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# COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA: A FAMILIAL AND GENETIC APPROACH

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ACADEMIC DISSERTATION

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**ABSTRACT**

Schizophrenia is a severe psychiatric illness that affects 1% of the world population. It is a brain disease manifesting in disruptions in the normal functioning of the human mind. Although schizophrenia has an evidenced genetic basis, the etiology of this complex disorder remains elusive. In addition to psychotic symptoms, cognitive dysfunction is one of the core symptoms of schizophrenia. Schizophrenia patients have impaired attention, memory and executive functioning, which are associated with the psychosocial consequences generally observed among the patients. The same dysfunctions, albeit in an attenuated form, may be present in some unaffected relatives of the patients, too.

Cognitive dysfunctions have been considered as one type of biological markers, or endophenotypes, that confer the vulnerability of the disorder and may be associated with the same genetic factors as the disorder. Based on this assumption, this thesis examined the neuropsychological functioning of a representative sample of schizophrenia patients and their family members. The aims of the study were to estimate the heritability of the cognitive traits and to evaluate the number of their contributing loci. Furthermore, the study aimed at detecting the effects of familial loading on the dysfunctions among the unaffected relatives of the patients, examinining the effect of age of onset and some other illness factors on cognition, and evaluating whether familial loading mediates the observed effects. In this way exploring the value of cognitive traits as endophenotypic markers, the study aimed at using them in a genomewide genetic linkage analysis to see whether this modeling would prove valid for the search of genes for the disorder. In order to detect more homogeneous subgroups for further genetic research, the study also aimed at identifying clusters of families with schizophrenia that show convergent cognitive functioning.

Impairment of several cognitive functions was heritable, such as dysfunction in visual working memory that also showed familial effects among both the patients, irrespective of the age of onset or chronicity of the illness, and the unaffected relatives. Verbal memory functions were observed to be contributed by several loci. In the genomewide linkage analysis, visual working memory showed suggestive linkage to chromosome 2q, and verbal memory functions showed at least modestly significant linkage to several markers on chromosome 4q. In the cluster analysis, three family groups were detected, among them one cluster with particularly poor cognitive performance among both the patients and relatives.

In conclusion, the results of the study suggested that the cognitive dysfunction observed in schizophrenia patients and their relatives is heritable and shows familial effects. The usability and validity of certain continuous cognitive traits, particularly verbal memory functions and visual working memory, was supported by the accentuated linkage evidence when compared with that previously detected in linkage analyses using the dichotomous diagnosis as the phenotype. Further studies may benefit from the results of the cluster analysis and include more homogeneous family groups in the analyses.

## TIIVISTELMÄ

Skitsofreniaan liittyvien kognitiivisten häiriöiden perinnöllisyydestä ja niiden esiintyvyydestä skitsofreniaa sairastavien perheissä. Helsingin yliopisto, psykologian laitos, 2005.

Skitsofrenia on vakava mielenterveyden häiriö, jota esiintyy noin yhdellä prosentilla koko maailman väestöstä. Vaikka geneettiset tekijät ovat skitsofrenian synnyssä keskeisiä, tämän monitekijäisen sairauden syytekijöitä ei tunneta. Skitsofreniaa pidetään sairautena, jossa normaalisti toimivien aivojen toiminta häiriintyy. Psykoottisten oireiden ohella kognitiiviset häiriöt ovat skitsofrenian keskeisiä oireita. Potilailla havaitaan muistin, tarkkaavaisuuden ja toiminnanohjauksen häiriöitä, jotka liittyvät myös sairaudesta aiheutuviin psykososiaalisiin ongelmiin. Myös joillakin skitsofreniapotilaiden terveillä perheenjäsenillä havaitaan häiriöitä kognitiivisissa toiminnoissa, jotka kuitenkin ovat potilaiden häiriöitä lievempiä. Kognitiivisen toiminnan häiriöitä pidetäänkin skitsofrenian ns. endofenotyyppeinä, jotka ovat merkki mahdollisesta geneettisestä alttiudesta sairaudelle sen puhkeamisesta riippumatta.

Tämä väitöstutkimus on osa laajempaa vakavien mielenterveyshäiriöiden geneettistä epidemiologiaa selvittävää tutkimusta, jota varten kerättiin edustava väestötasoinen perheaineisto skitsofreniaa sairastavista perheenjäsenistä sekä heidän terveistä vanhemmistaan ja sisaruksistaan. Yhteensä 975 henkilölle tehtiin diagnostinen haastattelu ja neuropsykologinen tutkimus. Väitöstutkimuksen tarkoituksena oli arvioida kognitiivisten häiriöiden periytyvyyttä sekä sitä vaikuttaako skitsofreniaa sairastavien perheenjäsenten määrä toisaalta perheenjäsenillä ja toisaalta sairastuneilla havaittujen kognitiivisten häiriöiden vaikeusasteeseen. Lisäksi tutkittiin sairastumisiän ja eräiden muiden kliinisten muuttujien vaikutusta kognitiivisiin häiriöihin sekä sairaiden perheenjäsenten määrän osuutta tähän. Ne neuropsykologiset muuttujat, joiden periytyvyydelle saatiin tukea, sisällytettiin koko genomin kattavaan geneettiseen kytkentäanalyysiin. Tarkoituksena oli tutkia tuottavatko sairauteen liittyvät jatkuvaluonteiset piirremuuttujat parempia kytkentätuloksia kuin aikaisempiin tutkimuksiin sisällytetty dikotominen diagnoosimuuttuja. Jatkossa tehtäviä geneettisiä tutkimuksia varten tehtiin vähintään kaksi skitsofreniaa sairastavaa potilasta ja heidän terveitä perheenjäseniään sisältävien perheiden klusterianalyysi, jonka tarkoituksena oli etsiä neuropsykologisissa testeissä samansuuntaisesti suoriutuvia perheitä.

