

# Neurocognitive Function in Schizophrenia

## A follow-up study

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### Abstract

Neurocognitive deficits are considered a core feature of schizophrenia. Deficits covering a wide range of functions have been well documented. However there are still relatively few longitudinal studies regarding the long-term development of neurocognitive impairment. The current study examined the effect of time in schizophrenic patients and controls concerning cognitive functions. A neurocognitive test-battery was administered on two occasions to 36 schizophrenic patients and 46 healthy controls with approximately 4.5 year interval. Results showed that schizophrenic patients performed significantly worse on all measures on both occasions. No significant decline was found over time for either group except for on Trail Making Test, part B. Improvement on Continuous Performance Test was found for affected patients and improvement on Rey Auditory Verbal Learning Test was found for controls. Age was related to outcome in controls and education was related to outcome in patients. The conclusion is drawn that neurocognitive measures are relatively stable over 4.5 years in patients with schizophrenia, in line with earlier research. The authors discuss the impact of age and education and limitations of the study.

### Introduction

Schizophrenia is a condition that affects about 1 % of the population during a lifetime worldwide. It is a significant cause of suffering for the affected individual with about 10 percent of patients committing suicide (Andreasen, 2000). No single sign or symptom defines schizophrenia, rather it's defined by the fact that people who suffer from the illness experience abnormalities in many different kinds of mental activities as well as biological features, family background and childhood. This heterogeneity is a part of what makes the illness such a puzzle for scientists, practitioners as well as relatives and friends of patients suffering from the illness (Heinrichs, 2001).

Schizophrenia impairs the ability to think creatively and imaginatively, to have close social relationships with other human beings, to use language to express ideas with clarity

or to experience and express a variety of emotions such as love and fear. Even though anti psychotic medication helps the majority of patients to control the hallucinations and delusions experienced, medical treatment is less effective with lack of motivation and flattened affect and most patients never recover enough to return to full-time work, sustain a long-term relationship or raise a family. Most are left with a life-long disability, leading the World Health Organization to place it on the list of the 10 most debilitating medical illnesses (Williamsson, 2005). It is therefore of great importance to learn more about this disease, its causes, development and treatment.

## *Schizophrenia: an overview*

### *History*

Emil Kraepelin, sometimes referred to as the father of modern psychiatry was a German psychiatrist who developed an influential classification of psychiatric disorders in the late nineteenth and early twentieth centuries. According to the classification there were two major types of psychotic disorders: manic depression and something he called “dementia praecox” (literally: early dementia). The major differences between these two groups were that the manic depression group seemed to recover much better than those suffering from dementia praecox. Kraepelin found that these patients were emotionally dull with a loss of interest and singular indifference toward others. They had “no real joy in life”, “no human feelings”, to them “nothing matters”, “everything is the same”, and they feel “no grief and no joy” (Williamsson, 2005). Kraepelin further described auditory, visual, olfactory and somatoform hallucinations as well as delusions of persecution and grandiose delusions.

The early term of dementia praecox implies a progressively deteriorating illness, something that a Swiss psychiatrist by the name of Eugen Bleuler reasoned against since he observed that many patients do not deteriorate. Bleuler instead named this condition “Schizophrenia” since he considered the splitting (schizo) of different psychic functions (phrene) to be one of its most important features (Green, 2001). Green further refers to the work of Bleuler who also made a distinction between fundamental and accessory symptoms of schizophrenia. The fundamental symptoms included affectivity, ambivalence and alternations in association, which combined ultimately lead to disturbances in attention. According to Bleuler, these were actually the underlying basic impairment in the diagnosis but were not the most obvious things to anybody observing a schizophrenic person. Instead the accessory symptoms which were derived from the fundamental symptoms and included hallucinations, delusions and a variety of behavioral and speech abnormalities were the most obvious and therefore the focus of attention (Green 2001). For some reason Bleulers description never really caught on and the focus through the last century has still been on the more overt symptoms of schizophrenia that Kraepelin described. Indeed, the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV) criteria, currently in use to make the diagnosis of schizophrenia has drawn heavily on Kraepelin's descriptions of dementia praecox.

Heinrich (2001) comments on the further developments of the diagnosis and states that since the pioneers Krapelin and Bleuler no new symptoms have been discovered or elicited. The only changes have been attempts to subcategorize and differentiate some aspects of the illness from others. Thus positive symptoms have been distinguished from negative symptoms. Positive symptoms include delusions and hallucinations. They seem to be abnormal additions to mental life, whereas negative symptoms are deficits, or losses, like reduced motivation, impoverished speech, or emotional withdrawal.

### *DSM IV criteria of schizophrenia*

In the Mini-D IV (2002) diagnostic criteria, five kinds of symptoms are identified as characteristic of schizophrenia. These include delusions, hallucinations and disorganized speech. The fourth symptom-related criterion grossly disorganized or catatonic behavior, involves odd movements and postures seen in some patients. The fifth criterion, negative symptoms includes emotional indifference, autistic withdrawal, as well as a loss of drive and initiative.

Only one of these criteria is required if the delusions are bizarre, if the hallucinations consist of a voice making a running commentary on the patient's behavior or thoughts or if two or more voices are talking to one another. Otherwise, two symptoms are required.

Further the Mini-D IV states that to be diagnosed with Schizophrenia, social or work-related dysfunction should coexist with symptoms. The symptoms must have lasted for 6 months with at least 1 month of continuous symptoms. It should also be ruled out that the symptoms are caused or connected to other conditions such as schizo affective syndrome or depression as well as being a result of intoxication of drugs or other physical illness (Mini-D IV, 2002).

### *Causes and development hypothesis*

The origin of schizophrenia is widely debated and over the years different theories have emerged. Since the typical onset of schizophrenia is during late adolescence or early adulthood, it is only logical to think that the illness has something to do with the rapid and immense brain development that occurs during this time, such as pruning, a phenomenon in which a large proportion of the huge quantity of synapses produced during the developmental stage disappears (Granger, 1997). This has led to one line of research concerning schizophrenia as a neurodegenerative illness (meaning that cells in the brain die). There is some evidence for this hypothesis (Lieberman 1999; Christopoulos et al., 2005) or that it may at least play a role in a subgroup of patients (Knoll et al., 1998).

However, a number of risk factors have been identified in patients that occur long before adolescence. During prenatal periods the risk factors may include: Mothers nutrition where malnutrition may lead to increased risk of developing schizophrenia, infection during second gestation period, season of birth where winter and spring months show

more people with schizophrenia, urban birth where children born and raised in urban areas show an increased risk of developing the illness and the presence of so called MPA's (minor physical anomalies) which are slight deviations in external physical characteristics such as low set ears, high arched palate or curved fingers. There are further risk factors such as obstetrical complications during birth and motor and social abnormalities during childhood as well as impairments in IQ and school performance during childhood and early adolescence (Lewis et al., 2002).

These findings imply that something goes awry in an early period of life that sets the stage for schizophrenia but for some reason the illness does not "break out" until early adulthood. Therefore, as opposed to the neurodegenerative theory another line of research has focused on schizophrenia as a neurodevelopmental disorder which posits that pathogenetic biological events or characteristics are present much earlier in life than the onset of the features of the illness. Something that also supports this view is the apparent absence of gliosis in schizophrenia (Lewis et al., 2002) which is commonly seen in other types of degenerative brain diseases, gliosis refers to the process that leads to scars in the central nervous system (<http://www.medterms.com>).

The neurodevelopmental hypothesis does not explain why the onset occurs many years later than the initial damage is done. Some theories have addressed this process but none are conclusive nor widely accepted. One theory is that the neural disruption involves brain regions that are not very active until the second or third decade of life such as the prefrontal cortex and so the illness only becomes visible when this part of the brain is suddenly more often required (Green, 2001).

