COGNITION IN RECENT ONSET SCHIZOPHRENIA

Cover: Ilse Holthausen
Print: Ridderprint Offsetdrukkerij Ridderkerk

The studies described in this thesis were performed at the Department of Psychiatry, University Hospital Groningen in collaboration with:
- Department of Psychiatry, University Medical Center Utrecht
- Department of Psychiatry, Academic Medical Center, University of Amsterdam

The research described in this thesis was made possible by a grant from ZonMw (940-33-015). Publication of this thesis was supported by The Graduate School of Behavioral, Cognitive and Neurosciences.

ISBN: 90-367-1876-7

RIJKSUNIVERSITEIT GRONINGEN

Cognition in recent onset schizophrenia

Proefschrift

ter verkrijging van het doctoraat in de
Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. F. Zwarts,
in het openbaar te verdedigen op
woensdag 15 oktober 2003
om 16.00 uur

door

Esther Anna Elizabeth Holthausen
geboren op 18 augustus 1971
te Son en Breugel

Promotores	:	Prof. dr. R.J. van den Bosch Prof. dr. D. Wiersma
Beoordelingscommissie	:	Prof. dr. J.M. Bouma Prof. dr. R.S. Kahn Prof. dr. A.H. Schene

Contents

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

Chapter 2

Schizophrenic patients without neuropsychological deficits: subgroup, disease severity or cognitive compensation?

Published
Holthausen, E.A.E., Wiersma, D., Sitskoorn, M.M., Hijman, R., Dingemans, P.M., Schene, A.H., van den Bosch, R.J., 2001. Psychiatry Research 112, 1-11.

Abstract

Some schizophrenic patients do not show clinically relevant cognitive deficits. The question remains whether this represents the existence of 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 ("brain reserve") capacity. A group of 23 out of 118 first onset patients was identified as cognitively normal. The cognitive profile of these patients was compared with that of 45 healthy controls. Next these patients were compared with the cognitively impaired patients on obstetric complications, premorbid adjustment, age at onset, PANSS ratings, social functioning and substance abuse. In addition both groups were compared on intelligence and educational level as indirect indicators of cognitive compensation capacity. There were no differences in obstetric complications, premorbid adjustment, age at onset, psychopathology or substance abuse between both patient groups. There was a significant difference in social functioning, which is a consequence rather than a cause of cognitive deficits. However, the cognitively normal patients scored significantly higher on measures of intelligence and educational level than the cognitively impaired patients. This suggests that a difference in cognitive compensation capacity could explain the existence of a cognitively normal patient group.

1. Introduction

It is generally accepted that cognitive deficits are a major characteristic of schizophrenia. They are often supposed to be the fundamental impairment, which causes psychopathology and social dysfunctioning (Andreasen, 1997; Goldman-Rakic, 1994; Hemsley, 1994). However, not all schizophrenic patients show cognitive deficits according to standard clinical norms. Several studies have identified a group of schizophrenic patients with cognitive functioning within normal limits (Bryson et al., 1993; Palmer et al., 1997; Silverstein and Zerwic, 1985; Kremen et al., 2000). Estimates of the proportion of patients without neuropsychological impairments vary from 23 % (Kremen et al., 2000) to 73 % (Bryson et al., 1993).

There are several possible explanations for this phenomenon. The "cognitively normal" (CN) patients might represent a subgroup within the schizophrenic population. An etiological theory, which could explain the existence of cognitively normal and cognitively impaired (CI) subgroups, comes from Murray et al. (1987; 1992). He proposes that in a subgroup of patients, the CI patients, the disease has a distinct neurodevelopmental cause, which has its origins in genetic defects and early risk factors such as obstetric complications. These patients are characterized by premorbid symptoms, such as motor and behavioral problems, cognitive deficits, poor social adjustment, an early onset and more negative symptoms. The CN group also has a vulnerability to decompensate into psychotic symptoms, but they show less evidence of a developmental disease and are less likely to show premorbid symptoms or cognitive deficits. Another explanation for the existence of CN patients would be a general effect of disease severity. The difference between cognitively normal and cognitively impaired patients could be an artificial distinction on a severity continuum. This would imply that CN patients are less severely affected but still show signs of cognitive decline at a subclinical level. It is also to be expected that the more severe the disease, the more severe are all its manifestations from early age on, with the CN group showing better premorbid functioning, less psychopathology, and better social functioning.

The few studies that examined the characteristics of CN patients all used chronic patient groups in which the effects of hospitalization, recurrent episodes and long-term medication can bias the results. Most studies looked at

differences in psychopathology. None of these studies analyzed differences in obstetric complications and premorbid functioning, other than premorbid IQ estimates (Kremen et al., 2000). Silverstein and Zerwic (1985) found that CN patients had more paranoid symptoms than patients with cognitive deficits. Kremen et al. (2000) also found a significantly higher proportion of the paranoid subtype in the CN group, although there was no significant difference in symptom ratings. Both Palmer et al. (1997) and Torrey et al. (1994) showed that CN patients had less negative symptoms than CI patients. These data are not entirely consistent, but they suggest that the two groups show predominantly positive and negative symptoms respectively. This would be in accordance with the first explanation, which suggests that the neurodevelopmental, cognitively impaired group shows more negative symptoms. However a study of Kremen et al. (2000) showed that a schizophrenic subgroup with neuropsychological test scores within normal limits actually performed significantly worse and had a different profile shape than normal controls, which would be more in accordance with a general effect of disease severity. Indirect evidence for subclinical cognitive decline in the CN group also comes from studies with discordant monozygotic twins, in which in almost all cases the schizophrenic twin was cognitively impaired compared to his or her co-twin, who represented the optimal level of cognitive achievement (Goldberg et al., 1990; 1995; Torrey et al., 1994).

According to the literature both explanations could be true, still there could be another explanation as well. It is also possible that all patients have some sort of underlying neuropathology, which causes cognitive deficits in CI patients, but does not cause the same deficits in CN patients because they have more capacity to compensate for brain dysfunction. This would be in accordance with the " brain reserve capacity" theory (BRC; Satz, 1993) used in dementia research. This theory argues that, because of environmental enrichment, genetic predisposition or both, some individuals develop a cognitive reserve that may increase the threshold for cognitive symptoms after acquired brain pathology. Because psychosocial studies have shown the protective as well as the risk effects of intelligence and education on adaptive behavior, aging and health (Gurland, 1981; Mortimer, 1988), a number of studies have used intelligence and educational level as indirect measures of BRC (Mortimer, 1997; Mortimer and Graves, 1993; Schmand et al., 1997; Schofield, 1999; Stern et al., 1996). Of

course one could argue that it is self-evident that individuals with greater intelligence and better education simply perform better on neuropsychological tests. However, several longitudinal studies have shown a link between higher educational attainment and resistance to cognitive change (Evans et al., 1993; Farmer et al, 1995). Joyce et al. (2002) found a dissociation between cognition and IQ in a group of schizophrenic patients who had premorbid and current IQ levels in the normal range but displayed working memory deficits. Weickert et al. (2000) found a separate IQ component in a principal component analysis of neuropsychological and intellectual test data in a group of schizophrenia patients. Although the BRC model comes from dementia research, in which it is applied to an acquired neurological disorder, it could be applicable to schizophrenia as well. Schizophrenia is believed to be a neurodevelopmental disorder, but there is evidence that the most remarkable decline in cognitive functioning takes place just before or during illness onset (Kelly et al., 2000; Rabinowitz et al., 2000).

Our main objective was to separate a group of first onset schizophrenia patients with cognitive functioning within normal limits from cognitively impaired patients, to study whether this distinction reflects a difference in disease severity, two different subgroups or a difference in cognitive compensation capacity. If the CN group shows no evidence of cognitive deficits, less obstetric complications, less negative symptoms but no difference in positive symptoms as compared to the CI group, and premorbid adjustment comparable to controls, then this could indicate an etiologically different subgroup. Cognitive decline at subclinical levels, less severe psychopathology and better premorbid adjustment in the CN group as compared to the CI group, could indicate a difference in disease severity. If the difference between cognitively normal and cognitively impaired patients is caused by a difference in compensation capacity, the most important difference between the groups would be in intelligence and education, as indirect measures of compensation. Both groups were also compared on measures of social functioning and substance abuse to study the association between these variables and cognitive functioning.

2. Method

2.1. Subjects

The study included 118 patients who had recently experienced a first or a second psychotic episode according to DSM-IV (American Psychiatric Association, 1994) and were diagnosed within the schizophrenia spectrum (schizophrenia, schizoaffective disorder, schizophreniform disorder). All patients participated in a Dutch multicenter study of the university hospitals of Groningen, Utrecht and Amsterdam. Diagnosis was based on a structured interview (SCAN; Wing et al., 1990 or CASH; Andreasen et al., 1992). Exclusion criteria were severe mental retardation and a known systemic or neurological illness. Eighty-seven males and thirty-one females were included. Mean age was 23 years (sd 5.3). Forty-five healthy controls, thirty-eight males and seven females, were included in order to establish standard scores on cognitive tests. Exclusion criteria for controls were a history of mental illness, mental retardation and a known systemic or neurological illness. Mean age was 24 years (sd 6.4). The healthy control group was recruited through announcements in the local newspapers. There were no significant differences between patients and controls for sex (χ^2 = 2.10, n.s.) or age ($F(1,161) = 0.29$, n.s.). Twenty-five patients used typical antipsychotics, seventy-five patients used atypical antipsychotics, eighteen patients did not use antipsychotic medication. Ten patients also used anticholinergic medication.

2.2. Procedures and instruments

Cognitive measures

All patients completed an extensive neuropsychological battery after being stabilized for at least six weeks on medication. Most cognitive measures in our study were chosen because of their widespread use in clinical practice. In addition, there should be evidence for their discriminatory power in studies of schizophrenic patients and normal controls on these measures (e.g. Keefe et al., 1995; Saykin et al., 1994; Van den Bosch et al, 1996). The cognitive measures were grouped into nine ability areas as presented in Table 1. Tests included a

double stimulus Continuous Performance Task (CPT; van den Bosch et al., 1996); a computerized STROOP task; form A, B and C of a new version of the Trail Making Test (Vink and Jolles, 1985); a Finger tapping test; the Dutch translation of the California Verbal Learning Test (Delis et al., 1987); the Rey Complex Figure Test (Rey, 1964); Verbal Fluency tasks (category and letter);

Table 1. Cognitive battery with tests grouped by ability area

Perceptual sensitivity
CPT d'
Attention-selectivity
STROOP interference score
Trail Making Test interference score
Perceptual and psychomotor speed
CPT RT (ms)
Trail Making A and B (s)
STROOP names (s)
STROOP colors (s)
Finger tapping
Memory-verbal-encoding
CVLT trial 1 to 5
Memory-verbal-consolidation
CVLT long term free recall minus trial 5
Memory-verbal-retrieval
CVLT short term free recall minus short term cued recall
CVLT long term free recall minus long term cued recall
CVLT difference between recognition and long term recall
Memory-visual
Rey Complex Figure Test percentage immediate recall
Rey Complex Figure Test percentage delayed recall
Spatial Working Memory Task immediate recall
Spatial Working Memory Task delayed recall
Verbal Fluency
Verbal Fluency Categories
Verbal Fluency Letters
Visuoconstruction
Rey Complex Figure Test copy

a computerized Spatial Working Memory Task (Keefe, 1995). When variables resembled the normal distribution, patients' test scores were transformed into z-scores using means and standard deviations of the normal control group. Otherwise normalized standard scores were used to establish cut-off points. In this procedure, the percentage of persons in the standardization sample falling at or above a raw score point is calculated. This percentage is transformed into a z score by reference to a normal distribution frequency table (Walsh and Betz, 1985). A patient was considered cognitively impaired if he had at least one z score of 2 or more below normal in one ability area. The z-scores and normalized standard scores were also used to compute the mean z-scores per domain for all three groups.

Obstetric complications, premorbid adjustment, age at onset

Information concerning obstetric complications (OCs) was obtained with a self-report questionnaire for the mother. Because the frequency of individual OCs is not very high, two sum scores representing the different reproductive periods (pregnancy and birth) were computed and used as dichotomous items in the

analyses. Because hypoxia is mentioned as an important factor in explaining the relation between OCs and schizophrenia in recent reviews (McNeil et al., 2000; Geddes et al., 1999), a special sum score for OCs related to hypoxia was also computed. OCs during pregnancy were: vaginal bleeding; early contractions; high blood pressure; rhesus incompatibility; pre-eclampsia; rubella; syphilis; substance abuse from the mother. OCs during birth were: gestational age less than 37 weeks; caesarian; labor longer then 36 hours; breech delivery; forceps delivery; vacuum extraction; epileptic seizures; incubator more then 4 weeks; birth weight lower then 2000 grams; placental anomalies; cord prolapse; cyanosis; slow heart rate; asphyxia; oxygen treatment. The latter five were also used to compute a hypoxia sum score. Premorbid adjustment was inferred from employment status and history of intimate relationships before inclusion. Data concerning premorbid adjustment and age at onset were gathered in a Case Record Form using all possible sources of information.

Psychopathology, substance abuse and social functioning

Symptoms were rated on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) within the same week as the neuropsychological assessment. These ratings were used to obtain dimensional scores by calculating the sum scores loading high on the positive, negative, disorganization, depression and excitement dimensions as described in Lindenmayer et al. (1995). The total PANSS score minus the disorganization dimension was used as a general measure of psychopathology. The disorganization dimension was left out of the computation because of a large overlap with cognitive measurements (Bryson et al.1999). Depressive symptoms were also rated with the Montgomery Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979). Not all variables resembled the normal distribution. If possible log and square root transformations were performed. Social functioning during the month preceding inclusion was assessed with the Groningen Social Disabilities Schedule (GSDS; Wiersma et al., 1988), a semi-structured interview that measures social role functioning on seven roles. Substance abuse or dependence was rated with the relevant section of the Composite International Diagnostic Interview (CIDI; WHO, 1990). Substance abuse or dependence was divided into four substance categories for analyses

Indirect measures of cognitive reserve capacity: education and intelligence

Level of education and performance on intelligence tasks were taken as indirect measures of compensation. All subjects were asked about their highest educational attainment, and whether they still received education at illness onset. The Dutch educational system differentiates already after primary school; therefore we have chosen a coding system other than years of education. This goes from 1: primary school up to 8: university or graduate school. Thirty seven percent of the patients still received education; for these patients we took the level they were aiming at minus half a point (e.g., a Law school student received a code of 7.5 instead of 8). A log transformation was performed on educational level in order to fit the normal distribution. Four subtests of the Dutch translation of the Wechsler Adult Intelligence Scale, (WAIS; Stinissen et al., 1970): comprehension, vocabulary, block design and picture arrangement, were administered to the patients. The mean subtest C-score of these four subtests was taken as a measure of intelligence. These C-scores go from 0 tot 10 with a mean of 5 and a standard deviation of 2. Because the Dutch translation of the WAIS is from 1970, we also give corrected mean C-scores in which we take account for an estimated IQ gain of 0.25 IQ points a year from 1971 to 1996 (Flynn, 1998). The corrected average C-score is 5.8 with a standard deviation of 2.

3. Results

A group of 23 patients (19%) without clinically relevant cognitive deficits was identified. The other 95 patients had deficits in at least one ability area (range 1-8). 34 of the 45 controls (76 %) had no cognitive deficits according to our criteria. If we use our criteria to predict group membership (schizophrenia versus healthy controls) 79 % of the subjects is correctly classified, the sensitivity is 81% and the specificity is 76 %. The CN group consisted of 15 men and 8 women; mean age was 24.8 years (sd 5.5), average parental education was at High School level. Four patients used typical antipsychotics, fourteen used atypical antipsychotics, five patients did not use antipsychotic medication. One patient also used anticholinergic medication. The CI group

consisted of 72 men and 23 women; mean age was 22.9 years (sd 5.2), average parental education was at High School level. Twenty-one patients used typical antipsychotics, sixty-one used atypical antipsychotics, eight patients did not use antipsychotic medication. Nine patients also used anticholinergic medication. There were no significant differences between CN and CI patients for sex (χ^2 = 1.07, ns.), age (F(1,116) = 2.43, ns.), parental education (F (1,98) = 1.85, ns.), type of medication (χ^2 = 3.05, ns.) or the use of anticholinergic medication (χ^2 = 0.63, ns.).

The question whether the CN group was really cognitively normal or showed cognitive deficits at subclinical levels was examined by independent-sample t-tests between CN patients and controls and visual inspection of cognitive profiles (Table 2 ; see also Figure 1).

Table 2. Cognitive ability area scores for CN and CI patients and effect sizes for the comparison between CN and CI patients and CI patients and controls

	Cognitively normal n= 32		**Cognitively impaired, n = 95**		**Effect size CN vs. CI patients**[1]	**Effect size CN vs. controls**[2]
	mean	sd	mean	sd		
1.Perceptual- sensitivity	-0.25	0.88	-1.68	1.37	1.04	-0.25
2. Attention-selectivity	0.04	0.83	-0.65	1.43	0.48	0.04
3. Speed	-0.60	0.45	-1.75	1.12	1.03	-0.60
4. Verbal encoding	-0.57	0.72	-1.42	1.09	0.78	-0.57
5. Verbal consolidation	0.46	1.46	-0.50	1.47	0.65	0.46
6. Verbal retrieval	0.06	0.78	-0.33	0.82	0.48	0.06
7. Visual memory	-0.00	0.63	-1.28	1.39	0.92	0.00
8. Verbal Fluency	-0.32	0.80	-1.00	0.68	1.00	-0.32
9. Visuoconstruction	-0.08	1.11	-1.08	2.06	0.49	-0.08

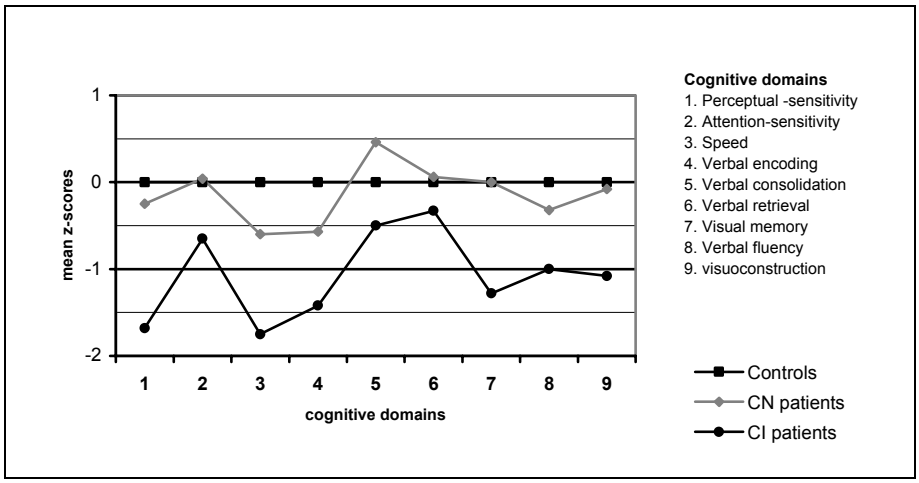
[1] Cohen's d based on the standard deviation of the CI group
[2] Cohen's d based on the standard deviation of the control group

The CN patients performed significantly worse than controls on perceptual and psychomotor speed (t (66) = 3.85, p < .000) and verbal encoding (t (66) = 2.44, p = .017), with medium effect sizes. The cognitive profile shape of the CN patients deviates from that of normal controls and follows that of CI patients, who performed worse than both controls and CN patients on all domains.

Although the profiles suggest that CN patients performed better than controls on verbal consolidation, this difference is not significant. Differences between CN and CI patients were also tested by independent sample t tests.

All differences were significant, with 5 effect sizes in the larger range; all other effect sizes were medium.

Figure 1. cognitive profiles



Differences between CN and CI patients on obstetric complications, premorbid adjustment and substance abuse were tested with chi-squared tests (table 3). Data concerning the employment status of normal controls were also available (17.8 % regular employment, 71.1 % study and 11.1 % unemployed). There was no significant difference between controls and CN patients, but there was a significant difference between controls and CI patients in employment status (χ^2 = 13.99, p = .001). Differences on age at onset, psychopathology, social functioning and indirect measures of compensation were tested with ANOVA or Mann-Whitney U tests. Differences in the percentage of subjects showing disabilities on individual social roles were tested with chi-squared tests (table 4). There were no significant differences in obstetric complications, employment situation before inclusion, history of intimate relationships or age at onset.

There was no significant difference on general psychopathology minus disorganization. Also no evidence for different symptom profiles was found. The CI patients only had a significantly higher score on the disorganization dimension ($F(1,116) = 4.93$, $p < .05$). No significant differences in substance abuse or dependence were found.

Table 3. Differences between patients with and without cognitive deficits on obstetric complications, premorbid adjustment and substance abuse.

	Cognitively normal n = 23 % patients	**Cognitively impaired n = 95** %patients	**Significance** (Chi-squared, two-tailed)
Obstetric complications			
Pregnancy	35.3	48.7	ns.
Birth	43.8	31.5	ns.
Hypoxia-related	31.3	20.5	ns.
Premorbid adjustment			
Employment status			
Regular	39.4	26.4	
Study	37.2	47.8	ns.
Sickness benefit, sheltered employment, unemployed	23.4	26.1	
History of intimate relationship			
Never	50.0	39.1	
< 6 months	27.7	21.7	ns.
> 6 months	22.3	39.1	
Substance abuse			
Alcohol	24.5	21.7	ns.
Cannabis	54.1	47.4	ns.
Sedatives	4.2	0	ns.
Miscellaneous	9.5	13.0	ns.

Both patient groups differed significantly in general social functioning, in favor of the CN group. This was significant for the self-care role ($\chi^2 = 4.46$, $p < .05$) and the work role ($\chi^2 = 8.09$, $p < .01$). CN Patients scored significantly higher on intelligence ($F(1,116) = 7.19$, $p < .01$) and level of education ($F(1,116) = 7.30$, $p < .01$) than CI patients. Mean level of education for the controls was 5.9 with a standard deviation of 1.5. The difference between CN patients and controls was not significant, the difference between CI patients and controls was significant ($t(138) = 6.39$, $p < .000$)

Table 4. Differences between patients with and without cognitive deficits on age at onset, psychopathology, social functioning, and indirect measures of cognitive compensation.

	Cognitively "normal" patients n = 23		**Cognitively impaired patients, n = 95**		**Significance** (two-tailed)
	mean	sd	mean	sd	
Age at onset	23.7	5.6	21.8	4.9	ns.
Psychopathology					
Positive *	2.0	1.1	2.3	1.0	ns.
Negative	2.0	0.7	2.4	1.0	ns.
Disorganization	1.6	0.3	1.9	0.7	.028
Depression	2.1	0.9	2.4	1.0	ns.
Excitement	1.4	0.6	1.7	0.8	ns.
PANSS total minus disorganization	47.4	12.9	53.8	16.2	ns.
MADRS total score	12.3	9.4	14.6	10.4	ns.
Social functioning					
Total score**	1.0	0.7	1.3	0.6	.035
Self care***	26.1		50.5		.029
Family role	69.6		78.9		ns.
Kinship role	52.2		67.4		ns.
Partner role	56.5		69.5		ns.
Citizen role	73.9		81.1		ns.
Social role	56.5		65.3		ns.
Work role	69.6		91.6		.010
Compensation					
level of education (1-8)	5.3	2.3	3.9	2.1	.011
mean WAIS C-score (1-10)	6.8	1.0	5.9	1.5	.008
Mean corrected WAIS C-score	6.1	1.0	5.4	1.5	.008

* Standardized PANSS ratings ranging from 1:absent to 7: extreme

** Standardized GSDS ratings ranging from 0: no disability to 3: extreme disability

** * Percentage of subjects showing disability

4. Discussion

In this study 19 % of the patients were found to have no cognitive deficits, which is lower than the percentage found in some other studies (63 % in Zilverstein and Zerwic, 1985; 42% and 73% in Bryson et al., 1993). We preferred a conservative approach, however. Patients with only one deficit were already classified as cognitively impaired, whereas the other studies used the

Luria-Nebraska or the Halstead-Reitan impairment scores, so patients had to perform weakly on several items to be classified as cognitively abnormal. There is a negligibly small difference with the studies of Palmer et al. (27%; 1997) and Kremen et al. (23%, 2000) who also used a composite neuropsychological battery and more stringent criteria. If the criteria for cognitive impairment were used to predict group membership, than all three studies would classify a fair amount of subjects correctly (respectively, 76 %, 85% and 79% in chronological order). Our study would be the most sensitive and the least specific. This means that our criteria for cognitive normality were most strict.

