Neurocognition
In Schizophrenia Spectrum Disorders

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“My mental illness is like a skunk,
People know very little about me
But neither do they care to know,
Interlinking lives can be enriching
And much can be learned from one another,
Fear from what has become as common knowledge
Prevents them from any involvement whatsoever
And even causes others to go out of their way
For the single purpose of avoiding me.”

Like a skunk by Barbara

http://www.squidoo.com/voices_of_schizophrenia

In memory of Margareta Wennerberg –

Mentor, colleague and friend.

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Studies

The dissertation is based on the following four original studies, which will be referred to in the text by their Roman numerals:

I Karilampi U, Helldin L, Hjärthag F, Norlander T, Archer T (2007) Verbal learning in schizopsychotic outpatients and healthy volunteers as a function of cognitive performance levels. *Archives of Clinical Neuropsychology, 22:*161-174.

II Karilampi U, Helldin L, Archer T (2011) Cognition and global assessment of functioning in male and female outpatients with schizophrenia spectrum disorders. *Journal of Nervous and Mental Disease, 199*:445-448.

III Karilampi U, Helldin L, Hjärthag F, Archer T (Submitted) Vigilance profiles and remission in schizophrenia.

IV Karilampi U, Odin A, Wentz K, Archer T (Submitted) The ecological validity of neurocognitive improvement in outpatients with schizophrenia spectrum disorders: a qualitative study.

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Abstract

The general purpose of this dissertation was to explore and describe the global and specific aspects of neurocognition and cognitive functioning in a cross-sectional, clinically representative group of outpatients with schizophrenia spectrum disorders, using healthy volunteers as a control group, whenever feasible.

Study I analyzed and compared neurocognitive test profiles related to different levels of verbal learning performance among patients with schizophrenia spectrum disorders and healthy volunteers in order to identify the major predictors of category assignment. Approximately four out of ten patients had normal levels of verbal learning performance. Despite equivalent levels of verbal learning in comparison with healthy volunteers, the patients performed worse on all subtests with the exception of working memory. All patients also presented equally poor visuomotor processing speed despite their level of verbal learning performance, indicating global neurocognitive retardation in speed-related processing.

Study II assessed the relationship between the global assessment of functioning (GAF) subscales and neurocognitive test performance in a cohort of outpatients with schizophrenia spectrum disorders, based on gender. The GAF associations with composite cognition varied as a function of sex, suggesting a complex relationship between these variables. Furthermore, the results indicated that executive functioning may have a greater impact on the symptom and function profiles of male patients than on those of female patients.

Study III analysed and compared vigilance-related performance profiles of male and female patients with schizophrenia spectrum disorders, in and out of remission, against healthy volunteers. There was a sex-related difference in signal detection scores in the healthy volunteer group but not in the patient group. Also, perceptual sensitivity was shown to be significantly affected for patients of both sexes, but the ratio was almost two times larger for male patients, suggesting a larger neurocognitive decline in the male patient population.

Study IV elicited how people with schizophrenia spectrum diagnoses evaluate their own cognitive ability, with main focus on psychometrically validated cognitive improvement. The patients found it hard to evaluate their cognitive improvement as the demands in their daily life were low. Also, they tended to ascribe concentration problems to feelings of anxiety and restlessness, or claimed them to be a side-effect of antipsychotic medication. The patients still felt it meaningful to receive feedback on their improved test results as the information made them feel more proud and empowered.

Sammanfattning

Avhandlingens syfte var att undersöka och beskriva globala och specifika aspekter av neurokognition i ett tvärsnittsstudie av kliniskt representativa öppenvårdspatienter med schizofrenispektrum störningar. Friska frivilliga har använts som kontrollgrupp i vissa delstudier.

Delstudie I analyserade och jämförde neurokognitiva testprofiler hos psykospatienter och friska frivilliga utifrån tre nivåer av verbal inlärning. Syftet var att hitta andra kognitiva faktorer som bäst kunde förutsäga grupptillhörighet. Ungefär fyra utav tio patienter fanns ha normal verbal inlärningsförmåga. Trots detta presterade patienterna sämre än friska frivilliga på samtliga test utom det för arbetsminne. Samtliga patienter, oavsett nivån av verbal inlärning, hade likvärdiga svårigheter i test för visuomotorisk snabbhet. Resultaten indikerar på en global neurokognitiv nedsättning i tidsrelaterade mentala processer.

Delarbete II studerade sambandet mellan global funktionsskattning och neurokognition hos manliga och kvinnliga patienter med schizofreni-spektrum störningar. De olika aspekterna av global funktionsskattning hade olika samband med kön, vilket tyder på ett komplext samband mellan dessa variabler. Resultaten gav också indikation på att exekutiv funktion kan ha en större betydelse för mäns symptom- och funktionsprofiler än för kvinnors.

Delarbete III analyserade och jämförde vigilans-relaterade prestationsprofiler hos friska frivilliga samt psykospatienter efter kön och remission. I friska frivilliggruppen fanns en könsrelaterad skillnad i signaldiskriminering, medan samma skillnad saknades i patientgruppen. Perceptuell känslighet var signifikant påverkad för båda könen, men skillnaden var betydligt större för män än kvinnor, indikerande på större neurokognitiv nedsättning hos män med schizofrenispektrum störningar.

Delarbete IV studerade hur personer med psykossjukdomar skattar sin egen kognitiva förmåga mot bakgrund av validerad förbättring av kognitiva testresultat. Patienterna fann det svårt att värdera sin kognitiva förbättring då de upplevde vardagens krav som låga. De hade lättare att berätta om kognitiva svårigheter, och menade att koncentrationsproblem berodde på ångest och rastlöshet eller medicinbiverkningar. Patienterna ansåg det dock värdefullt att få återkoppling om de förbättrade testresultaten som fick dem känna sig stolta och mer kapabla.

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Chapter 1: Introduction

Schizophrenia

Schizophrenia is a heterogeneous, multifactorial, complex biological and behavioral disorder, which manifests itself in cognitive dysfunction and other clinical symptoms. The disorder will not emerge without a congenital predisposition, but there are no guarantees as to who will develop the disease. Risk factors increase the chance of developing schizophrenia and protective factors decrease the chance (Green 2001, p.28). Risk factors can include adverse events early in life, for example maternal separation and social isolation, that via central stress dysregulation (Goel and Bale, 2009) profoundly affect brain development and adult behavior, thus contributing to the occurrence of psychiatric disorders in genetically predisposed individuals (Niwa et al, 2011).

Neurodegenerative or neurodevelopmental disorder?

Determining the characteristics of schizophrenia is of singular importance for understanding the pathophysiology of the disorder and its treatments. The clinical heterogeneity of schizophrenia has given way to considerations that the symptoms may constitute groups of diseases of generally common phenotypic [for definition, see page 2] expression but of different underlying etiopathology (Buckley et al, 2009). There has been much debate about whether or not schizophrenia is predominantly a neurodegenerative disorder or a neurodevelopmental disorder or incorporates elements of both (Andreasen, 2010; Archer, 2010). *Neurodegenerative* theories (Hulshoff Pol and Kahn, 2008) of schizophrenia posit that there are progressive structural changes in the brain after the debut of the illness, whereas *neurodevelopmental* theories (Fatemi and Folsom, 2009; Owen et al, 2011) posit that a brain insult takes place during the course of early normal development, disrupts developmental processes, and results in the various manifestations of the

illness. There seems to be a current tendency towards unifying models. Ho et al (2003) proposed that schizophrenia be called a *"progressive neurodevelopmental disorder"*. According to this model, schizophrenia occurs as a consequence of multiple aberrations in the process of brain development, with some occurring during fetal life or early childhood, whereas others occur during adolescence and young adulthood. The late neurodevelopmental mechanisms may continue to exert their damaging effects after onset and during the early years of the illness. However, the authors admit that the developmental neurobiological processes that explain these serial changes remain a puzzle. Gupta and Kulhara (2010) summarized that these theories are complementary rather than exclusive, because they can individually explain certain phenomena observed in the onset and course of schizophrenia, and put together, they can explain the onset as well as the course and outcome. According to Andreasen (2010), combining a recognition that abnormalities are present at onset (further evidence for neurodevelopment) with a recognition that changes also occur or continue after onset (neurodegeneration or *neuroprogression*) ceases to present problems.