Kognitiivisten häiriöiden periytyvyydelle skitsofreniaa sairastavissa perheissä saatiin tukea. Erityisesti työmuistihäiriöiden perinnöllinen osuus oli suuri, ja niitä näytti vastaavan rajattu määrä geenilokuksia. Verbaalisen muistin suhteen periytyvyys oli tässä tutkimuksessa epäselvempi. Perheen sairastuneiden määrä liittyi erityisesti visuaalisen työmuistin häiriöön. Varhaisempi sairastumisikä liittyi erityisesti verbaalisen muistin häiriöihin. Geneettisessä kytkentäanalyysissä työmuistimuuttuja antoi kiinnostavan kytkentätuloksen kromosomiin 2q. Useat verbaalisen muistin toiminnot näyttivät kytkeytyvän merkitsevästi kromosomi 4q:n lokuksiin. Klusterianalyysi tunnisti perheistä kolme ryhmää, joissa perheenjäsenet sairaudesta riippumatta menestyivät keskenään samankaltaisesti neuropsykologisissa tehtävissä. Ryhmät nimettiin hyvin menestyvien, huonosti menestyvien ja niiden väliin sijoittuvien perheiden klustereiksi.

Tutkimuksen tulosten perusteella perinnölliset tekijät selittivät merkittävän osan skitsofrenia-alttiuteen liittyvistä kognitiivisista häiriöistä. Neuropsykologisista testeistä saadut jatkuvaluonteiset muuttujat tuottivat merkitseviä tuloksia geneettisessä kytkentäanalyysissä. Kognitiivisen toiminnan suhteen samankaltaisten perheiden tunnistaminen voi hyödyttää jatkotutkimuksia sairauden monitekijäisen taustan selvittämisessä.

**CONTENTS**

## ABBREVIATIONS

| | |
|---|---|
| AF | All Finland |
| CI | Confidence Interval |
| cM | Centimorgan |
| Com | Complete Study Sample |
| COWAT | Controlled Oral Word Association Test |
| CVLT | California Verbal Learning Test |
| DNA | Deoxyribonucleic Acid |
| DRT | Delayed Response Test |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| DZ | Dizygotic |
| fMRI | Functional Magnetic Resonance Imaging |
| $h^2$ | Heritability |
| ICD | International Classification of Disorders |
| IS | Isolate |
| IQ | Intelligence Quotient |
| LOD | Logarithm of Odds |
| MCMC | Markov Chain Monte Carlo model |
| MRI | Magnetic Resonance Imaging |
| MZ | Monozygotic |
| NOS | Not Otherwise Specified |
| OCCPI | Operational Criteria Checklist for Psychotic Illness |
| OPCRIT | The Operational Criteria Checklist |
| p, p-value | Significance Probability |
| P300 | Cognitive Evoked Potential |
| QTL | Quantitative Trait Locus |
| SCID | Structured Clinical Interview for DSM |
| SD | Standard Deviation |
| SNP | Single Nucleotide Polymorphism |
| SPSS | Statistical Package for the Social Sciences |
| WAIS-R | Wechsler Adult Intelligence Scale-Revised |
| WCST | Wisconsin Card Sorting Test |
| WMS-R | Wechsler Memory Scale-Revised |
| Z | Two-point LOD score |
| Zmp | Multipoint LOD score |

## LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original articles, referred to in the text by Roman numerals I-V.

**I**    Tuulio-Henriksson A, Haukka J, Partonen T, Varilo T, Paunio T, Ekelund J, Cannon TD, Lönnqvist J. Heritability of neurocognitive functions and number of quantitative trait   loci contributing to them in families with schizophrenia. American Journal of Medical Genetics (Neuropsychiatric Genetics) 2002; 114:483-490.

**II**    Tuulio-Henriksson A, Arajärvi R, Partonen T, Haukka J, Varilo T, Schreck M, Cannon TD, Lönnqvist J. Familial loading associates with impaired visual span among healthy siblings of schizophrenia patients. Biological Psychiatry 2003; 54:623-628.