Our results suggest that the CN patients still show signs of cognitive decline at a subclinical level, because their cognitive profile deviates from that of normal controls and follows more or less the same direction as that of the CI patients. The CN patients performed significantly below the level of normal controls on perceptual and psychomotor speed and verbal encoding. They performed better, although not significantly, than controls on the verbal consolidation measure. This might be an artifact because consolidation is computed by subtracting the number of words on delayed recall from the number of words on immediate recall (verbal encoding). Since the CN patients already showed a weak performance on verbal encoding, they could not loose many words from memory. The subclinical deficits in the CN group and their almost similar profile shape suggest that the two patients groups do not represent etiologically different subgroups. It rather suggests that all patients experience cognitive dysfunctions at a certain level even if they are still within normal limits. The fact that no differences between both groups in obstetric complications, age at onset or premorbid adjustment were found, makes it even less likely that the CN patients represent an etiologically different subgroup.

However, no significant difference in the total level of psychopathology (minus disorganization because of conceptual redundancy) and age at onset was found. The only significant difference in psychopathology was found on the disorganization dimension. These findings reject a general effect of disease severity.

The only measures on which the CN group scored higher, apart from social functioning, were education and intelligence. The CN group had a score slightly above average on intelligence tests. Mean educational attainment was also reasonably high in this group, a level comparable with College. This is in

accordance with the brain reserve capacity theory (BRC; Satz, 1993), which states that people with greater BRC, measured indirectly by education and intelligence, are better able to compensate for the negative effects of brain pathology on cognition. There is evidence that not all domains of cognitive functioning are equally affected in schizophrenia. Several studies mention a generalized deficit with more pronounced impairment in verbal learning, attention-vigilance and speeded visual-motor processing (Censits et al., 1997; Saykin et al., 1991; 1994). Therefore it is possible that compensation in these more severely affected areas is not always conclusive, which could explain the significant differences on verbal learning and perceptual and psychomotor speed between CN patients and controls.

Cognitive deficits are associated with social dysfunctioning in schizophrenia (Dickerson et al., 1996; Green, 1996). Therefore it is to be expected that the CI group has more problems in social functioning. Indeed, both patient groups differed significantly in general social functioning in favor of the CN patients. Close inspection of the various social roles, however, revealed that this was mostly due to significant differences in self-care and work roles. These roles depend less on interpersonal interactions and more on the acquisition and execution of skills than the other roles. It is possible to function marginally in interpersonal contacts and still perform within normal limits on a job with less interpersonal demands. No significant differences in rates of substance abuse or dependence between the two patient groups were found. This suggests that the effect of chronic substance use on cognition is not very strong.

Because not much time had passed between onset of the current episode and time of testing it is possible that state-like effects have had their impact on cognitive performance. It seems unlikely that this will have significant effects on the results of this study because there is no reason to assume that both patient groups are differentially affected. Also, the BRC theory is applicable for both state and trait like effects of brain dysfunction on cognition. One could also argue that the differences in cognition between CN and CI patients are caused by the same amount of cognitive decline from different levels of cognitive functioning as is paralleled in differences in IQ and education. However, IQ and cognition are not identical as was shown by Joyce et al. (2002) and Weickert et al. (2000). And a decline from higher levels would implicate that premorbidly

CN patients would have performed above the level of normal controls on five of the nine domains, on which they now equal controls, which is highly unlikely.
The use of the BRC theory, normally used in research on progressive dementia, for a neurodevelopmental disorder as schizophrenia also raises some questions. In dementia the BRC predicts later onset of cognitive deficits for those with greater cerebral reserve. Because schizophrenia is not a progressive deteriorating brain disease, we suggest that cerebral reserve will be protective against the cognitive effects of neuropathology at any age. It could be argued that it is not justified to use education as an indirect measure of compensation capacity in schizophrenia because of premorbid attenuated educational attainment. It is not clear however at what developmental stage educational attainment is affected. In the NIMH discordant twin study for example school grades were strikingly similar between affected and well twins (Torrey et al., 1994). So it seems more likely that educational attainment is not severely affected during early development. The Dutch educational system, and hence our scoring system, is rather robust for this, because the Dutch system already differentiates after primary school into four levels.
Overall this study suggests that cognitive compensation could explain the existence of cognitive "normality" in schizophrenia. The evidence is rather indirect, because we cannot proof directly that CN patients truly resist the cognitive effects of brain pathology due to a larger compensation capacity. We did not have premorbid cognitive data or an estimate of premorbid intelligence. There were, however, no differences in other indicators of premorbid functioning (employment status or intimate relationships), which suggests that there were no large differences in general functioning other than intelligence and educational level between both groups before illness onset. This would make it less likely that CI patients already showed the severe cognitive deficits found in this study before illness onset. We think that compensatory mechanisms should be included in comprehensive models of cognitive dysfunction in schizophrenia.
This study also seems to challenge models of schizophrenia in which cognition is seen as the core deficit, and the cause of clinical symptoms (Goldman-Rakic, 1994; Hemsley, 1994), because CN patients performed significantly better than CI patients on all cognitive domains, while no significant differences in psychopathology were found.

References

American Psychiatric Association, 4th edn, 1994. Diagnostic and Statistical Manual of Mental Disorders. 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., 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.

Bryson, G., Bell, M., Greig, T., Kaplan, E., 1999. Internal consistency, temporal stability and neuropsychological correlates of three cognitive components of the Positive and Negative Syndrome Scale (PANSS). Schizophr. Res. 38, 27-35.

Bryson, G.J., Silverstein, M.L., Nathan, A., Stephen, L., 1993. Differential rate of neuropsychological dysfunction in psychiatric disorders: comparison between the Halstead-Reitan and Luria-Nebraska batteries. Percept. Mot. Skills 76, 305-306.

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.

Delis, D.C., Kramer, J.H., Kaplan, E., Ober, B.A., 1987. California Verbal Learning Test (CVLT) Manual. New York: the Psychological Corporation.

Dickerson, F., Boronow, J.J., Ringel, N., Parente, F., 1996. Neurocognitive Deficits and social functioning in outpatients with schizophrenia. Schizophr. Res. 21, 75-83.

Evans, D.A., Beckett, L A., Albert, M S., Hebert, L.E., Scherr, P.A., Funkenstein, H.H., Taylor, J.O., 1993. Level of education and change in cognitive function in a community population of older persons. Annals of Epidemiology 3, 71-77.

Farmer, M.E., Kittner, S.J., Rae, D.S., Bartko, J J., Regier, D.A., 1995. Education And change in cognitive function. The Epidemiologic Catchment Area Study. Ann. Epidemiol. 5, 1-7.

Lynn, J.R., 1998. WAIS-III and WISC-III IQ gains in the united states from 1972 To 1995: how to compensate for obsolete norms. Percept. Mot. Skills, 86, 1231 1239.

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

Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am. J. Psychiatry 153, 321-330.

Goldberg, T.D., Ragland, J.D., Torrey, E.F., Gold, J.M., 1990. Neuropsychological assessment of monozygotic twins discordant for schizophrenia. Arch. Gen. Psychiatry 47, 1066-1072.

Goldberg, T.E., Torrey, E.F., Gold, J.M., Bigelow, L.B., Ragland, R.D., Taylor, E., Weinberger, D.R., 1995. Genetic risk of neuropsychological impairment in schizophrenia: a study of monozygotic twins discordant and concordant for the disorder. Schizophr. Res. 17, 77-84.

Gurland, B.J., 1981. The borderlands of dementia: the influence of sociocultural characteristics on the rates of dementia occuring in the senium. In N.E. Miller and G.D. Cohe (Eds), Aspects of Alzheimer's disease and senile dementia. Raven Press, New york, pp. 61-80.

Hemsley, D.R., 1994. Cognitive disturbance as the link between schizophrenic symptoms and their biological basis. Neurol. Psychiatry Brain Res. (Abstract) 2, 163-170.

Joyce, E.M., Hutton, S.B., Mutsatsa, S.H., Webb, E., Paul, S., Barnes, T.R.E. 2002. Contribution of IQ to risk of schizophrenia and cognitive profile at first episode: the West London study (Abstract). Schizophr. Res. 53, 140.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The Positive and Negative Syndrom Scale (PANSS) for schizophrenia. Schizophr. Bull. 16,537-545.

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.

Kelly, C., Sharkey, G., Morrison, G., Allardyce, J., McCreadie, R.G., 2000. Nithsdale Schizophrenia Surveys 20; Cognitive function in a catchment-area based population of patients with schizophrenia. Br. J. Psychiatry 177, 348-353.

Kremen, W.S., Seidman, L.J., Faraone, S.V., Toomey, R., Tsuang, M.T., 1999. The question of neuropsychologically normal schizophrenia (Abstract). Schizophr. Res. 36, 140.

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

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

Montgomery, S.A., Åsberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382-389.

Mortimer, J.A., 1988. Do psychosocial factors contribute to Alzheimer's disease? In J. H. Henderson, A.S. Henderson (Eds), Etiology of dementia of Alzheimer's type. Wiley, New York, pp. 39-52.

Mortimer, J.A., 1997. Brain reserve and the clinical expression of Alzheimer's disease. Geriatrics 52 Suppl 2, S50-S53.

Mortimer, J.A., Graves, A.B., 1993. Education and other socioeconomic determinants of dementia and Alzheimer's disease. Neurology Vol 43, S39-S44.

Murray, R.M., Lewis, S.W., 1987. Is schizophrenia a neurodevelopmental disorder? Br. J. Psychiatry 295, 681-682.

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

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.

Rabinowitz, J., Reichenberg, A., Weiser, M., Mark, M., Kaplan, Z., Davidson, M., 2000. Cognitive and behavioral functioning in men with schizophrenia both before and shortly after first admission to hospital. Br. J. Psychiatry 177, 26-32.

Rey, A., 1964. L'examen clinique en psychologie. Presses Universitaires de France, Paris.

Satz, P., 1993. Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. Neuropsychology 7, 273-295.

Saykin, A.J., Gur, R.C., Gur, R.E., Mozley, P.D., Mozley, L.H., Resnick, S.M., Kester, D.B., 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.

Schmand, B., Smit, J.H., Geerlings, M.I., Lindeboom, J., 1997. The effects of intelligence and education on the development of dementia. A test of the brain reserve hypothesis. Psychol. Med. 27, 1337-1344.

Schofield, P., 1999. Alzheimer's disease and brain reserve. Australas. J. Ageing 18, 10-14.

Silverstein, M.L., Zerwic, M.J., 1985. Clinical psychopathologic symptoms in neuropsychologically impaired and intact schizophrenics. J. Consult. Clin. Psychol 53, 267-268.

Stinissen, J., Willems, P.J., Coetsier, P., Hulsman, W.L.L., 1970. Manual of the Dutch translation of the Wechsler Adult Intelligence Scale. Swets, Amsterdam.

Torrey, E.F., Bowler, A.E., Taylor, E.H., Gottesman, I.I., 1994. Schizophrenia and manic-depressive disorder. Basic Books, New York.

Van den Bosch, R.J., Rombouts, R.P., van Asma, M.J., 1996. What determines continuous performance task performance? Schizophr. Bull. 22, 643-651.

Vink, M., Jolles, J., 1985. A new version of the Trail making Test as an Information processing task. J. Clin. Neuropsychol. 7, 162.

Walsh, W. B., Betz, N. E., 1985. Tests and assessment. Prentice Hall, New Yersey.

Weickert, T.W., Goldberg, T.E., Gold, J.M., Bigelow, L.B., Egan, M.F., Weinberger, D.R., 2000. Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. Arch. Gen. Psychiatry, 57, 907-913.

Wiersma, D., DeJong, A., Ormel, J., 1988. The Groningen Social Disabilities Schedule: development, relationship with I.C.I.D.H., and psychometric properties. Int. J. Rehab. Res. 11, 213-224.

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.

World Health Organization. 1990. Composite International Diagnostic Interview (CIDI).WHO,Geneva

Chapter 3

Does frontal normality exist in schizophrenia? A saccadic eye movement study

Published:
Broerse, A., Holthausen, E.A.E., van den Bosch, R.J., den Boer, J.A., 2001.
Psychiatry Res. 103: 167-178, 2001

Abstract

Many observations have supported the general idea of impaired frontal function in schizophrenia. In particular neuropsychological studies have shown severe frontal deficits. However, other studies found normal cognitive function in a proportion of patients. Since saccadic tasks also provide an index of frontal function, we examined the presence of frontal deficits in patients by means of both neuropsychological and saccadic tasks, and compared the sensitivity of both approaches for frontal impairment. In addition, we examined the relationship between saccadic and neuropsychological measures. Twenty-four schizophrenic patients and twenty healthy controls completed an extensive neuropsychological battery and three saccadic tasks. Based on the neuropsychological battery alone, 42% of the patients showed frontal deficits, whereas combined use of neuropsychological and saccadic tasks resulted in 79% with frontal deficits. The antisaccade task appeared able to detect frontal deficits in patients who were without frontal impairment on the neuropsychological battery. Saccadic deficits were, however, not necessarily accompanied by deficits on frontal neuropsychological measures. This suggests that the saccadic and neuropsychological tasks used in the present study targeted different frontal functions. This view was supported by the lack of correlations between saccadic and frontal neuropsychological measures.

1. Introduction

Many observations have supported the general idea of impaired frontal function in schizophrenia. In particular, studies addressing frontal functions by means of neuropsychological (NP) tests have demonstrated severe cognitive deficits. It has, therefore, been proposed that frontal cognitive deficits are among the core deficits of schizophrenia (Goldman-Rakic 1994; Hemsley 1994). However, this assumption is not in accordance with studies that found a substantial proportion of patients with normal NP performance, including performance on frontal tasks (Silverstein & Zerwic 1985; Bryson et al. 1993; Palmer et al. 1997; Holthausen et al. 2002). Estimates of this proportion vary from 19% (Holthausen et al. 2002) to 73% (Bryson et al. 1993).

In order to determine if frontal impairment is a core deficit of schizophrenia, it seems worth the effort to evaluate frontal functions by means of an alternative method, namely the recording of saccadic eye movements. Saccades are fast eye movements, which are made to fixate objects on the fovea. These eye movements can be easily implemented in various cognitive tasks. An advantage of such tasks is that the neural systems subserving these tasks are well known from primate studies (Bruce & Goldberg 1985; Hikosaka & Wurtz 1991; Everling et al. 1999) and performance is not dependent on manual and verbal capacities. In addition, a smaller number of cognitive subprocesses are involved, since the visual stimuli are very simple and do not require complex integrative processing (in contrast to pictures, words, etc), and the eye movement response does not require cross-modal integration. Due to these characteristics, we presume that saccadic tasks target frontal functions rather specifically.

Saccadic tasks have proven to be a valuable tool in estimating functional impairment in certain psychiatric patient groups (Everling & Fischer 1998). In particular, in schizophrenic patients saccadic abnormalities were found (Thaker et al. 1989; Crawford et al. 1995; Hutton et al. 1998). With respect to these abnormalities, it is useful to make a distinction between visually guided (or externally driven) saccades and voluntary saccades, which are usually generated in (simple) cognitive paradigms (Tusa et al. 1986). Visually guided saccades require mainly spatial attention and the generation of a precise motor program, whereas voluntary saccades require intact higher order, executive functions. A

large number of studies have shown that schizophrenic patients perform accurately on visually guided saccades (Crawford et al. 1995; Hutton et al. 1998; Karoumi et al. 1998), whereas they have severe problems with voluntary saccades, as measured in, for example, the antisaccade and memory saccade task. On these tasks, patients show typical failures in suppressing response tendencies towards suddenly appearing stimuli (Crawford et al. 1995; McDowell & Clementz 1997).

Saccadic tasks and NP tasks have both been used to assess frontal functions. It is, therefore, not surprising that several studies have looked at the relationship between these tasks in psychiatric patient groups (Rosse et al. 1993; Crawford et al. 1995; Schreiber et al. 1995; Tien et al. 1996; Radant et al. 1997; Karoumi et al. 1998; Snitz et al. 1999; Nieman et al. 2000; Gooding & Tallent 2001). The majority of these studies, however, used only few NP tests. Moreover, the results were inconsistent, except for a positive association between antisaccade inhibition failures and performance on the Wisconsin Card Sorting Test (WCST; perseveration errors) (Rosse et al. 1993; Crawford et al. 1995; Tien et al. 1996; Radant et al. 1997; Karoumi et al. 1998) and a spatial working memory task (Gooding & Tallent 2001). These positive associations have been attributed to a common dependency on the (dorsolateral) prefrontal cortex (DLPFC), which has been reported to be crucially involved in each of these tasks (Berman et al. 1986; Goldman-Rakic 1994; O'Driscoll et al. 1995; Sweeney et al. 1996; Doricchi et al. 1997). Since neuroimaging studies have shown that various other NP tasks, like the Continuous Performance Task (Hager et al. 1998), the Stroop Task (Peterson et al. 1999), the Trail Making Test (Lesnik et al. 1998), and Verbal Fluency (Hugdahl et al. 1999), are also dependent on the (pre)frontal cortex, it remains to be elucidated why previous studies failed to find consistent associations between these tasks and saccadic tasks. The extent of DLPFC involvement in these NP tasks might determine whether significant relations are obtained.

The main goal of the present study was to evaluate the assumption that frontal impairment is a core deficit of schizophrenia, an assumption which implies that *all* patients show frontal deficits. Since the traditional use of NP tests has revealed inconsistent results, frontal function was examined by means of NP tasks as well as saccadic tasks, which were presumed to target frontal function more specifically. We examined whether adding saccadic tasks to a NP test

battery would increase the sensitivity to detect frontal impairment, and whether specific saccadic measures were more sensitive to frontal deficits than NP tasks. Therefore, we first established the number of patients with frontal deficits based on the NP tasks alone, and compared this with the number of patients obtained when NP tasks were combined with saccadic tasks. Second, we compared the performance on specific saccadic measures in patients *with* and *without* frontal impairment on the NP test battery. We also examined the number of patients showing deficits in two other, non-frontal domains, namely psychomotor speed and memory. Finally, we were interested in the relationship between saccadic measures, which were presumed to target frontal function, and frontal NP measures, since the literature provides inconsistent results on these correlations.

2. Methods

2.1 Subjects

The study included 24 patients (18 males and 6 females) who had recently experienced a first or a second psychotic episode according to DSM-IV (American Psychiatric Association 1994) and received a diagnosis within the schizophrenia spectrum (schizophrenia, n=12; schizophreniform disorder, n=11; schizoaffective disorder, n=1). The diagnosis was based on a structured interview (SCAN; Wing et al. 1990). Exclusion criteria were severe mental retardation, systemic or neurologic illness, severely impaired vision, medication other than antipsychotics, and severe tardive dyskinesia. The mean age was 26.54 (SD 8.47) years and average education was at high school level. Eighteen patients used atypical antipsychotic medication (olanzapine and risperidone), five patients used classic antipsychotic medication, and one patient was drug-free.

A control group of 20 healthy volunteers (15 males and 5 females), recruited from the local community, was included to evaluate the saccadic performance of patients. The mean age was 20.95 (SD 2.80) years and average education was at high school level.

The patient and control groups were matched for gender and level of education, whereas there was a difference for age ($p = .007$). The factor age is known to

have an influence on both cognitive (Elias et al. 1990) and saccadic performance (Fischer et al. 1997), however, the age difference between our groups was too small (5.6 years) to have a significant influence on performance.

2.2 Neuropsychological measures

An extensive NP test battery was completed. Tests included a double stimulus Continuous Performance Task (CPT; Van den Bosch et al. 1996), a computerized Stroop task (Stroop 1935), the Trail Making Test (TMT; Vink & Jolles 1985), a Finger Tapping test, the Dutch translation of the California Verbal Learning Test (CVLT; Delis et al. 1987), the Rey Complex Figure (RCF; Rey 1964), and Verbal Fluency (VF). Table 2 shows the 15 measures obtained by each of these tests. The following four measures were considered to reflect frontal functioning: CPT *d'*, Stroop interference, TMT interference, and VF items in category. The raw test scores were converted into *z* scores, and patients showing a *z* score below –2 on one of the four frontal measures were characterized as 'frontally impaired' (FI), whereas the other patients were characterized as 'frontally normal' (FN). This criterion for group assignment was chosen, because of its frequent use in clinical settings. A similar procedure was used to determine the presence of deficits in two non-frontal domains, psychomotor speed and memory. The following five measures were considered to reflect psychomotor speed: CPT reaction time, Stroop word reading and color naming, TMT trail A, and Finger Tapping, whereas memory function was presumed to be reflected in: CVLT encoding, consolidation, retrieval, total intrusions, and RCF percentage recall.
In order to examine the relationship between saccadic measures and NP performance in the frontal, psychomotor speed, and memory domains, we calculated three composite scores for each of these domains. These were based on the mean *z* scores of the NP measures described above.

2.3 Saccadic eye movement recording

Subjects were comfortably seated 90 cm in front of a color monitor in a darkened room. Eye movements were recorded using an infrared limbus reflection device (Iris Skalar, Skalar Medical, B.V.), and head movements were restrained by an adjustable headrest. Visual stimuli, small green squares of approximately 3 mm, were presented against the darkened color monitor. Before presentation of the tasks, subjects were presented with calibration stimuli and a series of 20 practice trials. Saccades were identified using interactive software (developed at the University Maastricht, The Netherlands) which enabled the rejection of artifacts due to, for example, eye blinks.
Saccade detection was based on a velocity criterion of 30°/s in addition to an acceleration across three consecutive samples. Since the minimum latency of a visually guided saccade is approximately 100 ms (Fischer & Ramsperger 1984), the first saccade of at least 3° made 100 ms after target onset was scored as the response.

2.4 Saccadic measures

Three saccadic tasks were completed: a visually guided saccade task, an antisaccade task and a memory saccade task (Figure 1).
Visually guided saccade task After central fixation (800 ms), a stimulus was randomly presented 7.5° or 15° to the left or right for 1000 ms. Subjects were expected to respond with a rapid and accurate eye movement. Intertrial interval was 1000 ms, and 48 trials were completed. This task required the integration of spatial attention, visual perception, and a precisely targeted motor program, but placed few demands on higher order, executive functions. The performance was evaluated for latency of saccadic onset and the number of too early anticipations on stimulus behavior.
Antisaccade task After central fixation (800 ms), a stimulus was randomly presented 7.5° or 15° to the left or right for 2000 ms. Subjects were required to direct a saccade towards the spatial position in the visual field opposite to that of the stimulus. There was no intertrial interval, and 48 trials were completed. The task required both the suppression of the reflexive saccade that would

normally be generated in response to a novel visual target and the generation of a volitional saccade to the opposite hemifield. The performance was evaluated for the number of inhibition errors (reflecting a failure in the ability to suppress a response tendency), the latency of appropriate saccades, and the latency of the inhibition errors.

Memory saccade task After central fixation (800 ms), a stimulus was randomly presented 7.5° or 15° to the left or right for 200 ms. Subjects were required to suppress the reflexive saccade to the stimulus and delay the saccade for 700 ms (until fixation point offset). There was no information on the location of the previously presented stimulus at the moment of saccade initiation. Intertrial interval was 3000 ms, and 48 trials were accomplished. This task examined the ability to generate an internal representation of space as well as the programming of a volitional motor action and the ability to delay (inhibit) the saccadic motor program during the memorization period. The task also examined the inhibition of an immediate saccadic reflex to the stimulus. However, this inhibition was relatively easy when compared to the antisaccade task, since the fixation point remained on during stimulus presentation, which facilitates the engagement of attention.