Endophenotypes

Another recent line of focus is the concept of endophenotypes. *Genotypes* are at the level of DNA base pairs and can be measured with techniques of molecular biology, whereas a *phenotype* represents observable characteristics of an organism, which are the joint product of both genotypic and environmental influences. *Endophenotypes* are described as internal phenotypes and may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological in nature (Gottesman and Gould, 2003). They are seen as closer to genetic variation than are clinical symptoms of schizophrenia, and are thereby closely linked to heritable risk factors (Braff et al, 2007). Thus, endophenotypes are expected to be associated with the clinical disorder but not part of its diagnosis; heritable; present before the onset of active illness or during remission; co-segregating with illness in families; and found in unaffected family members at a higher rate than in the general population (Jablensky, 2010). Endophenotypes are quantitative measures that reflect genetically influenced stable changes in brain function (Courtet et al, 2011). For example, suicide could be categorized as a *phenotype*, gene coding for the serotonin receptor as a *genotype*, and the tendency to impulsive-aggressive behavior as an *endophenotype* (Mann et al, 2009).

Neurocognitive findings in schizophrenia may qualify as endophenotypes. For example, working memory has been found to be compromised in patients with schizophrenia (Horan et al, 2008), and researchers have identified gene and

chromosomal regions possibly involved in working memory (Paunio et al, 2004). Combining cognitive tasks such as working memory with imaging techniques, thereby localizing the deficit to a particular neural circuit, refines the endophenotypical level of analysis more than measuring working memory performance alone as measured by neuropsychological testing (Gottesman and Gould, 2003; Thaker, 2007). On the other hand, it has to be proven that the studied dysfunction is differential for a particular subtype of psychosis, i.e., schizophrenia, only. Some studies suggest that neurocognitive dysfunction can be a vulnerability factor to psychotic disorders in general, rather than specific of schizophrenia (Mulet et al, 2007). Others claim that while cognitive deficits are present in all psychotic disorders, they are most severe and pervasive in schizophrenia and least pervasive in bipolar disorder and mania (Zanelli et al, 2010).

Cognition in schizophrenia

In the 1990's, the phenomenology of schizophrenia expanded beyond symptoms altogether, to include a strong emphasis on neurocognitive aspects of schizophrenia (Green and Nuechterlein, 1999). Cognitive deficits are since then accepted as a core feature of schizophrenia, rather than an epiphenomenon of the illness state (Jablensky, 2010). It has been proposed that the well-known diversity of schizophrenia in terms of functional outcome and recovery from the illness is best characterized by cognitive deficits, not by the classical symptoms (Reichenberg, 2010).

Patients with schizophrenia perform as a group 1½ to 2 standard deviations below healthy controls on various neurocognitive tests (Keefe, 2008). Seven separable cognitive factors have been replicable across studies and represent fundamental dimensions of cognitive deficit in schizophrenia: speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and verbal comprehension (Nuechterlein et al, 2004). There is compelling evidence that cognitive deficits are significantly correlated with impairments in activities of daily life (Jablensky, 2010), but still, as Keefe (2008) points out, psychiatrists rarely consider cognitive function in their evaluation of patients with schizophrenia. One of the reasons behind this is that cognitive functioning is best assessed by neuropsychological testing, which requires a trained psychologist. Several studies (Good et al, 2004; Hofer et al, 2007; Keefe, 2008) have suggested that clinical rating of cognitive symptoms, using for example the PANSS (*Positive and Negative Syndrome Scale:*

Kay et al, 1989), is not suitable to replace neuropsychological testing in schizophrenic patients, irrespective of the stage of the illness.

There may be some episode-related cognitive deterioration. Controlling for premorbid IQ, Eberhard et al (2003) showed that on average, schizophrenic patients had lost one standard deviation in most cognitive tests, except for vocabulary, after their first psychotic episode. This drop remained static but for two neuropsychological indices: simple reaction time and verbal short term memory, that deteriorated by new episodes. In contrast, an Israeli study (Caspi et al, 2003) found no changes between a first assessment while in good mental health (draft board aptitude assessment) and a second assessment following the manifestation of the first psychotic episode. However, the patients performed worse than the healthy comparisons on both assessments. According to the authors, the results indicate that most of the cognitive impairment exhibited by first-episode schizophrenic patients precedes the first psychotic episode. A meta-analysis of 53 longitudinal studies of cognition in schizophrenia (Szöke et al, 2008) even indicated that for some cognitive domains, improvement is possible after the onset of the disorder. Rund (2009) summed it up in pointing out that there is an established decline in neurocognitive functioning prior to and in connection with the onset of illness, but there is currently no convincing evidence that there is a cognitive decline *after* onset of illness.

Global versus specific deficits

One of the controversies that developed in the early years of research on cognition in schizophrenia was, and still remains, whether or not all schizopsychotic patients perform equally poor on every cognitive test that they attempt, producing a global intellectual deficit, or have greater deficits in one or more critical aspects of functioning. A related question is whether *all* patients with schizophrenia have a specific deficit, similar to all patients with Alzheimer's disease expressing a memory deficit (Harvey and Sharma, 2002, p.5). This debate can be tied to the debate about neurodegeneration versus neurodevelopmental. Deficits that are stable could reflect a possibly neurodevelopmental condition, while others could be state dependent, fluctuating with psychopathology (Brewer et al, 2006). Green (1998, p.53) concluded that patients with schizophrenia have deficits in multiple domains, but a single generalized deficit fails to account for the range and pattern of findings.

Alternatively, there can be multiple subtypes of patients with schizophrenia, each with their own characteristic pattern of neurocognitive deficits (Green, 1998, p.51). Attempts to find subtypes have been based on symptom profiles (Seltzer et al, 1997), degree of memory impairment (Abi-Saab et al, 2005; McDermid Vaz and Heinrichs, 2002), skills on problem-solving tests (Horan and Goldstein 2003), and general intelligence (Potter and Nestor, 2010), just to name a few.

Gender aspects

The existence of gender specificity in different aspects of schizophrenia has been disputed and the conclusions have been conflicting, if not confusing. The inconsistency may be due in part to methodological and/or cultural artifacts. Plausible results may be affected, for example, by the duration and phase of the illness. A Danish study (Køster et al, 2008) of 269 persons with first episode psychosis, with a follow-up two years later, showed women to have a longer duration of illness before treatment and more affective symptoms, while men had more negative symptoms and were more socially isolated. A review (Large and Nielssen, 2008) of studies of the duration of psychosis in schizophrenia spectrum disorders from high-income countries showed men to have a longer duration of psychosis than women. In contrast, most studies from lower-income countries showed the opposite trend, with women having a longer mean duration of psychosis than men.

The best replicated sex-related difference in schizophrenia is the tendency for male patients with schizophrenia to manifest the disease around five years earlier than female patients with schizophrenia. This observation may be due to the sex-related differences found in the structural abnormalities that occur in schizophrenia, with greater abnormalities found in male brains (Arango et al, 2008). These differences may exist already at a genetic level. A study by Schumacher et al (2009) showed sex-specific effect in genetic linkage in a large European population of schizopsychotic patients, with different markers for men and women.