**III**    Tuulio-Henriksson A, Partonen T, Suvisaari J, Haukka J, Lönnqvist J. Age of onset and cognitive functioning in schizophrenia. British Journal of Psychiatry 2004; 185:215-219.

**IV** Paunio T, Tuulio-Henriksson A, Hiekkalinna T, Perola M, Varilo T, Partonen T, Cannon TD, Lönnqvist J, Peltonen L. Search for cognitive trait components of schizophrenia reveals a locus for verbal learning and memory on 4q and for visual working memory on 2q. Human Molecular Genetics 2004; 13:1693-1702.

**V**    Hoti F[1], Tuulio-Henriksson A[1], Haukka J, Partonen T, Holmström L, Lönnqvist J. Family-based clusters of cognitive test performance in familial schizophrenia. BMC Psychiatry 2004; 22:4:20.

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[1] Equal contribution

# 1 INTRODUCTION

The present thesis is an exploration on cognitive impairments in patients suffering from schizophrenia, and in their unaffected first-degree relatives. The framework is in psychiatric genetics, a methodology that is used to understand why a mental disorder occurs in some families but not in others. In the present thesis, the psychiatric genetic framework is used in studying familiality and genetics of cognitive deficits in schizophrenia. Family is the basic unit of analysis in psychiatric genetics, following from the axiom that families influence the mental health of their members (Faraone et al 1999b). Furthermore, "genes do not act in isolation from other genes or from a person´s psychologic or physical environment. Think of genes as actors and the environment as their stage. Together they tell the story of human development. As psychiatric geneticists watch the play of psychopathology, they seek to identify the actors and learn how their behavior changes with the surrounding scene" (Faraone et al 1999b, p. 4).

Schizophrenia is a devastating psychotic illness characterized by positive symptoms (delusions, hallucinations, and disordered thought), negative symptoms (withdrawal, avolition, apathy), and cognitive impairments such as attention and memory deficits. Schizophrenia tends to run in families. It has an indisputable genetic basis, although there is still absence of definitive genes, and the pathogenic molecular mechanisms remain unknown. As schizophrenia, like most mental disorders, shows complex inheritance, the transmission of the disorder most likely implies several genes and environmental factors that transmit the predisposition to the illness but not necessarily its expression.

In many family studies, impaired performance in neuropsychological tests has been observed in both schizophrenia patients and their relatives, suggesting that these impairments may be biological markers indicating illness vulnerability. Consequently, many studies have concluded that these impairments may turn out to be valid endophenotypes - biological traits that confer vulnerability to the development of a disorder - to be included in genetic studies. However, only a few previous studies have actually used them in genetic analyses. Here, the heritability of certain cognitive traits was estimated, the association of familial loading and age of onset on cognitive traits was studied, and finally, the cognitive test variables were used as endophenotypes in a genomewide linkage study. For future genetic studies, a cluster analysis was conducted in order to identify such families in which both schizophrenia patients and their unaffected relatives performed convergently in neuropsychological tests.

## 2 REVIEW OF THE LITERATURE

2.1 SCHIZOPHRENIC DISORDERS

Schizophrenic psychoses include schizophrenia, schizophreniform disorder, and schizoaffective disorder. In addition, schizoid personality disorder and schizotypal personality disorder are included in the so called schizophrenia spectrum disorders.

2.1.1 Schizophrenia

Schizophrenia is a severe psychiatric disorder with complex and multifactorial etiology. The prevalence of schizophrenia is about 1% worldwide. The onset of the disorder occurs usually at a young age, but it may appear at any age. The risk of illness is similar in females and males, but men tend to have an earlier onset than females, and the illness is often more severe in males. No single sign or symptom defines schizophrenia. The clinical picture is thus heterogeneous and expressed in several subtypes of the disorder (Andreasen 2000).

Patients with schizophrenia have psychotic symptoms by definition, and continue to demonstrate ongoing and often profound mental status changes even in remission. The disease includes a severe disruption of personality and cognitive capacity, along with psychotic positive and psychotic negative symptoms (Fuller et al 2003). The positive symptoms are presence of such phenomena that should not be present in a normal individual. Typical positive symptoms are delusions and hallucinations, and disorganized thought and behavior. Negative symptoms are diminution or loss of functions or aspects of life that should be present in a normal individual. Typically, negative symptoms include withdrawal from social relationships, avolition, apathy and unattentivity. According to the Diagnostic and Statistical Manual of Mental Disorders, fourth version (DSM-IV) (American Psychiatric Association 1994), some signs of the disturbance must persist for a continuous period of at least six months, during which at least two of the following symptoms persist at least one month: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, or negative symptoms. Table 1 shows the DSM-IV diagnostic criteria of schizophrenia.

**Table 1. Diagnostic criteria for schizophrenia (**DSM-IV, American Psychiatric Association 1994**)**

A. Characteristic symptoms: Two or more of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

      1. Delusions
      2. Hallucinations
      3. Disorganized speech
      4. Grossly disorganized or catatonic behaviour
      5. Negative symptoms

Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices are conversing with each other.