Research has shown that males are more frequently and severely affected, the illness tends to run in families and has a strong hereditary tendency and despite the fact that a majority of people with schizophrenia do not marry or have children, the disease persists in the human population (Andreasen, 2000).

Andreasen has proposed a working model for the etiology and pathophysiology of schizophrenia where multiple convergent factors such as DNA, gene expression, viruses, toxins, nutrition, birth injury and psychological experiences all play a part in the pathophysiology occurring in brain development from conception to early adulthood through processes such as neuron formation, migration, synaptogenesis, pruning, apoptosis (functional cell death) and activity dependent changes. Disturbances in these processes lead to anatomic and functional disruption in neuronal connectivity and communication which in turn cause impairment in a fundamental cognitive process. This further impairs on more second-order cognitive processes such as attention, memory, language and emotion which ultimately lead to the manifestation of symptoms of schizophrenia like hallucinations, delusions, negative symptoms and disorganized speech (Andreasen, 2000).

Green states that people are born with a certain predisposition for schizophrenia. Some have more of a predisposition than others, and there are no guarantees as to who will develop the disease. Whether or not schizophrenia develops depends not only on the

person's genetic predisposition but also on factors that are related to an increased risk of developing the illness and on factors related to a decreased risk (Green, 2001). Green further describes the underlying development as neurodevelopmental abnormality leading to disrupted neural connectivity and further to mild neurocognitive indicators. After these steps however, it depends on the degree of initial risk (genetic) and amount of protective/potentiative factors present, who will go on to the worsening of neurocognitive deficits and functional impairment that we call schizophrenia and who will stay at this level with a vulnerability only (Green, 2001).

Another theory of what is the underlying cause of schizophrenia is the research involving disturbances in the neural circuits in the brain, more specifically the so called CCTCC (cortico– cerebellar–thalamic– cortical circuit) which encompasses the communication between these different brain regions. Andreasen et al. (1999) observed that patients with schizophrenia have abnormalities in neural connectivity and that this appears to affect the circuitry used to integrate information from cortical and sub cortical regions. They proposed that that the CCTCC performs a monitoring and coordinating in the fluid execution of mental activity and that a disruption in the activity of this circuit leads to cognitive dysmetria, and ultimately, to the disordered cognition and the clinical symptoms of schizophrenia. The term cognitive dysmetria was defined as “a disruption in the fluid coordination of mental activity that is the hallmark of normal cognition” by Schmahmann (as cited by Andreasen 1999). Other studies support the role of a disrupted circuit involving the cerebellum and/or the effect of lesions on the cerebellum resulting in behavior common to schizophrenia such as hallucinations, delusions, and loss of volition (Andreasen et al., 1997; Schmahmann 2004; Nopoulos et al., 1999).

It stands relatively clear that at this point in time there is not a singular explanation of what causes schizophrenia. The most likely theory is one of multiple factors where both biological and environmental factors interact to produce vulnerability in patients who in further interaction with the environment during childhood and adolescence can (but not necessarily) cumulate until ultimately an “outbreak” occurs at a certain time point. No theories are mutually exclusive, for example it is still possible that some patients may develop schizophrenia from an early brain lesion, which does not degenerate, whereas other patients may develop a more progressive form (Williamson, 2005).

### *Morphology*

A range of research has shown that the brains of patients with schizophrenia differ in their morphology from the brains of healthy controls. These differences include abnormalities throughout all basal ganglia structures in at least a subgroup of schizophrenic patients (Hokama et al., 1995), significant reductions of gray and white matter volumes in the temporal regions, smaller white matter volumes in the cerebrum and increased CSF (cerebrospinal fluid) volumes in the frontal and the temporal regions as well as the cerebrum in males (Okugawa et al., 2002).

In line of support for the neurodegenerative hypothesis of schizophrenia a number of studies have shown a progressive, degenerative process in the brain of patients with

schizophrenia such as reduction in frontal lobe volume (Gur et al., 1998), accelerated frontotemporal cortical gray matter decline and cortical sulcal and lateral ventricular expansion (Mathalon et al., 2001; Lieberman et al., 2001), significant decreases in gray matter volume over time in the left superior temporal gyrus (Kasai et al., 2003), changes in whole-brain volume (Wood et al., 2001; DeLisi et al., 1997), significant difference in the rate of change in the overall volumes of right cerebellum and greater enlargement of the left cerebral ventricle (DeLisi et al., 1997).

Contrary to the above findings, a longitudinal study of patients with schizophrenia compared to healthy controls with a 5 and 10 year follow up conducted by DeLisi and Hoff (2005) came to the conclusion that there were no significant differences in total temporal lobe or Superior Temporal Gyrus (STG) volumes between patients and controls at any of the three time points. There were also no significant changes over time when patients were compared with controls. However there was a significant main effect of time. The rate of change in the temporal lobe for each subject was not significantly greater in patients than in the controls and similarly for the STG. They also found that whole brain volume changes over time in both patients and controls failed to find progressive temporal lobe volume decreases 10 years subsequent to a first episode of schizophrenia (DeLisi et al., 2005). Another study of hippocampal volume in first episode psychosis and chronic schizophrenia found no evidence for progressive loss of either hippocampal or temporal lobe volume in patients with chronic schizophrenia or first episode psychosis (Wood et al., 2001; Lieberman et al., 2001).

The morphology of patients with Schizophrenia is related to their performance on neuropsychological tests. For example Lawyer et al. (2006) found that frontal lobe gray matter volumes were associated with verbal learning, parietal lobe gray matter volumes were associated with working memory and parietal and temporal lobe gray matter volumes were associated with executive function. Their results also supported earlier findings on involvement of cerebellar structures in cognitive brain function. Considerable evidence demonstrates that cerebellar structures are involved in diverse cognitive functions, including working memory, motor skill learning, explicit memory, and language (Schmahmann, 2004; Nopoulos et al., 1999; Andreasen et al., 1996). Further, volume reduction of lobes has been associated with decreased performance on neurocognitive measures and especially the temporal lobe (Gur et al., 1998).

### *Neuropsychology in schizophrenia*

High-level psychological functions are what separate us from other primates. Activities like planning for the future, learning and storing large amounts of complex information, and having elaborate and dynamic social relationships are dependent on these high level cognitive functions. When these cognitive functions are interfered with, other intrinsically human activities are impaired (Harvey & Sharma, 2002).

Impaired cognitive functioning is generally considered to be a primary characteristic of schizophrenia and a core feature of the illness (Harvey & Sharma, 2002) which was recognized already by both Kraepelin and Bleuler (Bozikas et al., 2006). Students of Kraepelin were actually the first to investigate cognition of schizophrenia, interestingly the topics that they studied 100 years ago, still remain of interest to researchers to day (Harvey & Sharma, 2002). Bleuler believed that deficits in critical cognitive processes were in fact the underlying cause of the central impairments in the illness (Harvey & Sharma, 2002). Later development regarding the view of cognitive deficits is a deeper understanding of the importance of cognitive deficits, including their functional implications and their potential to influence other aspects of the disorder (Harvey & Sharma, 2002).

Although cognitive deficits have been described for years there have been questions lingering regarding if these deficits reflect a central feature or if they are a consequence of other aspects of the disorder (Harvey & Sharma, 2002). Several lines of research have addressed this topic, of which five are presented below.

First, is cognitive impairment caused by positive symptoms? Several lines of investigation show results that have given a general opinion of the answer no to this question. It has been shown by Addington et al. (1991) that positive symptoms are not correlated with the severity of cognitive impairments. Yet another study carried out among geriatric schizophrenic patients support the findings that cognitive impairments rather than positive symptoms correlate with poor outcome in schizophrenia (Davidson et al., 1995). Results of other studies that evaluate the same patient when they are psychotic and then again when they are not, have gathered evidence that impairments in memory and attention are very similar in the acute episode and in remission of the acute episode, which has been reported by Harvey and Sharma (2002) (Harvey et al., 1990; Nuechterlein et al 1986). Several studies have also shown that cognitive impairments are present before, during and after occurrences of psychotic symptoms such as hallucinations (Harvey & Sharma, 2002). However Hoff et al. (1999) found some improvement in cognitive measures correlated with the decrease in positive symptoms.