Few studies have addressed gender differences in premorbid cognitive performance. An Israeli historical-prospective study (Weiser et al, 2000) showed that in apparently healthy adolescents who will develop schizophrenia in the future, premorbid cognitive performance was poorer in women, as compared to men. The follow-up period was up to age 26, by which age more men than women will have manifest schizophrenia. The authors concluded that it is possible that the early onset women identified in their study have a particularly severe form of illness. Mortiarty et al (2001) studied a group of poor outcome patients with lifelong

schizophrenia and found no gender differences in cognitive functioning. Their findings suggest that the association of cognitive deficits with gender may be found only in patients with better functional outcome. This finding could imply that differences in gender may reflect a different etiology for the illness and for associated cognitive impairments as well. Nevertheless, there remains one critical aspect to gender differences that must be borne in mind throughout: that any eventual between-gender differences are generally overshadowed hugely by the enormity of the within-gender differences. For example, epidemiological evidence from the Australian National Study of Low Prevalence (Psychotic) Disorders showed differences between women across the diagnostic groups to be more pronounced than differences between women and men within a diagnostic group (Morgan et al, 2008).

Aims of the dissertation

The general aim of this dissertation was to explore and describe the global and specific aspects of neurocognition and cognitive functioning in a cross-sectional, clinically representative group of outpatients with schizophrenia spectrum disorders, using healthy volunteers as a control group, whenever feasible.

Study I analyzed and compared neurocognitive test profiles related to different levels of verbal learning performance among patients with schizophrenia spectrum disorders and healthy volunteers, in order to identify the major predictors of category assignment.

Study II assessed the relationship between the global assessment of functioning subscales and neurocognitive test performance in a cohort of outpatients with schizophrenia spectrum disorders, based on gender.

Study III analyzed and compared vigilance-related performance profiles of male and female patients with schizophrenia spectrum disorders, in and out of remission, against healthy volunteers.

Study IV elicited how people with schizophrenia spectrum diagnoses evaluate their own cognitive ability, with main focus on psychometrically validated cognitive improvement.

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Chapter 2: Summary

All data collected and analyzed in this dissertation comes from a wider research project called the *Clinical Long-Term Investigation of Psychosis in Sweden* (CLIPS). It is an ongoing, long-term naturalistic follow-up study of persons with schizophrenia spectrum disorders. The CLIPS study was initiated by the Department of Psychiatry, NU Health Care in Trollhättan, Sweden. During the baseline years 2000 to 2004, a research team of one psychologist and three nurses collected data from all eleven outpatient centres in the catchment area (with a population of approximately 272 000). From the year 2005 and on, data in CLIPS is annually collected from all outpatient centres by the local staff of nurses, occupational therapists and psychologists.

Patient population

The outpatient settings in the NU Health Care catchment area have a population of about 670 patients with the diagnoses schizophrenia, schizoaffective disorder or delusional disorder according to DSM-IV and ICD-10. Out of the total number, 516 patients were considered to be in a stable phase of the disorder as assessed from the patients' medical records and observations of the psychiatric personnel, personnel from the community psychiatry and relatives. These patients were not presenting co-morbidity of other symptoms, such as dementia, that could influence the result. In total, 284 patients volunteered for the investigation and were presented with an extensive clinical test and interview battery, including study of their medical records. After 20 patients had been excluded due to having other diagnoses than those allowed, 264 patients remained. Of these, 233 had completed at least one of the neurocognitive tests administered. Missing value analysis resulted in a final group of 196 patients with complete results from all neurocognitive testing. One of these patients had completed only the neurocognitive testing with no other evaluations made.

Healthy volunteer population

The healthy volunteers originated from a standardization study conducted by undergraduate students at Karlstad University, Sweden, during the spring semesters of 2004 and 2005. Recruitment of healthy volunteers was carried out through direct contact with employees of various organizations, university students, pensioners, and through advertisements in the local newspapers. A heterogeneous population with regard to sex, age and education was sought after. All subjects were informed that their participation was anonymous and on a volunteer basis and that all the material collected would be treated with complete confidentiality. Each participant was tested singly over an interval of about one hour. All experimental testing was performed by altogether eight undergraduate psychology students, all of whom had completed a basic course in application of the neuropsychological test battery. A standardized procedure was observed carefully by each of the experimenters. Ten persons were excluded from the original group of 302 subjects: six persons who reported suffering from mental illness, and four persons who had a close relative with psychosis. After missing value analysis, 26 persons were removed from the group, reducing the healthy volunteer group to 266 persons.

Instruments

Neuropsychological tests

The patients were tested with a semi-computerized neuropsychological test battery, the *Cognitive Performance Indicator*, CPI. CPI was constructed in the late 1990's by Michael Green, Phil Harvey and Håkan Nyman for Janssen AB in Sweden for use in clinical trials and gives an overview of important cognitive functions in patients with schizophrenia. It consists of seven classical neuropsychological tests, six that measure aspects of cognition known to be reduced in the course of schizophrenia, plus one that estimates the subjects' premorbid level of functioning. The tests were administrated in a standardized order (as presented below). The patients received immediate, individualized feedback on their test results. The results were immediately entered into in a database.

Verbal learning and memory

The *Rey Auditory Verbal Learning Test* (RAVLT) is a commonly used clinical measure of verbal learning and memory (Rey, 1964; Schmidt, 1996) that measures immediate memory span, provides a learning curve, reveals the presence or absence of learning strategies, elicits retroactive and proactive interference tendencies and tendencies to confusion or confabulation on memory tasks, measures both short-term and longer-term retention following interpolated activity, and allows for a comparison between retrieval efficiency and learning (Lezak, 1995, p. 438). RAVLT consists of a 15-item word list that is presented five times, always in the same order, with an assessment of recall immediately after each presentation. Thereafter an interference list is presented, followed by a request to recall the original list without further presentation of the original list words. Finally, a delayed recall test is presented after 20 minutes. The RAVLT total score (the number of words correctly recalled, summed across the five immediate recall trials) was used as a measure of verbal learning.

Attention/Vigilance

The *Continuous Performance Test – Identical Pairs* version (CPT-IP) is a computerized vigilance test (Cornblatt et al, 1988; Rosvold et al, 1956), presented in monochrome mode on a laptop computer. 450 stimuli (four-digit numbers) were presented in three sequences or 'blocks', with 150 stimuli in each. Stimuli were flashed on the computer screen at a constant rate of one per second, with a stimulus 'on' time of 50 milliseconds. The target stimulus was the second of a pair of consequential identical numbers. Subjects were instructed to keep the left mouse button pressed down until the target stimulus appeared whereby they were to release the mouse button and quickly press it down again. All trials were continuously administered at a constant pace, with no formal breaks between the blocks. The total *d'* score (a measure of perceptual sensitivity or attentional capacity, i.e. the participants ability to discriminate targets from non-targets) for the 450 trial condition was used as a measure of vigilance.

Speed of processing

The *Trail Making Test*, originally part of the *Army Individual Test Battery*, is one of the most widely used and most sensitive brief examinations for brain impairment (Reitan, 1958). In *Part A* (TMT-A), subjects are required to join consecutive numbers with paper and pen under the pressure of doing the task as rapidly as possible. The test was scored as introduced by Reitan (Lezak, 1995, p. 381). The time to completion (in seconds) for the *Part A* condition was used as a measure of visuomotor processing speed/efficacy. Note that the scales are inverted, as lower scores stand for better performance.

Cognitive flexibility

In *Trail Making Test Part B* (TMT-B), subjects are required to alternate between two sets, connecting numbers and letters with paper and pen under the pressure of doing the task as rapidly as possible. The test was scored as introduced by Reitan (Lezak, 1995, p. 381). The time to completion (in seconds) for the *Part B* condition was used as a measure of cognitive flexibility. Note that the scales are inverted, as lower scores stand for better performance.