B. Social/occupational dysfunction: for a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or, when the onset is in childhood or adolescence, failure to achieve the expected level).

C. Duration: Continuous signs of the disturbance persist for at least 6 months, of which at least one month should be of symptoms that meet Criterion A. The 6 months may include periods of prodromal and residual symptoms.

D. Schizoaffective and mood disorder exclusion: Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms, or if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the active and residual periods.

E. Substance/general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance or a general medical condition.

F. Relationship to a pervasive developmental disorder: if there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Schizophrenia involves dysfunction in one or more major areas of functioning (e.g. interpersonal relations, work or education, or self-care). Educational progress is frequently disrupted, and the individual may be unable to finish school. Many individuals can not hold a job, and become easily unemployed, or employed at a lower level than their parents. The interpersonal relationships tend to remain few, and marriage occurs only in 30-40 % cases. The dysfunction persists for a substantial period of the disorder and does not appear to be a direct cause of any single feature (American Psychiatric Association 1994). Probably no other chronic illness similarly debilitates functioning as schizophrenia (Schultz and Andreasen 1999). Moreover, schizophrenia is associated with markedly increased age-adjusted mortality (Brown 1997).

Prodromal symptoms often precede the active phase of the disorder, and residual symptoms follow the acute phase of the disorder (Häfner and an der Heiden 2003). These symptoms may be milder forms of the psychotic symptoms, such as peculiar (but not bizarre) behavior, mumbling to oneself, or up to severe negative features, such as withdrawal from social contacts, loss of interest in previously pleasant activities, or spending most of the time in bed (American Psychiatric Association 1994).

The first-degree relatives of patients with schizophrenia have a risk for the disorder about 10 times greater than that of general population. The risk for schizophreniform disorder or schizoaffective disorder, as well as schizoid and schizotypal personality disorder may also be increased in these subjects. On the other hand, risk of schizophrenia is increased in relatives of individuals with schizophreniform disorder or schizoaffective disorder (American Psychiatric Association 1994).

2.1.2 Schizophreniform disorder

Schizophreniform disorder is essentially identical to schizophrenia, except that the total duration of the illness (including prodromal, active, and residual phases) is at least one month but less than six months. Furthermore, the diagnosis of schizophreniform disorder does not require the impairment in social and occupational functioning that is one of the criteria in schizophrenia. This diagnosis is "provisional" in the sense that if the symptoms persist beyond six months, the diagnosis would be changed to schizophrenia (American Psychiatric Association 1994).

### 2.1.3 Schizoaffective disorder

Schizoaffective disorder comprises both the full criteria of the active phase of schizophrenia and a major depressive episode lasting at least two weeks, or a manic or mixed episode lasting for at least one week. During the same period of illness, there must be an at least two weeks period of delusions and hallucinations without any prominent mood symptoms. The mood symptoms have to be present for a substantial portion of the entire period of illness, including the active and residual symptoms. The total duration of the psychotic symptoms must be at least one month (American Psychiatric Association 1994).

### 2.1.3 Schizoid and schizotypal personality disorder

Schizoid personality disorder is characterized by detachment from social relationships, and a restricted range of emotions in interpersonal settings. It does not occur exclusively during the course of schizophrenia or another psychotic disorder. The essential feature of schizotypal personality disorder is a pervasive pattern of social and interpersonal deficits. This disorder involves cognitive or perceptual distortions, and eccentricities of behavior, thinking and communication. However, overt psychosis is absent (American Psychiatric Association 1994).

### 2.2 COGNITIVE IMPAIRMENT AND SYMPTOMS IN SCHIZOPHRENIA

Cognitive impairments are one type of core symptoms in schizophrenia. The schizophrenia patients show deficits in attention, memory, and executive functions. The severity of cognitive dysfunction associates specifically with negative and to a lesser extent with disorganized symptoms, but usually not with the presence of delusions and hallucinations (Addington et al 1991; O'Leary et al 2000; Rund et al 2004). Furthermore, improvement in symptom ratings has not been observed to associate with improved cognitive test performance (Hughes et al 2003). Negative symptoms associate with poor performance in verbal learning and memory, impaired conceptual thinking, object naming, visual and verbal long-term memory, and with verbal fluency (O'Leary et al 2000). Disorganized symptoms associate particularly with poor concentration and immediate recall of e.g. word lists (O'Leary et al 2000).

Dysfunctions are related to several aspects of symptomatology and may prevent patients from attaining an optimal adaptation in their everyday life (Green 1996). Impairments in executive processes, including planning, problem solving and

enterprising, play a relevant role in restricting patients ability to retain, acquire, or relearn skills that are needed for psychosocial functioning (Keefe 1995). Generally, impaired cognition has been more closely than the clinical symptoms linked to community outcome, social problem solving and social skill acquisition (Green et al 2000). Furthermore, the psychosocial and other functional consequences of the disorder seem to be most clearly related to impairments in verbal memory functions (Green 1996).