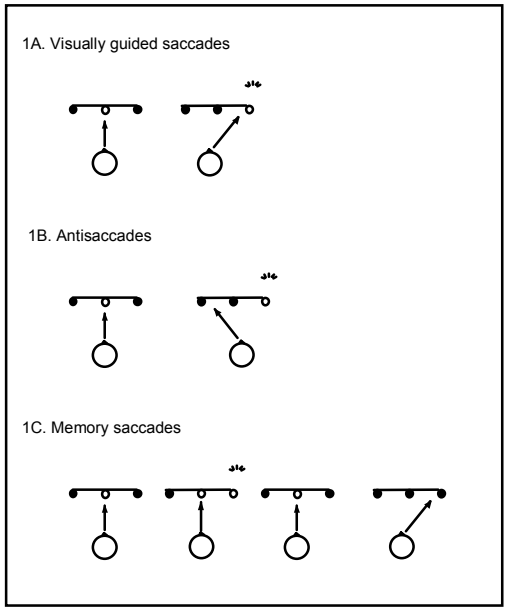


Figure 1. Saccadic paradigms
1A: A visual stimulus is presented in a random sequence to the left or right of a central fixation point and subjects are instructed to respond with a rapid and accurate eye movement
1B: Antisaccades are directed towards a spatial position in the opposite visual filed tot that of the stimulus. The paradigm requires suppression of the refexive saccade that would normally be generated in response to a novel visual target, and the generation of a volitional saccade to the opposite hemifield.
1C: Subjects are instructed to suppress the normal reflexive eye-movement in response to a novel stimulus, and to delay the saccade until the offset of the central light. There is no visual information on the location of the previously presented target at the moment of saccadic initiation

Performance on this task was evaluated for two parameters. First, the number of immediate inhibition errors (reflecting a failure in the ability to suppress a response tendency), which occur in the early phase of the delay period (0 to 250 ms), and second, the number of delay errors (reflecting a defect or weakness in inhibition mechanisms which normally prevent an already prepared saccadic motor program from being directly initiated), which occur in the late phase of the delay period (250 to 700 ms).
Based on animal studies (Funahashi et al. 1993; Everling & Munoz 2000) and studies in patients with brain lesions (Pierrot-Deseilligny et al. 1991a,b), the following measures from the antisaccade and memory saccade task were considered to reflect frontal function: antisaccade inhibition errors, memory saccade inhibition errors, and memory saccade delay errors. The raw test scores on these measures were converted into *z* scores, and patients showing a *z* score below –2 on at least one of these measures were regarded as showing frontal saccadic impairment.

2.5 Statistical analyses

Differences between the FI and FN group on major demographic variables (age, gender, and level of education) were examined by means of *t* tests or chi-square analyses. Differences between the FI, FN and control groups on saccadic and NP measures were examined by one-way analysis of variance (ANOVA) followed by post hoc testing (Fishers' protected T tests, alpha .05). When variables did not resemble the normal distribution, non-parametric Kruskal-Wallis tests followed by Mann-Whitney *U* tests were performed. The relationships between saccadic and NP performance were examined in the total sample with Pearson correlation coefficients.

3. Results

3.1 Presence of frontal, psychomotor speed, and memory deficits in patients

Table 1 shows how deficits in the frontal, psychomotor speed, and memory domains were distributed within the patient sample when the NP test battery was considered alone and when the NP tasks were combined with the three putatively frontal saccadic measures. Based on the NP tasks alone, 10 patients (42%) showed frontal impairment, whereas combined use of NP and saccadic tasks revealed 19 patients (79%) with frontal deficits. Combined use of NP and saccadic tasks also revealed that none of our patients were without cognitive deficits.

Table 1. Cognitive deficits in the frontal, psychomotor speed, and memory domain in patients.

Defective cognitive domain	Number of patients	
	NP tasks alone	*NP + saccadic tasks*
None	1	0
Frontal [a]	1	2
Speed [a b]	5	2
Memory [a]	5	2
Frontal + Speed	1	4
Frontal + Memory	1	4
Speed + Memory	3	1
Frontal + Speed + Memory	7	9
Overall frontal (either with or without deficits in other domains)	10	19
Overall speed (either with or without deficits in other domains)	16	16
Overall memory (either with or without deficits in other domains)	16	16

[a] no deficits in the other two domains.
[b] speed=psychomotor speed.

3.2 NP test performance of the FI, FN, and control groups

Based on the NP test battery, 10 patients were characterized as 'frontally impaired' (FI group), while 14 patients were characterized as 'frontally normal' (FN group). No significant differences were found in age, gender, or level of

education between the FI, FN, and control groups. Table 2 shows the performance of these groups on all NP measures included in the test battery.

Table 2. Neuropsychological performance in the FI, FN, and control group.

	FI patients (n=10) Mean (SD)	**FN patients (n=14)** Mean (SD)	**Controls (n=20)** Mean (SD)	**Sign**	**Post hoc**
CPT					
d'	2.74 (1.04)	3.86 (.35)	4.25 (.51)	.000	FI<FN+CS
RT (ms)	546.6 (116.19)	495.14 (73.69)	441.85 (65.94)	.007	FI>CS
Stroop					
Word reading (s)	43.8 (7.72)	40.62 (5.57)	37.03 (4.39)	.011	FI>CS
Color naming (s)	45.71 (7.60)	37.50 (5.96)	34.41 (5.12)	.000	FI>FN=CS
Interference (s)	10.45 (5.82)	6.95 (3.35)	8.58 (5.97)	.284	
Trail Making					
Trail A (s)	46.00 (22.36)	35.57 (10.50)	25.05 (6.66)	.000	FI>CS
Interference	70.58 (57.96)	37.10 (25.00)	45.71 (22.65)	.065	
Verbal Fluency					
Category words	16.25 (2.63)	17.92 (3.36)	22.05 (6.38)	.008	FI<CS
Finger tapping					
Number of taps	52.1 (10.18)	56.16 (13.41)	64.54 (11.40)	.020	FI<CS
CVLT					
Encoding (trial 1-5)	38.80 (8.64)	48.64 (7.39)	55.20 (6.26)	.000	FI<FN<CS
Consolidation	1.80 (2.04)	1.64 (2.02)	2.40 (1.60)	.462	
Retrieval	5.40 (2.95)	5.57 (1.87)	5.15 (1.84)	.849	
Total intrusions	6.20 (5.94)	4.36 (5.26)	1.16 (1.20)	.007	FI>CS
RCF					
Copy	30.22 (4.63)	32.36 (4.14)	32.98 (2.2)	.155	
Percentage recall	45.43 (23.91)	62.17 (24.0)	70.39 (16.92)	.018	FI<CS

FI=frontally impaired; FN=frontally normal; CS=controls.

3.3 Saccadic performance of the FI, FN and control group.

The FI, FN and the control groups differed significantly for 3 of the 7 saccadic measures (Table 3): the number of inhibition errors on the antisaccade task ($F=7.87$, $p=.001$), the number of inhibition errors on the memory task ($\chi^2=6.85$, $p=.033$), and the number of delay errors on the memory task ($F=3.79$, $p=.032$). Both the FI and FN group showed significantly more inhibition errors on the antisaccade task than controls (p values of .016 and .003 respectively). With respect to the memory task, the FI group showed significantly more inhibition errors ($p=.022$) and delay errors ($p=.025$) than the control group, whereas

differences between the FI and FN group and the FN and control group were not significant.

Table 3. Saccadic performance in the FI, FN, and control group.

	FI patients (n=10) Mean (SD)	FN patients (n=14) Mean (SD)	Controls (n=20) Mean (SD)	Sign	Post hoc
Visually guided task					
Latency	197.32 (30.11)	199.13 (35.05)	196.04 (25.10)	.958	
Early anticipations	7.8 (8.69)	5.71 (5.37)	2.75 (2.31)	.376	
Antisaccade task					
Latency	387.63 (78.17)	369.22 (62.37)	330.55 (58.79)	.064	
Inhibition errors	28.89 (15.56)	31.04 (20.82)	12.59 (7.35)	.001	FI=FN>CS
Latency Inhibition errors	247.19 (58.15)	237.29 (41.20)	221.00 (40.56)	.331	
Memory task					
Inhibition errors	8.67 (5.81)	9.28 (11.49)	3.40 (4.89)	.033	FI>CS
Delay errors	21.25 (19.63)	14.22 (9.24)	8.31 (5.40)	.032	FI>CS

* FI=frontally impaired; FN=frontally normal

3.4 Presence of deficits on *frontal* saccadic and *frontal* NP measures in patients.

Table 4 shows that patients with impaired performance on frontal NP measures did not necessarily perform poorly on frontal saccadic measures, and vise versa. Three patients with normal saccadic performance showed impaired performance on NP measures, while nine patients with impaired saccadic performance showed normal NP performance.

Table 4. Presence of deficits on frontal saccadic and frontal NP measures in patients.

		Frontal *saccadic* performance**	
		normal	*impaired*
Frontal *NP* performance*	*normal*	5	9
	Impaired	3	7

* performance on CPT *d'*, Stroop interference, TMT interference, and Verbal Fluency.

** performance on antisaccade inhibition errors, memory saccade inhibition errors, and memory saccade delay errors.

3.5 Frontal saccadic measures, frontal NP measures, psychomotor speed and memory.

The signs of the raw data were adjusted so that a lower value on any measure represented poorer performance. Using a Bonferroni correction, only two-tailed p values smaller than .003 were considered significant for correlation coefficients. As shown in Table 5, antisaccade inhibition errors were significantly correlated with CPT *d'* (r=.45, p=.002) and with the composite score for psychomotor speed (r=.49, p=.001), while inhibition errors on the memory saccade task were significantly correlated with the composite score for memory (r=.47, p=.001).

Table 5. Correlations between frontal saccadic measures and NP measures.

	Antisaccade ***Inhibition errors***	**Memory saccade** ***Inhibition errors***	**Memory saccade** ***Delay errors***
Frontal (composite score)	.32	.24	-.03
CPT *d'*	.45 *	.22	.28
Stroop interference	.14	.33	-.14
TMT interference	-.04	.10	-.21
VF items in category	.11	.17	.003
Psychomotor speed **(**composite score**)**	.49**	.33	.40
Memory (composite score)	.35	.47 *	.41

* = p<.002
**** = p<.00**

4. Discussion

In order to examine whether frontal impairment is a core deficit of schizophrenia, we examined frontal function with two different approaches. In addition, we examined whether combined use of traditional NP and saccadic tasks would increase the sensitivity to detect frontal impairment. Based on the NP tasks alone, 42% of our patients demonstrated frontal deficits, whereas combined use of NP and saccadic tasks revealed frontal impairment in 79% of our patients. This suggests that addition of saccadic tasks to the NP measures

used in the present study significantly increased the sensitivity to detect frontal impairment.

The question whether the saccadic measures were more sensitive to frontal impairment than NP tasks, was addressed by comparing the performance on saccadic measures in patients *with* and *without* frontal impairment on a NP battery. A high level of antisaccade inhibition errors was obtained in FN patients, who were presumed to have intact frontal function. Apparently, the antisaccade task was able to reveal frontal deficits which were not detected by the frontal NP tasks used in the present study. This might be due to a strong stimulus-response compatibility (Gale & Holzman 2000) and the absence of verbal and manual task components. These characteristics might imply a relatively short and restricted pathway in the brain, which probably reduces the impact of (inhibitory) control mechanisms. With respect to the memory saccade task, the performance of the three groups revealed a pattern similar to that of the NP tasks. This suggests that the memory task is less sensitive to frontal impairment than the antisaccade task, which might be due to the fact that, although both tasks address inhibitory functions, the memory task addresses them in a less stringent way. In the memory task, visual targets are presented while the fixation point remains on, which implies that the orienting system is not fully prepared for immediate action. In the antisaccade task, however, fixation point offset results in disengagement of attention, which renders subjects more vulnerable to an immediate response to novel targets. The memory task also requires a larger number of cognitive processes, which provides the opportunity to compensate for problems in one task process by investing more effort in others. In combination with its slower pace, this makes the memory task is a better comparison to the NP tasks.

Although the high antisaccade error rate in the FN group suggests that this task is more sensitive to frontal impairment than the NP tasks, a closer look at the presence of *frontal saccadic* and *frontal NP* deficits in individual patients revealed that patients with impaired performance on frontal saccadic measures not necessarily performed poor on frontal NP measures, and vise versa. These findings suggest that the frontal saccadic and NP tasks address, at least to some extent, different frontal functions. This was interpreted as evidence for the notion that combined use of NP and saccadic tasks is the most favorable method to assess frontal function. Future studies using, for example, functional brain

imaging techniques should provide evidence for the idea that our frontal saccadic and NP measures indeed target different frontal functions.

The finding that 21% of our patients did *not* show frontal impairment on either the NP or the saccadic tasks, contradicts the notion of frontal deficits as a core deficit of schizophrenia. On the other hand, all our patients suffered from deficits in either the frontal, speed, or memory domain, which strongly suggests that *cognitive* deficits (instead of *frontal* deficits) are a core deficit of the disease.

A related issue, is the ongoing debate as to whether the cognitive deficits in schizophrenia should be characterized as a *generalized* cognitive deficit or as deficits in *specific* cognitive domains. The common view is that schizophrenic patients suffer from specific deficits against a background of generalized cognitive dysfunction, with specific impairment in verbal learning, vigilance, speeded visual-motor processing (Saykin et al. 1991, 1994; Censits et al. 1997) and executive functioning (Mohamed et al. 1999). The present study did not support the idea of cognitive deficits being a generalized deficit, since only nine patients showed deficits in all three domains. We also failed to find evidence for the existence of specific deficits in either the frontal, psychomotor speed, or memory domain, since deficits in these three domains were present in respectively 79%, 67% and 67% of the patients.

With respect to the relationship between saccadic performance and NP performance within the frontal, psychomotor speed, and memory domain, our main finding was a remarkable lack of significant association between frontal saccadic measures and the composite score for frontal NP function. With respect to individual frontal NP measures, however, we found a strong correlation between antisaccade inhibition errors and CPT d'. Apparently, antisaccade performance and the sensitivity to detect targets in a memory-load CPT depend on a common function, and thus probably on common brain regions. This idea is supported by neuroimaging studies reporting that the CPT is associated with brain activation in the right DLPFC and the mesial frontal cortex (Hager et al. 1998), while these areas have also been found to be active during the antisaccade task (Sweeney et al. 1996; Doricchi et al. 1997). For the other frontal NP measures, we found, however, no significant association with saccadic measures, which suggests a lack of overlap in the frontal functions addressed by both type of measures. This is also suggested by our finding that

deficits on frontal saccadic measures were not necessarily accompanied by deficits on frontal NP measures. It should be noted here, that our patients showed a remarkable accurate performance on two putative frontal NP measures, namely Stroop interference and TMT interference. Other studies have also failed to observe an association between frontal saccadic measures and frontal NP measures, except for the WCST and a working memory task. We hypothesize that, compared to NP tests, voluntary saccades depend on a relatively limited set of brain regions, with crucial involvement of the DLPFC. The probably limited DLPFC dependence of our NP tasks might have resulted in only marginal associations with the saccadic measures, as compared to NP tasks with large DLPFC involvement, like the WCST and tests of spatial working memory.

Another intriguing finding was that psychomotor speed-abilities were significantly associated with antisaccade inhibition errors. This was unlikely to be caused by an underlying defect in basic oculomotor processes, since the performance on visually guided saccades was accurate. It appeared that all psychomotor speed measures were significant contributors to the association, except for Finger Tapping. This suggests that a general slowness in information processing was underlying the association rather than a deficit in motor abilities. Slow processing of incoming information, and probably also slow rehearsal of task instructions, might have resulted in greater problems to overcome response tendencies.

With respect to the significant correlation between memory saccade delay errors and performance in the memory domain, it appeared that encoding deficits were mainly responsible for the significance of the association. This may be because of the relatively slow pace of the memory saccade task (trial duration of 4.5 s, as compared to 2.8 s in the antisaccade task), which required active rehearsal of the task instruction *not* to initiate the saccade before fixation point offset. However, the oculomotor program for the saccade was prepared immediately after stimulus presentation. Poor encoding of the task instruction might, therefore, have rendered patients vulnerable to early initiation of saccades.

In sum, the present study does not support the view that frontal impairment is a core deficit of schizophrenia, but our results do support the notion that *cognitive* deficits are a core feature of the disease. We did not found evidence for the existence of either a generalized deficit or deficits in specific cognitive domains.

The use of traditional NP measures in combination with saccadic tasks appeared to increase the sensitivity to detect frontal impairment. In particular the antisaccade task appeared able to reveal frontal deficits. Frontal saccadic measures were, however, only marginally associated with frontal NP measures.

References

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

Berman, K.F., Zec, R.F., Weinberger, D.R., 1986. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. II. Role of neuroleptic treatment, attention, and mental effort. Arch. Gen. Psychiatry 43, 126-135.

Bruce, C.J., Goldberg, M.E., 1985. Primate frontal eye fields. I. Single neurons discharging before saccades. J. Neurophysiol 53, 603-635.

Bryson, G.J., Silverstein, M.L., Nathan, A., Stephen, L., 1993. Differential rate of neuropsychological dysfunction in psychiatric disorders: comparison between the Halstead-Reitan and Luria-Nebraska batteries. Percept. Mot, Skills 76, 305-306.

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.

Crawford, T.J., Haeger, B., Kennard, C., Reveley, M.A., Henderson, L., 1995. Saccadic abnormalities in psychotic patients. I. Neuroleptic-free psychotic patients. Psychol. Med. 25, 461-471.

Delis, D.C., Kramer, J.H., Kaplan, E., Ober, B.A., 1987. California verbal Learning Test (CVLT) Manual. New York: The Psychological Corporation.

Doricchi, F., Perani, D., Incoccia, C., Grassi, F. , Cappa, S.F., Bettinardi, V., Galati, G., Pizzamiglio, L., Fazio, F., 1997. Neural control of fast-regular saccades and antisaccades: an investigation using positron emission tomography. Exp. Brain Res. 116, 50-62.

Elias, M.F., Podraza, A. M., Pierce, T.W., Robbins, M.A., 1990. Determining neuropsychological cut scores for older, healthy adults. Exp. Aging Res. 16, 209-220.

Everling, S., Dorris, M.C., Klein, R.M., Munoz, D.P., 1999. Role of primate superior colliculus in preparation and execution of anti-saccades and pro-saccades. J. Neurosci, 19, 2740-2754.

Everling, S., Fischer, B., 1998. The antisaccade: a review of basic research and clinical studies. Neuropsychologia, 36, 885-899.

Everling, S., Munoz, D.P., 2000. Neuronal correlates for preparatory set associated with pro saccades and anti-saccades in the primate frontal eye field. J. Neurosci., 20, 387-400.

Fischer, B., Biscaldi, M., Gezeck, S., 1997. On the development of voluntary and reflexive components in human saccade generation. Brain Res. 754, 285-297.

Fischer, B., Ramsperger, E., 1984. Human express saccades: extremely short reaction times of goal directed eye movements. Exp. Brain Res. 57, 191-195.

Funahashi, S., Bruce, C.J., Goldman-Rakic, P.S., 1993. Saccade-related activity in the primate prefrontal cortex and it's role in working-memory processes. Biomed. Res. 14, 85-88.

Gale, H.J., Holzman, P.S., 2000. A new look at reaction time in schizophrenia. Schizophr. Res., 46, 149-165.

Goldman-Rakic, P.S., 1994. Working memory dysfunction in schizophrenia. J. Neuropsychiatry Clin. Neurosci. 6, 384-357.

Gooding, D.C., Tallent, K.A., 2001. The association between antisaccade task and working memory task performance in schizophrenia and bipolar disorder. J.Nerv. Ment. Dis. 189, 8-16.

Hager, F., Volz, H.P., Gaser, C., Mentzel, H.J. , Kaiser, W.A.,Sauer, H., 1998. Challenging the anterior attentional system with a continuous performance task: a functional magnetic resonance imaging approach. Eur. Arch. Psychiatry Clin. Neurosci. 248, 161-170.

Hemsley, D.R., 1994. Cognitive disturbance as the link between schizophrenic symptoms and their biological basis. Neurology Psychiatry Brain Res. 2, 163-170.

Hikosaka, O., Wurtz, R.H., 1991. The basal ganglia. In R.H. Wurtz M.E. Goldberg (Eds), The neurobiology of saccadic eye movements (pp. 257-282). Amsterdam: Elsevier.

Holthausen, E.A.E., Wiersma, D., Sitskoorn, M.M., Hijman, R., Dingemans, P.M., Schene, A.H., van den Bosch, R.J.,2002. Schizophrenic patients without neuropsychological deficits: subgroup, disease severity or cognitive compensation? Psychiatry. Res. 112, 1-11.

Hugdahl, K., Lundervold, A., Ersland, L., Smievoll, A.I., Sundberg, H., Barndon, R., Roscher, B.E., 1999. Left frontal activation during a semantic categorization task: an fMRI-study. Int. J. Neurosci. 99, 49-58.

Hutton, S.B., Crawford, T.J., Puri, B.K., Duncan, L.J., Chapman, M., Kennard, C., Barnes, T. R., Joyce, E. M., 1998. Smooth pursuit and saccadic abnormalities in first-episode schizophrenia. Psychol. Med. 28, 685-692.

Karoumi, B., VentreDominey, J., Vighetto, A., Dalery, J., dAmato, T., 1998. Saccadic eye movements in schizophrenic patients. Psychiatry Res. 77, 9-19.

Lesnik, P.G., Ciesielski, K.T., Hart, B.L., Benzel, E.C., Sanders, J.A., 1998. Evidence for cerebellar-frontal subsystem changes in children treated with intrathecal chemotherapy for leukemia: enhanced data analysis using an effect size model. Arch. Neurology 55, 1561-1568.

McDowell, J.E., Clementz, B.A., 1997. The effect of fixation condition manipulations on antisaccade performance in schizophrenia: studies of diagnostic specificity. Exp. Brain Res. 115, 333-344.

Mohamed, S., Paulsen, J.S., O'Leary, D., Arndt, S., Andreasen, N., 1999. Generalized cognitive deficits in schizophrenia: a study of first-episode patients. Arch. Gen. Psychiatry, 56, 749-754.

Nieman, D.H., Bour, L.J., Linszen, D.H., Goede, J., Koelman, J.H., Gersons, B.P., Ongerboer, D.V., 2000. Neuropsychological and clinical correlates of antisaccade task performance in schizophrenia. Neurology, 54, 866-871.

O'Driscoll, G.A., Alpert, N.M., Matthysse, S.W., Levy, D.L., Rauch, S.L., Holzman, P.S., 1995. Functional neuroanatomy of antisaccade eye movements investigated with positron emission tomography. Proc.Natl. Acad. Sci. U.S.A. 92, 925-929.

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.

Peterson, B. S., Skudlarski, P., Gatenby, J. C., Zhang, H., Anderson, A. W., Gore, J.C., (1999). An fMRI study of Stroop word-color interference: evidence for cingulate subregions subserving multiple distributed attentional systems. Biol. Psychiatry, 45, 1237-1258.

Pierrot-Deseilligny, C., Rivaud, S., Gaymard, B., Agid, Y., 1991a. Cortical control of reflexive visually-guided saccades. Brain, 114 1473-1485.

Pierrot-Deseilligny, C., Rivaud, S., Gaymard, B., Agid, Y., 1991b. Cortical control of memory-guided saccades in man. Exp. Brain Res. 83, 607-617.

Radant, A.D., Claypoole, K., Wingerson, D.K., Cowley, D.S., & Roy-Byrne, P.P., 1997. Relationships between neuropsychological and oculomotor measures in schizophrenia patients and normal controls. Biol. Psychiatry. 42, 797-805.

Rey, A., 1964. L'examen clinque en psycholgie. Paris: Presses Universitaires de France.

Rosse, R.B., Schwartz, B.L., Kim, S.Y., Deutsch, S.I., 1993. Correlation between antisaccade and Wisconsin Card Sorting Test performance in schizophrenia. Am. J. Psychiatry, 150, 333-335.

Saykin, A.J., Gur, R.C., Gur, R.E., Mozley, P.D., Mozley, L.H., Resnick, S.M. , Kester, D.B., 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.

Schreiber, H., Rothmeier, J., Becker, W., Jurgens, R., Born, J., Stolz, B.G., Westphal, K.P., Kornhuber, H.H.,1995. Comparative assessment of saccadic eye movements, psychomotor and cognitive performance in schizophrenics, their first-degree relatives and control subjects. Acta Psychiatr. Scand. 91, 195-201.

Silverstein, M.L., Zerwic, M.J., 1985. Clinical psychopathologic symptoms in neuropsychologically impaired and intact schizophrenics. J. Consult.Clin. Psychol. 53, 267-268.

Snitz, B.E., Curtis, C.E., Zald, D.H., Katsanis, J., Iacono, W.G., 1999. Neuropsychological and oculomotor correlates of spatial working memory performance in schizophrenia patients and controls. Schizophr. Res. 38, 37-50.

Stroop, J.R., 1935. Studies of interference in serial verbal reactions. J. Exp. Psychol. 18, 643-662.