Working memory

The *Letter-Number Sequencing* (LNS), now a supplementary subtest in the *Wechsler Adult Intelligence Scale-Third Edition* (WAIS-III) (Wechsler, 1997), is often used for assessment of auditory working memory performance (Gold et al, 1997). It requires the subjects to sort out letters from numbers within a row of alternating letters and numbers that are read to them, and to separately recall the letters and numbers in successive order. The subjects can either pass or fail on each trial. The number of trials on which the subjects were successful in producing the information correctly was used as a measure of working memory.

Verbal facility

The *Vocabulary* subtest from the *Wechsler Adult Intelligence Scale-Revised* (WAIS-R) has been identified as the single best measure of both verbal and general mental abilities (Wechsler, 1981). The subject is asked the meaning of words,

arranged in order of difficulty, and their explanation is given 0, 1 or 2 points. The sum score was used as a measure of verbal facility.

Executive function

The *Wisconsin Card Sorting Test* (WCST) has increasingly been employed as a clinical neuropsychological instrument and can be considered a measure of executive function (Heaton et al, 1993). The WCST consists of four stimulus cards and 128 response cards that depict figures, colors, and numbers. The subject is instructed to match each consecutive card from the deck with one of the stimulus cards by pressing a computer key. A message on the computer screen tells the subject whether each response is right or wrong. Once the subject has made a specified number of consecutive correct matches to the initial sorting principle, the sorting principle is changed without warning. The WCST proceeds in this manner through a number of shifts in sorting principle among the three possible sorting categories. The computer program calculates the test scores. The total number of completed categories was used as a measure of executive functioning.

Clinical rating scales

Global functioning

The *Global Assessment of Functioning* (GAF) is used to evaluate overall severity of psychiatric disturbance. It combines evaluation of symptoms as well as relational, social, and occupational functioning on a single axis. The rating does not include impairment in functioning due to physical or environmental limitations (APA, 1987). The scale runs from 1 to 100 and is divided into 10 equal parts providing defining characteristics, both symptoms and social functioning, for each 10-point-interval. A low rating reflects worse symptoms and a poorer level of functioning, whereas a high rating reflects less symptoms and a better level of functioning. As the two GAF assessments measure different aspects of a patient's condition, at times they provide a large difference in the scores in either direction. This situation caused the Norwegian administration to split the GAF scale into one symptom and one function score in 1998 (Pedersen et al, 2007), thereby introducing the split version of the GAF (the Split-GAF). The Split-GAF instrument is common in psychiatric clinical practice in Sweden and is applied in this dissertation.

Remission

Remission was defined through the application of an adapted Swedish translation of *The Positive and Negative Syndrome Scale* (PANSS) (Kay et al, 1987; Lindström et al, 1994), a structured clinical interview for schizophrenia, whereby eight chosen items, representing core symptoms diagnostically characteristic for the condition (delusions, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerism/posturing, blunted affect, passive/apathetic social withdrawal, lack of spontaneity and flow of conversation), should be reduced to such an extent (a value not exceeding 3 points out of maximum 7 points) as to be solely regarded as mild without affecting the individual's level of functioning (Andreasen et al, 2005; Helldin et al, 2007). The criteria of the condition having remained stable for at least six months could not be applied in this thesis, as no previous systematic assessments had been made.

Ethics and consent

The CLIPS study was ethically approved in 1999 under its original study name RIS-SWE-21. The procedures followed were in accordance with the standards of the Ethical Research Committee at the University of Gothenburg, and with the latest revision of the Helsinki Declaration of 1975. When recruited, the participants received both oral and written information about the study. All participation in the study was preceded by written informed consent. In the cases a subject gave an oral consent but did not want to sign the form, the subjects case manager witnessed the oral consent and signed the form for the subject. All participation was on a free volunteer basis and could be terminated whenever the subject so wished and without having to provide any rationale, with no consequences for the subjects treatment. On completion of the investigation, each participant was awarded a raffle ticket (worth 50 Swedish crowns, about 5 Euro).

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Study I

Participants

196 outpatients (116 men, 80 women) with schizophrenia spectrum disorders between the ages of 19 and 74 years (46.31 ± 11.76) and 196 healthy volunteers (78 men, 118 women) from 20 to 80 years (47.81 ± 18.09) participated in this study. 64.8 % of the patients were diagnosed with schizophrenia, 22.4 % with schizoaffective disorder and 12.8 % with delusional disorder. All but nine patients were on antipsychotic medication, with one of the nine prescribed medication the patient did not take. Five patients were about to be released from a psychiatric ward at the time of the testing; the others were living in the community.

The healthy volunteer group was reduced from 266 persons to 196 persons in order to match the size of the patient group. Before reducing the group size, all healthy volunteers with low scores on the main parameter RAVLT were saved, as there were only 27 of these in the whole volunteer group. Thereafter, a supplementary random selection was made in order to obtain a total group size of 196 healthy volunteers.

Design

The main purpose of this study was to identify major predictors of verbal learning category assignment in patients with schizophrenia spectrum disorders relative to that of healthy volunteers. The participants were examined with the RAVLT, along with the six other neurocognitive tests in CPI. The dependent variables were the measures from the six neurocognitive instruments. Verbal learning performance level and group (patients/healthy volunteers) were used as grouping variables. The main variable emerged during an unpublished pre-study when all neurocognitive variables were entered into the multivariate analysis data program SIMCA-P (by Umetrics), and verbal learning turned out to have the highest variable importance. In order to produce the main variable ‘verbal learning performance level’, the schizopsychotic and healthy volunteer groups were combined into one single group of 392 persons. The total number of words correctly recalled, summed across RAVLT trials I through V, were used as a learning summary score. This summary score is widely used (Schmidt, 1996), has

good test-retest reliability (Geffen et al, 1994), has been shown to discriminate mixed groups of neurological patients from normal subjects (Powell et al, 1991), and memory impairment from memory intact patients (Rosenberg et al, 1984; Ryan and Geisser, 1986). The RAVLT summary scores for the combined group were converted into standardized scores by the statistics program. The combined group scores were then divided into three subgroups (high-level, medium-level, low-level) with -/+ 0.5 standard deviations as fixed markers. These markers was chosen according to Harvey and Sharma (2002, p.17), who have defined 0.5 to 1.0 standard deviations below mean as representing a mild level of cognitive deficit. The three levels of verbal learning performance were then analyzed for predictor variables.

Instruments

All participants had been tested with the CPI test battery. In this study, the RAVLT total score was solely used to form the main variable 'verbal learning performance level'.

Statistics

A comparison of background variables (sex, education and civil status) for the patient group and healthy volunteer group were conducted with Mann-Whitney U-test and t-test. In order to analyze the effect of age and education on verbal learning performance, one-way analysis of variance (ANOVA) and chi-square were used. Multivariate analysis of variance (MANOVA) was used to compare the effect of verbal learning performance level, study group and sex on the combined cognitive test variable. In order to identify the best combination of cognitive variables to predict the level of verbal learning performance, discriminant function analysis was conducted separately for each study group and each level of verbal learning performance. The Mahalanobis distance method was used in the analyses, which were then cross-validated with Press's Q test.