2.3 COGNITIVE DYSFUNCTIONS IN SCHIZOPHRENIA

An important component of schizophrenia involves compromized performance in most of the cognitive domains: working memory, executive function, verbal declarative memory, and attention. Although not all schizophrenia patients show impaired cognitive functioning, often a generalized deficit is observed. However, no specific "neurocognitive profile" exists for schizophrenia (Mohamed et al 1999; Bilder et al 2000).

Attenuated impairment is present already before the illness onset. Many subjects with prodromal symptoms show cognitive deficits, particularly in attention (Cornblatt and Malhotra 2001; Klosterkotter et al 2001), and although there is not one specific deficit that predicts the onset of the disorder, some dysfunction in cognition often precedes it (Cornblatt et al 1999). Usually schizophrenia symptoms break out together with a marked reduction in several critical cognitive domains (Riley et al 2000). The impairments do not directly associate with age, severity of symptoms, length of the illness, or medication (Aleman et al 1999), and they do not progress but remain stable (Heaton et al 2001; Hijman et al 2003; Kurtz 2005), showing generally no more worsening than what ageing normally brings along (Hyde et al 1994). Executive functions, however, may show a more accelerated decline (Fucetola et al 2000).

Whether certain cognitive impairments are specific for schizophrenia has remained unresolved (Mohamed et al 1999). In their meta-analysis, Heinrichs and Zakzanis (1998) reported that individuals with schizophrenia score between one-half to one-and-a-half standard deviations below the control mean in a wide variety of neuropsychological domains including attention, memory, intelligence, motor speed, spatial ability, executive functioning and verbal fluency, thus showing a generalized deficit. Some patients do not show impairments compared with controls, but it may be that also their cognitive functioning has deteriorated from the premorbid level (Kremen at al 2000; Keefe et al 2005).

2.3.1 Attention

Attention refers to processes of how an individual becomes receptive for external or internal stimuli (Lezak et al 2004). The critical attributes of attention are focus, selectivity, exclusiveness, and vigilance. To select from the stream of stimuli and to sustain attention are fundamental for all cognitive functioning.

Since the early days when schizophrenia was first described, deficits in attention have been noted among the core cognitive impairments of this disorder. Individuals suffering from schizophrenia display a broad array of attention impairments, irrespectively of their clinical state (Cornblatt and Keilp 1994; Cornblatt et al 1999). However, these impairments do not deteriorate as the illness progresses, suggesting that they are resulting from an early brain insult (Cornblatt et al 1997). It is also unlikely that they explain but a small portion of the variance in other cognitive functions (Kenny and Meltzer 1991). Impairments in attention seem not to be due to medication, as they can be observed in unmedicated patients as well. In fact, in some patients with antipsychotic medication, attention may improve (Serper et al 1994), and even conventional neuroleptics, often considered to impair cognition, may also enhance attention (Mishara and Goldberg 2004). Impaired attention is likely to be a marker of biological liability to schizophrenia, as individuals with vulnerability to this disorder display deficits in attention long before the appearance of other symptoms. These deficits also function as good predictors of the later developing schizophrenia in children with high risk of the disorder (Erlenmeyer-Kimling et al 2000).

2.3.2 Declarative memory

Memory is the outcome of learning. The human memory is a complex system by which an individual registers, stores, retains, and retrieves information (Lezak et al 2004). The memory system is usually divided into short-term and long-term memories. Short-term memory can be divided into immediate and working memory, and long-term memory includes declarative (explicit) memory and nondeclarative (implicit) memory.

There exists a consensus about global memory impairment in schizophrenia patients (Aleman et al 1999). In particular, impairments are detected in episodic memory, a subsystem in declarative memory, even to an extent of being the relatively greatest against the global cognitive dysfunction (Saykin et al 1991; Saykin et al 1994; Heinrichs and Zakzanis 1998; Mohamed et al 1999; Cirillo

and Seidman 2003). People with schizophrenia learn less than healthy individuals, e.g. when presented word lists. They do not use effective learning strategies, such as semantic clustering, not even when told to cluster the information. However, they tend to show intact recognition memory (Conklin et al 2002), thus suggesting more impairment in explicit compared with implicit memory (Sponheim et al 2004).

Cirillo and Seidman (2003) reviewed the literature from years 1999 to 2001 inclusive on the dysfunction in verbal declarative memory in schizophrenia. They concluded that verbal declarative memory seems to be among the most impaired neuropsychological functions in the patients with this disorder. Based on the reviewed literature, particularly the encoding stage seemed to account for the deficits. In a meta-analysis on the relative sensitivity and reliability of different measures and findings across the studies on neurobiology and brain function in schizophrenia, the most powerful and robust case-control differences pertain to cognitive and psychophysiological aspects of brain function rather than to neuroanatomical or neurochemical findings (Heinrichs 2004). In the ranking list of the best measures, general verbal memory impairment received the second highest effect sizes of all measures (Heinrichs 2004).