Sweeney, J.A., Mintun, M.A., Kwee, S., Wiseman, M.B., Brown, D.L., Rosenberg, D. R., Carl, J.R., 1996. Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. J. Neurophysiol. 75, 454-468.

Thaker, G.K., Nguyen, J.A., Tamminga, C.A., 1989. Increased saccadic distractibility in tardive dyskinesia: functional evidence for subcortical GABA dysfunction. Biol. Psychiatry, 25, 49-59.

Tien, A.Y., Ross, D.E., Pearlson, G., Strauss, M.E., 1996. Eye movements and psychopathology in schizophrenia and bipolar disorder. J. Nerv. Ment. Dis. 184, 331-338.

Tusa, R.J., Zee, D.S., Herdman, S.J., 1986. Effect of unilateral cerebral cortical lesions on ocular motor behavior in monkeys: saccades and quick phases. J. Neurophysiol., 56, 1590-1625.

Van den Bosch, R.J., Rombouts, R.P., van Asma, M.J., 1996. What determines Continuous Performance Task performance? Schizophr. Bull. 22, 643-651.

Vink, M., Jolles, J., 1985. A new version of the Trail making Test as an informationprocessing task. J. Clin. Neuropsychology 7, 162.

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

Chapter 4

Long-Term Memory Deficits in Schizophrenia: Primary or Secondary Dysfunction?

Accepted for publication in Neuropsychology: Holthausen, E.A.E., Wiersma, D., Sitskoorn, M.M., Hijman, R., Dingemans, P.M., Schene, A.H., van den Bosch, R.J.

Abstract

Long-term memory impairment is often found in schizophrenia. The question remains whether this is caused by other cognitive deficits. One hundred eighteen first episode patients 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. Deficits were found in general verbal learning performance and retrieval in episodic memory and semantic memory. Processing speed reduced disease related variance in all memory variables. Coordination, organization of information, and speed of processing were the best predictors for long-term memory deficits in patients. The amount of explained variance, however, is small, especially in general verbal learning performance.

1. Introduction

Although no single neurocognitive test or construct completely separates schizophrenic patients and controls (Heinrichs & Zakzanis, 1998), long-term memory impairment is often found in schizophrenia. Some researchers even suggest that schizophrenia patients have a specific deficit in long-term memory against a background of more generalized cognitive dysfunctioning (Saykin, Gur, et al., 1991; Saykin, Shtasel, et al., 1994). Memory impairments, especially impairments in long term memory, are also associated with a variety of functional outcome measures, such as vocational outcome, community functioning and quality of life, in schizophrenia (Green, 1996; Green, Keen, Braff & Mintz, 2000).

Memory, however, is not a unitary concept and can be divided into several systems and processes (Schacter & Tulving, 1994). Long-term memory can be divided into episodic and semantic memory systems. 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 or learning of new information; storage of information; 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 of information from semantic memory. In contrast to these explicit memory systems, there is also implicit memory, which deals with the automatic cognitive and motor processes, which do not require conscious attention.

Some diseases are characterized by specific memory deficits. Storage deficits in episodic memory, for example, are typical for patients with Alzheimer's or Korsakov disease. Impaired initiation of retrieval strategies on the other hand is typically found in patients with Huntington's and Parkinson's disease (Paulsen et al., 1995). In schizophrenia, however, impairments in explicit memory are prominent, while lesser impairments in implicit memory are found (e.g. Clare, McKenna, Mortimer & Baddeley, 1993; Goldberg, Hyde, Kleinman & Weinberger, 1993; Kazes et al., 1999). Many studies report problems in episodic memory, but most of them only find learning and retrieval deficits, while storage is relatively spared (e.g. Aleman, Hijman, de Haan & Kahn, 1999;

Brebion, Amador, Smith & Gorman, 1997; Hawkins Sullivan & Choi, 1997; Paulsen et al., 1995). Although the majority studied verbal memory only, visual memory impairments are found as well, and there is no evidence for a difference between both modalities (Aleman et al., 1999). There is also evidence for semantic memory deficits (McKay et al., 1996). This seems to be caused by inefficient access to the semantic store, which could be labeled as a retrieval deficit (Joyce, Collinson & Chrichton, 1996). In sum, the memory deficits found in schizophrenia are explicit, verbal as well as visual and mostly concern active memory processes, such as learning and retrieval processes in long term memory systems. These systems are at least partly dependent on other cognitive functions, such as speed of information processing, and central executive processes. Should the memory impairments in schizophrenia be understood as pure memory deficits or as the result of another underlying cognitive deficit? Because different brain regions mediate these cognitive functions, this is an important question in the search for basic mechanisms in schizophrenia.

Several studies have described a slowing of processing speed on a number of cognitive tasks as a major cognitive deficit in schizophrenia (Nelson et al, 1990; Schatz, 1997; Van der Does Dingemans, Linszen, Nugter & Scholte, 1996). Most studies make a distinction between sensorimotor speed and cognitive speed. The latter requires controlled information processing and is more impaired in schizophrenia than simple sensorimotor speed (Nelson et al., 1990; van Hoof, Jogems-Kosterman, Sabbe, Zitman & Hulstijn, 1998). The influence of processing speed on other cognitive functions has been studied extensively in aging research by Salthouse (1996). He found evidence that age-related slowing of processing speed influences other cognitive measures, such as memory. A few studies have examined the relation between processing speed and memory measures in schizophrenia. Brébion, Amador, Smith and Gorman (1998) and Brébion et al. (2000) concluded that memory deficits may be partly accounted for by a slowing of processing speed.

Executive functions are thought to play a role in effortful cognitive processes. Recent research suggests that the central executive has different component functions (Baddeley, 1996; 1998; Nathaniel-James, Brown & Ron, 1996; Salamé, Danion, Peretti & Cuervo, 1998), such as: coordination of performance; switching of strategies to handle a task; selective attention and inhibition,

organization of information. Although the central executive is thought to play an important role in schizophrenia (Goldman-Rakic, 1994), the results are not always consistent, probably due to a large variance in the patient group. And it is not clear what component of the central executive is related to memory in schizophrenia (Salamé et al., 1998). Organization of information however, is a good candidate because strategic processes, such as organization of to-be-learned information, play a role in the encoding of new information (Fletcher and Henson, 2001). Recall is better for word lists that can be organized in semantic categories for example, and a strategic approach in a visual copy and memory task, such as the Rey Complex Figure, leads to better results on the reproduction part of this task (e.g. Chiulli, Haaland, La Rue & Garry, 1995). Therefore organization of information might be an important determinant of memory performance within schizophrenia as well.
In this study, we examined long-term memory in a large group of first episode schizophrenia patients. Because slowing of processing speed is often found in schizophrenia, we analyzed the relations between long-term memory and basic cognitive functions to test our first hypothesis that differences in processing speed explain the differences in memory measures between patients and controls. Next we examined whether variance in memory measures within the patient group is explained by differences in central executive functions, especially organization of information.

2. Method

2.1. Subjects

The study included 118 patients who had recently experienced a first or a second psychotic episode according to DSM-IV (American Psychiatric Association, 1994) and received a diagnosis within the schizophrenia spectrum (schizophrenia, schizoaffective disorder, schizophreniform disorder). All patients participated in a Dutch multicenter study of the university hospitals of Groningen, Utrecht and Amsterdam. Diagnosis was based on a structured interview (SCAN; Wing et al., 1990 or CASH; Andreasen, Flaum & Arndt 1992). Exclusion criteria were mental retardation according tot DSM-IV

(American Psychiatric Association, 1994) and a known systemic or neurological illness. Subject characteristics of patient are given for the entire group and the three different diagnostic groups in table 1. No differences in memory or cognitive measures were found between the diagnostic categories. Accordingly they were treated as one group. Ninety-five subjects had their first episode, 23 subjects experienced their second episode. Twenty-five patients used typical antipsychotics, seventy-five were on atypical antipsychotics and eighteen patients did not use antipsychotic medication. Ten patients also used anticholinergic medication. Twenty-eight patients had a diagnosis for alcohol abuse, 55 for cannabis abuse and 16 for other drug abuse. No significant differences on memory measures between patients with and without a substance abuse diagnosis were found, except for the patients with alcohol abuse, who performed significantly better on general verbal learning performance: $F(1,117) = 7.76$, $p = .006$. Forty-five healthy controls were included in order to establish standard scores on memory tests. Thirty-eight males and seven females were included. Mean age was 24 years (SD 6.4). There were no significant differences between patients and controls for sex: χ^2 (1, 1 63) = 2.10, ns, or age: $F(1, 161) = 0.29$, ns. Patients and controls were not matched on education level. The Dutch educational system differentiates already after primary school into four levels, therefore we have chosen a coding system rather than years of education. This goes from 1: primary school up to 8: university or graduate school. Because thirty seven percent of the patients still received education, we took the level they were aiming at minus half a point. Mean education level for controls was 5.9 (SD 1.5). There was a significant difference between patients and controls: $F(1.161) = 30.45$, $p < .000$. The most likely explanation is that a number of patients quit school before finishing one of the four different high school levels, due to prodromal symptoms. Therefore they only received the code for primary school. All control subjects finished at least one of the additional high school options. Although subjects from both groups are represented at the highest level (university or graduate school), the mode of the control group is at a higher level than that the mode of the patients group. Therefore education is entered as a covariate in the analyses of the differences between patients and controls and it is treated as a possible confounder in the regression analyses.

Table 1. Subject characteristics of patients by diagnosis

Subject characteristics	**All patients n = 118** M (SD)	**Schizophrenia (a), n = 84** M (SD)	**Schizophreniform (b), n= 19** M (SD)	**Schizoaffective (c), n = 15** M (SD)	**F** Post-hoc [c]
Age	23.30 (5.27)	22.45 (4.54)	26.63 (6.81)	23.80 (5.56)	5.30** a<b
Education (range 1-8)	4.0 (2.2)	3.8 (2.2)	4.7 (2.2)	4.1 (2.0)	1.37
PANSS (range 30-210)	61.85 (18.03)	65.24 (18.48)	51.53 (13.91)	56.20 (14.08)	5.75** a>b
Positive[a]	2.22 (1.06)	2.44 (1.07)	1.60 (0.85)	1.83 (0.85)	6.83** a>b
Negative	2.33 (0.95)	2.46 (1.02)	1.89 (0.72)	2.18 (0.63)	2.99
Disorganization	1.86 (0.68)	1.95 (0.72)	1.64 (0.56)	1.61 (0.46)	2.87
Depression	2.34 (0.95)	2.32 (0.93)	2.21 (1.09)	2.63 (0.89)	0.90
Excitement	1.61 (0.73)	1.69 (0.74)	1.44 (0.73)	1.40 (0.68)	1.53
MADRS (range 10-60)	14.13 (10.22)	14.39 (10.50)	12.06 (8.69)	15.20 (10.71)	0.48
Age at onset	22.18 (5.11)	21.26 (4.18)	26.28 (6.93)	22.01 (4.95)	7.98*** a<b
Sex m/f	87 / 31	66 / 18	12 / 7	9 / 6	3.57[b]

[a] Standardized PANSS ratings ranging from 1: absent to 7: extreme. [b] χ^2 test. [c] Tamhane. * $p < .05$. ** $p < .01$. *** $p < .001$.

2.2. Procedures and Instruments

Memory measures.

All patients were tested after being on stable medication for at least six weeks. Table 2 gives an overview of the memory measures. The Dutch translation of the California Verbal Learning Tests (CVLT; Delis, Kramer, Kaplan & Ober, 1987) was used to asses long-term verbal episodic memory. The CVLT is a list-learning task in which 16 words from 4 categories (list A) are presented over 5 immediate recall trials. Following the five trials, a second list (B) is presented for one interference trial. Directly after this presentation, short delay free and cued recall of list A are assessed. After 20 minutes long delay free and cued recall are assessed, immediately followed by a yes-no recognition task with 28 distracters. The total sum of words over the first five learning trials was taken as a measure of general verbal learning performance. The difference between long-term free recall and immediate recall trial on 5 was taken as a measure of storage. Retrieval was computed by subtracting the standardized score of long term free recall from the standardized score on the recognition task. Because it is difficult to find a visual memory task with measures for encoding, storage and retrieval, and there is no evidence for a difference between verbal and visual memory in schizophrenia, we decided to use the recall measures from the Rey

Complex Figure Test (RCFT; Rey, 1964) only. Subjects were administered a copy trial, an immediate recall and a delayed recall trial in which they had to draw the complex figure. The RCFT was scored using explicit scoring criteria from Duley, Wilkins, Hamby and Hopkins (1993) based on the method developed by Osterrieth (1944). The mean percentage correct from the immediate and the delayed recall (recall: copy x 100) was used as a visual memory measure. Retrieval from semantic memory was measured with a category fluency task in which subjects had to name as many words from one category (animals and professions) as possible in one minute. Although it cannot be denied that frontal functions play a role in category fluency, several studies also prove that the performance on category fluency is also influenced by the contents of the semantic store or semantic memory or the access to the semantic store. (Joyce et al., 1996; Chertkow & Bub, 1990).

Basic cognitive variables that may influence memory.

These additional measures were collected in the same test session (see table 2). The time in seconds on word reading and color naming of a computerized STROOP task were taken as measures of processing speed. A modified version of the Trailmaking Test (Vink & Jolles, 1985) was administered as a second task for processing speed. This version consists of three parts. In part A, the subject must connect consecutively numbered circles from 1 to 26. In part B, the subject must connect circles with the letters A through Z. In part C the subject must connect 26 consecutively numbered and lettered circles, by alternating between the two sequences. Time on part A and part B were taken as measures of processing speed. All speed measures correlated highly with each other in the total group of subjects (r ranging from .50 to .91, with $p < .000$). Therefore they were averaged after a z-transformation, to create one processing speed score. Five different measures were used in order to examine different component processes of the central executive. The Continuous Performance Task used in this study (CPT; Van den Bosch, Rombouts & Asma, 1996) is a double stimulus version, with a memory load, in which a subject has to react when the number seven appears on a computer screen after the number 3. Patients have to remember the last stimulus, the task instruction, and stay alert to react to the new stimulus. The sensitivity index (d') of this double-stimulus CPT was used to assess the ability to coordinate the allocation of processing

capacity (Coordination). In another study of our group (Broerse, Holthausen, van den Bosch & den Boer, 2001), significant correlations were found between CPT d' and the percentage of inhibition errors on an antisaccade task, which is an established frontal executive task. The interference score of the Trailmaking Test (interference = C- ½ (A + B) / ½ (A + B)) was taken as a measure of the ability to switch between search strategies (Switching). The STROOP interference score (STROOP color word – STROOP color naming) was used to assess selective attention and inhibition (Selective attention). We had two measures for organization. The semantic cluster score from the CVLT was taken as a measure of organization of verbal information. Regarding visual memory we decided to take the method of drawing as a measure of organization. We used a binary approach wherein a drawing strategy in which the main figure was drawn first was coded as normal and a drawing strategy with a fragmented approach was labeled as abnormal (Chiulli et al., 1995; Lezak, 1983).

Psychopathology.

Symptoms were rated on the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein & Opler, 1987) within the same week as the neuropsychological assessment. These ratings were used to obtain dimensional scores by calculating the sum scores loading high on the positive, negative, disorganization, depression and excitement dimensions as described in Lindenmayer, Bernstein Hyman, Grochowski and Bark (1995). Depressive symptoms were also rated with the Montgomery Åsberg Depression Rating Scale(Montgomery and Åsberg, 1979). Symptom ratings are given in table 1.

3. Results

All variables were inspected to see if they resembled the normal distribution. If not, log transformations were performed. This was the case for STROOP interference and the positive and disorganization dimensions from the PANSS. Differences between patients and normal controls on all memory and cognitive variables were tested with ANCOVA with education as covariate. If the effect of the covariate was significant, estimated marginal means are given, which are

corrected for education (with raw means in parentheses). Effect sizes were computed for the differences between controls and patients on all memory and cognitive measures using Cohen's d, with the standard deviation of the control group (table 2). Patients performed significantly worse on all long term memory measures, except storage of verbal information, which was left out of further analyses. The effect sizes showed that general verbal learning performance and semantic memory were especially disturbed, with large effect sizes (according to Cohen, 1969). Patients also performed significantly worse on most basic cognitive measures, with large effect sizes except for Trail Making interference (small) and CVLT semantic clustering (medium).

Table 2. Long-term memory and other cognitive variables in patients and controls.

Cognitive measures	Controls n = 45 M ± SD	Patients n = 118 M ± SD	F-value	Effect sizes Cohen's d
Memory Measures				
CVLT trial 1-5	56.38 ± 8.52	45.69 ± 9.21	45.59****	-1.25
CVLT storage	-0.68 ± 1.49	-1.15 ± 2.25	1.66	-0.32
CVLT retrieval	0.11 ± 1.65	1.18 ± 1.77	12.01**	-0.65
RCFT immediate recall	70.50 ± 16.21	61.71 ± 20.19	5.86*	-0.54
RCFT delayed recall	68.39 ± 16.46	61.31 ± 18.37	5.11*	-0.43
Category fluency	22.68 ± 5.09	18.06 ± 4.27	33.96****	-0.91
Estimated marginal means[a]				
STROOP names (time)	38.33 ± 4.59 (36.76)	47.29 ± 9.91 (47.91)	28.70****	-1.95
STROOP colors (time)	33.77 ± 5.68 (34.42)	44.72 ± 9.14 (45.27)	32.55****	-1.58
Trailmaking A (time)	26.71 ± 7.54 (25.13)	38.13 ± 15.08 (38.88)	19.81****	-1.51
Trailmaking B (time)	26.87 ± 9.68 (24.62)	37.19 ± 15.78 (38.38)	14.85****	-1.07
CPT d '	4.14 ± 0.55 (4.29)	3.60 ± 0.77 (3.53)	17.23****	-0.98
CVLT semantic clustering	2.05 ± 0.99 (2.05)	1.61 ± 0.66 (1.57)	8.98**	-0.44
Raw means				
Trailmaking interference	41.51 ± 30.05	48.31 ± 44.31	1.11	-0.23
STROOP interference	7.43 ± 5.17	11.59 ± 11.44	2.17*	-0.80
RCFT organization type (% normal)	84%	62%	7.50[b]**	-

[a] Means adjusted for the covariate education, raw means without adjustment are shown within parenthesis.
[b] χ^2 test. * p < .05. ** p < .01. ***p < .001. **** p < .0001.

Correlations between all memory and cognitive variables and education for all subjects and for the patient group separately are given in table 3 and 4.

Table 3: Correlations between memory measures and cognitive measures for the whole group (patients and controls, N = 163)

	2	3	4	5	6	7	8	9	10	11	12
1.Verbal learning	.223**	.347***	.365***	.415***	.460***	.362***	.160*	.061	.419***	.300***	.277***
2. Verbal storage	-	.465***	.184*	.245**	.176*	.189*	.074	.128	.178*	.303***	.086
3. Verbal retrieval		-	.197*	.369***	.357***	.300***	.137	.185*	.297***	.257**	.181*
4. Visual memory			-	.231**	.323***	.301***	.095	.076	.129	.346***	.148
5. Semantic memory				-	.571***	.423***	.125	.064	.335***	.255**	.288***
6. Speed of processing					-	.577***	.236**	.040	.340***	.289***	.436***
7. Coordi-nation						-	.159*	.136	.245**	.262**	.429***
8. Selective attention							-	.139	.089	.100	.159*
9. Switching								-	.055	.096	.109
10. Verbal organization									-	.265**	.299***
11. Visual organization										-	.213**
12. Education											-

* p < .05. ** p < .01. ***p < .001.

There are significant correlations between all memory measures in the whole subject group, and between most memory measures in the patient group. As for the cognitive measures, speed, coordination and verbal and visual organization are significantly associated. Correlations between memory variables and psychopathology measures were computed. Only two significant correlations were found for semantic memory and the negative and disorganization dimensions respectively ($r = .262$, $p = .005$; $r = .228$, $p = .014$)

In order to examine whether speed explains the difference in memory measures between patients and controls, we used the method suggested by Salthouse (1996). In the original method, which is based on regression analysis, group is first entered as a predictor, to calculate the amount of variance predicted by group membership for each memory measure, the so-called disease related variance. Secondly, in a new analysis, speed is entered as a first predictor before group, to see if the amount of variance explained by group is reduced considerably. We altered this method slightly to control for the possible confounding effect of education. First group is entered as a predictor, as in the original method. Secondly education was entered after group.

Table 4. correlations between memory measures and cognitive measures for patient group (n = 118)

	2	3	4	5	6	7	8	9	10	11	12
1.Verbal learning	.200*	.231*	.337***	.294**	.222*	.242**	.118	.018	.236*	.189*	.188*
2. Verbal storage	-	.297**	.191*	.151	.127	.186*	.036	.079	.193*	.303**	.083
3. Verbal retrieval		-	.178	.301**	.248**	.255**	.098	.151	.255**	.189*	.109
4. Visual memory			-	.153	.318**	.314**	.054	.060	.046	.298**	.099
5. Semantic memory				-	.436***	.382***	.090	.008	.228*	.173*	.240**
6. Speed of processing					-	.439***	.239*	.129	.234*	.203*	.310**
7. Coordi-nation						-	.140	.136	.144	.204*	.319***
8. Selective attention							-	.113	.060	.086	.232*
9. Switching								-	.045	.078	.046
10. Verbal organization									-	.150	.207*
11. Visual organization										-	.175
12. Education											-

* p < .05. ** p < .01. ***p < .001.

If the coefficient of group changed more than 10 %, education was treated as a confounder. This was the case for visual and semantic memory. For these variables we conducted two separate analyses. In the first group was entered after speed, to see how much the disease related variance is reduced by speed. In the second group was entered after education to see how much the disease related variance is reduced by education (table 5). Entering processing speed in the model reduced disease-related variance in all memory variables.

Table 5: Reduction of disease related variance after entering speed and education as a first predictor for the whole group (patients and controls, N = 163).

Memory Measures	***Disease related variance*** R^2 group	**Δ R^2 for group, after speed as a first predictor**	**Δ R^2 for group, after education as a first predictor**
Verbal learning	.22 ****	.07****	-
Verbal retrieval	.07****	.01	-
Visual memory	.04 *	.00	.02
Semantic memory	.18 ****	.01	.11****

* p < .05. ** p < .01. ***p < .001. **** p < .0001.

And although education is a confounder for disease related variance in visual and semantic memory, speed still reduced more of the disease related variance than education.

Finally, with hierarchical multiple regression analysis with forced entry, the best fitting regression model for the whole group is computed, using all cognitive variables: speed, coordination, selective attention, switching, verbal and visual organization. Education was also entered in the model to examine for possible confounding. There was no confounding, so education was left out of the analyses. Results are presented in table 6.

Table 6: Hierarchical multiple regression analyses for long term memory variables in all subject (n = 163), schizophrenic patients (n = 118) and controls (n= 45)

Memory measures	Predictors	B	β	R^2
All subject (N = 163)				
Verbal learning	Speed	2.58	.38 ****	.30 ****
	Organization[a]	3.93	.31 ****	
Verbal retrieval	Speed	0.41	.30 ****	.20 ****
	Organization[a]	0.46	.20 *	
	Switching	0.01	.19 *	
Visual memory	Organization[b]	3.93	.29 ****	.17 ****
	Speed	3.41	.24 **	
Semantic memory	Speed	2.08	.54 ****	.35 ****
	Organization[a]	0.88	.14 *	
Patients (n = 118)				
Verbal learning	Organization[a]	3.26	.23 *	.10 **
	Coordination	2.31	.20 *	
Verbal retrieval	Coordination	0.51	.22 *	.11 **
	Organization[a]	0.60	.22 *	
Visual memory	Speed	1.47	.26 **	.18 ****
	Organization[b]	3.47	.23 *	
Semantic memory	Speed	1.41	.38 ****	.25 ****
	Coordination	1.10	.20 *	
Controls (n = 45)				
Verbal learning	Organization[a]	0.46	.46**	.39****
	Speed	0.49	.37**	
Visual memory	Organization[b]	1.05	.39 **	.16**
Semantic memory	Speed	2.63	.40**	.16**

[a] Organization of verbal material (CVLT semantic clustering). [b] Organization of visual material (RCFT organization type). * p < .05. ** p < .01. ***p < .001. **** p < .0001.

A combination of processing speed and organization made the best prediction for all memory variables.