Results

For distribution of schizopsychotic patients and healthy volunteers in the three

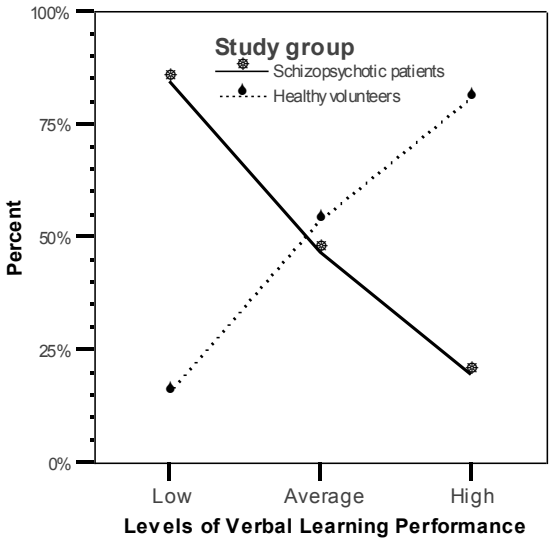

Figure 1. Distribution (in percent) of schizopsychotic patients and healthy volunteers in the three levels of verbal learning performance.

levels of verbal learning performance, see *Figure 1.*

The general results showed the healthy volunteer group to have better cognitive function than the schizopsychotic patient group in all domains except working memory. Men across the groups had better vigilance then women, whereas women across the groups had slightly better executive function than men. Comparing the different levels of verbal learning performance across the groups, the higher level had superior performance and the lower level inferior performance in all domains except visuomotor processing speed/efficacy, where no effect of verbal learning level was found.

When analyzing the predictors for group membership, the best predictor of the level of verbal learning performance in the patient group was working memory. In the healthy volunteer group, working memory was also found to be the best

predictor, paired with cognitive flexibility. Looking to predict the level of verbal learning performance across the patient and healthy volunteer groups, the higher level was predicted by cognitive flexibility, and to some degree even executive functioning. The intermediate level was also best predicted by cognitive flexibility, and secondly by vigilance. The lower level was predicted by both vigilance and executive function, and to some degree even verbal facility.

Study II

Participants

Subjects were 195 medicated outpatients with a diagnosis of schizophrenia, schizoaffective disorder or delusional disorder who had completed all aspects of the relevant parameters of the investigation. 59 % of the sample were men and 41 % were women. The average age of the male patients was 44.11 ± 10.48 years, and the average age at their first psychiatric hospital registration was 28.11 ± 9.12 years. The average age of the female patients was 49.39 ± 12.87 years, and the average age at their first psychiatric hospital registration was 32.36 ± 13.16 years. Five patients (three males and two females) were about to be released from a psychiatric ward at the time of the testing; the others were living in the community.

Design

The main purpose of this study was to assess the gender-based relationship between GAF and neurocognitive test performance in a cohort of outpatients with schizophrenia spectrum disorders. The hypothesis was that a gender effect would be found. Three main variables were used: the two GAF subscales and a composite cognition score that was created from the CPI. These three were the main dependent variables. The dependent variables were analyzed for gender effects and the relationships between the variables were investigated by gender. Finally, a separate analysis was employed to determine if the underlying neurocognitive measures in the composite cognition score had a predictive, gender-related value on the GAF subscales.

Instruments

The participants had been tested with the CPI test battery and evaluated with the GAF.

Statistics

All statistical analysis was performed on the Statistical Package for the Social Sciences (SPSS) version 15.0 for Windows. The composite cognition score was created by transforming individual test scores to *z* scores using the patient sample and then averaging across tests (Nuechterlein et al, 2008). Independent-samples t-test was used to check for gender differences in the main variables. Stepwise multiple regression analysis was used to assess the predictive value of GAF Symptom and GAF Function on composite cognition. Additional stepwise multiple regression analyses were run to check for the effects of the individual neurocognitive tests against GAF Symptom and GAF Function. All variables were entered into separate analyses for men and women.

Results

A comparison of GAF Symptom, GAF Function, and composite cognition scores between men and women showed no significant difference. Correlating these scores to each other, however, unearthed marked gender differences, see *Table 3*. For male patients, GAF Symptom subscale showed only a negative correlation for cognitive flexibility, whereas GAF Function subscale showed a positive correlation for executive function and negative correlations for cognitive flexibility and composite cognition. For female patients, GAF Symptom subscale showed negative correlations for both cognitive flexibility and composite cognition, but positive correlations for vigilance, executive function, working memory and verbal facility, whereas GAF Function subscale showed only positive correlation for working memory. Taken together, the results of the correlation analyses show notably different relationships between GAF subscales and cognition with regard to gender. Stepwise multiple regression analysis showed better composite cognition to be predicted by higher function levels in male patients and lower symptom levels in female patients. Reversed, GAF Symptom scores were best predicted by cognitive

flexibility in male patients and verbal facility in female patients. GAF Function scores were best predicted by executive function in male patients and working memory in female patients.

Table 3. Correlation indices (Pearson's r, 2-tailed) between GAF subscales and cognitive variables for male and female outpatients with schizophrenia spectrum disorders.

Variable	GAF Symptom		GAF Function	
	Male patients (N = 115)	***Female patients (N = 80)***	***Male patients (N = 115)***	***Female patients (N = 80)***
Composite cognition		0.40*	0.32*	
Vigilance		0.31*		
Cognitive flexibility	-0.24*	-0.31*	-0.26*	
Working memory		0.33*		0.31*
Verbal facility		0.36*		
Executive function		0.30*	0.32*	

* $p = 0.01$

Study III

Participants

195 patients (115 men, age 44.43 ± 10.42 years; 80 women, age 49.41 ± 12.82 years) were recruited from the CLIPS study. Applying the severity, but not the time component of the remission criteria proposed by Andreasen et al (2005), it was established that 37 % of the male patients had achieved remission, whereas 63 % male patients had not. Likewise, 53 % of the female patients had achieved remission and 47 % had not. All but nine patients (4 men, 5 women) were on antipsychotic medication, with one of the females prescribed medication she did

not take. Five patients (3 men, 2 women) were about to be released from a psychiatric ward at the time of the testing; the others were living in the community.

275 healthy volunteers (115 men, age 47.11 ± 17.63 years; 160 women, age 47.66 ± 18.30 years) from the general population took part in a standardization study conducted by undergraduate psychology students at Karlstad University, Sweden. All volunteers completed the same neuropsychological test battery as the patient group.

Design

The main purpose of this study was to analyze and compare vigilance-related performance profiles of male and female patients with schizophrenia, in and out of remission, to male and female healthy volunteers. With the earlier described eight items from the PANSS instrument as a starting point, it was established which patients had achieved remission severity criteria and which patients had failed to fulfil the criteria for remission. The *d'* for the three blocks in CPT-IP were used as dependent variables. First, the impact of sex on vigilance was studied. Secondly, sex-related profile analyses were done with age as co-variate to determine whether the patient group and the volunteer group had different performance over the three blocks in CPT-IP, and whether remission had an effect on vigilance test performance profiles.

Instruments

All participants had been tested with the CPT-IP, and the patient group was also evaluated with the PANSS for remission. As the focus was on serial performance profiles over the three CPT-IP blocks, the *d'* for the total test was not used in this study.

Statistics

Pearson's chi-square test, Mann-Whitney U-test and t-test were conducted for a comparison of demographic variables. Within-sex-related differences in signal detection scores were calculated with one-way analyses of variance (ANOVA).

Repeated measures multivariate analyses of covariance (MANCOVA), with group and sex as between-subjects factors and age as covariate, were used to analyze performance profiles (Tabachnick and Fidell, 2007) over the three blocks of CPT-IP in patients with schizophrenia spectrum disorders and healthy volunteers. The confidence intervals were Bonferroni adjusted. All statistical analysis was performed on the Statistical Package for the Social Sciences (SPSS Inc, Chicago, Illinois) software, version 15.0 for Windows. Alpha levels of 0.05 were used, but as the study was explorative, nearby levels are reported when of major interest.

Results

The men in the healthy volunteer group had better test performance than men in the patient group. The same pattern applied to the women. Men had better signal detection scores than women, but only in the healthy volunteer group. There was no difference between male and female test scores in the patient group.