2.3.3 Working memory

Working memory refers to a multicomponent cognitive system that is serving to hold a limited amount of information "online" for a short period of time, and to simultaneously manipulate the information so that it is available for further cognitive processing, or to guide response selection, relevant for a specific context (Baddeley 1992). The subsystems of working memory comprise the central executive with two short-term slave stores: the visuospatial scratch-pad for visual information, and the articulatory loop for phonological information (Baddeley 1996). The central executive is responsible for the coordination of the processing of material in the slave systems and has access to long-term memory.

It has been argued that impaired working memory is the core cognitive deficit in schizophrenia, associating with the clinical picture and the functional consequences of the disorder (Goldman-Rakic and Selemon 1997; Goldman-Rakic 1999). Both verbal and nonverbal working memory are dysfunctional in schizophrenia (Park and Holzman 1992; Conklin et al 2000; Okada 2002). It has even been suggested that core symptoms of schizophrenia may emerge as a result from a breakdown in the working memory processes (Goldman-Rakic 1999).

Albeit a discrete cognitive function, working memory can also be considered a capacity for a wide range of complex cognitive functions, such as comprehension, learning, reasoning, and planning. Working memory plays an important role during the encoding process. Seidman et al (1998) found that during a verbal learning task in which the words can be semantically clustered, the differences between schizophrenia patients and healthy controls were eliminated when the results were controlled for scores in a working memory task. It is likely that abnormalities in working and strategic memory contribute substantially to the verbal encoding deficit in schizophrenia, as well as to other cognitive functions.

2.3.4 Executive function

Executive functions involve the use of information rather than the fundamental processing of information, and refer to the processes by which an individual realizes purposeful behavior (Lezak et al 2004). Executive functioning includes the ability to solve problems, formulate strategies, evaluate, select and discard useless strategies. It also refers to a flexible ability to alternate between competing strategies and adaptively shift to new strategies.

Schizophrenia patients have shown impairments in many areas of executive functioning. They have difficulties in abstraction, set shifting and response to feedback (Gold et al 1997). The deficits in executive functions aggravate the schizophrenia patients´ capacity to deal with everyday activities, and to adapt to novel situations. Usually the patients perform poorly in such tests measuring executive functioning as Wisconsin Card Sorting Test, the Trail Making Test, the Stroop test, or the Verbal fluency test (Elliott et al 1995; Chan et al 2004).

2.4 SPECTRUM DISORDERS AND COGNITIVE IMPAIRMENTS

Individuals with schizophreniform disorder or schizoaffective disorder have cognitive deficits in the same domains and comparable with those in schizophrenia patients (Cadenhead et al 1999; Townsend et al 2001; Goldstein et al 2005), being present in the first episode of these disorders (Addington et al 2003). Furthermore, in a recent report, Matsui et al (2004) studied patients with schizotypal personality disorders and compared them with schizophrenia patients and controls. They found that patients with schizotypal personality disorder showed similar impairments in verbal memory and visuomotor ability than

patients with schizophrenia, while the latter scored lower than the former in tests assessing executive functioning. Differences between patients and the control group were consistent in all measures (Matsui et al 2004). In a twin study, Johnson et al (2003) found that schizotypal symptoms in co-twins with schizophrenia were associated with increased risk of impairment in attention, working memory, verbal memory, and executive functioning. This was not observed in twins without a schizophrenic co-twin, which suggested a genetic association between the cognitive impairment in schizophrenia and schizotypal personality disorder (Johnson et al 2003).

2.5 SCHIZOPHRENIA AND BIPOLAR DISORDER – SIMILAR OR DIFFERENT COGNITIVE IMPAIRMENT?

Symptomatic patients with schizophrenia and bipolar disorder have been found to display similar degree of cognitive deficits, particularly in tasks of attention and problem solving (Zihl et al 1998). Similar results have also been obtained by Hoff et al (1990), who failed to differentiate between the deficits of schizophrenia and bipolar patients in acute psychosis, after controlling for age, sex, education, duration and severity of illness, and medical status.

Both acute schizophrenia patients and acute manic patients have been found to show working memory deficits in a spatial task (McGrath et al 2001). However, in remission only schizophrenia patients were impaired, which suggests that this deficit may act as a trait marker on schizophrenia, but in mania it may be more state dependent (McGrath et al 2001). In another study (Rossi et al 2000), a group of euthymic bipolar patients were compared with schizophrenia patients and control subjects using Wisconsin Card Sorting Test (WCST) (Heaton 1981), which involves multiple cognitive processes, working memory and problem solving included. Bipolar patients performed better than patients with schizophrenia, but worse than controls even in remission (Rossi et al 2000). Dickerson et al (2001) found that schizophrenic and bipolar outpatients differed only in immediate verbal memory, when a comprehensive neuropsychological test battery was employed. The bipolar patients were as impaired as schizophrenia patients in overall social functioning, but not in social effectiveness or verbal social skills. The better social effectiveness in bipolar patients may be due to their less impaired declarative verbal memory, which is a good measure in assessing the functional consequences of psychosis (Green 1996).