Secondly we analyzed the influence of basic cognitive variables on long term memory within the patient group with hierarchical multiple regression analyses

with forced entry, using all cognitive variables (speed, coordination, selective attention, switching, verbal and visual organization). Because the role of disease severity on memory is not clear, psychopathology dimensions were also entered in the model. Results are presented in table 6. The coordinating component of the central executive (CPT d') is the best predictor for both general verbal learning performance and verbal retrieval. Processing speed is the best predictor for visual memory and semantic memory, but CPT d' still explains additional variance of these variables. Organization is a significant predictor for all three episodic memory measures but not for semantic memory. As for the role of disease severity, the psychopathology dimensions were not significant predictors.
The influence of basic cognitive variables on long-term memory within the control group was also analyzed with hierarchical multiple regression analyses with forced entry. Results are presented in table 6. Organization is the best predictor for general verbal learning performance and visual memory. Speed is the best predictor for semantic memory and also explains some variance in general verbal learning.

4. Discussion

The long-term memory deficits in schizophrenia found in this study correspond to a large extent with those reported in other studies (e.g. Aleman et al., 1999; Paulsen et al., 1995), in which learning and retrieval deficits were reported but no storage deficits. In contrast with the results of two large meta-analyses (Aleman et al.; Heinrichs & Zakzanis, 1998) verbal memory deficits in our patients appeared more severe than visual memory deficits. Although some studies suggest a differential deficit in verbal learning and memory in schizophrenia (e.g. Saykin et al., 1991) most of these studies, including ours, used a non-verbal memory task that is not comparable to word list learning. A recent study of Tracy et al. (2001) showed similar results on verbal and non-verbal memory tasks in schizophrenia with a non-verbal memory task, which produced the same memory component measures as the CVLT. Therefore we think that the difference in effect sizes on verbal and visual memory measures are caused by differences in task characteristics and not by modality specific

deficits. There were also significant differences between patients and controls on basic cognitive variables, thought to influence memory. These differences were most apparent for processing speed and the coordinating component of the central executive. Although significant, the differences were less pronounced for the selective attention and the organization components of the central executive. There was no significant difference between patients and controls on the switching component of the central executive, suggesting that a distinction between different central executive components is valid indeed. Although there was a difference in education between patients and controls in this study, the differences in cognitive variables were still clearly significant after controlling for the effect of education.

Because of the difference in education between patients and controls, the possible confounding effects of education were examined for all regression analyses. Education only was found to be a confounder for disease related variance in visual and semantic memory. However, education was not a confounder for the regression of cognitive variables on memory measures in the whole group. Our first hypothesis was partly confirmed. Processing speed did reduce the disease-related variance in all memory variables, suggesting that part of the differences in long-term memory performance between schizophrenic patients and controls could be due to a slowing of processing speed in schizophrenia. Although education reduced part of the disease related variance in visual and semantic memory, speed still reduced a larger part of the disease related variance than education. For general verbal learning performance, group membership, however, still explained some of the variance after entering processing speed as first predictor. This remained significant even after entering organization as a second predictor. This could point to a special role of verbal learning deficits in schizophrenia. Processing speed still was the best predictor for all verbal memory measures in the total subject group, and second to organization for visual memory. Switching was the only central executive measure with additional predictive power, in this case for verbal retrieval. The total amount of variance explained is limited to a maximum of 35 % for semantic memory.

Our second hypothesis was also partly confirmed. The combination of coordination and organization of information gave the best prediction for long-term verbal episodic memory measures in patients. Processing speed together

with coordination and organization respectively gave the best prediction for semantic memory and visual memory. The other central executive components, on which patients performed almost at a normal level, did not predict long-term memory in schizophrenia. This suggests that only central executive components that are affected by the disease, mediate memory performance in schizophrenia. An additional analysis of the control group, which performed well on all central executive measures, revealed that the coordination component did not influence memory performance; organization however did. An association between organization of information and encoding in normal subjects is found in other studies as well (Fletcher, Shallice & Dolan, 1998). We suggest a differential influence of central executive components on long-term memory, in which some components, such as organization, always influence long term memory performance, while others, such as coordination only have a negative influence when they break down. One should keep in mind, however, that the amount of explained variance in the patient group is modest, especially for episodic memory performance, suggesting that basic cognitive functions only have a limited influence on long-term memory functions. Data presented in other publications confirm our results. Brébion et al. (1998) presented correlations of processing speed and working memory with long-term memory measures ranging from .39 to .50, indicating a maximum of 25 % explained variance in long-term memory.

Psychopathology did not influence memory performance in this study. This is in contrast with the general trend that shows a moderate influence of negative symptoms on memory performance (Aleman et al., 1999). Some correlational longitudinal studies found memory measures to be partly related to active episodes (Censits, Ragland, Gur & Gur, 1997; Hoff et al., 1999). This could explain our negative results, because symptom ratings were rather mild, and patients were in a relatively stable phase of the disease.

Organization of information, coordination and especially speed were the best predictors for long-term memory in this study. This raises the question what is meant by “speed of processing”. The neurophysiology behind this construct is still unknown. Simple reaction times tend to be long relative to transduction and transmission times (Hanes and Schall, 1996). Speed could refer to efficiency of information processing, and therefore is likely to reflect some kind of executive process. Speed and central executive components were correlated in this study

but they explained different parts of the variance in long-term memory. These speed related "executive processes" probably operate in such a short time interval that they are almost impossible to assess with executive tasks. Electrophysiological and functional imaging studies could help to clear this issue.

The main conclusion is that the influence of more basic cognitive deficits on long-term memory in schizophrenia is modest, especially for verbal learning. It seems that the long-term memory deficits in schizophrenia are primary deficits. The question remains what sub processes of memory are to be held responsible. Because learning of information is most impaired, the early perceptual encoding of stimuli or the establishment of memory traces are the most likely candidates.

Imaging studies of verbal encoding point to a special role for the prefrontal cortex and the medial temporal regions including the hippocampus (Cabeza & Nyberg, 2000). In an excellent review of neuropathological and functional studies, Harrison (1999) postulates that the pathofysiology of schizophrenia reflects aberrant activity in, and integration of, the components of a distributed circuitry involving the prefrontal cortex, hippocampus and certain subcortical structures. Although the concept of localized dysfunctions still dominates research in schizophrenia, a growing body of evidence indicates that deficits in connectivity between and within the different components of the suggested circuitry, which are supposed to be involved in coordination and organization of information, are more likely. Because the process of establishing memory traces depends on the coordinated forming of associations between several features it is conceivable that deficits in connectivity also cause memory deficits, especially in the phase of encoding of information.

References

Aleman, A., Hijman, R., de Haan, E.H.F., Kahn, R.S., 1999. Memory impairment in schizophrenia: A meta-analysis. Am. J. Psychiatry 156, 1358-1366.

American Psychiatric Association. 1994. Diagnostic & Statistical Manual of Mental Disorders. Washington DC: American Psychiatric Association.

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.

Baddeley, A., 1996. Exploring the central executive. Quarterly Journal of Experimental Psychology: Human Experimental Psychology, 49A, 5-28.

Baddeley, A., 1998. Recent developments in working memory. Curr. Opin Neurobio., 8, 234-238.

Brebion, G., Amador, X., Smith, M.J., Gorman, J.M., 1997. Mechanisms underlying memory impairment in schizophrenia. Psychol. Med. 27, 383-393.

Brebion, G., Amador, X., Smith, M.J., Gorman, J.M., 1998. Memory impairment and schizophrenia: the role of processing speed. Schizophr. Res. 30, 31-39.

Brebion, G., Smith, M.J., Gorman, J.M., Malaspina, D., Sharif, Z., Amador, X., 2000. Memory and schizophrenia: differential link of processing speed and selective attention with two levels of encoding. J. Psychiatr. Res. 34, 121-127.

Broerse, A., Holthausen, E.A.E., Van den Bosch, R.J., Den Boer, J.A., 2001. Does frontal abnormality exist in schizophrenia? A saccadic eye movement study. Psychiatry Res. 103, 167-178.

Cabeza, R., Nyberg, L., 2000. The neural bases of learning and memory: functional neuroimaging evidence. Curr. Opin. neurology 1350-7540.

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.

Chertkow, H., Bub, D., 1990. Semantic memory loss in dementia of Alzheimer's type. What do various measures measure? Brain, 113, 397-417.

Chiulli, S.J., Haaland, K.Y., La Rue, A., Garry, P.J., 1995. Impact of age on drawing the Rey-Osterrieth Figure. Clin. Neuropsychologist l9, 219-224.

Clare, L., McKenna, P.J., Mortimer, A.M., Baddeley, A.D., 1993. Memory in schizophrenia: What is impaired and what is preserved. Neuropsychologia, 31, 1225-1241.

Cohen, J., 1969. Statistical power analysis for the behavioral sciences. New York: Academic Press.

Delis, D.C., Kramer, J.H., Kaplan, E., Ober, B.A., 1987. California Verbal Learning Test (CVLT) Manual. New York: the Psychological Corporation.

Duley, J.F., Wilkins, J.W., Hamby, S.L., Hopkins, D.G., 1993. Explicit scoring criteria for the Rey-Osterrieth and Taylor complex figures. Clin. neuropsychologist, 7, 29-38.

Fletcher, P.C., Shallice, T., Dolan, R.J., 1998. The functional roles of prefrontal cortex in episodic memory. I. Encoding. Brain, 121, 1239-1248.

Fletcher, P.C., Henson, R.N., 2001. Frontal lobes and human memory: insights from functional neuroimaging. Brain, 124, 849-881.

Goldberg, T.E., Hyde, T.M., Kleinman, J.E., Weinberger, D.R., 1993. Course of schizophrenia: neuropsychological evidence for a static encephalopathy. Schizophr. Bull. 19, 797-804.

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

Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am. J. Psychiatry 153, 321-330.

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

Hanes, D. P., Schall, J. D., 1996. Neural control of voluntary movement initiation. Science, 274, 427-430.

Harrison, P.J., 1999. The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain, 122, 593-624.

Hawkins, K.A., Sullivan, T.E., & Choi, E.J., 1997. Memory deficits in schizophrenia: inadequate assimilation or true amnesia? Findings from the Wechsler Memory Scale-revised. J. Psychiatry Neurosci. 22, 169-179.

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

Hoff, A.L., Sakuma, M., Wieneke, M., Horon, R., Kushner, M., DeLisi, L.E., 1999. Longitudinal neuropsychological follow-up study of patients with first-episode schizophrenia. Am. J. Psychiatry 156, 1336-1341.

Joyce, E.M., Collinson, S.L., Crichton, P., 1996. Verbal fluency in schizophrenia: relationship with executive function, semantic memory and clinical alogia. Psychol. Med. 26, 39-49.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261-276.

Kazes, M., Berthet, L., Danion, J.M., Amado, I., Willard, D., Robert, P., Poirier, M.F., 1999. Impairment of consciously controlled use of memory in schizophrenia. Neuropsychology, 13, 54-61.

Lezak, M.D., 1983. Neuropsychological assessment. Oxford: Oxford university Press.

Lindenmayer, J.P., Bernstein-Hyman, R., Grochowski, S., Bark, N., 1995. Psychopathology of Schizophrenia: initial validation of a 5- factor model. Psychopathology, 28, 22-31.

McKay, A.P., McKenna, P.J., Bentham, P., Mortimer, A.M., Holbery, A., Hodges, J. R., 1996. Semantic memory is impaired in schizophrenia. Biol. Psychiatry 39, 929-937.

Montgomery, S.A., Åsberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry, 134, 382-389.

Nathaniel-James, D.A., Brown, R., Ron, M.A., 1996. Memory impairment in schizophrenia: its' relationship to executive function. Schizophr. Res. 21, 85-96.

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

Osterrieth, P.A., 1944. Test of copying a complex figure; contribution to the study of perception and memory. Archives de Psychologie, 30, 206-356.

Paulsen, J.S., Heaton, R.K., Sadek, J.R., Perry, W., Delis, D.C., Braff, D., Kuck, J., Zisook, S., Jeste, D.V., 1995. The nature of learning and memory impairments in schizophrenia. J. Int. Neuropsychol. Soc. 1, 88-99.

Rey, A., 1964. L'examen clinique en psychologie. Paris: Presses Universitaires de France.

Salame, P., Danion, J.M., Peretti, S., Cuervo, C., 1998. The state of functioning of working memory in schizophrenia. Schizophr. Res. 30, 11-29.

Salthouse, T.A., 1996. The processing-speed theory of adult age differences in cognition. Psychol. Rev. 103, 403-428.

Saykin, A.J., Gur, R.C., Gur, R.E., Mozley, P.D., Mozley, L.H., Resnick, S.M., Kester, D.B., 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., Tulving, E., 1994. What are the memory systems of 1994. In D.I. Schacter & E. Tulving (Eds.). Memory systems 1994 (pp. 1-38). Cambridge: MIT Press.

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

Tracy, J.I., Mattson, R., King, C., Bundick, T., Celenza, M.A. & Glosser, G. (2001). A comparison of memory for verbal and non-verbal material in schizophrenia. Schizophrenia Research 50, 199-211.

Van den Bosch, R.J., Rombouts, R.P., van Asma, M.J., 1996. What determines continuous performance task performance? Schizophr. Bull. 22, 643-651.

Van der Does, A.J., Dingemans, P.M., Linszen, D.H., Nugter, M.A., Scholte, W.F., 1996. Symptoms, cognitive and social functioning in recent-onset schizophrenia: a longitudinal study. Schizophr. Res. 19, 61-71.

Van Hoof, J.J., Jogems-Kosterman, B.J., Sabbe, B.G., Zitman, F.G, & Hulstijn, W., 1998. Differentiation of cognitive and motor slowing in the Digit Symbol Test (DST): differences between depression and schizophrenia. J. Psychiatr. Res. 32, 99-103.

Vink, M., Jolles, J., 1985. A new version of the Trail making Test as an information processing task. J. Clin. Neuropsychology, 7, 162.

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.

Chapter 5

Psychopathology and cognition in schizophrenia spectrum disorders: the role of depressive symptoms

Published:
Holthausen, E.A.E., Wiersma, D., Knegtering, R.H., van den Bosch, R.J., 1999. Schizophr. Res. 39, 65-71.

Abstract

The cognitive correlates of five symptom dimensions based on PANSS ratings were examined in a group of 50 recent onset psychotic patients, using both objective and subjective cognitive measures. We were particularly interested in the depression dimension, since it has not been studied extensively thus far. The depression dimension showed a fairly high number of correlations with both objective and subjective cognitive measures, such as problems with simple and divided attention, psychomotor slowing and subjectively experienced distractibility, overload and diminished attentional control. The other dimensions, including the negative symptoms, had less cognitive correlates. It is possible that previous studies based on a three-dimensional model confounded correlates of negative symptoms with correlates of depressive symptoms. The results of this study suggest the need for more research into the mechanisms underlying the relationship between depressive symptoms and cognitive functioning in schizophrenia, and that patients with depressive symptoms are less efficient in information processing, but can compensate by investing more mental effort. Because subjective cognitive measures were related to mental effort in previous research they can be a useful tool in future research.

1. Introduction

Although schizophrenia is associated with a diversity of cognitive impairments, such as deficits in attention, memory, motor functioning and executive functioning (Gold and Harvey, 1993; Gourovitch and Goldberg, 1996; Rossel and David, 1997), it is not possible to specify a typical cognitive profile. This is partly due to the heterogeneity of the disease. Attempts to group patients into different subtypes of schizophrenia have not led to a solution. However, during the last decade a more promising dimensional approach has emerged, which categorizes symptoms instead of patients (Andreasen and Carpenter, 1993). Studies have consistently identified a positive, a negative and a disorganization dimension (Andreasen et al., 1994). Some, using a wider range of symptom ratings, also found excitement and depression-anxiety dimensions (Bell et al., 1992, 1994; Kay and Sevy, 1990; Lindenmayer et al., 1994, 1995). It has been suggested that the dimensions represent different pathological processes (Liddle et al., 1987; 1992). If this is true, it is likely that the symptom dimensions have specific cognitive correlates.

A number of studies have addressed the cognitive correlates of these dimensions of schizophrenia (Addington et al., 1991; Berman et al., 1997; Brown and White, 1992; Liddle, 1987; Liddle and Morris, 1991; Norman et al., 1997; Van der Does et al., 1996). Most included only positive, negative and disorganization symptom dimensions. The negative dimension has been shown to correlate with poor generation or execution of cognitive strategies, slow responses on simple attention tasks, poor abstract reasoning and impaired set shifting. The positive dimension appears to correlate mainly with poor verbal memory, and the disorganization dimension has been shown to correlate with attentional dysfunction and inhibition problems. Only two studies examined cognitive correlates of depressive symptoms, focusing on attention and verbal memory respectively. Van der Does et al. (1996) found a significant correlation with poor selective attention and Brebion et al. (1997) found that depressive symptoms correlated significantly with poor semantic encoding and reduced verbal recall and recognition.

It is well established that a proportion of the patients, ranging from 11% to 55% (Palmer et al., 1997), do not show cognitive deficits on neuropsychological or objective cognitive measures, although they often complain about their

cognitive functioning. It is possible that these individuals perform below the level they could have achieved if not ill. Another explanation might be that they are able to compensate for their cognitive deficits on neuropsychological tasks by investing more mental effort. These tasks usually measure basic cognitive functions over a short period, in a structured way, whereas in daily life patients probably reach their limits because the pressure on their information processing capacity is much larger. Ratings of subjective cognitive experiences could be helpful in obtaining an indirect measure of mental effort, because a recent study has shown that self-report ratings of increased mental effort are associated with subjective experiences of mental overload and distractibility (Van den Bosch & Rombouts, 1998).

Subjective cognitive deficits are failures or difficulties experienced by a person in the perception and processing of internal and external information, which are usually measured with self-report questionnaires. A small number of studies have examined subjective cognitive functioning in schizophrenia. These studies report a high prevalence of subjective cognitive deficits (Liddle et al., 1988; Peralta and Cuesta, 1998; Van den Bosch et al., 1993). There is a striking lack of correlation between objective and subjective measures. Williams et al. (1984) did not find a relation between self-report of cognitive difficulties and a choice reaction time task. Van den Bosch and Rombouts (1998) found no correlation between subjective cognitive dysfunctions and vigilance performance.

Our main objective in this study was to examine whether the five psychopathology dimensions have different cognitive correlates in recent onset psychotic patients. We were particularly interested in the depression dimension, because there is good evidence for its independent existence and it has not been studied extensively thus far. Although we do not know which specific cognitive functions are associated with this dimension, we hypothesized that it would have at least some cognitive correlates. Neuropsychological tasks addressed attentional, memory, executive and motor speed functions. To get an indirect measure of the amount of mental effort people invest to compensate for their cognitive deficits, we also included subjective ratings of cognitive functioning.

2. Method

2.1. Subjects

The study included fifty psychiatric patients who had recently experienced a first or second psychotic episode. Psychiatric diagnosis according to DSM-IV (American Psychiatric Association, 1994) was based on all information available, including a structured interview (Schedules for Clinical Assessment in Neuropsychiatry, SCAN; Wing et al, 1990). This study was part of a larger epidemiological study for which they gave informed consent. Exclusion criteria were severe mental retardation and a known systemic or neurological illness. Subject characteristics are given in table 1. There were no significant differences between the schizophrenic patients and patients with another psychotic disorder for sex (Chi-square = 0.02, ns), age (F = 0.12, ns), or educational level (F = 1.62, ns).

Table 1. Demographic characteristics of patients by diagnosis.

Diagnosis	**n**	**age**		**sex**	**educational level***	
		m	sd	m / f	m	sd
schizophrenia	32	24.8	6.3	22 / 10	3.8	1.3
schizophreniform disorder	10	23.7	6.3	7 / 3	2.4	0.7
delusional disorder	2	28.5	4.9	2 / -	4.0	1.4
brief psychotic disorder	2	18.	2.1	- / 2	3.5	0.7
psychotic disorder NOS	4	31.8	9.4	3 / 1	4.8	1.9
Total	50	25.0	6.6	34 / 16	3.6	1.4

* educational level goes from 1: primary school, up to 6: university degree

The average daily dosage of antipsychotic drugs was 6.1 mg haloperidol equivalents (range 1.0 - 20.0 mg). Seven patients were drug-free. Fifteen patients also used antiparkinsonian drugs.

2.2. Procedures and instruments

During the first week after admission patients were interviewed with the SCAN. Psychiatric diagnosis was made at a consensus meeting, seven weeks after admission. Only subjects with a diagnosis within the schizophrenia spectrum (schizophrenia, schizophreniform disorder, delusional disorder, brief psychotic

disorder, psychotic disorder NOS) were included. Patients were tested after a period of six weeks on stable medication. Within the same week their symptoms were rated on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). Dimensional scores were obtained by calculating sum scores of symptoms loading high on the five dimensions described in a large factor analytical study (Lindenmayer et al., 1995).

Objective cognitive functioning was measured using a neuropsychological battery measuring attention, memory, executive functioning and motor speed. Vigilance was measured with the sensitivity index d' of a double stimulus Continuous Performance Task (CPT; Van den Bosch et al, 1996). A computerized STROOP task measured reaction time in two simple (names, colors) and one complex selective attention task (interference). Forms A and B of a computerized version of the Trail Making Test were used to measure simple and divided attention respectively. The Digit Span subtest of the Wechsler Adult Intelligence Scale (WAIS; Stinissen et al., 1970) was used to measure immediate verbal memory, and the delayed recall score of the Dutch translation of the Rey Auditory Verbal Learning Task (RAVLT; Rey, 1964) was used to measure long-term verbal memory. Executive functioning was measured as the number of steps taken on a computerized Maze task and motor speed was measured by Fingertapping.

Subjective cognitive functioning was measured with the Test of Attentional Style (TAS; Van den Bosch et al., 1993). The TAS is a self-report questionnaire of 31 items containing five subscales. Responses are on a five point scale ranging from 1: "never" to 5: "always". The first two subscales refer to cognitive problems and are called (1) Distractibility and (2) Overload. The other three subscales measure perceived cognitive efficacy and are named (3) Processing capacity; (4) Attentional Control and (5) Conceptual Control. The last subscale was left out of analysis because it does not distinguish patients from normal controls (see Van den Bosch et al, 1993, for a more extensive description).

3. Results

Table 2 presents the data on the symptom dimensions and the cognitive measures. The symptom ratings, especially on the excitement and the disorganization dimensions, were fairly low. This is no surprise because patients were rated after a period of six weeks on stable medication.

	Mean	SD
Symptom dimensions		
positive (5 PANSS items)	9.9	5.0
negative (6 PANSS items)	12.4	5.0
disorganization (5 PANSS items)	7.7	2.7
depression (4 PANSS items)	9.3	3.3
excitement (3 PANSS items)	3.7	1.1
Neuropsychological tests		
CPT d'	3.6	0.9
STROOP names (s)[1]	53.6	9.1
STROOP colors (s)	50.4	9.3
STROOP interference (s)	68.0	15.3
Trail Making A (s)[1]	84.6	39.2
Trail Making B (s)	103.3	40.6
Mazes number of steps[2]	280.5	108.0
Fingertapping (10 s)	50.9	12.5
Digit Span WAIS	12.8	3.6
Delayed recall RAVLT	9.4	2.6
Subjective Cognitive Functioning[3]		
Distractibility	23.1	4.7
Overload	16.8	4.6
Processing Capacity	17.8	3.4
Attentional Control	15.2	2.3

Table 2.Symptom dimensions, neuropsychological tests and subjective cognitive functioning six weeks after admission.

The excitement dimension was left out of analysis because of the very low variability in scores. We do not give the norm-scores for the objective cognitive variables because the tasks were standardized on different groups. In general the STROOP, Trail Making and Maze tasks were performed poorly. Performance on the CPT, Fingertapping, Digit Span and verbal learning tasks where within the normal range. All variables resembled the standard normal distribution, except the positive and the disorganization dimensions, which were skewed to the left. Therefore we used parametric as well as nonparametric correlation analysis. Because we predicted higher levels of symptomatology to be associated with poorer cognitive performance, one-tailed tests of significance were used (table 3).

The depression dimension in particular correlated significantly with a number of objective and subjective cognitive variables: slow performance on STROOP colors, Trailmaking A and B, Fingertapping and subjectively experienced distractibility, overload and diminished attentional control. The other symptom

[1] This computerised version takes longer then the paper and pencil test.
[2] Minimum number of steps, which means an excellent performance, is 205.
[3] For mean scores and standard deviations of a normal control group see: Van den Bosch et al (1993).

dimensions showed less significant correlations with these variables. The positive dimension correlated with poor delayed verbal recall and slow Trailmaking B, as well as subjective overload experiences. The disorganization dimension correlated with subjective distractibility and overload experiences, but not with objective test measures. The negative dimension correlated with poor Fingertapping and the subjective experience of distractibility and diminished processing capacity.