Second, empirical studies does not show that medication has an impact on the majority of important cognitive functions in schizophrenia. However there are a few exceptions to this trend, for example there is some evidence that improvement subsequent to treatment in the domain of motor skills in a study by Blyler and Gold (2000) (Harvey & Sharma, 2002) and limited measure of attention (Serper et al., 1994). Other areas that support the limited effect of medication on cognitive function is that deficits in cognitive function were reported and well documented before the introduction of antipsychotic medication (Harvey & Sharma, 2002). There is also contemporary evidence that unmedicated patients perform similarly to patients who have previously been medicated for years (Saykin et al., 1994). Longitudinal studies of patients who are medicated with typical neuroleptics did not show significant deterioration nor improved cognitive measures correlated to medication (Hoff et al., 1999). However it has been proposed by Mortimer (1996) that atypical neuroleptics could have the capacity to remediate cognitive

impairment in schizophrenia but conventional neuroleptics effect on cognitive function are minor.

A third aspect that has been discussed regarding performance on neuropsychological measurements is poor motivation (Harvey & Sharma, 2002). After a workshop on the topic of motivation summarized by Barch (2005) it was stated that “Any individual who has worked extensively with people who have schizophrenia knows that, although cognitive dysfunction is prominent, these individuals can also display a host of emotional and motivational deficits” Several studies have shown that performance on cognitive tasks such as for example Wisconsin Card Sorting Test can be improved via the use of monetary incentives however several other studies using monetary incentives found contradicting evidence in this matter (Barch, 2005). Gorissen et al. (2005) found evidence that a lack of effort in schizophrenic patients explained a significant amount of variance in neuropsychological test performance. Furthermore a lack of effort was related to negative symptoms (Gorissen et al., 2005). However Harvey and Sharma (2005) argue that motivation and effort alone can not explain normal and impaired performance across different cognitive measures. The role that motivation plays in impaired cognitive task performance in schizophrenia is still unclear and further research needs to be conducted on this topic (Barch, 2005).

Fourth, negative symptoms are related to, but not the cause of cognitive deficits according to Harvey and Sharma (2005). Measures from many different domains of cognitive functioning are more likely to be associated with the severity of negative symptoms than positive symptoms (Harvey & Sharma, 2002). In one study it was concluded that negative symptoms are a major source of disability for schizophrenic out-patients and that it is also associated with cognitive function (Villalta-Gil et al., 2006). Harvey et al. (1996) have suggested that negative symptoms and cognitive functions are related but separable dimensions of symptoms in Schizophrenia (Harvey et al., 2006). Several studies of patients with the presence of negative symptoms have shown that cognitive decline can occur in the absence of worsening in negative symptoms (Chemerinski et al., 2006) suggesting that negative symptoms and cognitive impairments are related and that they considerably overlap (Harvey et al., 1996).

Fifth, according to Harvey and Sharma (2002) “poor cognitive performance is not caused by global intellectual deficits”. Instead neuropsychological patterns in schizophrenia tend to be consistent at different IQ levels. Kremen et al. (2001) investigated neuropsychological performance at different intelligence Quotient levels in schizophrenia. Schizophrenic patients were matched with normal controls, and the results found that schizophrenic patients with normal current IQs manifested substantial neuropsychological compromise relative to their general intellectual ability compared to controls with same IQ. From these results the authors concluded that neurocognitive deficits are core deficits of schizophrenic illness (Kremen et al., 2000; Kremen et al., 2001).

To summarize, cognitive deficits are central aspects of schizophrenia and are not caused by, but might be related to other features of the illness, especially negative symptoms.

### *Specific function deficits associated with schizophrenia*

Five domains have been documented to be of special interest in schizophrenic patients (Lawyer et al., 2006). A short resume of these functions and their relevance to the neuropsychology of Schizophrenia will be presented below.

#### *Working memory*

Working memory is commonly defined as the capacity for “temporary storage and manipulation of the information necessary for such complex cognitive tasks as language comprehension, learning and reasoning” (Baddely, 1992). A recent re-conceptualization elaborates on the storage and manipulation aspects of working memory by characterizing tasks as transient online storage and retrieval or executive function working memory (Perry et al., 2001). The transient type of memory is measured by “hold and repeat” tests in which the subject creates and maintains an internal representation of the internal stimuli (Twamley et al., 2006). Impairment in working memory in patients suffering from schizophrenia that has been well documented in the literature and has been considered important in the cognitive profile of schizophrenia (Twamely et al., 2006). It has been shown by several authors that patients with schizophrenia have impaired performance on a variety of working memory tasks. These findings have also been used to support the hypothesis that the prefrontal cortex is impaired in schizophrenia spectrum patients (Perry et al., 2001; Gold et al., 1997)

#### *Executive functions*

Executive functions are the most complex of behaviors and are important to respond in an adaptive manner to novel situations and also the basis of many cognitive, emotional and social skills (Lezak, 2004 ). Executive function is a diverse collection of cognitive abilities, it refers to the ability to solve problems, use abstract concepts and manage cognitive skills and resources (Harvey & Sharma, 2002). Moreover it also includes the ability to solve problems, including formulation of strategies, evaluation of their usefulness, selection of the best strategy, avoiding the effects of irrelevant information, and discarding strategies when they lose their usefulness. Executive function also refers to the ability to effectively alternate between competing demands and adaptively shift effort in doing so (Harvey & Sharma, 2002).

#### *Psycho motor speed*

Psycho motor speed refers to the amount of time it takes a person to process a signal, prepare a response and execute that response and is commonly measured by reaction time.

Patients with schizophrenia have slowed performance on various psychomotor measures meaning that their movements and reaction time are slower than healthy controls. This is one of the most consistent findings in the illness and has been demonstrated independent of medication and is also associated with negative symptoms and, to a lesser extent, with positive and depressive symptoms (Morrens et al., 2007).

### *Verbal memory/Verbal learning*

Patients of schizophrenia manifest a number of impairments in memory functions. When read a story or list of words they remember much less than healthy controls (Saykin et al., 1991). If the list or story is repeated, schizophrenic patients learn much less than healthy controls (Davidson et al., 1996). Lezak (2004) claims that wordlists are among the most sensitive verbal memory test formats because of the relative freedom from associative context compared with for example prose material. As opposed to the research above, Karilampi et al (2007) found that 43.9% of schizo-psychotic patients had normal learning ability as measured by RAVLT.

### *Attention/vigilance*

Vigilance is the ability or capacity to maintain attentional activity over a period of time (Lezak, 2004). It is well known that patients with psychosis and schizophrenia often have disturbances in this ability and that this is of great importance for their possibilities to retain or develop social abilities. Attentional impairments appear to persist after remission of acute psychotic episodes (Harvey & Sharma, 2002).