A recent study with severely ill chronic schizophrenia and bipolar patients found that the patient groups had similar neuropsychological impairments, which,

however, were more severe in the schizophrenia group (Seidman et al 2002a). In this study, both patient groups had suffered from the disorders from about the same age and had the same number of hospitalizations, although on individual level schizophrenia patients scored worst on these dimensions. The differences in cognitive impairment between the patient groups were quantitative rather than qualitative, and the authors concluded that their results support the view of clinical continuum but not necessarily the etiological similarity of these dysfunctions (Seidman et al 2002a).

Mojtabai et al (2000) detected a significantly worse neuropsychological test performance in schizophrenic first episode patients than in affective patients with psychotic symptoms. Subjects with schizophrenia expressed more generalized deficits and performed worse than bipolar patients, particularly in tests of attention, concentration and mental tracking. In a study comparing patients with schizophrenia and major affective disorder in their first episode of illness, a dysfunction in a broad range of functions was found among groups in patients with psychotic symptoms (Albus et al 1996). Frontal dysfunction, which is typical for chronic psychotic patients, was not so pronounced in the psychotic first episode patients. Affective disorders without psychotic symptoms were not associated with cognitive dysfunction as compared with controls.

In the study by Fleck et al (2001) acutely ill patients with bipolar disorder, schizophrenia, and healthy controls were compared using a test of sustained attention with degraded stimuli, and although no differences between the patient groups were found in sensitivity measures (i.e. hit/false alarm quotient), the schizophrenia patients showed a significantly longer hit reaction time than the bipolar patients. In all measures, patients performed worse than the healthy controls. The authors emphasize that information processing speed as one aspect of attentional capacities may be important in characterizing attentional dysfunction in major psychiatric disorders (Fleck et al 2001). Earlier, Brébion et al (1998) suggested that slowing of information processing may indeed be the factor that limits the effectivity of working memory in schizophrenia patients. A generalized slowing of information processing is commonly thought to be the source of many cognitive decrements (Salthouse 1996), and has recently been found to mediate test performance in bipolar patients, too (Kieseppä et al 2005).

2.6 PSYCHOPHARMACOLOGICAL TREATMENT AND COGNITION IN SCHIZOPHRENIA

The conventional antipsychotic medication has shown the best treatment responses on the positive symptoms of the illness, with much less impact on negative symptoms, mood symptoms, or cognitive deficits (Keefe et al 1999). However, the functional disability of schizophrenia is strongly associated with negative symptoms that correlate with the cognitive impairment but not with the positive symptoms. During recent years, the psychopharmacological research has focused on developing such new generation antipsychotic drugs that are targeted in the treatment of negative symptoms and cognition (Elvevåg and Goldberg 2000).

It has still remained controversial whether the novel antipsychotic medication enhances cognition over the conventional treatment, and whether there are differences across the novel drug preparations (Freedman 2003). The conventional drugs may have heavier side-effects than the atypical drugs, requiring own treatment such as anticholinergics that show impairing effects on cognition, too (Davidson et al 1995). In a meta-analysis, Keefe et al (1999) concluded that atypical neuroleptic treatment was more effective in producing cognitive improvement than the conventional treatment. Compared with placebo treatment, the novel drugs have been associated with enhanced performance in several cognitive tests, although with differential effect on different cognitive domains (Weickert et al 2003).

However, also the conventional antipsychotic drugs may enhance cognition. In a recent meta-analysis "opening the closed book" on the effects of conventional neuroleptic treatment on cognition, Mishara and Goldberg (2004) found a modest to moderate enhancing effect on most cognitive domains, although motor function was adversely impacted. Interestingly, they did not find any significant relationship between improvement of symptoms and enhanced cognition, suggesting that both symptoms and cognition may improve, but they do not covary. In a study comparing neuropsychological test performance of unmedicated first-episode patients with their test scores after 1,5 years of treatment, no impairments or improvement was observed, irrespective of their decreased symptom ratings (Censits et al 1997).

It is not clear, whether the beneficial effect on cognition of the atypical antipsychotics observed in some studies emerges from the absence of the side-effects of the large doses of the typical (conventional) neuroleptics that require additional medication. Recently, Keefe et al (2004) published a comparison of olanzapine (atypical) and haloperidol (typical). They found that although

olanzapine was beneficial on cognitive functioning in first-episode psychosis, low doses of the typical drug showed almost similar effects.

2.7 ETIOLOGY OF SCHIZOPHRENIA

2.7.1 The neurodevelopmental theory of schizophrenia

A theory of schizophrenia as a complex illness should explain the etiology of the illness, the timing of the illness, and the heterogeneous character of the illness (Heinrichs 2001). The basic questions concerning the etiology of schizophrenia are: Does the neuropathology of schizophrenia stem from genetic influences, from the physical environment, or from both in some weighted combination? Regarding the onset, questions arise: What determines the timing of the illness, why the illness onset is so rare in childhood and so common in the third decade of life - what noxius combination of events causes the high incidence right at the time of young adulthood and physical maturity? Family influences are regarded as important stresses and mediating forces in the life of patients with schizophrenia, but they are not regarded as causes of psychotic illness (Heinrichs 2001).