Table 3. Correlations between symptom dimensions and cognitive variables.

cognitive variables	positive dimension †	disorganization dimension †	negative dimension ‡	depression dimension ‡
Objective				
CPT d'	0.10	-0.05	-0.04	0.06
STROOP names	0.01	0.03	0.08	0.23
STROOP colors	0.13	0.09	0.13	**0.35****
STROOP interference	0.07	0.02	0.09	0.23
Trail Making A	0.15	0.04	0.12	**0.26***
Trail Making B	**0.32***	0.17	0.24	**0.29***
Mazes number of steps	-0.08	0.05	0.12	0.15
Fingertapping	-0.19	-0.02	**-0.25***	**-0.28***
Digit Span WAIS	-0.01	-0.05	-0.18	-0.17
Delayed recall RAVLT	**-0.33***	-0.05	0.07	0.19
Subjective				
Distractibility	0.20	**0.24***	**0.30***	**0.49*****
Overload	**0.31***	**0.25***	0.22	**0.44****
Processing Capacity	0.05	0.03	**-0.26***	-0.07
Attentional Control	-0.11	-0.09	-0.12	**-0.33****

† Spearman rank-order correlation coefficients; ‡ Pearson product-moment correlation coefficients.
One-tailed significance, *p < .05, **p < .01, ***p < .001

The associations between objective and subjective cognitive measures were examined with one-tailed tests for significance on the Pearson product-moment correlations. Distractibility correlated significantly ($p < .05$) with the STROOP interference (0.27), Fingertapping
(-0.25) and Digit Span (0.34). Processing capacity correlated significantly ($p < .05$) with Trail Making B (0.30), and Attentional control correlated significantly with Delayed verbal recall (0.35). The subjective experience of Overload had no objective cognitive correlates.

4. Discussion

In this study on recent onset psychotic patients we found significant correlations between several symptom dimensions and subjective as well as objective cognitive variables. Depressive symptoms were associated with a fairly high number of cognitive ratings such as problems with simple and divided attention, psychomotor slowing and subjective experiences of distractibility, overload and diminished attentional control. The other symptom dimensions showed fewer cognitive correlates, with some overlap with the depression dimension. Negative symptoms correlated with psychomotor slowing and the experience of distractibility, as did the depressive symptoms. However, there was a unique correlation with the experience of diminished processing capacity. Somewhat surprisingly, disorganization symptoms correlated only with subjective experiences of distractibility and overload but not with objective cognitive measures. Positive symptoms correlated with problems in divided attention and subjective experiences of overload, like depressive symptoms, but there was a unique correlation with poor verbal recall. The last finding is in accordance with other studies (Berman et al., 1997; Norman et al., 1997), whereas the findings concerning negative and disorganization symptoms are not. In most studies these dimensions correlate with executive and attentional tasks (Addington et al., 1991; Berman et al., 1997; Brown and White, 1992; Liddle, 1987; Liddle and Morris, 1991; Norman et al., 1997; Van der Does et al., 1996). Our negative findings regarding objective cognitive correlates of the disorganization dimension might be due to the fact that our patients had relatively few of these symptoms because they were on stable medication. There are several possible explanations for the lack of objective cognitive correlates of the negative symptoms in this study. First, in other studies this dimension usually correlates with less structured executive tasks like Verbal Fluency and Wisconsin Card Sorting, while we used an executive task (Mazes) which forces the subject to find the only possible solution. Second, the patient group also differed from other studies, most of which were based on more chronic patients. Studies of recent onset patients are not confounded by long-term medication or hospitalization, but these patients have a higher prevalence of depression (Addington et al., 1998; Koreen et al., 1993). This makes it more likely that cognitive correlates of depressive symptoms are identified. Moreover, studies

based on a three-dimensional model of symptomatology are likely to confound correlates of negative symptoms with correlates of depressive symptoms. Most studies have only looked at negative, positive and disorganization dimensions.
The evidence in favor of an independent dimension of depressive symptoms in schizophrenia is quite strong, as is shown by several factor analytical studies (Bell et al., 1992; 1994; Kay and Sevy, 1990; Lindenmayer et al., 1994; 1995), correlational studies (Kuck et al., 1991; Newcomer et al., 1989), and studies investigating the differences between schizophrenic patients with and without depression (Kohler et al., 1998; Lindenmayer et al., 1991). It is important to study these symptoms and their cognitive correlates in addition to the core symptoms of psychosis. If the causal mechanisms of the symptom dimensions and their cognitive correlates are the same regardless of the diagnostic category, then the causal mechanisms of some cognitive problems of psychotic patients with depressive symptoms could be the same as those in affective disorder patients. Depressive patients are less efficient in effortful information processing, and this would show in a slowness in reacting and responding (King and Caine, 1996). This agrees well with our findings on objective cognitive tasks.
The correlations of depressive symptoms with subjective cognitive complaints are also interesting. There is a relationship between depressive symptoms and subjective experiences of distractibility and mental overload. Previous research showed that in schizophrenic patients these subjective complaints were strongly related to ratings of the amount of mental effort people felt they had to spent on cognitive tasks (Van den Bosch & Rombouts, 1998). It could be speculated that depressive symptoms are accompanied by less efficient information processing, as a result of which patients have to invest more effort, which, in turn, results in subjective cognitive complaints in spite of normal results on neuropsychological tasks. This points to the importance of subjective measures for cognitive research. There were some correlations between subjective and objective cognitive tasks, but subjective mental overload had no objective cognitive correlates. This could mean that this scale addresses problems, which cannot easily be assessed by neuropsychological tasks.
The results of this study suggest that more research should be directed at the mechanisms behind the relationship between depressive symptoms and cognitive dysfunctioning in schizophrenia. In this study, the depression

dimension of the PANSS was used. In future research more sophisticated depression scales might be used. Subjective cognitive ratings and psycho physiological measures of mental effort could be helpful in unraveling the relationship between depressive symptoms and cognition.

References

Addington, J.D., Addington, D., Maticka-Tyndale, E., 1991. Cognitive functioning and positive and negative symptoms in schizophrenia. Schizophr. Res. 5, 123-124.

Addington, D., Addington, J., Patten, S., 1998. Depression in people with first-episode schizophrenia. Br.J.Psychiatry. Suppl. 33, 90-92.

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

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

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 Psychiat. Scand. Suppl. 384, 51-59.

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.

Bell, M.D., Lysaker, P.H., Beam Goulet, J.L., Milstein, R.M., Lindenmayer, J.P., 1994. Five-component model of schizophrenia: assessing the factorial invariance of the positive and negative syndrome scale. Psychiat. Res. 52, 295-303.

Berman, I., Viegner, B., Merson, A., Allan, E., Pappas, D. Green, A.I., 1997. Differential relationships between positive and negative symptoms and neuropsychogical deficits in schizophrenia. Schizophr. Res. 25, 1-10.

Brebion, G., Smith, M.J., Amador, X., Malaspina, D., Gorman, J.M., 1997. Clinical correlates of memory in schizophrenia differential links between depression, positive and negative symptoms, and two types of memory impairment. Am. J. Psychiatry 154, 1538-1543.

Brown, K.W., White, T., 1992. Syndromes of chronic schizophrenia and some clinical correlates. Br. J. Psychiatry 161, 317-322.

Gold, J.M., Harvey, P.D., 1993.Cognitive deficits in schizophrenia. Psychiat. Clin. North. Am. 16,295-312.

Gourovitch, M.L., Goldberg, T.E. 1996. Cognitive deficits in schizophrenia: attention, executive functions, memory and language processing. In C. Pantalis, H.E. Nelson, T.R. Barnes. (Eds.). Schizophrenia: a neuropsychological perspective. (pp 71-87). Wiley, Chichester, pp 71-87.

Kay, S.R., Fiszbein, A., Opler, L.A.,1987. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261-276.

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

King, D.A., Caine, E.D., 1996. Cognitive impairment and major depression: beyond the pseudodementia syndrome. In I.Grant, K.M. Adams (Eds.). Neuropsychological assessment of neuropsychatric disorders. Oxford University Press, New York, pp 200-217.

Kohler, C., Gur, R.C., Swanson, C.L., Petty, R., Gur, R.E., Mozley, L.H., 1998. Depression in schizophrenia: Association with neuropsychological deficits. Biol. Psychiatry 43, 173-180.

Koreen, A.R., Siris, S.G., Chakos, M., Alvir, J., Mayerhoff, D., Lieberman, J., 1993. Depression in first-episode schizophrenia. Am.J.Psychiatry 150, 1643-1648.

Kuck, J., Zisook, S., Moranville, J.T., Heaton, R.K., Braff, D.L., 1992. Negative symptomatology in schizophrenic outpatients. J.Nerv.Ment.Dis. 180, 510-515.

Liddle, P.F., 1987. Schizophrenic syndromes, cognitive performance and neurological dysfunction. Psychol. Med. 17, 49-57.

Liddle, P.F., Barnes, T.R., 1988. The subjective experience of deficits in schizophrenia. Compr. Psychiatry 29, 157-164.

Liddle, P.F., Morris, D.L., 1991. Schizophrenic syndromes and frontal lobe performance. Br. J. Psychiatry 158, 340-345.

Liddle, P.F., Friston, K.J., Frith, C.D., Hirsch, S.R., Jones, T., and Frackowiak, R.S. , 1992. Patterns of cerebral blood flow in schizophrenia. Br.J.Psychiatry 160, 179-186.

Lindenmayer, J.P., Grochowski, S., Kay, S.R., 1991. Schizophrenic patients with depression: psychopathological profiles and relationship with negative symptoms. Compr.Psychiatry 32, 528-533.

Lindenmayer, J.P., Bernstein Hyman, R., Grochowski, S. A., 1994. A new five factor model of schizophrenia. Psychiat. Quart. 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.

Newcomer, J.W., Faustman, W.O., Yeh, W., Csernansky, J.G., 1990. Distinguishing depression and negative symptoms in unmedicated patients with schizophrenia. Psychiat. Res. 31, 243-250.

Norman, R.M., Malla, A.K., Morrison Stewart, S.L., Helmes, E., Williamson, P.C., Thomas, J., Cortese, L., 1997. Neuropsychological correlates of syndromes in schizophrenia. Br. J. Psychiatry 170, 134-139.

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.

Peralta, V., Cuesta, M.J., 1998. Subjective experiences in psychotic disorders: diagnostic value and clinical correlates. Compr. Psychiatry 39, 11-15.

Rey, A., 1964. L'examen clinique en psychologie. Presses Universitaires de France, Paris.

Rossel, S.L., David, A.S., 1997. The neuropsychology of schizophrenia: recent trends. Curr. Opin. Psychiatry 10, 26-29.

Stinissen, J. Willems, P.J., Coetsier, P., Hulsman, W.L.L., 1970. Manual of the Dutch translation of the Wechsler Adult Intelligence Scale. Swets, Amsterdam.

Van den Bosch, R.J., Rombouts, R.P., Asma, M.J.O., 1993. Subjective cognitive dysfunction in schizophrenic and depressed patients. Compr.Psychiatry 34, 130-136.

Van den Bosch, R.J., Rombouts, R.P., and van Asma, M.J.O., 1996. What determines continuous performance task performance? Schizophr.Bull. 22, 643-651.

Van den Bosch, R.J., Rombouts, R.P., 1998. Causal mechanisms of subjective cognitive dysfunction in schizophrenic and depressed patients. J.Nerv.Ment.Dis. 186, 364-368.

Van der Does, A.J., Dingemans, P.M., Linszen, D.H., Nugter, M.A., and Scholte, W.F., 1996. Symptoms, cognitive and social functioning in recent-onset schizophrenia: a longitudinal study. Schizophr.Res. 19, 61-71.

Williams, R.M., Alagaratnam, W., Hemsley, D.R., 1984. Relationship between subjective self-report of cognitive dysfunction and objective information processing performance in a group of hospitalized schizophrenic patients. Eur. Arch. Psychiat. Neurol. Sci. 234, 48-53.

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.

Chapter 6

The limited predictive value of cognition for outcome in schizophrenia

Submitted:
Holthausen, E.A.E., Wiersma, D., Cahn, W., Kahn, R.S., Dingemans, P.M., Schene, A.H., van den Bosch, R.J.

Abstract

Objective: This study examined the predictive value of cognitive functioning in a first episode group for course of illness and functional outcome in schizophrenia. ***Method***: One hundred and eighteen first episode patients were tested on a cognitive battery. One hundred and three patients participated in the follow-up two years after inclusion. Data were gathered to predict course of illness, social role functioning, competitive employment, and need for care. Differences in outcome between cognitively normal and cognitively impaired patients were also analyzed. ***Results***: Cognitive measures at inclusion did not predict relapse rate, social functioning or competitive employment. Time in psychosis or in full remission, as well as need for care were partly predicted by specific cognitive measures. Although statistically significant, the predictive value of cognition was very limited, explaining a maximum of six percent of the variance in these measures. There was a significant difference between patients with and without cognitive deficits in general on competitive employment status and the work role. ***Conclusions***: Although cognitive deficits in a global sense may affect work performance, the predictive value of specific cognitive measures for outcome in schizophrenia is quite limited. This challenges the idea that cognitive impairment should be considered as the core of the disease and suggests that the relation between cognition and outcome is not that straightforward, and might be affected by other mechanisms, such as mental effort and compensation.

1. Introduction

There is no doubt that cognitive deficits are often found in schizophrenia. As for the nature of the cognitive deficits in schizophrenia, most authors agree that there are specific deficits against a background of generalized cognitive dysfunctioning (Saykin et al., 1994). In an extensive meta-analyses the largest differences between schizophrenia patients and healthy controls were found for verbal memory, performance IQ and vigilance (Heinrichs and Zakzanis, 1998).
Schizophrenia often runs a chronic course, which is difficult to predict. One of the most important course specifiers is relapse rate. Relapse rate in the first year is relatively low but rises substantially in the following years. Five years after first contact it varies around 70 – 80% (Robinson et al., 1999; Wiersma et al., 1998). Common sense suggests that cognitive competence is likely to be a predictor of course of illness. One reliable study so far has investigated the predictive value of cognitive measures on course of illness. No significant effect was found (Robinson et al., 1999).
Functional outcome is multidimensional, consisting of several domains such as interpersonal functioning, functioning in community settings, performance of basic daily activities, occupational functioning. Although only a modest percentage of patients end up staying in a psychiatric hospital or living in sheltered accommodation (14% in a six-site 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. The onset of schizophrenia is also associated with a pronounced decline in employment (Mueser et al., 2001).
Although an increasing number of studies investigate the association between cognitive functioning and functional outcome in schizophrenia (see Green et al., 2000 for a review), only a few have investigated the longitudinal predictive value of cognition on functional outcome (Goldman et al., 1993; Johnstone et al., 1990, Addington and Addington, 2000; Fujii and Wylie, 2002; Velligan et al., 2000). The results are rather inconsistent. Two of these studies find no association (Johnstone et al., 1990, Addington and Addington, 2000). The other three found some significant cognitive predictors for several outcome domains (Goldman et al., 1993; Fujii and Wylie, 2002; Velligan et al., 2000). However, only one of these studies used a first episode group, while prediction is most

relevant early in the disease. No association was found, but in this study only two cognitive measures were used as a predictor.
Because of the lack of cognitive prediction studies in first episode groups, the aim of this study was to investigate the predictive value of cognitive functioning in recent onset group for course of illness, social role functioning, occupational functioning and need for care two years after inclusion.

2. Method

2.1. Subjects

The study included 118 patients who had recently experienced a first or a second psychotic episode according to DSM-IV and were diagnosed within the schizophrenia spectrum (schizophrenia, schizoaffective disorder, schizophreniform disorder). All patients participated in a Dutch multicenter study of the university hospitals of Amsterdam, Groningen and Utrecht. This study 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 in- or outpatient treatment over a period of 1.5 years (1997-1998). After complete description of the study to the subjects, written informed consent was obtained. Diagnosis was based on a structured interview (SCAN; Wing et al., 1990 or CASH; Andreasen et al., 1992). Exclusion criteria were severe mental retardation and a known systemic or neurological illness. Hundred and three patients participated in the follow-up after two years (87%). There were no significant differences in age, sex, cognitive measures, and psychopathology at illness onset between these 103 patients and the 15 lost to follow-up. There was a significant difference in level of education ($F = 6.82$, $df = 1, 116$, $p = .010$) and mean abbreviated WAIS score ($F = 6.05$, $df = 1, 116$, $p = .015$) in favor of the patients who completed the follow-up assessment. At follow-up seventy-seven males and twenty-six females were included. Mean age at inclusion was 23.6 years (sd 5.5).
Forty-five healthy controls, thirty-eight males and seven females, were included in order to establish standard scores on cognitive tests. Exclusion criteria for

controls were a history of mental illness, mental retardation and a known systemic or neurological illness. Mean age was 23.8 years (sd 6.4). There were no significant differences between patients and controls for sex (χ^2 = 1.67, df = 1, 146, n.s.) or age (F = 0.63, df = 1, 146, n.s.). At inclusion twenty-four patients used typical antipsychotics, sixty-seven patients used atypical antipsychotics, eight patients did not use antipsychotic medication, and the medication data from four patients were missing. Ten patients also used anticholinergic medication.

2.2. Procedures and instruments

Cognitive measures

All patients completed an extensive neuropsychological battery after being stabilized for at least six weeks on medication. The cognitive measures in our study were chosen because of their widespread use in clinical practice, evidence for their discriminatory power in studies of schizophrenia patients and normal controls (Keefe et al., 1995; Saykin et al., 1994; van den Bosch et al., 1996) and some evidence for prediction of outcome according to former studies (Goldman et al., 1993; Fujii and Wylie, 2002; Velligan et al., 2000). Vigilance was assessed with the sensitivity index (d') of a double stimulus Continuous Performance Task. Processing speed was assessed with a compound scores of times in seconds on word reading and color naming on a computerized Stroop task and time on part A and part B of a modified version of the Trailmaking Test (Vink and Jolles, 1985). This version consists of three parts: part A with numbers 1 to 26, part B with letters A through Z and part C with 26 numbers and letters alternately. All speed measures showed high intercorrelations in the total group of subjects. Therefore they were averaged after a z-transformation based on the scores of the healthy controls, to create one score. Selective attention and inhibition was assessed with the Stroop interference score (Stroop color word minus Stroop color naming). General verbal learning performance (verbal encoding) was assessed with the total sum of words over the first five learning trials of the Dutch translation of the California Verbal Learning Test (Delis et al., 1987). Verbal Fluency was operationalized as the mean number of words over two categories in one minute (animals and professions). Intelligence

was assessed with four subtests of the Dutch translation of the Wechsler Adult Intelligence Scale (Stinissen et al., 1970): comprehension, vocabulary, block design and picture arrangement. The mean C-score of these four subtests was taken as a measure of intelligence. These C-scores go from 0 to 10 with a mean of 5 and an S.D. of 2. Because the Dutch translation of the WAIS is from 1970, we also give corrected mean C-scores in which we take into account an estimated IQ gain of 0.25 points a year from 1971 to 1997 (Flynn, 1998). The corrected mean C-score is 5.6 with an S.D. of 1.5, which is on an average level compared to the general population. Table 1 gives the scores on these cognitive predictors for patients and controls. Patients performed significantly below the level of controls on all cognitive measures, except for the WAIS score. To investigate whether having a cognitive impairment in a global sense at inclusion influenced outcome, we also analyzed the differences in outcome measures between "cognitively normal" (CN) and "cognitively impaired" (CI) patients. In order to assign patients to these groups, scores on a large neuropsychological battery were transformed into z-scores using means and SD's from the controls. A patient was considered cognitively impaired if he had at least one z-score of two or more below the control group (for more details: Holthausen et al., 2002).

Table 1. Means and standard deviations for cognitive predictors; patients compared with normal controls

	Patients N = 103	**Controls N = 45**	**Sign.**
Vigilance (CPT d')	3.53 (0.77)	4.29 (0.55)	.000
Speed of processing *	-1.9 (1.4)	0.0 (1.0)	.000
Selective attention (STROOP interference)	11.6 (11.4)	7.4 (5.2)	.037
Verbal encoding (CVLT trial 1-5)	45.7 (9.2)	56.4 (8.5)	.000
Verbal fluency (number of words)	18.0 (4.3)	22.7 (5.1)	.000
Intelligence (mean WAIS C-score 1-10)**	6.2 (1.5)		
Mean corrected WAIS C-score	5.6 (1.5)		

* Mean z-score on CPT reaction time, Trailmaking A, STROOP 1 and 2.
** Mean WAIS subtest score on Comprehension, Vocabulary, Block design, Picture arrangement.

Course of illness

Data were gathered with a case record form, using all possible sources of information. Data were analyzed over a mean period of 25 months (range 20-32). A relapse was defined as a period in which the patient experienced

delusions, hallucinations or conceptual disorganization, which interfered with daily life. These symptoms had to be severe enough to obtain a score of 4 (moderate) or higher on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). In order to score a new relapse, there had to be a previous period of 30 days without these psychotic symptoms. Only relapses after inclusion were counted. Thirty-eight patients (37%) experienced a psychotic episode at inclusion. Therefore we also looked at the percentage of time in psychosis. Remission was defined as a period without psychotic symptoms that would justify
a score of four or higher on the PANSS. We made a distinction between full and partial remission. Full remission was defined as a period without any psychiatric symptoms (PANSS scores < 2). Partial remission was defined as a period without severe psychotic symptoms, but with other psychiatric symptoms or less severe psychotic symptoms (PANSS scores < 4). The percentage of time in full remission was used for analyses.

Social functioning, competitive employment and need for care

Social functioning was assessed with the Groningen Social Disabilities Schedule (GSDS; Wiersma et al., 1988), a semi-structured interview that measures social role functioning on seven roles for the month preceding the interview. Social functioning was assessed at inclusion and at the follow-up. Mean social role score and the percentage of subjects showing disability on individual social roles were taken as outcome measures. Data concerning competitive employment were also gathered using the case record form. Competitive employment was defined as having a job, which enabled the person to make a living, or studying with a scholarship, because these students are required to fulfill certain standards concerning their study performance.
Need for care during the month preceding the follow-up was rated with the Camberwell Assessment of Needs (CAN; Slade et al., 1996). This is a structured interview in which the interviewer rates the need for care according to the patient on 22 topics on a 3-point scale (no problem, no problem /moderate problem due to help given, serious problem). We grouped the needs into four domains: ADL, mental health care, rehabilitation, services (Wiersma and Buschbach, 2001). The total number of needs (score ≥ 1), and the mean score on each of the four domains were taken as outcome measures.

2.3. Statistical analyses

All cognitive predictor variables were inspected to see if they resembled the normal distribution. A log transformation was performed for Stroop interference. The outcome data that were measured on an interval scale were also checked for normality of distribution. Relapse rate, time in psychosis, time in full remission, ADL-, rehabilitation- and service needs all had a positive skew and could not be normalized with the appropriate transformations. The other outcome measures resembled the normal distribution. Because hierarchical multiple regression analysis is rather robust for violation of the assumption that the criterion variable has to resemble the normal distribution we still used this method for analysis. For relapse rate, we also used logistic regression because the distinction between having no relapses at all and having one or more relapses appears to be most important. The predictive value of cognition for separate social roles, improvement or deterioration of social functioning over two years and competitive employment was analyzed with logistic regression. In order to investigate whether a cognitive impairment in a general sense at inclusion influenced outcome, differences in outcome between CN and CI patients were analyzed with one-way ANOVA's and $\chi 2$ tests. All tests were two-tailed.

3. Results

3.1. Outcome two years after inclusion

Course of illness

Seven of the 103 patients were psychotic during the entire follow-up period. Forty-nine patients had one or more relapses after inclusion. The mean percentage of time in psychosis for the whole group was 32%; the mean percentage of time in full remission was 25%. Fifty-three patients never were in full remission. The mean percentage of time in psychosis for these patients was 40%.

Social functioning, competitive employment and need for care

Table 2 gives the differences in social functioning between inclusion and follow-up. There was a significant improvement of the mean role score. Overall 69 % of the patients showed an improvement in social functioning, 29 % showed a deterioration, 2% remained stable. There were no differences in sex, age or course of illness between both groups. There was also a significant increase in the number of patients without social disabilities, from 2 patients at inclusion to 12 patients at follow-up ($p = .013$). Both at inclusion and follow-up, most patients showed disabilities in the work role.