### *Cognitive deficits and functional outcome in schizophrenia*

There are several dimensions of functional deficits in Schizophrenia. Patients show marked impairments in independent living, social functioning, occupational skills, and self-care (Harvey and Sharma, 2002). The neuropsychological impairments are in themselves interesting since they are highly related to functional outcome (Green et al., 2000). The neurocognitive domains most consistently related to functional outcome include secondary verbal memory or what is referred to in this study as verbal learning (Lezak 2004) and memory measured by RAVLT. Also immediate or working verbal memory, executive functioning measured with card sorting, and vigilance is considered to correlate with functional outcome. In a study conducted by Green et al (2004) it was found that certain functions were directly related to certain outcomes. To mention a few: Secondary verbal memory or verbal learning was related to success in psychosocial skill acquisition, laboratory assessment of instrumental skills and social problem-solving ability and community outcome/daily activities. Card sorting was related to community outcome/daily activities and immediate/short-term verbal memory was related to success in psychosocial skill acquisition (Green et al., 2000). Another study by Bowie et al. (2008) examined the different predictive relationships between neuropsychological domains, functional competence, social competence, symptoms, and real-world behavior in domains of work skills, interpersonal relationships, and community activities. The authors found evidence that processing speed and attention/working memory predicted social competence. The attention/working memory domain was also directly related to work skills. Executive functions had a direct effect on interpersonal behaviors and processing speed had an effect on all three “real-world” behaviors investigated in this study. The relationship between neuropsychological measures and functional outcome has been shown to be continual. A review of 18 studies that examined the relationship

between cognitive performance at baseline and community outcome with at least a 6 month follow up came to the conclusion that “it is reasonable to conclude that cognitive performance at baseline tends to be related to community outcome months or years later” (Green et al., 2004).

Another functional consequence of impaired cognitive functioning, especially deficits in memory skills (Harvey and Sharma 2002) and vigilance (Kern et al 1992) (Bowen et al. 1994) may be predictors of functional deficits as well as “rate-limiters” for acquisition of skills in the therapeutic method of social skills training.

### *Cognitive functions evolvement over time*

Neurocognitive impairments do not seem to deteriorate significantly over time, implying that schizophrenia is not likely a degenerative process. Hoff et al. (2005) conducted a ten year follow up of neuropsychological functioning subsequent to a first episode of schizophrenia and found that patients did not deteriorate significantly more than controls. But they did find that the healthy controls increased their scores on verbal intellectual functioning, delayed verbal and nonverbal recall, and cognitive inhibition. They concluded that most first episode patients have had considerable cognitive decline by the time of their first hospitalization and that most cognitive change takes place early in this illness but its exact timing still remains unknown (Hoff et al., 2005). In an earlier study by Hoff et al. (1999) some neurocognitive improvement was found even in patients except for verbal memory scores and no significant change in cognitive functioning was otherwise found between the patients and the healthy controls (Hoff et al., 1999). The stability of neuropsychological performance over time has also been shown by Censits et al. (1997) consistent with the neurodevelopmental model of schizophrenia.

Some studies have focused on investigating schizophrenia patients and healthy controls across age groups. In a study conducted by Fuecola et al. (2000) the authors investigated the effect of aging on executive functions. They discovered that patients with schizophrenia demonstrated similar age-related declines across most neuropsychological functions as healthy controls, with the exception of abstraction ability in which there was significant evidence of a more accelerated decline. The authors concluded that the results indicated similar age effects on most aspects of cognition in schizophrenia patients and healthy adults but supported the hypothesis that a degenerative process may result in a more accelerated decline of some executive functions in older age in schizophrenia (Fuecola et al., 2000). Another study conducted by Bowie et al. (2007) found evidence for age associated cognitive worsening on the more complex components of an information processing test but not in other neuropsychological tests. These results suggest that age-related changes in cognitive function in schizophrenia may be a function of both the course of illness and the processing demands of the cognitive measure of interest (Bowie et al., 2007).

A review by Rund of 15 studies of cognitive functions in schizophrenia with a follow-up period of at least 1 year found the majority of functions to be highly or moderately stable and some even to improve. These functions included for example general IQ, verbal

memory, short-term memory and attention. The only functions found to show significant decline were attentional span (1 study) and to a certain degree shifting capacity (Rishovd Rund, 1998). A study conducted by Friedman et al. (2001) came to the similar conclusion, no cognitive decline was found in patients during a follow-up period of six years. This result was particularly interesting because the authors singled out patients with poor prognosis as the few studies that have been conducted with truly elderly schizophrenic patients have focused on poor-outcome populations with long histories of hospitalization, possibly skewing the picture of cognitive decline over time (Harvey et al., 1999). Further, Gold et al. (1999) found improvement in performance and full-scale IQ and no change in verbal IQ or WCST or other tested skills during a follow-up period of five years.

It has been shown that chronic patients perform worse than first-episode patients, implying that cognitive function can decline over time (Bilder et al., 1992). However, this interpretation must be done with caution since as mentioned above, other factors, such as hospitalization, may have influenced elderly schizophrenic patients cognitive abilities.

### *The aim of this study*

Given the heterogeneity of symptoms in schizophrenia it has been proposed that cognitive approaches hold most of the promise for understanding the variability in the neurobiological substrates of the disorder (Mortimer, 2005). Byrne et al. (2003) concluded that there is a state of vulnerability manifested by neuropsychological impairment inherited, and that these deficits occur in far more individuals than go on to develop the disorder.

Research that examines the role of cognitive decline over time in patients with schizophrenia is highly relevant since it seems to be strongly related to functional outcome. The purpose of this study is to generate and analyze data concerning neuropsychological functioning and its development after a period of 2.5-6.5 years. The investigation should be considered as a part of a greater project designed by a group of researchers in Stockholms läns landsting and further to be correlated to morphology as described below.

This report is a follow-up study to a previous paper by Lawyer et al. (2006). The authors correlated morphological features to cognitive dysfunction in schizophrenia with Bayesian regression (a statistical procedure). The subjects were part of the large cohort described below and their results were the baseline to which our results were compared in this study. Our intention is to investigate if any changes in the neuropsychological functions have occurred over a time-span of 2.5 to 6.5 years in patients with schizophrenia compared to healthy controls.

The aim of this study was twofold, the first question was in what way the two groups differ in their results on the second test occasion compared to their previous results on

measures of neuropsychological functioning. We intended to explore any changes over time within the two groups and if they existed, to what extent they might differ significantly from one other. Secondly the intention was to see what other factors might be linked to the results of patients with schizophrenia, specifically considering age of onset, duration of illness, number of hospitalizations and education.

## Method

### *Subjects*

The subjects that participated in the previous study (Lawyer et al., 2006) were drawn from a larger, previously described cohort (Jönsson et al., 2003). They were unrelated Caucasian individuals living in the north-western part of Stockholm County. Subjects were assessed for life-time psychiatric diagnosis and geographical origin using reviews of hospital case notes, clinical and/or structured interviews, and parish register data. Only patients fulfilling a DSM-III-R diagnosis or DSM-IV of schizophrenia were included. All reviews of hospital case notes, interviews and diagnostic formulations were performed by a psychiatrist or a psychiatry resident (Jönsson et al., 2003). The patients were tested on the same neuropsychological functions as in the present study and underwent a MRI scan.

The patients of the present study consisted of those who participated in the previous study described above and who had gone through a second MRI scan at the time of follow-up. They were contacted via phone by a research assistant and asked to participate. A natural selection then took place where some could not participate on grounds of personal choice, moving, death or other reasons. The patients of this study had to be stable in their diagnosis in order to participate.

Healthy controls were found through a letter sent to the population by random lists (for example national registration) where they were asked if they were interested in participating in the project. The letters were then followed up by a telephone call. Everyone that wanted to participate went through a screening for any current or former psychiatric diagnosis, any traumatic injury to the head, any illness affecting the nervous system and for any abuse or extensive use of alcohol and/or drugs. The controls tested in the follow-up study were a sample drawn from the sample of the previous study conducted by Lawyer et al. (2006) where the appropriate time for a second testing had passed and where the controls were willing to undergo a second procedure of MRI scans and neuropsychological evaluation.

The previous study examined 71 patients and 65 control subjects. For this follow-up-study the results of 36 patients and 46 control subjects were obtained.

## *Procedure*

Patients and healthy controls were contacted by a nurse specialized in research and asked if they were willing to participate in the study once before every test occasion, agreement of time and place was also decided at this time. For their trouble patients and controls were offered two cinema tickets each.

The testing took place at different locations within the Karolinska Institute and was administrated by 4 undergraduates in psychology with training in test administration over a time period of 2 years. Administration of the test battery took approximately 1 hour. Forty of the follow-up measurements were administered by the authors of this report.