A specific vigilance test performance profile was found in the healthy volunteer group, with performance improving after the first block. No difference in performance across the three test blocks was found in the patient group, see *Figure 1*.

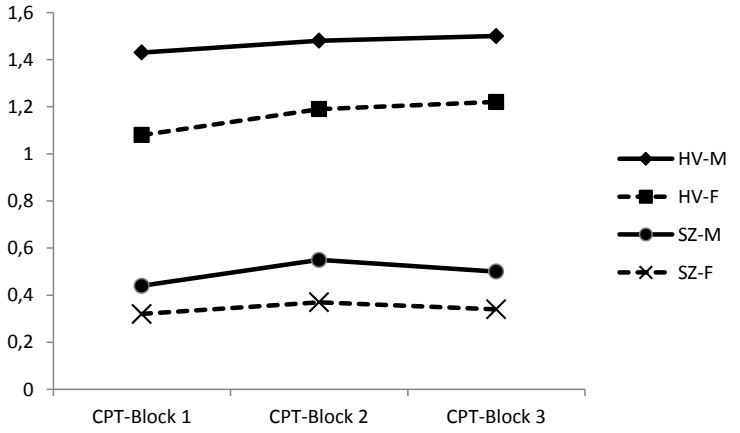

Figure 1. Performance profiles for *d'* over the three blocks of CPT-IP for healthy male (HV-M) and female (HV-F) volunteers, and for male (SZ-M) and female (SZ-F) patients with schizophrenia spectrum disorders.

Patients not in remission performed on a lower level than patients in remission. This remission-related difference in performance levels was somewhat stronger among male patients than female patients. On the other hand, female patients not in remission displayed worse performance during later stages of the vigilance test than male patients not in remission, see *Figure 2*.

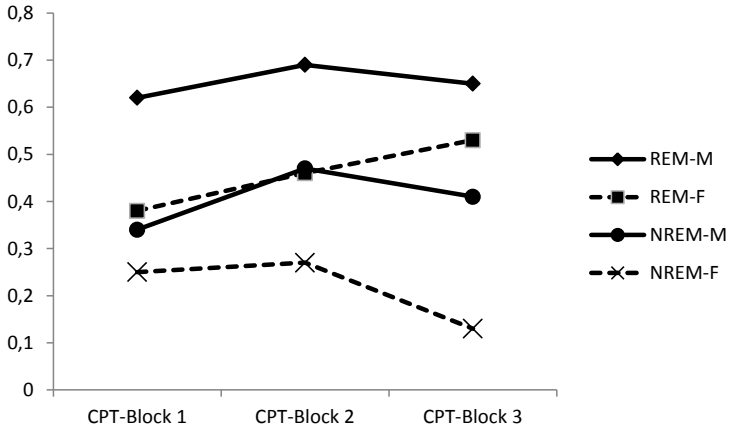

Figure 2. Performance profiles for *d'* over the three blocks of CPT-IP for male patients with schizophrenia in remission (REM-M) and not in remission (NREM-M), and for female patients with schizophrenia in remission (REM-F) and not in remission (NREM-F).

Study IV

Participants

As a part of the CLIPS investigation, the patients completed a neuropsychological test battery when entering the study, and were re-tested some years later. In spring 2010, 99 out of 296 patients had been re-tested, whereof 38 patients at the largest outpatient centre. Out of these 38 patients, 24 had improved test results in one or more of the neuropsychological tests; simultaneously, 16 of

them had also deteriorated results in some of the tests. These 24 patients were considered eligible for inclusion in this study and were consecutively asked to participate in extra interviews until finally ten patients were accepted. The interviewed patients were aged between 31 and 63 years old. Seven of them were men, three were women. Seven of the patients were diagnosed with schizophrenia, two with schizoaffective disorder and one with delusional syndrome. The baseline tests were conducted about eight years prior to the interviews, and the latest re-testing about two years prior to this study. Four of the patients had statistically significant improvement in one or two of the seven tests from test to re-test, while the rest of the patients had mixed results.

Design

The main purpose of this study was to elicit how patients with schizophrenia spectrum diagnoses evaluate their own cognitive functioning, using a qualitative methodology so that novel knowledge could emerge and existing concepts might be examined in the light of the patients' experiences. The main focus was on psychometrically validated improvement on cognitive testing. Schizophrenia spectrum patients who had been tested with the CPI twice and had improved test results on at least one of the neurocognitive measures were eligible for this study. The patients were interviewed with the help of an interview schedule that centered on the patients' self- perceived cognitive functioning in everyday life and in the test situation. The main focus was how patients evaluated and explained their own cognitive functioning, and whether they had noticed any improvement in cognitive functioning. The semi-structured interviews were audiotaped and then transcribed verbatim. *Interpretative Phenomenological Analysis* (IPA) (Smith et al, 2003; Smith et al, 2009) was applied to further describe the patients' experience of cognitive functioning in everyday life. The overall aim of IPA is to translate the themes into a narrative account, attempting to find interesting and essential points in the material, seeking to understand, rather than explain or predict, participants' worlds, as they are revealed in narratives.

Instruments

All patients had been tested with the CPI twice, about six years apart. Semi-structured qualitative interviews were conducted about two years after the second testing. IPA was used for analysis of the data from the interviews.

Results

All patients could, in varying degrees, still remember how they perceived the neuropsychological test situation. All but one patient could also relate perceived difficulties in the testing situation to similar difficulties in their everyday life. Despite this, most of the participants had trouble trying to figure out what meaning the documented neurocognitive improvement had in their daily life. Some of the patients thought that any test improvement was just a random effect or simply mood-related.

Eight major themes emerged from the data.

1. Fast processing strains learning, memory and attention

Tasks that require quick processing, for example the computerized vigilance test, strained the patients' cognitive performance and could quickly become unmanageable. Even the list of random words in the verbal learning test was perceived as demanding, hindering one participant from using a compensatory strategy. This reminded some participants of how teachers had "thrown words at them" at school and how large amounts of information quickly overwhelmed them, leading to fatigue and a need to rest. Social situations were also perceived as demanding as they require concentrating on many things at once.

2. The ability to concentrate is blocked by anxiety and adverse effects

Several participants described substantial problems with concentration in everyday life. These problems were ascribed to feelings of anxiety and restlessness, causing a sense of powerlessness in the participants. A few of the participants had problems with the paper-and-pen trail making tests which require visuomotor coordination. These participants complained about physical weakness and problems with coordinating their movements, claiming this to be a side-effect of antipsychotic medication. Some of the participants had such profound difficulties with concentration during the whole test situation that they did not perceive any improvement from baseline testing.

3. Non-demanding or unchanged daily life makes evaluation difficult

Several participants said that the demands in their daily life were so low in domains such as memory, attention, and problem solving that it was difficult to evaluate the actual degree of cognitive dysfunction or improvement. Many of them had worked before and compared their current life situation with their working life. A number of participants felt that any cognitive improvement would be observable only if the demands of daily life changed or increased.

4. Test improvement was just a random effect or simply mood-related

Some of the participants thought that any test improvement was just related to their general mood, how they had slept, or any other random cause. A few of the participants had not experienced any changes in their everyday lives since they entered the study. These participants found it hard to find any meaning in their improved test performances. One of them was satisfied with daily life remaining unchanged; another was depressed over persistent everyday difficulties. Some participants said that they had little knowledge about the tests they took or the test results. They thought that the results probably had some meaning, but they were uncertain about what it was.

5. Problem solving strategies are sometimes successful

Some of the participants were aware of memory problems and aspired to compensate with paper-and-pen. They took notes in class, wrote down what to say on the answering machine, made a note of dates to remember, and wrote shopping lists. Most of the time these simple memory aids were sufficient, but sometimes they failed. Problem solving strategies worked better when the participant felt that life was more structured than before.