Only 21 patients (21 %) fulfilled the criteria for competitive employment at follow-up. Of the remaining 81 patients (79%), 19 had regular activities, but depended on social welfare or their family to make a living. Five patients reported no problems for which they experienced a need for care. Most patients (67%) did have a need for care on 1 to 4 areas. The mean number of needs was 3.5, mostly concerning mental health care.

Table 2. Differences in social role functioning between inclusion and Follow-up

	Inclusion	Follow-up	Sign.
Mean role score*	1.2 (0.6)	0.9 (0.7)	.000
Self care**	44.7	22.5	.000
Family role	75.7	52.4	.000
Kinship role	60.2	50.0	ns.
Partner role	65.0	61.0	ns.
Citizen role	78.6	62.1	.012
Social role	62.1	58.3	ns.
Work role	86.4	68.0	.003

* Standardized GSDS ratings ranging from 0: no disability to 3: extreme disability.

** Percentage of subjects showing disability, differences between inclusion and follow-up were tested with the McNemar test, using the χ^2 distribution.

3.2. Prediction of course of illness, social functioning, competitive employment and need for care with cognitive variables

Cognition did not predict relapse rate. Even if the seven chronic psychotic patients were left out of the analysis, cognition still did not predict relapse rate. Selective attention and verbal fluency were significant predictors for time in psychosis. Verbal fluency was also a significant predictor for time in full

remission. Cognitive measures did not predict the mean social role score, disabilities on separate social roles, the distinction between improvement or deterioration in social functioning over two years or competitive employment. Vigilance did predict the number of needs and speed of processing predicted the need for care in the domain of rehabilitation (table 3).

Table 3. Hierarchical multiple regression on course of illness and need for care

	R	R^2	% explained variance	Beta	Sign.
Time in psychosis					
Selective attention	.23	.05	5	-.25	.010
Verbal Fluency				-.23	.020
Time in full remission					
Verbal Fluency	.20	.04	4	.20	.049
Number of needs					
Vigilance	.24	.06	6	.24	.018
Rehabilitation needs					
Speed of processing	.24	.06	6	-.24	.012

3.3. Differences between CN and CI patients

Table 4 gives an overview of the differences between CN and CI patients on all outcome measures. There were significant differences on the work role, competitive employment, the number of needs for care and the need for mental health care. We computed the odds ratios (OR) for the influence of cognitive impairment on the dichotomic outcome measures. The OR for CI patients showing impairment on the work role was 1.8. The OR for CI patients having no competitive employment was 1.4.

Table 4. Differences between CN and CI patients on all outcome measures

	CN patients (n = 20)	CI patients (n = 83)	Test	Significance (two-tailed)
Relapse rate (% patients)				
No relapse	65 %	52 %		
Relapse after inclusion	30 %	41 %	$\chi^2 = 1.133$	n.s.
Chronic psychotic	5 %	7 %		
Course of illness				
% of time psychotic	27 (36)	33 (33)	F = 0.575	n.s.
% of time full remission	27 (35)	24 (31)	F = 0.241	n.s.
Social functioning				
Total score[a]	0.79 (0.91)	0.83 (0.59)	F = 0.062	n.s.
Self-care[b]	26.3	20.0	$\chi^2 = 0.366$	n.s.
Family role	36.8	56.8	$\chi^2 = 2.458$	n.s.
Kinship role	52.6	48.8	$\chi^2 = 0.933$	n.s.
Partner role	47.4	64.6	$\chi^2 = 1.906$	n.s.
Citizen role	47.4	65.4	$\chi^2 = 2.131$	n.s.
Social role	52.6	58.0	$\chi^2 = 0.183$	n.s.
Work role	42.1	74.1	$\chi^2 = 7.228$	.007
Need for care				
Number of needs	2.5 (2.1)	3.8 (2.6)	F = 3.967	.049
Mental health care	0.17 (0.15)	0.28 (0.19)	F = 6.453	.013
ADL	0.05 (0.10)	0.11 (0.21)	F = 1.689	n.s.
Rehabilitation	0.20 (0.30)	0.26 (0.36)	F = 0.481	n.s.
Services	0.07 (0.12)	0.15 (0.23)	F = 1.991	n.s.
Competitive employment[c]	40	16	$\chi^2 = 5.734$	.017

[a]: Standardized GSDS ratings ranging from (0) no disability to (3) extreme disability
[b]: Percentage of subjects showing disability
[c]: Percentage of subjects with competitive employment

4. Discussion

In this longitudinal study the predictive value of cognitive functioning for course of illness and functional outcome in first onset schizophrenia was investigated.

As was expected, the patients as a group performed below healthy controls on all cognitive measures at inclusion. Both course of illness and functional outcome after two years in our sample illustrate the generally poor outcome of schizophrenia. Half of the patients had one or more relapses and a large part of the patients had psychiatric symptoms during most of the follow-up period. Only 21 percent of the patients were able to obtain competitive employment or to follow some kind of study. This is in accordance with the competitive employment rate mentioned in literature (Mueser et al., 2001). Although the majority of patients showed an improvement in social functioning at follow up

as compared to inclusion, most patients (82 %) still had social disabilities. Most patients experienced some need for care, especially in the area of mental health care.

Our main finding was that the predictive value of cognition at illness onset on course of illness and functional outcome is very limited. One of the most important course specifiers, relapse rate, was not predicted by cognitive performance at inclusion. Selective attention and verbal fluency at inclusion predicted time in psychosis during the follow-up period and verbal fluency predicted time in full remission. Although significant, the predictive value of these cognitive measures was very limited, explaining five and four percent of the variance in these outcome measures respectively. These results are roughly in accordance with the only other study, which investigated the predictive value of cognition on course of outcome and found no significant effects (Robinson et al., 1999).

Cognitive measures at inclusion did not predict social functioning. This is not surprising, in view of the rather inconsistent results of other longitudinal prediction studies. However, there seems to be a sharp contrast with the conclusions of the meta-analysis of Green et al. (2000), which suggests that several cognitive functions have significant cross-sectional relationships with functional outcome. This could partly be due to inclusion of studies with laboratory assessment of social skills, in which similarities between neuropsychological test conditions and social skill assessment might have caused an overestimation of the real correlations between these constructs. A closer look at the results of the cross-sectional studies focusing on the association of cognition with social functioning in daily life, also shows that the results in this area are positive but not impressive (Goldman et al., 1993; Addington and Addington, 1999; Addington et al., 1998; Buchanan et al., 1994, Heslegrave et al., 1997; Jaeger and Douglas., 1992). Most studies find some significant correlations, but the p-values are all in the .01 - .05 range, which in view of the number of analyses in these studies, are not likely to survive a Bonferroni correction. The same holds for the association between cognition and work related variables (Addington and Addington, 1999; Addington et al., 1998; Bellack et al., 1999; Breier et al., 1991; Dickerson et al., 1996; Brekke et al., 1997; Lysaker et al., 1995).

Cognition seems to have some predictive value for need for care. Vigilance at inclusion did predict the number of needs for care a patient had at follow up. Speed of processing did predict the needs in the rehabilitation domain. The predictive value of these cognitive measures was also very limited, explaining 6 percent of the variance for both outcome measures. We cannot exclude the possibility that the subjective nature of the instrument used to assess need for care in this study has influenced this association. Most patients have told us during interviews that cognitive deficits, which were assessed at inclusion and subsequently explained to them, still played a role in their lives. It is conceivable that this affects their self-confidence in a negative way and therefore increases their subjective experience of need for care.

In a general sense, cognitive deficits appear to be associated with problems with the work role and with competitive employment at follow up. The risk of work-related impairments was almost twice as large for patients with cognitive impairments compared to patients without cognitive impairments at inclusion, and their chances on having competitive employment were reduced to a similar degree. It seems that having a cognitive deficit in general, regardless of the nature of the deficit, may affect work performance, and acts as a limiting factor for occupational functioning.

There are limitations to this study. First cognition was only measured at the beginning of the disease. It is possible that cognitive performance in our sample has deteriorated and that cognition at follow-up is associated with outcome. There is, however, evidence that cognitive deficits are relatively stable early in the disease (Rund, 1998). Secondly, the functional outcome measures are valid for the month preceding the follow-up, and might therefore be considered more or less a random indication. However, a closer look at the socio-demographic data gathered with case record forms shows that the social situation is rather stable for most patients after the initial months of the disease. Another limitation is that the effects of different kinds of anti-psychotic medication taken during follow-up are not known.

Our results suggest that the predictive value of cognition on course of illness and functional outcome is not that large and challenge the idea that cognitive impairment is the core of the disease. Nevertheless, most patients show obvious cognitive deficits and many of them indicate that they are bothered by these deficits in daily life. It is possible that the relation between cognitive test

performance and functional outcome is obscured by compensation-mechanisms, which enable some patients to partly conceal their cognitive problems by investing more effort during test performance. In daily life however, when there is a constant appeal to many different cognitive functions, this compensation is likely to fail. This is in accordance with results from functional imaging studies, suggesting that schizophrenia patients show neural inefficiency, which shows as elevated activity on performance-corrected tasks (Ramsey et al., 2002). We think that future studies on the relation between cognition and outcome in schizophrenia should include measures to assess this compensation during cognitive testing, such as subjective ratings of mental effort, psycho physiological parameters or brain imaging patterns of compensatory cortical activation.

References

Addington, J., Addington, D., 1999. Neurocognitive and social functioning in schizophrenia. Schizophr. Bull. 25, 173-182.

Addington, J., Addington, D., 2000. Neurocognitive and social functioning in schizophrenia: a 2.5 year follow-up study. Schizophr. Res. 44, 47-56.

Addington, J, McCleary L, Munroe-Blum H: Relationship between cognitive and social dysfunction in schizophrenia. Schizophr Res 1998; 34: 59-66.

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.

Bellack, A.S., Gold, J.M., Buchanan, R.W.,1999. Cognitive rehabilitation for schizophrenia: problems, prospects and strategies. Schizophr. Bull. 25, 257-274.

Breier, A., Schreiber, J.L., Dyer, J., Pickar, D., 1991. National Institutes of Mental Health longitudinal study of chronic schizophrenia: prognosis and predictors of outcome. Arch. Gen. Psychiatry 48, 239-246.

Brekke, J.S., Raine, A., Ansel, M., Lencz, T., 1997. Neuropsychological and psychophysiological correlates of psychosocial functioning in schizophrenia. Schizophr. Bull. 23, 19-28.

Buchanan, R.W., Holstein, C., Breier, A., 1994. The comparative efficacy and long-term effect of clozapine treatment on neuropsychological testperformance. Biol. Psychiatry, 36: 717-725.

Delis, D.C., Kramer, J.H., Kaplan, E., Ober, B.A., 1987. California Verbal Learning Test (CVLT) Manual. New York, the Psychological Corporation.

Dickerson, F., Boronow, J.J., Ringel, N., Parente, F., 1996. Neurocognitive deficits and social functioning in outpatients with schizophrenia. Schizophr. Res. 21, 75-83.

Flynn, J.R., 1998. WAIS-III and WISC-III IQ gains in the United States from 1972 to 1995: how to compensate for obsolete norms. Percept. Mot. Skills 86, 1231 –1239.

Fujii, D.E., Wylie, A.M., 2002. Neurocognitive and community outcome in schizophrenia: long-term predictive validity. Schizophr. Res. 59, 219-223.

Goldman, R.S., Axelrod, B.N., Tandon, R., Ribeiro, S.C.M., Craig, K., Berent, S., 1993 Neuropsychological prediction of treatment efficacy and one-year outcome in schizophrenia. Psychopathology 126, 122-126.

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

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

Heslegrave, R.J., Awad, G., Voruganti, L.N.P., 1997. The influence of neurocognitive deficits and symptoms symptoms on quality of life in schizophrenia. J. Psychiatry Neurosci. 22, 235-243.

Holthausen, E.A.E., Wiersma, D., Sitskoorn, M.M., Hijman, R., Dingemans, P.M., Schene, A.H., van den Bosch, R.J.,2002. Schizophrenic patients without neuropsychological deficits: subgroup, disease severity or cognitive compensation? Psychiatry. Res. 112, 1-11.

Jaeger, J., Douglas, E., 1992. Neuropsychiatric rehabilitation for persistent mental illness. Psychiatr. Q. 63, 71-94.

Johnstone, E.C., Macmillan, J.F., Frith, C.D., Benn, D.K., Crow, T.J., 1990. Further investigation of the predictors of outcome following first schizophrenic episodes. Br. J. Psychiatry 157, 182-189.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr. Bull. 16, 537-545.

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.

Lysaker, P.H., Bell, M., Beam-Goulet, J., 1995. Wisconsin Card sorting Test and work performance in schizophrenia. Psychiatry Res. 56, 45-51.

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

Ramsey, N.F., Koning, H.A.M., Welles, P., Cahn, W., van der Linden, J.A., Kahn, R.S., 2000. Excessive recruitment of neural systems subserving logical reasoning in schizophrenia. Brain 125, 1793-1807.

Robinson, D., Woerner, M.G., Alvir, J.M.J., Bilder, R., Goldman, R., Geisler, S., Koreen, A., Sheitman, B., Chakos, M., Mayerhoff, D., Lieberman, J.A., 1999. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch. Gen. Psychiatry 56, 241-247.

Rund, B.R., 1998. A review of longitudinal studies of cognitive functions in schizophrenia patients. Schizophr. Bull. 24, 425-435.

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.

Slade, M., Phelan, M., Thornicroft, G., Parkman, S., 1996. The Camberwell Assessment of Need (CAN): comparison of assessments by staff and patients of the needs of the severe mentally ill. Soc. Psychiatry Psychiatr. Epidemiol. 31, 109-113.

Stinissen, J., Willems, P.J., Coetsier, P., Hulsman, W.L.L., 1970. Manual of the Dutch translation of the Wechsler Adult Intelligence Scale. Amsterdam, Swets en Zeitlinger.

Van den Bosch, R.J., Rombouts, R.P., van Asma, M.J., 1996. What determines continuous performance task performance? Schizophr. Bull. 22, 643-651.

Velligan, D.I., Bow-Thomas, C.C., Mahurin, R.K., Miller, A.L., Halgunseth, L.C., 2000. Do specific neurocognitive deficits predict specific domains of community function in schizophrenia? J. Nerv. Ment. Dis.188, 518-524.

Vink, M., Jolles, J., 1985. A new version of the Trail making Test as an information processing task. J. Clin. Neuropsychology7, 162.

Wiersma, D., Busschbach, J., 2001. Are needs and satisfaction of care associated with quality of life? An epidemiological survey among the severely ill in the Netherlands. Eur. Arch. Psychiatry Clin. Neurosci. 251, 239-246.

Wiersma, D., De Jong, A., Ormel, J., 1988. The Groningen Social Disabilities Schedule: development, relationship with I.C.I.D.H., and psychometric properties. Int. J. Rehabil. Res. 11, 213-224

Wiersma, D., Nienhuis, F.J., Slooff, C.J., Giel, R., 1998. Natural course of schizophrenic disorders: a 15-year follow-up of a Dutch incidence cohort. Schizophr. Bull. 24, 75-85.

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 centres. 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.

Chapter 7

Summary and general discussion

Summary and general discussion

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.

References

Agelink, M.W., Majewski, T., Wurthmann, C., Lukas, K., Ullrich, H., Linka, T., Klieser, E., 2001. Effects of newer atypical antipsychotics on autonomic neurocardiac function: a comparison between amisulpiride, olanzapine, sertindole and clozapine. J. Clin. Psychopharmacol. 21, 8-13.

Aleman, A., Hijman, R., de Haan, E.H.F., Kahn, R.S., 1999. Memory impairment in schizophrenia: A meta-analysis. Am. J. Psychiatry 156, 1358-1366.

Andreasen, N.C., Paradiso, S., O'Leary, D.S., 1998. "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? Schizophr. Bull. 24, 203-218.

Benson, D.F., Stuss, D.T., 1990. Frontal lobe influences on delusions: a clinical perspective. Schizophr. Bull. 16, 403-411.

Carpenter, W.T., Gold, J,M., 2002. Another view of therapy for cognition in schizophrenia. Biol. Psychiatry 51, 969-971.

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.

Chapman, L.J., Chapman, J.P., 1978. The measurement of differential deficit. J. Psychiatr. Res. 14, 303-311.

Gold, S., Arndt, S., Nopuolos, P., O'Leary, D.S., Andreasen, N.C., 1999. Longitudinal study of cognitive function in first-episode and recent-onset schizophrenia. Am. J. Psychiatry 156, 1342-1348.

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

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

Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am. J. Psychiatry 153, 321-330.

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"? Schizophr. Bull. 26, 119-136.

Green, M.F., Marder, S.R., Glynn, S.M., McGurk, S.R., Wirshing, W.C., Wirshing, D.A., Liberman, R.P., Mintz, J., 2002. The neurocognitive effects of low-dose haloperidol: a two-year comparison with risperidone. Biol. Psychiatry 51, 972-978.

Harrison, P.J., 1999. The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain 122, 593-624.

Harvey, P.D., Keefe, R.S., 2001. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. Am. J. Psychiatry 158, 176-184.

Heaton, R.K., Gladsjo, J.A., Palmer, B.W., Kuck, J., Marcotte., T.D., Jeste, D.V., 2001. Stability and course of neuropsychological deficits in schizophrenia. Arch. Gen. Psychiatry 58, 24-32.

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

Hoff, A.L., Sakuma, M., Wienke, M., Horon, R., Kushner, M., Delisi, L.E., 1999. Longitudinal neuropsychological follow-up study of patients with first-episode schizophrenia. Am. J. Psychiatry 156, 1336-1341.

Holden, C., 2003. Deconstructing schizophrenia. Science 299, 333-335.

Hughes, c., Kumari, V., Soni, W., Das, M., Binneman, B., Drozd, S., O'Neil, S., Mathew, V., Sharma, T., 2002. Longitudinal study of symptoms and cognitive function in chronic schizophrenia. Schizophr. Res. 59, 137-146.

Kuperberg, G., Heckers, S., 2000. Schizophrenia and cognitive function. Curr. Opin. Neurobiol. 10, 205-210.

Meltzer, H.Y., McGurk, S.R., 1999. The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. Schizophr. Bull. 25, 233-255.

Mortimer, A., 1997. Cognitive function in schizophrenia-do neuroleptics make a difference? Pharmacol. Biochem. Behav. 56, 789-795.

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.

Ramsey, N.F., Koning, H.A.M., Welles, P., Cahn, W., van der Linden, J.A., Kahn, R.S., 2002. Excessive recruitment of neural systems subserving logical reasoning in schizophrenia. Brain 125, 1793-1807.

Rund, B.R., 1998. A review of longitudinal studies of cognitive functions in schizophrenia patients. Schizophr. Bull. 24, 425-435.

Van den Bosch, R.J., Rombouts, R.P., 1998. Causal mechanisms of subjective cognitive dysfunction in schizophrenic and depressed patients. J. Nerv. Ment. Dis. 186, 364-368.

Williams, R.M., Alagaratnam, W., Hemsley, D.R. 1984. Relationship between subjective self-report of cognitive dysfunction and objective information processing performance in a group of hospitalized schizophrenic patients. Eur. Arch. Psychiat. Neurol. Sci. 234, 48-53.

Zakzanis, K.K., Heinrichs, W., 1999. Schizophrenia and the frontal brain: a quantitative review. J. Int. Neuropsychol. Soc. 5, 556-566.

Zanello, A., Huguelet, P., 2001. Relationship between subjective cognitive symptoms and frontal executive abilities in chronic schizophrenia outpatients. Psychopathology 34, 153-15

Hoofdstuk 8

Nederlandse samenvatting

Inleiding

Schizofrenie is een ernstige psychiatrische ziekte, met afwijkingen in denken, taal, waarneming, gedrag, emotie, motivatie en cognitie (verwerking van informatie). Het ziektebeeld verschilt per patiënt en geen enkel symptoom is op zichzelf typerend voor de ziekte. Psychotische episodes met wanen, hallucinaties en vaak bizar gedrag worden afgewisseld met periodes waarbij negatieve symptomen, zoals initiatiefverlies, psychomotorische armoede en emotionele vervlakking op de voorgrond staan. Er is meestal ook sprake van een duidelijke achteruitgang in het sociaal functioneren. De gemiddelde leeftijd waarop men ziek wordt is rond de vijfentwintig jaar voor mannen, en rond de dertig jaar voor vrouwen. Ongeveer een kwart van de patiënten herstelt volledig na een of twee psychotische episodes, de helft herstelt slechts gedeeltelijk met terugkomende psychotische episodes, terwijl het overgebleven kwart een chronisch beloop heeft. Het is tegenwoordig algemeen geaccepteerd dat schizofrenie wordt veroorzaakt door een stoornis in de hersenen. Cognitie wordt vaak gezien als een niveau dat tussen de neurobiologische afwijkingen en de hogere niveaus van functioneren, zoals zelfbewustzijn en sociaal functioneren, inzit. Volgens sommige onderzoekers zijn cognitieve stoornissen zelfs de oorzaak van de ziekte.

Cognitieve stoornissen komen vaak voor bij schizofrenie. Als groep laten schizofrene patiënten afwijkingen zien op alle cognitieve functies, waarbij de verbale geheugenfunctie en de snelheid van informatieverwerking het meest verstoord lijken te zijn. Tussen patiënten zijn er echter grote verschillen. Sommige patiënten bijvoorbeeld laten in een standaard neuropsychologisch onderzoek helemaal geen afwijkingen zien. Binnen de groep met cognitieve afwijkingen zijn de verschillen ook erg groot. Sommigen hebben alleen maar een probleem met een enkele cognitieve functie, zoals bijvoorbeeld met het aanleren van verbaal materiaal of het langdurig alert blijven reageren, anderen hebben stoornissen in verschillende cognitieve domeinen. Een van de belangrijkste onderzoeksvragen is dan ook hoe men om moet gaan met deze cognitieve heterogeniteit. In groepsvergelijkingen tussen patiënten met schizofrenie en gezonde controles gaat veel informatie verloren door de grote onderlinge verschillen in cognitief functioneren binnen de patiëntgroep. Dit zou

kunnen worden veroorzaakt door het bestaan van subgroepen van patiënten. Hier is tot op heden echter weinig bewijs voor gevonden.
Misschien is een dimensionele aanpak van cognitief functioneren bij schizofrenie nog de beste manier. Hierbij gaat men ervan uit dat verschillende continu verdeelde cognitieve functies min of meer aangetast kunnen zijn bij individuen met schizofrenie.
Deze dimensionele aanpak ziet men ook terug in het onderzoek naar de verschillende symptomen bij schizofrenie. Over het algemeen worden drie tot vijf symptoomdimensies onderscheiden: positieve symptomen, negatieve symptomen, desorganisatie symptomen en vaak depressieve en agitatie symptomen. Er zijn verschillende onderzoeken gedaan naar de relatie tussen deze psychopathologie dimensies en het voorkomen van bepaalde cognitieve stoornissen. Er zijn wel enige relaties gevonden, maar de onderzoeksresultaten zijn niet erg consistent en de gevonden verbanden zijn niet erg sterk.
Ditzelfde geldt voor de relatie tussen cognitie en alledaags functioneren, waarbij met name de relatie tussen cognitie en sociaal en beroepsmatig functioneren is onderzocht.
In de studies die in hoofdstuk twee tot en met zes worden gepresenteerd is het cognitief functioneren bij patiënten met schizofrenie op verschillende manieren met verschillende instrumenten onderzocht. Tevens is er gekeken naar de relaties tussen cognitie en andere niveaus van functioneren bij schizofrenie, zowel op hetzelfde meetmoment als over een langere periode.
De studies die in hoofdstuk twee, vier en zes worden beschreven zijn gebaseerd op de gegevens van de “multicenter" studie naar neurobiologische en neuropsychologische predictoren van functionele status bij eerste episode schizofrenie”. Deze studie was een samenwerking tussen academische ziekenhuizen van Groningen, Amsterdam en Utrecht. In eerste instantie deden honderd achtendertig patiënten mee. Honderd achttien van deze patiënten deden mee aan het cognitieve testonderzoek en van deze groep deden honderd en drie patiënten mee aan het vervolg onderzoek twee jaar later.
In hoofdstuk zeven worden deze onderzoeksresultaten samengevat en vergeleken met de meest belangrijke bevindingen uit de literatuur, met de bedoeling meer te kunnen zeggen over de aard en de gevolgen van cognitieve stoornissen bij schizofrenie.