### *Cognitive Performance Indicator (CPI) Test battery*

For measuring the neuropsychological performance The Cognitive Performance Indicator (CPI, a brief neuropsychological test battery used in Lawyer et al., (2006) was administrated as a follow-up measurement. CPI is a semi-computerized test battery, constructed to give an overview of critical cognitive functions in patients with Schizophrenia (Lawyer et al., 2006). The tests are well known standardized tests, which have been used extensively in neuropsychological examinations. In CPI the administration of sub tests and the registration of data are guided by a computer program, which makes it easy to use in clinical as well as research settings. CPI comprises Rey Auditory Verbal Learning Test, a 150 item version of Continuous Performance Test-Identical pairs, Trail Making Test, Letter-Number-Sequencing, WAIS-R Vocabulary, and the 64 card version of the Wisconsin Card Sorting Test.

In the current study five of the six domains from CPI test battery were used to investigate the performance of patients and healthy controls. The Vocabulary from WAIS-R used in the previous investigation was excluded since it is regarded as a “hold test” for roughly assessing pre-morbid functional level. The five domains included verbal learning as measured by Rey Auditory Verbal Learning Test, attention/vigilance as measured by Continuous Performance Test-Identical pairs, psycho motor speed measured by the Trail Making Test A and B, working memory measured by Letter Number Sequencing and executive functions measured by Wisconsin Card Sorting Test (completed categories, number of errors, preservative errors and preservative responses).

RAVLT, Rey Auditory Verbal Learning Test measures the ability to learn a series of words, the ability to exclude the words being learnt from a similar series of interference words as well as the ability to retain and actively pick out the learnt words after 20 minutes (CPI manual, 2000). The administrator presented a list (list A) of 15 words at a rate of one word per second after which the subjects were required to reproduce as many words as they could recall. The same list was then repeated four more times with the subjects required to do the same after each reading (trials 1-5). On completion, another

list (list B), with 15 new words was read aloud and the subjects were again required to reproduce as many words as they could recall from the new list. Upon completion the subjects were asked to reproduce as many words as they could recall from the list A. Before this request, no list was read aloud. After a delay of 20 minutes the subjects were asked again to recall as many words as possible from list A. In our results, 9 measures were collected: RAVLT 1-5 (total recall for each trial), RAVLT TOT (total recall over all 5 trials), RAVLT B (total recall from list B), RAVLT 6 (total recall from list A after reading of list B) and RAVLT 7 (total recall after 20 minutes delay).

CPT, Continuous Performance Test-Identical pairs is a classic test to measure vigilance, however, the identical pairs version of the CPT can be redefined in terms of working memory functions, because the currently presented stimulus must be compared with the immediately preceding stimulus represented in memory (Pukrop et al., 2003). A low result means that the person probably is strongly fluctuating in their attention and/or is easily distracted of irrelevant stimuli from the surroundings and the own organism and manage only to maintain adequate attention and concentration for a shorter time. Subjects were required to hold a mouse button down while presented with a series of four-digit-numbers on a computer screen. When successively presented stimuli were identical, subjects had to lift their finger off the mouse button and as quickly as possible press the button down again. The total  $d'$  ( $d$  prime) score was used to measure the capacity of attention. The total  $d'$  score is a measure of perceptual sensitivity or attentional capacity or the participant's ability to discriminate targets from non-targets (Karilampi et al., 2007).

Trail making test A and B examines both psychomotor speed and the ability to sustain flexibility while working under time constraints (Harvey & Sharma, 2002). The patient must draw lines between consecutively numbered circles on a worksheet on part A and on part B consecutively connect circles with letters and numbers (Lezak, 2004).

Trail Making Test A measures mostly motor speed and coordination of visual scanning and movements of the hand. Low results point to reduced ability to control and coordinate different motorical systems under time pressure. This test says less about the ability to perform when time is not an important factor. A low result in TMT-A should be interpreted as an expression of lower motor speed. Subjects were required to connect as quickly as possible randomly arranged numbers from 1 to 25 in successive order on a sheet of paper with a pen.

Trail Making Test B is a component of executive function and measures the ability to control behavior in a flexible way as well as attention and working memory. If the result in TMT-B is markedly lower than in TMT-A it's generally interpreted as the executive functions being disturbed. If both A and B are low one can not interpret the executive functions as being disturbed for sure, since the whole observation might be caused by disturbances in motor speed and mental processing. Subjects were required to connect as quickly as possible randomly arranged numbers (from 1 to 13) and letters (from A to L) alternately in successive order on a sheet of paper with a pen.

LNS, “Executive function” working memory is measured by tests that require transient working memory as well as additional processing or manipulation of the information held in mind (Twamley et al., 2006) such as in the measure of Letter-number Sequencing. It has been described by Twamley et al. (2006) as a function of “executive function” working memory. L-N-S measures this capacity by exposing the subject to longer series of letters and numbers that are to be organized in numerical and alphabetical order. In this way the information must be maintained in short term memory while the letters and numbers are organized. Patients that have difficulties with working memory will probably experience that they have difficulties keeping up in more complex contexts and might say that they have difficulties concentrating, are too tired to listen, think etc (CPI manual, 2000).

Subjects were required to sort out letters from numbers within a row of alternating letters and numbers that was presented to them verbally, and to separately recall the letters and numbers in successive order. The test ranges from two to seven items with three trials at each level. Only when the subject could not correctly recall all three items of the level the test was over.

WCST, Wisconsin Card Sorting Test measures some of the most critical executive functions needed for behavior to be adjusted and adapted for shifting conditions in the surroundings (CPI manual, 2000). This test was developed in the late 40’s and has been used for over 50 years to examine schizophrenic patients. Wisconsin Card Sorting Test involves matching cards which vary along the dimensions of color, shape and number (Harvey & Sharma, 2002). One of the executive components that can be involved in the processing is the ability to choose and use a strategy to find the correct sorting principle. Another executive function measured is surveillance, involving two components, part one the ability to observe the environment and stop the ongoing behavior and choices when the conditions change. The second part is that the aspect of working memory that keeps the ongoing behavior in the direction chosen must be active since there will otherwise be errors of another kind occurring namely switching sorting principle, although there is no signal in that direction from the surroundings. On another level the ability to abstract thinking is involved to distinguish the different sorting principles available.

Subjects had to sort 64 cards against a set of four stimulus cards according to a certain undisclosed rule: colour, shape, or number of symbols on the cards. Once the subject had made a specified number of consecutive correct matches to the initial sorting principle, the sorting principle was changed without warning. The WCST proceeds in this manner through a number of shifts in sorting principle among the three possible sorting categories. The subjects were presented with a computer screen on which four cards appeared along the top and one card that the subjects were required to sort appearing at the bottom. The subjects dragged and dropped the card onto one of the four cards where they best considered it to belong. They then received direct feedback if their choice was correct or incorrect in form of the words “correct” or “incorrect” appearing on the screen. The computer program then calculated four test scores: total categories completed, total errors, preservative errors (shifting sorting principle despite positive feedback on chosen principle) and preservative responses (continuing to respond with same principle despite feedback that the sorting principle is wrong).

*Table 1: Overview of CPI, the function measured, name of test and measurement*

Function	Test	Measure
Learning	RAVLT	total number of correctly reproduced words
Distractor		number of words reproduced from list B
Memory		number of words reproduced after 20 minutes
Attention	CPT (150 item version)	d'
Motor speed	TMT A	seconds
Shift	TMT B	seconds
Working memory	LNS	number of correctly reproduced sequences
Executive functions	WCST (64 card version)	number of categories completed number of preservative responses number of total errors number of preservative errors

### *Data Analysis*

A series of 2 x 2 repeated measures ANOVA's were conducted with the first factor being group (patients or controls) and the second factor being time (baseline or follow-up) and the dependent variable being the 17 test scores.