6. Antipsychotic medication improves thinking

Most of the participants believed that antipsychotic medication was the main reason for the improved test results. At the same time, many of them were troubled

by adverse effects such as fatigue. Despite these complaints, almost all participants said that antipsychotic medication was a necessity that they experienced as helpful. Switch to medicines that had less adverse effects was perceived as one possible cause to improved test results. One participant thought his cognitive improvement was, besides new medication, due to changes in his everyday life having become more well-settled and tranquil than before.

7. Cognitive improvement parallels a more full or tranquil life

Several participants described that their lives had become more active and meaningful since baseline testing. Some of them had started to work or study since their first test and thought that this might have had a positive effect on their cognitive functioning. Going back to work or working more hours than before improved finances and enabled having a hobby. Work also gave a sense of belonging to a group, being useful, and making an essential contribution. Other daily activities such as reading, crossword puzzles, and computer use were seen as possible causes to improved cognition. One of the participants said that he thought his test results had improved as he had "studied more" in the period between baseline testing and re-testing. Thanks to his studies, he felt his memory had improved.

8. Feedback gives inspiration and empowerment

Despite that the meaning of the psychometrically improved test results was unclear for most of the patients, many of them talked about the meaningfulness of receiving information about the improvement. The patients saw the improvement as a confirmation on their own feeling of having better mental health than before. Patients reacted with joy or relief to the news. Some of the participants described how the news about improved cognition made them feel proud and empowered. It meant that they "maybe can manage something out there". The results were felt as encouraging and gave "inspiration to fight" to achieve desired goals in life. Even one patient who initially described the neurocognitive tests as "shallow" said that the results gave him a little more self-confidence and made him dare to take a small step forward in some area of his life.

3

Chapter 3: Discussion

The present research was designed to be an exploratory analysis of neurocognitive test profiles in a clinically representative population of patients with schizophrenia spectrum disorders. The study was performed in a naturalistic setting at the outpatient clinics the patients were enlisted at, and they were recruited through their case managers. The findings can be generalized to clinical reality.

Impaired and unimpaired profiles

In comparison to healthy volunteers, schizopsychotic patients as a group will always perform worse than the healthy volunteer group on any given test (Palmer et al, 2009). However, anyone who has met and tested a large population of schizopsychotic patients will have noticed the substantial variability in their test performance. While there unquestionably is a large group of patients with low test results, there is also a group of patients that will pass on some of the tests, and still another group who will perform as well as the healthy volunteer group. This has been established in several studies (Abi-Saab et al, 2005; Badcock et al, 2005; Rund et al, 2006) and is replicated in **Study I**. Green (1998, p.51) points out in his book that the proportion of patients in this range depends on the severity of the patient sample and the selection of the cut-off score, but is often around 50 %. Thus, all patients are not equally impaired, suggesting the presence of at least two neurocognitive subgroups: impaired versus unimpaired.

Study I found 43.9 % of the schizopsychotic patients to have normal (average or high) levels of verbal learning performance. Does this imply that approximately four out of ten schizopsychotic patients function overall equal to normal controls?

Same, but still different

Despite equivalent levels of verbal learning in comparison with healthy volunteers, the schizopsychotic patients in **Study I** performed worse on all subtests with the exception of working memory. The connection between verbal learning and working memory may be expected, as research has indicated working memory capacity to be an important moderating variable of learning (Psychological Corporation, WAIS-III WMS-III technical manual, 2002, p. 7). This applies to both the patient and volunteer groups, as working memory was a significant predictor of verbal learning performance level in both groups. Higher scores on the working memory test were associated with higher verbal learning performance levels for both study groups.

Another finding was that the schizopsychotic high level verbal learning performers presented a level of vocabulary that was comparable with that of the healthy volunteers, which suggests that superior verbal learning might be facilitated by a good word comprehension. This level of verbal learning performance/level of vocabulary relationship seems applicable only to the patient group since no differences in the verbal facility of the volunteers, despite the level of verbal learning performance, existed. Vocabulary scores are thought to reflect the subjects' socio-economic and cultural origins rather than their academic achievement (Lezak, 1995, p. 540). However, in this respect an initial inspection of the schizopsychotic patients showing high level verbal learning performance revealed no obvious demographic pattern that could account for this verbal learning/vocabulary connection. But despite similar capacity in verbal learning, working memory and vocabulary, the high verbal learning performance schizopsychotic patients did not perform on an overall level equal to the healthy volunteers.

All the schizopsychotic patients presented equally poor visuomotor processing speed/efficacy, despite their level of verbal learning ability, as no significant differences were found within the patient group. This finding indicates retarded visuomotor processing speed, which has been suggested to be a generalised characteristic of the schizophrenic process (Badcock et al, 2004). Thus, even patients with intact learning ability, working memory and vocabulary appear to share this global neurocognitive retardation in speed-related processing, although it may not always be perceived as a prominent feature but as more of a background

influence against which there may or may not be impairment in other specific domains.

Gender as a subgroup

One notion underlying the reasoning behind the Split-GAF scale, i.e. one symptom and one function score, was the bidirectional differences in scoring (Pedersen et al, 2007). The findings in **Study II** lend further credence to that application of the instrument. According to Gaite et al (2005), the notion of GAF as a bidimensional index of functioning incorporates distinctions between clinical and sociofunctional dimensions. This approach leads to a further requirement of attending to symptom profiles and functional profiles in undertaking provision of a diagnosis (Archer et al, 2008; Palomo et al, 2008). The utility of the Split-GAF scale achieves further applicability with regard to the results pertaining to distinctions between male and female patients. On the one hand, composite cognition scores were predicted by GAF Symptom levels in the female patients; on the other hand, composite cognition scores were predicted by GAF Function levels in the male patients. The above pattern of results regarding GAF Symptom, GAF Function and Global Cognition suggests that there is a complex relationship between these variables.

In a meta-analysis by Ventura et al (2009), both neurocognitive functioning and functional outcome were found to be significantly related to negative symptoms, supporting a model in which negative symptoms partially mediate the relationship between these two variables. In their model, neurocognition was still a primary causal variable that influences outcome. Therefore, they proposed neurocognition to have both direct and indirect effects on functional outcome.

A study of the predictive validity of underlying cognitive variables in the composite cognition score suggested that, in addition to above, there may be a gender-specific difference in the neurocognitive components. Executive functioning may have a greater impact on the symptom and function profiles of schizopsychotic males than on schizopsychotic females.

A study by Urbanek et al (2009) found an aspect of executive functioning (conflict inhibition) to differ significantly between patients and controls. This difference mainly resulted from a gender-specific reduction of the conflict effect and the conflict ratio in schizophrenic men. The same variables were elevated,

though not significantly, in schizophrenic women. Executive control of attention is involved in self-regulation of cognitions and emotions. The executive network involves the anterior cingulate cortex and lateral prefrontal cortical regions and is modulated by dopamine, with individual variations in executive attention related to genetic polymorphisms in genes related to dopamine (Wang et al, 2005). Neuhaus et al (2007) proposed that dysfunctional anterior cingulated cortex activation during executive processing may be a neurophysiologic endophenotype candidate of schizophrenia.

Taken together, the consensus of these results implies that there appear to be one or more mediating factors between neurocognition and global functioning that remain unidentified. Gender is known to modulate the onset and therefore the clinical course of schizophrenia, but there is limited knowledge regarding whether gender also influences the cognitive and functional profiles, and if so, to what degree. And, might these differences vary over ethnicity and culture? Further research is needed to solve this issue, but it is certainly necessary to consider the relative contribution of sex/gender in determining the functional expressions of the etiopathogenesis of schizophrenia spectrum disorders.