Hoofdstuk 2

Dit hoofdstuk beschrijft een studie naar de kenmerken van patiënten die volgens de klinische normen geen cognitieve stoornissen zouden hebben. De vraag was of het bestaan van deze groep verklaard wordt door algemene verschillen in de ernst van de ziekte, het bestaan van een etiologisch afwijkende subgroep of dat er in principe wel cognitieve stoornissen zijn maar dat deze klinisch niet significant zijn omdat men ervoor kan compenseren.
Drieëntwintig van de honderd en achttien patiënten die recent een eerste of tweede psychotische episode hadden gehad werden als cognitief normaal bestempeld (CN). Deze groep werd vergeleken met patiënten met cognitieve stoornissen (CI: "cognitively impaired") wat betreft geboorte of zwangerschap complicaties, premorbide functioneren, leeftijd waarop men ziek is geworden, psychopathologie, sociaal functioneren en middelenmisbruik. Bovendien werden intelligentie en opleidingsniveau van beide groepen vergeleken als indirecte maten voor cognitieve compensatie capaciteit. Het cognitief functioneren van de CI en de CN groep werd vergeleken met een groep van vijfenveertig gezonde controles. CN patiënten presteerden gemiddeld als groep onder het niveau van gezonde controles en hadden ook min of meer hetzelfde cognitieve profiel als CI patiënten, maar dan op een hoger niveau. Er werden geen verschillen tussen beide patiëntgroepen gevonden, behalve op sociaal functioneren, wat eerder als een consequentie dan als een oorzaak van cognitieve stoornissen moet worden gezien. Dit verwerpt de hypothese dat een verschil in ernst of het bestaan van aparte subgroepen het bestaan van een CN groep zou verklaren. De CN patiënten scoorden echter beduidend hoger dan de CI patiënten op intelligentie en opleidingsniveau. Mogelijk kan een verschil in cognitieve compensatie capaciteit het bestaan van de CN groep verklaren.

Hoofdstuk 3

In dit hoofdstuk wordt de hypothese dat schizofrenie wordt veroorzaakt door afwijkingen in de frontale gebieden van de hersenen getoetst door de

aanwezigheid van zogenaamde “frontale dysfuncties” met behulp van neuropsychologisch onderzoek en oogbewegingstaken te onderzoeken.
Tevens werd de relatie tussen deze taken bestudeerd. Vierentwintig eerste episode patiënten namen deel aan dit onderzoek. Op de “frontale” neuropsychologische taken liet slechts de helft van de patiënten een gestoorde prestatie zien. Indien dit gecombineerd werd met de “frontale” oogbewegingstaken liet bijna tachtig procent een gestoorde prestatie zien. Dit betekent echter ook dat er bij twintig procent van de patiënten geen aanwijzingen zijn voor “frontaal dysfunctioneren” op beide meetmethodes, dit verwerpt de hypothese dat schizofrenie wordt veroorzaakt door afwijkingen in frontaal functioneren.
De associatie tussen de beide meetmethodes die in dit onderzoek werden gebruikt was ook niet erg groot. Dit zou kunnen betekenen dat beide methodes een beroep doen op verschillende frontale functies.

Hoofdstuk 4

Hoofdstuk vier onderzoekt de vraag of de vaak voorkomende stoornissen in het lange termijngeheugen bij schizofrenie primaire stoornissen zijn, of dat ze worden veroorzaakt door andere cognitieve beperkingen. Honderd en achttien patiënten die recent een eerste of tweede psychotische episode hadden gehad werden vergeleken met vijfenveertig gezonde controles op verschillende geheugenmaten om na te gaan op welke maten patiënten de meeste beperkingen laten zien. Vervolgens werd gekeken in hoeverre beperkingen in de snelheid van informatieverwerking en executieve of sturende functies van invloed waren op deze geheugenstoornissen. Omdat een vertraging van de informatieverwerking vaak voorkomt bij schizofrenie werd de hypothese getoetst dat deze vertraging van de informatieverwerking de geheugenstoornissen zou veroorzaken. Dit werd getoetst met regressie analyses op alle subjecten, waarbij werd gekeken of snelheid van informatieverwerking de ziekte-gerelateerde variantie in de geheugenmaten vermindert. Tevens werd nagegaan of verschillen in geheugenmaten binnen de patiëntgroep kunnen worden verklaard door verschillen in executieve functies. De grootste beperkingen werden gevonden in het aanleren van verbaal materiaal en het

ophalen van informatie uit het geheugen voor aan tijd en plaats gebonden informatie en het geheugen voor algemene informatie. Snelheid van informatieverwerking verklaarde inderdaad een deel van de verschillen tussen patiënten en controles bij alle geheugenmaten.
Coördinatie van cognitie, organisatie van informatie en snelheid van informatieverwerking waren de beste voorspellers van stoornissen in het lange termijn geheugen binnen de patiëntgroep. De hoeveelheid verklaarde variantie was echter vrij klein, vooral voor beperkingen in het aanleren van verbale informatie, een van de meest gestoorde geheugenfuncties bij schizofrenie. Het lijkt erop dat de stoornissen in het lange termijngeheugen bij schizofrenie toch vooral primair zijn en slechts voor een heel klein deel beïnvloed worden door andere cognitieve beperkingen.

Hoofdstuk 5

In dit hoofdstuk wordt de relatie tussen verschillende psychopathologie dimensies en cognitieve maten onderzocht. Hierbij waren we met name geïnteresseerd in het verband tussen depressieve symptomen en cognitie bij schizofrenie omdat dit nog nauwelijks was onderzocht. Bij een groep van vijftig patiënten die recent een eerste of tweede psychose hadden doorgemaakt werd met behulp van de PANSS, een gestructureerd interview naar psychopathologie, de score op vijf psychopathologie dimensies bepaald. Tevens werd bij alle patiënten een neuropsychologisch onderzoek en een vragenlijst voor subjectieve cognitieve klachten afgenomen. Er werd ook gekeken naar de relatie tussen deze objectieve en subjectieve maten voor cognitief functioneren. De score op de depressie dimensie was meer dan de andere psychopathologie dimensies gerelateerd aan zowel objectieve als subjectieve cognitieve maten. Het verband tussen depressieve symptomen en cognitie was echter niet heel erg sterk. Tussen objectieve en subjectieve maten voor cognitie werd nauwelijks enig verband gevonden.

Hoofdstuk 6

Hoofdstuk zes kijkt naar de predictieve waarde van cognitieve maten op het ziektebeloop en functioneren op de lange termijn bij eerste episode patiënten. Honderd en achttien patiënten die recent een eerste of tweede psychose hadden doorgemaakt, werden getest met een uitgebreide cognitieve testbatterij.
Van deze groep deden uiteindelijk honderd en drie patiënten mee aan het follow-up onderzoek twee jaar later. Hierbij werden gegevens verzameld over het ziektebeloop gedurende deze twee jaren, sociaal functioneren, beroepsmatig functioneren en zorgbehoefte. De voorspellende waarde van cognitie voor deze uitkomst maten werd geanalyseerd met behulp van logistische en multivariate regressie. Tevens werd er gekeken naar de verschillen tussen patiënten met en zonder cognitieve stoornissen (CI en CN, zie hoofdstuk 2). De cognitieve maten hadden geen voorspellende waarde voor het aantal nieuwe psychotische episodes, sociaal functioneren of beroepsmatig functioneren. Ze waren wel voorspellend voor de tijd dat men psychotisch was tijdens de follow-up periode en de behoefte aan zorg. De voorspellende waarde was echter minimaal, slechts zes procent van de variantie in deze maten binnen de patiëntgroep werd voorspeld door cognitieve variabelen. Er was een significant verschil tussen CN en CI patiënten in het beroepsmatig functioneren. Patiënten zonder cognitieve beperkingen hadden twee keer zoveel kans op het vinden van regulier werk dan patiënten met cognitieve beperkingen. Hoewel het hebben van een cognitieve beperking in het algemeen van invloed is op beroepsmatig functioneren, is de predictieve waarde van de afzonderlijke cognitieve maten voor het functioneren op de lange termijn beperkt. Dit is niet in overeenstemming met de theorie dat cognitieve stoornissen de oorzaak van schizofrenie zouden zijn. Er wordt gesuggereerd dat de relatie tussen cognitie en andere niveaus van functioneren niet zo eenvoudig is als vaak wordt gedacht en dat deze relatie mogelijk wordt beïnvloed door andere mechanismen zoals mentale inspanning en compensatie capaciteit.

Hoofdstuk 7

In dit hoofdstuk worden de resultaten uit de verschillende hoofdstukken samengevat en vergeleken met de bevindingen uit de literatuur om te zien of dit nieuwe inzichten oplevert over de aard en de gevolgen van cognitieve stoornissen bij schizofrenie. Het hoofdstuk wordt afgesloten met suggesties voor toekomstig onderzoek.

Samenvattend kan worden gezegd dat cognitieve stoornissen, met name stoornissen in het opslaan van verbaal materiaal en in de snelheid van informatieverwerking, vaak voorkomen bij schizofrenie. In tegenstelling tot wat vaak wordt beweerd is er geen bewijs voor een specifiek defect in executieve functies.

Belangrijker is echter dat er grote verschillen zijn in cognitief functioneren tussen patiënten. Deze verschillen worden niet veroorzaakt door het bestaan van verschillende subgroepen of verschillen in ernst van de ziekte. Cognitie is ook niet of nauwelijks gerelateerd aan andere domeinen van functioneren, zoals psychopathologie of sociaal functioneren.

Men kan zich afvragen of cognitie wel zo'n belangrijke rol speelt bij schizofrenie. Het antwoord is nog steeds bevestigend, cognitieve stoornissen hebben een negatieve invloed op werkprestatie en uit de gesprekken met patiënten bleek dat velen het gevoel hebben dat hun cognitieve beperkingen een duidelijke rol spelen in het dagelijks leven. Om de rol die cognitie daadwerkelijk speelt in deze ziekte te kunnen onderzoeken moeten er wel enige conceptuele veranderingen worden gemaakt in het denken over schizofrenie.

Ten eerste lijkt het beter om cognitieve functies als aparte dimensies te behandelen die geen direct causaal verband hebben met psychopathologie of sociaal functioneren. Doordat er zulke grote verschillen zijn binnen de patiëntgroep lijkt het beter om onderzoek met name te richten op intra-individuele veranderingen in cognitief functioneren en de relaties met andere domeinen van functioneren, bijvoorbeeld door de predictieve waarde van individuele veranderingen in cognitie bij eerste episode patiënten te onderzoeken.

Ten tweede moeten beschermende en risicofactoren, die de expressie van in aanleg aanwezig cognitieve beperkingen kunnen beïnvloeden, ook goed worden onderzocht. Een mogelijke beschermende factor is de cognitieve compensatie

capaciteit, waardoor men beter kan presteren door zich mentaal meer in te spannen. Een mogelijke risicofactor is het niveau van algehele mentale vermoeidheid. Beide factoren kunnen op verschillende manieren worden bestudeerd. Bijvoorbeeld door het gebruik van subjectieve vragenlijsten of schalen voor mentale inspanning en mentale vermoeidheid tijdens cognitief testonderzoek. Of door het gebruik van fysiologische maten voor mentale inspanning of vermoeidheid, zoals veranderingen in de systolische bloeddruk of veranderingen in hartslag variabiliteit. Zeer interessant is het functional imaging onderzoek naar patronen van corticale compensatie capaciteit op cognitieve taken, waarbij voor taakprestatie wordt gecorrigeerd. In dit soort onderzoek werd gevonden dat als patiënten hetzelfde presteerden als controles er bij deze patiënten meer corticale activiteit werd waargenomen.

Ten derde blijkt dat veel patiënten na een paar jaar leren leven met hun beperkingen en hun leven dan ook op een dusdanige manier inrichten dat situaties waar zij moeite mee hebben zoveel mogelijk worden vermeden, bijvoorbeeld door werk te zoeken waarbij men weinig te maken heeft met andere mensen, door in de weekenden veel te rusten of door een partner te kiezen die hen veel taken uit handen neemt. Veel uitkomst maten houden geen rekening met dit soort mechanismen, waardoor factoren die de relatie tussen cognitie en uitkomst vertroebelen niet worden opgemerkt.

Samenvattend, zowel experimentele studies naar de relatie van cognitieve compensatie en mentale vermoeidheid met cognitie als grote longitudinale studies naar de effecten van cognitieve veranderingen vroeg in het ziekteproces op het uiteindelijk functioneren in een meer stabiele fase van de ziekte lijken interessant voor toekomstig onderzoek

Dankwoord

Op deze plaats wil ik alle mensen bedanken die mee hebben gewerkt aan dit onderzoek of die op enige andere wijze het leven een stukje aangenamer hebben gemaakt in de afgelopen paar jaar. Hierbij bestaat altijd het gevaar dat ik onbewust vergeet iemand te noemen. Bij deze daarvoor mijn excuses, het werd wel gewaardeerd!

In de eerste plaats wil ik alle patiënten bedanken voor hun medewerking aan dit onderzoek. Niet alleen hebben zij tot twee maal toe meer dan een dag lang allerlei tests gemaakt en vragen beantwoord, een groot deel van de mensen in Groningen en Utrecht doet nu, vijf jaar na het begin, nog steeds mee aan vervolgonderzoek. Mensen bedankt, ik heb steeds meer bewondering gekregen voor de manier waarop jullie, ondanks je ziekte, toch iets van het leven maken.

Dan natuurlijk mijn eerste promotor, Rob van den Bosch. Beste Rob, bedankt voor de prettige samenwerking waarbij ik alle vrijheid kreeg om zelf mijn gang te gaan. Door onze besprekingen moest ik mijn gedachten zodanig op scherp stellen dat ik uiteindelijk tot betere ideeën kwam. En mijn andere promotor, Durk Wiersma. Durk, misschien heb je in het begin wat moeten wennen aan mijn zuidelijke temperament, ik heb de samenwerking echter altijd als bijzonder prettig ervaren. Door jou heb ik ook kunnen zien dat psychiatrie vele facetten heeft en verder gaat dan alleen maar ziektebeelden, hersenen en cognitie.

De dames van kamer 1.124, eerst Keete Hale en later Stynke Castelein, dankzij jullie liep de coördinatie en organisatie van de multicenter studie veel soepeler dan ik had durven hopen. Peter de Jong, bedankt voor de coördinatie en organisatie in de eerste fase van dit onderzoek.

De medewerkers van het psychosecluster van het AZG wil ik bedanken voor hun inzet bij het de opvang maar ook het interviewen van de patiënten in de eerste fase van dit onderzoek. Gelukkig mag ik nog steeds langskomen om psycho-educatie te geven. De heren doktoren, Rikus Knegtering en Richard Bruggeman, bedankt voor de hulp bij het werven van patiënten en het creëren van een afdeling waar patiëntzorg en onderzoek goed samengaan.

De mensen die een groot deel van de psychologische onderzoeken af hebben genomen. In de eerst plaats Gerda Falkena, die me in het begin ook een beetje wegwijs heeft gemaakt bij psychiatrie. Gerda, na mijn promotie gaan we toch eindelijk die lang besproken borrel drinken. Theo Deddens die ook een deel van

de onderzoeken voor zijn rekening heeft genomen. En de stagiaires van het eerste uur, Maya Schroevers, Marion Verkade, Geke Taymour-Spijker en Erna Berends, die aardig wat werk hebben verzet.
Annelies Broerse, jou had ik op verschillende plaatsen in dit dankwoord kunnen zetten, wegens je aangename gezelschap op congressen, het samen schaatsen, skaten of skieën, maar je hebt ook een aanzienlijke bijdrage geleverd aan dit proefschrift door het schrijven van hoofdstuk drie. Ik kan me nog goed herinneren hoe we dit ooit samen bedacht hebben op een terrasje in Santa Fé.
De initiatiefnemers van de multicenter studie in Amsterdam en Utrecht, prof. dr. Aart Schene en prof. dr. René Kahn, en natuurlijk alle andere medewerkers uit Amsterdam: Peter Dingemans, Ria Lenior, Jiska Wolthaus, en Utrecht: Wiepke Cahn, Esther Caspers, Neeltje van Haren, Ron Hijman, Diana Laponder, Elleke Lems, Adriaan Lemstra en Margriet Sitskoorn, bedankt voor de prettige samenwerking.
Alle medewerkers van de afdeling sociale psychiatrie wil ik bedanken voor de prettige werksfeer. En in het bijzonder de secretaresses Liesbeth en Martha die altijd bereid zijn even te luisteren, advies te geven of bij te springen in tijden van grote klunzigheid. Laura, Hugo, Henk-Jan, Elske, Karlien, voor de gezellige lunches, borrels, roddels etc. Sietse, die daarbij ook nog eens stapels literatuur voorzien van bijpassend commentaar voor me op heeft gehaald. En Janet voor de assistentie bij het nieuwe onderzoek. En natuurlijk alle andere collega's die maken dat "de vijfde" toch wel een hele gezellige afdeling is.
De (ex)AIO's van het eerste uur, Jacqueline, Kathelijne, Lucia, Marjan van den Berg, Marjan Nielen, Marjolein, Richard, Sascha, ik zal ons AIO-weekend in Hattem niet snel vergeten!
De leden van de leescommissie wil ik bedanken voor het lezen en beoordelen van dit proefschrift.
Gelukkig was er ook veel tijd voor ontspanning op, in of onder het water. Alle dames met wie ik de afgelopen jaren geroeid heb, Jolanda, Laura, Monique en Petra en natuurlijk Janneke en Sacha met wie ik nog steeds uitvaar wil ik hiervoor bedanken. In de eerste jaren heeft coach Dirk een poging gedaan om dit in goede banen te leiden, later is dit overgenomen door Jeroen, die ondertussen al heel wat zeergeleerde dames heeft begeleid. Heren, bedankt.

En dan de heren die mij iets hebben geleerd over de prachtige wereld onderwater, ik denk daarbij vooral aan Bert, Harry en Edo, en natuurlijk nog een aantal andere wisselende buddy's.
Geke bedankt voor alle schaatsuurtjes, eens zullen wij ook in die binnenbocht rijden.
En dan natuurlijk mijn paranimfen, Harmen, wat een lol hebben we gehad op de Kostersgang. Ook al wonen we niet meer samen, gelukkig is er nog tijd genoeg om van alles samen te ondernemen. Bij deze wil ik ook graag je moeder, Fenneke bedanken voor haar hulp bij het maken van de omslag.
En Ellen, dankzij jou is er een wereld voor mij opengegaan, na mijn eerste duikje met jou in zwembad de Frosk in Zwaagwesteinde, was ik verslaafd. Omgekeerd heb ik jou het roeien geleerd, alsof we al niet genoeg hadden om over te kletsen!
Mijn zus Ilse, bedankt voor alles en natuurlijk voor de prachtige schaal die je voor de voorkant van dit proefschrift hebt gemaakt. Ook de andere medewerkers van Henrika en Twinkelbel wil ik bedanken, Erik, Gemma, Jotte, Karin, Kok-Pan, Marko, Ruud en Susan het was erg gezellig om dit bij jullie te regelen en ik kom graag nog eens een dagje "glazuren".
Mijn ouders wil ik bedanken voor alle steun, hulp en interesse. Pa en ma, ondanks de afstand kon ik altijd op jullie rekenen, bedankt! En dan natuurlijk Rob, mijn "vaste buddy". Rob, bedankt voor je aanwezigheid, steun, sponsoring, verdraagzaamheid en al die mooie reizen die we hebben gemaakt. Laten we er snel nog een paar aan vastplakken!

Esther

Curriculum Vitae

Esther Holthausen werd op 18 augustus 1971 geboren in Son en Breugel. Na het behalen van haar VWO diploma aan de Gemeentelijke Scholengemeenschap Woensel in Eindhoven begon zij in 1990 met haar studie psychologie aan de Katholieke Universiteit Nijmegen. In april 1996 behaalde zij haar diploma in de afstudeerrichting neuro- en revalidatie psychologie. Tijdens haar studie heeft zij stage gelopen in het Elkerliek ziekenhuis in Helmond op de afdeling psychologie, waar zij vanaf september 1995 tot maart 1996 ook heeft gewerkt als psychodiagnostisch medewerker. Daarna heeft zij tot september 1996 gewerkt als psychodiagnostisch medewerker bij het Vincent van Gogh instituut in Venray. Hier werd haar interesse voor de psychiatrie gewekt en dan met name voor psychotische ziektebeelden. Vanaf oktober 1996 tot en met oktober 2000 heeft zij als onderzoeker in opleiding gewerkt op de multicenter studie naar neurobiologische en neuropsychologische predictoren van functionele status bij eerste episode schizofrenie, op de afdeling Psychiatrie van de Rijksuniversiteit Groningen. Gedurende deze periode heeft zij van juni 1997 tot en met januari 1999 ook deeltijd als psycholoog verbonden geweest aan het Academisch ziekenhuis Groningen. Vanaf oktober 2000 tot heden is zij werkzaam als post-doc op het vervolg van de multicenter studie.

Publications

Holthausen, E.A.E., Wiersma, D., Knegtering, H., van den Bosch., 1999. Psychopathology and cognition in schizophrenia spectrum disorders: the role of depressive symptoms. Schizophrenia Research 39, 65-71.

Holthausen, E.A.E., Wiersma, D., Sitskoorn, M.M., Hijman., Dingemans, P.M., Schene, A.H., van den bosch, R.J., 2001. Psychiatry Research 112, 1-11.

Holthausen, E.A.E., Wiersma, D., Sitskoorn, M.M., Hijman, R., Dingemans, P.M., Schene, A.H., van den Bosch, R.J., 2003. Long-term memory deficits in schizophrenia: primary or secondary dysfunction? Neuropsychology

Holthausen, E.A.E., Wiersma, D., Cahn, W., Kahn, R.S., dingemans, P.M., Schene, A.H., van den Bosch, R.J. The limited predictive value of cognition for outcome in schizophrenia. (submitted for publication).

Holthausen, E.A.E., Wiersma, D., Van den Bosch, R.J. Objective and subjective cognitive correlates of psychopathology in first episode patients. (abstract) Schizophrenia research. 30 (1998).

Holthausen, E.A.E., Wiersma, D., Van den Bosch, R.J. Depressive symptoms and cognition in first episode schizophrenia. (abstract).Schizophrenia research. 36 (1999), 134-135.

Holthausen, E.A.E., Wiersma, D., Van den Bosch, R.J. Psychopathology and social functioning in psychotic patients with and without cognitive deficits. (abstract). Schizophrenia research. 36 (2000), 135.

Holthausen, E.A.E., Wiersma, D., Knegtering, R.H., Van den Bosch, R.J. Do schizophrenic patients without neuropsychological deficits still show signs of cognitive decline? (abstract) Schizophrenia Research. 41 (2000), 269.

Holthausen, E.A.E., Broerse, A., den Boer, J.A., Van den Bosch, R.J. Cognition and saccadic eye movements in first onset schizophrenia. (abstract) Schizophrenia Research. 41 (2000), 295.

Holthausen, E.A.E., Wiersma, D., Knegtering, R.H., Van den Bosch, R.J. Compensation of neurocognitive deficits: influence on course of illness in schizophrenia. (abstract). Schizophrenia Research. 47 (2001).

Holthausen, E.A.E., Wiersma, D., Knegtering, H., Van den Bosch, R.J. Does cognition predict outcome and course of illness in schizophrenia? (abstract). Schizophrenia Research. 53 (2002), 127.

Holthausen, E.A.E., Wiersma, D., Knegtering, H., Van den Bosch, R.J. Are long term memory deficits a primary dysfunction in schizophrenia? (abstract). Schizophrenia Research. 53 (2002), 130.

Broerse, A., Holthausen. E.A.E., van den bosch, R.J., den Boer, J.A., 2002. Does frontal normality exist in schizophrenia? A saccadic eye movement study. Psychiatry Research 103, 167-178.

Wolthaus, J.E.D., Dingemans, P.M.A.J., Schene, A.H., Linszen, D.H., Knegtering, H., Holthausen, E.A.E., Cahn, W., Hijman, R., 2000. Component structure of the Positive and Negative Syndrome Scale (PANSS) in patients with recent onset schizophrenia and spectrum disorders. Psychopharmacology 150, 399-403.