A paired-samples t-test was calculated for the within group scores of the 17 tests to see if the eventual significant main effect of time was based on one groups significant difference and not the others.

For 2 demographic variables (age and years of education) an independent samples t-test was conducted to find any significant differences between groups. These variables (with the addition of sex) were then correlated to the 17 mean scores for each group at both baseline and follow-up using Pearsons and Spearman's correlations with two-tailed significance. Each of the remaining demographic variables (age of onset, illness duration and number of hospitalizations) was then correlated with the 17 test scores for patients at baseline and follow-up to see if any significant correlations would appear, using Pearsons correlation with two-tailed significance.

We set the alpha level to 0.05 for all statistical analysis.

## Results

Below the results of our analysis are presented. First the demographic variables are presented and after that, the results from varying statistical analysis.

*Table 2: demographic variables, mean scores, standard deviation in brackets*

	Patients	Controls	Total
Number	36	46	82
Sex*			
Males	32	28	60
Females	4	18	22
Age at baseline	40 (8)	42 (8)	41 (8)
Age at follow-up	45 (8)	46 (8)	45,5 (8)
Time between baseline and follow-up*	4,5 (1)	4 (1)	4,3 (1)
Education*	12,2 (2,3)	13,6 (2,8)	13 (2,7)
Illness duration at baseline	16,5 (8,5)		
Illness duration at follow-up	21 (8,5)		
Number of hospitalizations	11,8 (10,8)		
Age of onset	23,5 (4)		

\* significant difference between groups at  $p = < 0,05$

To identify change in the different measures over time, change between groups and interaction between these variables, an ANOVA was performed. Results are presented in Table 3.

*Table 3: Mean, standard deviation in brackets (raw scores) and F values for main effect of group, main effect of time and interaction time/group on each test for patients and controls.*

	Patients		Controls		F values		
	Baseline	Follow-up	Baseline	Follow-up	group	time	group/time
RAVLT 1	5,7 (1,5)	5,9 (1,7)	7,0 (1,4)	8,1 (1,9)	33,5***	9,3**	4,9*
RAVLT 2	8,1 (2,5)	8,4 (2,3)	10,0 (1,9)	11,1 (1,9)	29,7***	10,0**	3,7
RAVLT 3	9,4 (2,6)	9,3 (3,1)	11,9 (1,7)	12,3 (1,9)	37,9***	,257	,51
RAVLT 4	10,4 (2,6)	10,7 (3,0)	12,9 (1,7)	12,9 (1,8)	27,4***	1,0	,41
RAVLT 5	11,0 (2,8)	10,6 (3,0)	13,8 (1,2)	13,7 (1,3)	45,0***	2,0	,81
RAVLT TOT	44,6 (10,8)	44,9 (11,7)	55,7 (6,5)	58,2 (7,6)	42,6***	3,0	1,9
RAVLT B	5,2 (1,5)	4,9 (2,1)	7,0 (1,5)	6,9 (1,9)	34,1***	,403	,58
RAVLT 6	8,8 (3,2)	9,0 (3,0)	12,0 (2,3)	12,2 (2,5)	35,0***	,378	,00
RAVLT 7	9,2 (3,5)	8,7 (3,2)	12,1 (2,3)	12,5 (2,3)	33,4***	,054	2,6
CPT	0,81 (0,71)	1,06 (0,89)	1,35 (0,79)	1,53 (1,0)	8,0**	7,3**	,38
TMTA	32,0 (12,1)	37,2 (25,7)	23,5 (8,0)	25,4 (6,8)	14,6***	3,9	,86
TMTB	94,5 (57,5)	109,2 (70,9)	55,1 (19,8)	62,4 (25,7)	19,3***	13,7***	1,5
LNS	9,4 (2,6)	9,1 (3,0)	11,5 (2,6)	11,6 (3,0)	17,5***	,129	,57
WCST -TC	2,7 (1,7)	2,6 (1,9)	3,6 (1,6)	3,7 (1,4)	9,1**	,000	,87
WCST -TE	22,3 (12,2)	21,3 (12,5)	15,2 (9,4)	14,1 (9,3)	10,6**	,977	,00
WCST -PE	11,5 (7,3)	9,9 (6,6)	7,3 (4,5)	7,1 (5,1)	8,9**	2,3	1,3
WCST -PR	12,8 (8,5)	10,9 (7,8)	7,8 (5,3)	7,6 (5,9)	8,8**	2,2	1,2

\* p = < 0,05 \*\* p = < 0,01 \*\*\* p = < 0,001

There was a significant difference between groups on all test scores at baseline (p varies from 0,000-0,020). Likewise, there was a significant difference between groups on all test scores at follow-up (p varies from 0,000 to 0,036).

Results of the ANOVA showed that on RAVLT 1 there was a significant main effect of time (p = 0,003) as well as a significant main effect of group (p = 0,0001). There was also a significant interaction time/group effect where the controls performed better than patients at both times but more so during the second testing (p = 0,028). On RAVLT 2 there was also a significant main effect of time (p = 0,002). On CPT there was a significant main effect of time (p = 0,008) and the same result was found for TMT B (p = 0,0001).

There were no significant main effects of time or interaction effects on RAVLT 3, RAVLT 4, RAVLT 5, RAVLT TOT, RAVLT B, RAVLT 6, RAVLT 7, LNS, WCST TC (total categories), WCST TE (total errors), WCST PE (preservative errors) and WCST PR (preservative responses).

To examine change over time in patients and controls a paired samples t-test was performed and the results are presented below.

*Table 4: t-value and significance for change over time on each test for controls and patients*

	Controls	Patients
	t	t
RAVLT 1	-3,775***	-,601
RAVLT 2	-3,764***	-,854
RAVLT 3	-1,076	,120
RAVLT 4	-,340	-1,012
RAVLT 5	,509	1,297
RAVLT TOT	-2,600*	-,212
RAVLT B	,215	,975
RAVLT 6	-,425	-,439
RAVLT 7	-1,062	1,240
CPT	-1,597	-2,202*
TMT A	-1,681	-1,371
TMT B	-2,905**	-2,500*
LNS	-,287	,788
WCST -TC	-,650	,695
WCST -TE	,751	,664
WCST -PE	,298	1,832
WCST -PR	,288	,1708

\* p = < 0,05 \*\* p = < 0,01 \*\*\* p = < 0.001

The healthy subject controls had significantly increased their scores on the first two trials of RAVLT ( $p = 0,0001$ ) whereas the patients had not. The controls also show a significant increase in the total score of RAVLT ( $p = 0,013$ ) as opposed to the patients. Patients showed a significant increase on the CPT ( $p = 0,035$ ). Both patients and controls show a significant decrease in performance on the TMT B over time (patients  $p = 0,017$  and controls  $p = 0,006$ )

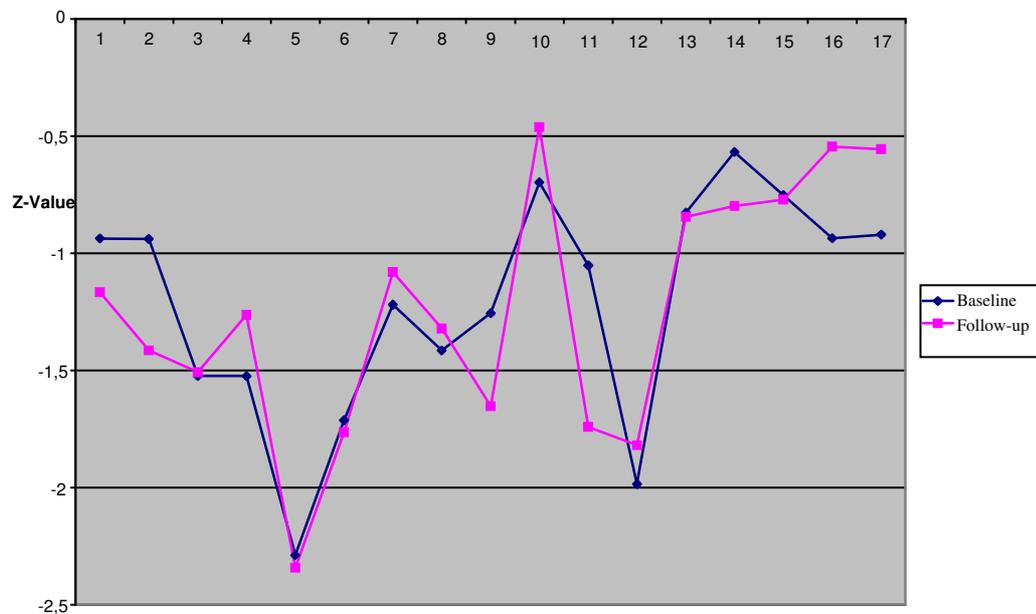
To see how patients differ from controls in their performance on chosen tests, a standardized z score was calculated. The results are presented in Table 5.