Are studies involving neurocognitive performance by different populations of schizophrenic patients comparable?

There are basic methodological differences between studies of neurocognition in schizophrenia, the first of them being the composition of the patient group. In classical randomized clinical trials there are extensive exclusion criteria. Together with commonly used multi-center study designs, the schizopsychotic patient population is highly selected and does not resemble the patients met in everyday clinical practice. A naturalistic, observational cohort approach on the other hand has fewer restrictions, and the participation retention is higher than in randomized clinical trials.

Even though the relationships between psychotic symptoms and neurocognition are usually quite modest in strength (Green, 1998, p.89), **Study III** showed that

male patients in symptomatic remission performed significantly better on a vigilance test than male patients not in remission. The same difference was not significant for female patients, but they did display some remission-related variability in their performance patterns. Thus, remission may play a significant role in interpreting the results of neurocognitive testing and should be taken in consideration when reporting these results.

Another issue is the choice of neuropsychological tests. Some studies use conventional neuropsychological tests, while others use modified or newly created tests. The included cognitive dimensions vary, making it difficult to compare results. More recently, the *National Institute of Mental Health's Measurement and Treatment Research to Improve Cognition in Schizophrenia* (MATRICS) initiated the development of a consensus cognitive battery for clinical trials of cognition-enhancing treatments for schizophrenia through a broadly based scientific evaluation of measures (Nuechterlein et al, 2008). Four out of the seven chosen domains (speed of processing, attention/vigilance, working memory, and verbal learning) are covered in the present study, while no tests within the other domains (visual learning, reasoning and problem solving, and social cognition) are used. The main reason is that the present study is not a clinical trial but a naturalistic, observational study that does not have the same time limit as clinical trials do. For clinical trials, high test-retest reliability is vital as retesting is done after a relatively short time span.

Nevertheless, as Jaeger et al (2006) indicated, conventional neuropsychological tests are polyfactorial, in that task performance is influenced by multiple cognitive operations, and all testing requires a basic capacity of attention, learning and memory. Hence, it is difficult to pinpoint exactly for which cognitive operations a low scoring subject may have a low level of functionality.

Insight, from different perspectives

Self- and expert-rated clinical outcomes rely on different assumptions and differ markedly. Karow et al (2011) found that in only 18 % of the cases do patients with schizophrenia, relatives and psychiatrists agree in their assessments of remission. Furthermore, symptomatic remission as assessed by the standardized criteria plays a secondary role for patients and relatives in daily clinical practice. Good subjective

well-being was the most important for remission estimated by patients; good subjective well-being and symptom reduction by family members; and finally, better symptom scores, well-being and functioning by psychiatrists. The authors conclude that a more thorough consideration of patients' and caregivers' perspectives should supplement the experts' assessment.

Likewise, **Study IV** found that patients with schizophrenia had difficulties trying to relate their cognitive test performance to their everyday life. Cognitive capacity seems to be validated by tangible changes towards a more comprehensive life, in general mental health or in daily functioning. Patients who had not had any positive change in their daily life in the period between test and re-test did not perceive any improvement in their cognitive functions, nor did they think that the test results had any effect on or meaning in their lives. In general, it was far easier for the patients to describe cognitive difficulties than cognitive improvement. However, this focus is not specific for patients with schizophrenia spectrum disorders. Bayard et al (2009) found that patients with schizophrenia, after controlling for level of depressive symptoms, did not express abnormally high cognitive complaints when compared to data gathered in healthy controls matched for age and education. As concluded by Medalia et al, specific education about cognitive symptoms may be necessary for compliance with cognitive remediation and/or cognitive enhancing medications. The results may endow the neurocognitive test battery a valuable psycho-educational instrument to facilitate patient functioning.

Staging in schizophrenia spectrum disorders

The *clinical staging* model has been used to describe illnesses which develop in a complex way, such as cancer. Stages describe not only a particular point in the course of the disease, but also the appropriate treatment for that stage. A clinical staging model makes three key predictions: pathologic measures should be more abnormal in more severe stages; patients who progress between the stages should show change in the same pathologic measures; and treatment should be more effective in the earlier stages, as well as more benign (Wood et al, 2011).

It has been suggested that the model can be useful in planning the treatment of other complex illnesses such as schizophrenia, contributing to early identification, diagnosis, and treatment (Archer et al, 2010). The stages that have been proposed in the development of schizophrenia are the prodrome, the first episode, and the long-term chronic phase (Agius et al, 2010). Staging may allow a more efficient integration of the biological, social and psychological vulnerability factors involved in development of mental illness into what may ultimately resemble a

clinicopathological staging model (McGorry, 2010). Clinical staging of schizophrenia spectrum disorders is facilitated through the systematic neurocognitive performance profiles, so that comprehensive considerations of diagnosis, prognosis and treatment enjoy greater availability. The patient situation is complicated by a multitude of genetic predispositions, epigenetic forces, symptoms and syndromes, early-onset and prodromal phases, recurrences and relapses that remain to be solved, possibly through multicenter efforts (Archer et al, 2011). Qualitative analyses derived from patients' awareness/non-awareness of self provide a valuable ancilliary to neurocognitive profiles of clinical staging.

Observations and impressions

Despite the time-consuming aspect of testing this singularly large population of patients, single-handed, the rare opportunity of personal access to a wide variety of schizopsychotic patients presented opportunities for many insights pertaining to the expressions of the disorder. Some patients failed on every given cognitive test, while others passed with flying colors. What were the factors contributing to the observed variance in the patients' test performances and what were the possible consequences for the functional roles that each patient maintained in his/her everyday life? The resulting association could not possibly be a linear function. Some of the patients, who had great difficulties with the tests, had, with support from family, friends and communal service, enjoyed an active life that they were fully satisfied with. Thus, cognitive prowess seems not to be a necessary prerequisite, and does not need to predict the patient's subjective quality of life; nor is it necessarily related to vocational outcome. For example, one young man with excellent cognitive performance had to have his case manager wake him up in the morning and drive him to the workplace, thereby posing questions regarding general functionality. Society offers very few job opportunities to people with chronic mental illness, and most patients cannot compete on the open work market. What is their greatest hindrance?

It seems to be the case, increasingly, that stress, both as vulnerability and precipitating factor, constitutes a major obstacle for schizopsychotic patients. Taking a test at the outpatient clinic is a rare and well-structured situation in which the patients can take all the time they need on tests that are not time-limited. The atmosphere is benevolent and supportive, and no matter what the results are, the patient gets credit for having gone through the testing. Nevertheless, under constant

time pressure or multiple demands, the schizopsychotic patient's brain appears to be susceptible to strain, which taxes its capacity for optimal function.

Due to inherited or acquired deficits, the schizopsychotic patient's brain is vulnerable to external and internal stress. Possibly, the notion of "vulnerability" constitutes the underlying general deficit that neuroscientists and clinicians have been searching for with the diligence of the 'quest for the Holy Grail'. Vulnerability is, after all, a non-specific constellation of deficits whose presence is noted indirectly by a lower threshold for symptom manifestation and/or a higher threshold for adequate cognitive performance, both of which contribute to the expressions of disorder in the phenotype. These impairments may lead to global neurocognitive retardation in speed-related processing. Against this general background, different cognitive profiles may emerge. These profiles could be expected to covariate with the degree of experienced stress. Thus, the specific cognitive deficits profile for a given patient would be different when in a psychotic episode as opposed to while in remission.

In summary, neurocognitive functioning is an important factor to be considered in planning the treatment of schizopsychotic patients and, following current notions, the clinical staging of the disorder. Further research should focus on studying longitudinal cognitive profiles of schizopsychotic patients in order to determine which functions remain stable and which domains vary as a function of the 'waxing and waning' of the psychotic disorder.

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