Table 5: Patients z- values on tests at baseline and follow-up with controls z-value set to 0

	Baseline	Follow-up
1. RAVLT 1	-0,9375	-1,1658
2. RAVLT 2	-0,9393	-1,4145
3. RAVLT 3	-1,5235	-1,5076
4. RAVLT 4	-1,5240	-1,2625
5. RAVLT 5	-2,2892	-2,3432
6. RAVLT TOT	-1,7129	-1,7645
7. RAVLT B	-1,2191	-1,0806
8. RAVLT 6	-1,4140	-1,3208
9. RAVLT 7	-1,2555	-1,6536
10. CPT	-0,6976	-0,4627
11. TMT A	-1,0521	-1,7411
12. TMT B	-1,9853	-1,8195
13. LNS	-0,8275	-0,8453
14. WCST -TC	-0,5677	-0,7986
15. WCST -TE	-0,7523	-0,7718
16. WCST -PE	-0,9358	-0,5450
17. WCST -PR	-0,9210	-0,5559

On the tests where a high score represents a worse result we simply added a minus in front of the Z-value (applicable for tests 11, 12, 15, 16 and 17).

Graph 1: Standardized mean value (z) of patients scores on each test at baseline and follow-up, numbers refer to individual tests (see table 5)





## Discussion

The significant difference between controls and patients over all tests at baseline and follow-up are expected results in line with earlier research. A considerable amount of reports have found patients with schizophrenia to perform on average between 0.5 and 2 standard deviations below average on the tests included in CPI (Bonilha et al., 2007; Yamashita et al., 2005; Pukrop et al., 2003; Barrantes-Vidal et al., 2007; Perry et al., 2001; Wang et al., 2007).

The significant difference in years of education between controls and patients seen in our sample is expected and has been shown by others (Birkett et al., 2007). Since our results have not shown a large discrepancy between controls and patients in longitudinal cognitive functions, this difference is of little importance.

The significant difference in time elapsed between baseline and follow-up for patients and controls might have been a confounding factor if the patients had performed significantly worse on many tests. Since this did not happen, we consider this variable to be of marginal importance.

RAVLT, the controls showed a significant increase in their score on trial 1, 2 and Total where the patients did not. On RAVLT 1 there was also a significant interaction effect of time/group which indicates that controls performed better than patients at both times and significantly more so at follow-up. Rather than reflecting a real change in verbal memory this might imply that controls had a better advantage of having taken the test at baseline than patients. There has been considerable research done on the practise effects of RAVLT where healthy controls show a small but statistically significant practise effect in longitudinal studies (Mitrushina et al., 2005). Most of them have however only investigated the effects over a time period not longer than 1 year. Since this follow-up is considerably longer our results may still reflect a real improvement in verbal learning memory over time but this interpretation should be made with caution. It is more likely that controls have taken advantage of being exposed to the test before where the patients have not since it has been found that patients with schizophrenia improve less with practice than normal individuals (Blyler and Gold, 2002). The patients did not perform significantly worse on any RAVLT score indicating stability over time in verbal memory, which is consistent with earlier research (Hoff et al., 2005).

For the same scores of RAVLT 1, 2 and Total there was a significant correlation with age for the control group but not the patients. Studies consistently demonstrate an effect of age on recall in RAVLT in healthy controls (Mitrushina et al., 2005) and so the findings for that group are not surprising. The correlation is not found for the patient group possibly implying that the illness effect may dominate over the normal effect of ageing.

For the controls a significant correlation of education at follow-up and RAVLT 3 was found. The effect of education on RAVLT in the literature is unclear, with contradicting findings (see Mitrushina et al., 2005 for overview). Since this correlation was the only one found for education at both baseline and follow-up and any RAVLT scores at both

times for controls there is a great possibility that this is a random finding of little importance. For the patients however a significant correlation between education at baseline and RAVLT 1, 4, 5 and Total was found. In addition a significant correlation was found between education at follow-up and RAVLT 1, 3, 4, 5, Total and list B. These results might imply that education is of more importance for the maintaining of neuropsychological functions in patients with schizophrenia than in the healthy population.

CPT, patients significantly improved their performance on CPT at follow-up whereas the controls did not. This is in contrast to Censits et al. (1997) who found no significant improvement or decline over time in patients or controls on CPT. However, Liu et al. (2007) conducted a longitudinal study of attention in patients with schizophrenia measured with CPT over 4-7 years. They divided patients into three groups based on their performance at baseline (no impairment, moderate impairment and severe impairment) and analysed their separate trajectories. The group with no impairment was stable over time as were most of the severely impaired but a subgroup of these along with those moderately impaired fluctuated markedly, mainly towards the better (Liu et al., 2005). This concludes that most patients are stable over time and if there is a change it tends to be positive rather than negative which renders our findings reasonable.

Chen et al. (1998) have shown that there is a practise effect on CPT when the test is administrated with one week apart. This is of little implication for the results of this study, since the time elapsed between test occasions in the current study is greater. If practise effects were responsible for the improvement in CPT seen in our patients one would expect a similar and/or even greater effect for the healthy controls which was not found. This indicates that patients actually improved their performance on CPT over time whereas healthy controls did not.

Older age has been associated with worse performance on CPT (Chen et al., 1998; Birkett et al., 2007). Our results replicate this in the healthy controls but not among patients, suggesting that the effect of schizophrenia strikes out the normal effect of ageing on functions measured by CPT. Likewise education has been linked to performance on CPT with longer education yielding better results (Chen et al., 1998). This was true for the patient group but not for the control group which did not show any correlation between education and CPT performance. This is an interesting finding that is in line with the earlier results from RAVLT in this study, possibly enhancing the effect of education on test performance for patients.

TMT, both controls and patients showed significant decline on TMT B over time. There is little evidence for any practise effect of TMT over longer time-periods than 3 months but there is considerable evidence for the effect of ageing where increased age is related to poorer test scores. The association between age and TMT scores is present in both the normal population and patients but appears to be of smaller magnitude in brain-damaged samples (Mitrushina et al., 2005). In our data the significant decline in scores is larger in controls than in patients which support the above mentioned notion.

Since the relationship between ageing and TMT scores is so prevalent and because both groups showed decline without any interaction effect, there is no evidence of abnormal decline in the patient group compared to healthy controls in our sample.

However, when the results of TMT-B were correlated with age, controls but not patients showed a significant relationship. And only at the time of the follow-up measurement. Hence, our findings contrast the widely accepted effect of age on TMT B but this might be due to our relatively small sample rather than a decline of scores due to other factors than age.

Furthermore a significant correlation between illness duration at baseline and TMT B for the patients was found. Since this finding was not replicated at follow-up it might be a random finding. It is however possible that TMT B performance declines to a certain degree depending on illness duration but that the effect comes to a plateau with time, so that patients with shorter illness duration become worse within a few years but the ones with longer durations of illness have come to a normal ageing process where the illness ceases to speed up the performance decline. This might be a question for further research to answer.

Earlier research has found a relationship between TMT and education, where higher education is linked to better test performance in normal individuals (Mitrushina et al., 2005). The present study failed to find and replicate this result. However, this relationship was found in the patient group where patients with more extended education outperformed those with fewer years of education. As in the correlations of education and RAVLT this might propose that education is of more importance for the patient group than the control group, perhaps as a mitigating or protective factor for cognitive decline.

LNS, there was no significant decline in the scores of LNS for either group, indicating that no improvement or decline in working memory occurred within either group.

Performance on LNS is highly dependent on both age and education (Mitrushina et al., 2005) so a relationship should be expected. For the patients a significant correlation was found for education but not age, and for the controls no correlations were found with either variable. This is interesting because our sample is relatively well distributed over both age and education in both groups. It might be that our sample of controls is too small, but it might also strengthen our previously described hypothesis of education being more important for patients compared to controls.

WCST, neither group showed any significant differences in results at baseline or follow-up on any of the WCST scores. This is in line with earlier research (Censits et al., 1997; Gold et al., 1999) however it should be stated that few longitudinal studies have examined schizophrenic patients' performance on WCST.

WCST performance seems to vary by schizophrenia subtype and/or symptoms (Mitrushina et al., 2005) which may have corrupted our findings. Since we have not

compared different subtypes or symptoms within our patient group it is possible that significant decline has occurred for subtypes in the group.

There is a well documented affect of age on the WCST but it seems to become relevant only after approximately 60 years of age or even later (Mitrushina et al., 2005). In our study we found that controls age and WCST correlated significantly at baseline for preservative errors and preservative responses but this correlation was lost at follow-up indicating that it might be a random finding or possibly that our sample was too small. In our patient group however, age correlated with all four scores of WCST at follow-up and three at baseline, indicating that older patients performed worse than younger at both times. Since the mean age did not differ significantly between the groups this is an interesting finding, perhaps implying that the ageing process might speed up cognitive decline for the patients where it does not for controls.

There is a similar effect of education on WCST in the normal population where its effect is most evident after 15 years of formal education (Mitrushina et al., 2005). Since both our groups had mean education levels under 15 years it would not be predicted to have a strong effect. What we found is that once again, the patient group showed significant correlations on WCST and education where the controls generally did not. This has been found in some other studies regarding education and WCST (Mitrushina et al., 2005) but is not a well documented occurrence.

A correlation between illness duration and the four scores from WCST at follow-up for patients was also found while controlling for age, indicating that patients perform worse with elapsed illness. There is no clear evidence regarding the effects of illness duration on WCST, with some findings reporting relationships and some not (Vega et al., 2005; Mitrushina et al., 2005). Our findings are therefore neither unique nor well documented.

### *Limitations of the study*

The results should be considered with certain aspects in mind. These are aspects that might have influenced the results of this study. The sample of patients was for example not controlled for the type of medication used so we expect there to be a variety in the medication represented in the patient-sample. However previous findings have shown that regular neuroleptics do not in general affect the performance on neuropsychological measures (Harvey & Sharma, 2002).

Regarding the reliability of the collection of neuropsychological measurements used, the tests have been generally used for the purpose of examining cognitive functioning in schizophrenia because of patient's sensitivity to these measures. For this reason we consider the chosen tests to be adequate measures of neuropsychological functions.

Factors that could have affected the outcome of individual performances might be that several test administrators have been involved in collecting data, as well as the fact that

different locations have been used for the purpose of collecting the neuropsychological data.

The patients had to be stable in their diagnosis in order to participate in our study. This means that they represent a group of patients that have chronic schizophrenia which are stable on their medication, in their social setting and/or other life circumstances. This may have skewed our results since severely ill and high-functioning patients may not have participated and subgroups might be differently represented. Therefore our sample group might have moderate difficulties and so our results are possibly limited to this group.

In the sample of this study there was also a significantly skewed sex distribution with more males than females. Among the patients this is fairly representative since schizophrenia is more prevalent in men (Aleman et al., 2003) and even so, there have been studies conducted that show no robust sex differences in neuropsychological performance in schizophrenic patients (Hoff et al., 1998). However since our controls were not matched for sex, the relatively large proportion of females in that sample might have implications for our results since research has shown a small but relatively constant advantage for females on verbal learning tests (Mitrushina et al., 2005; Reite et al., 1993) and more specifically on RAVLT (Messinis et al., 2007).

The fact that we found so few correlations between controls age and their performance on tests might indicate that our sample was too small. If this finding was to be replicated however, in a larger sample it could warrant further research.

Another possible source of skewing in our results is that we could not control for what reasons some patients decided not to participate during this second testing. It may be that a considerable amount of them had undergone other cognitive changes that would have influenced our findings in a different direction.

The tests that constitute CPI are chosen in the purpose of enlightening specific critical areas of function where patients with schizophrenia often have difficulties. Our purpose with this study was to examine these functions evolvment over time. However, it is important to bear in mind that a subject showing great performance on the different sub tests of the battery might still show limitations in functions not covered by CPI. Examples of such areas of functions are non-verbal learning and memory, several aspects of visuo-spatial construction function and verbal flow. Dysfunction in these areas might be of just as great importance for a person's ability to take care of him or herself, socialize with others and work as the functions covered by CPI test battery.

Another limitation in this study was that specific subtypes of schizophrenia were not at hand and so they have not been matched to the results of patients. Such analysis might have yielded more in depth information in the matter of specific patterns connected to different subgroups. Previous research has shown that the specific symptoms correlated to cognition in schizophrenia are mostly negative symptoms, foremost displayed in one subtype of schizophrenia that is largely characterized by negative symptoms (Harvey &

Sharma 2002). Data concerning the display of negative symptoms in the patient group has not been available to the authors of this study.

### *Summary and conclusions*

Our findings point to a relationship between education and test performance among patients but not among controls. One must bear in mind that the relationship is not determined in any one direction, so it might be that patients with better cognitive functioning from the beginning were able to acquire longer education and therefore also perform better on CPI, not necessarily that education per se is a protective factor, although there is some research pointing to this conclusion (Vega et al., 2005). The correlation becomes more interesting when one sees that the usual correlation between performance on tests and education in the healthy population is not found in our sample to the expected degree. In part this might be due to a relatively small sample, however many reports have fewer participants than ours and so we consider this area to be of interest to further investigation. It might imply that education plays a more important roll for maintaining cognitive function in patients than in controls.

Generally people perform worse on cognitive tests with older age and this is consistent with our results for the controls but the same was not found for our patients, a finding that to some extent has been previously found (Vega et al., 2005). Our findings give further support to the notion that schizophrenia as an illness might strike out the normal age related performance seen in controls.

Research has shown a relationship between morphology and performance on neuropsychological tests (Lawyer et al., 2006). The results of the current study are intended to be further investigated in regard to a follow-up study of morphological features. The same sample being investigated in this report underwent a second MRI scan and the results are to be analyzed further.

Overall, our findings confirm previous studies of longitudinal change in neuropsychological functioning in patients with schizophrenia (Censits et al., 1997; DeLisi et al., 2005). The patients show a cognitive profile that is well below that of the controls across a range of tests at baseline and at follow-up but no significant decline has occurred compared to healthy controls. The patients have significantly improved their score on CPT and the controls have significantly improved their scores on RAVLT trials 1, 2 and Total. Both groups have decreased their scores on TMT B. We also found significant correlations between neuropsychological measures and education for patients but not controls. This is rather rare, further research regarding this topic might be of interest. Furthermore, the effect of age was more prominent for the controls than patients except for the scores of WCST where the opposite relationship was found. The findings are in line with earlier research and concludes that neuropsychological functioning in schizophrenia is relatively stable over a time period of 4,5 years.

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