Although neither Kraepelin nor Bleuler, the early theoreticians of schizophrenia, provided a comprehensive theory of schizophrenia, both noted that individuals suffering from this illness may have shown premorbid changes many years before the illness had actually emerged. Furthermore, Kraepelin was aware that early insults in brain development may have been implicated in schizophrenia. However, the modern forms of the neurodevelopmental theory were first presented year 1987 when Weinberger published his landmark paper on the issue (Weinberger 1987). In this paper, he suggested that a prenatal or perinatal event or lesion could disturb the normal sequence of brain development. This early disruption was thought to be clinically silent until after puberty, when maturational events lead to the emergence of the symptoms of schizophrenia. The static alterations in brain sturucture, the correlations with problems in early life adaptation, the findings of cytoarchitectural disorganization of cortex, and the absence of gliosis have been thought to be consistent with the possibility of a developmental anomaly (Weinberger 1995; Andreasen 1999). The profound behavioral and cognitive symptoms of the disease may ultimately be explained by neurodevelopmental disruptions and subsequent changes in complex aspects of brain function (Tamminga 1999). Thus there is an interaction between genetic and environmental factors during critical early periods of brain development that adversely impacts on adult mental health.

Converging data warrant the assumption that schizophrenia is a neurodevelopmental disorder, and individuals who manifest schizophrenia in adulthood, suffer from some form of subtle cerebral maldevelopment during the time of pregnancy or infancy (Lencz et al 2001; Lewis and Levitt 2002). Furthermore, schizophrenia has not been found to be associated with an increased frequency of Alzheimer´s disease or any other known neurodegenerative disorder, which gives support to the model of the neurodevelomental origin of schizophrenia (Harrison and Weinberger 2005).

Recently, Sullivan et al (2003) published a meta-analysis on twin studies of schizophrenia. That analysis, based on 12 published studies, supported the view that schizophrenia is a complex disorder with substantial genetic effects, plus with a small but significant contribution of shared environmental effects. The point estimate of heritability was found to be 81% (95% confidence interval, 73%-90%), while the shared environmental influences in liability was 11% (95% CI, 3%-19%). As the environments of twins are most similar in utero and immediately after birth, the common environmental effects on liability to schizophrenia most likely occur early in life. Along with consistent evidence of prenatal and perinatal insults such as pregnancy and obstetric complications for the risk of schizophrenia, the authors conclude their result further supporting the neurodevelopmental etiology of schizophrenia (Sullivan et al 2003).

2.7.2 Environmental factors

Several environmental risk factors may increase the risk of developing schizophrenia in persons with genetic susceptibility to the disorder. Maternal influenza during the second trimester of pregnancy (Mednick et al 1988), rubella (Brown et al 2001), malnutrition (Susser and Lin 1992), polio virus (Suvisaari et al 1999), as well as the effects of Rhesus incompatibility (Hollister et al 1996), are among the suggested prenatal risk factors, although results in any of these factors have remained controversial (Brown and Susser 2002). Perinatally, obstetric complications such as hypoxia, and low birthweight caused by intrauterine growth retardation, may increase the risk of schizophrenia (Hultman et al 1997; Cannon et al 2002b). It is not yet known whether the high occurrence of obstetric complications is a result of abnormal brain development that is reflecting genetic vulnerability to the disorder, or an additive environmental factor (Mueser and McGurk 2004).

Socio-economic factors, such as poverty and lower social class have been found to be linked to high occurrence of schizophrenia. This may arise either from the

association between stressful environmental conditions and an increased risk, or from the decreasing effect of schizophrenia on social and occupational functioning (Häfner et al 1999). Urban births have been suggested as risk factors (Marcelis et al 1998; Haukka et al 2001), as well as winter births (Battle et al 1999), although results are partly controversial (Davies et al 2003; Suvisaari et al 2004). Severe instability of the childhood rearing environment, and deviant communication between parents, may be among he later risk factors for development of schizophrenia (Wahlberg et al 1997; Tienari et al 2004).

2.7.3 Genetic factors

Twin and adoption studies have shown that the genetic basis of schizophrenia is high, with heritability estimates up to 80% (Cannon et al 1998; Cardno et al 1999; Sullivan et al 2003). In families, the genetic distance to a schizophrenic patient affects on the risk of the illness of a relative. Sharing 50% of the genes, parents of a patient have a 6 % risk, siblings a 9 % risk and children a 13% risk to be affected. The prevalence in an adopted offspring of schizophrenia mothers, reared by unaffected mothers, is the same as siblings reared by their affected mothers, indicating that the familiality of the disorder is not explained by the family environment (Gottesman and Shields 1982).

A recent study by Tienari et al (2004) compared the effect of family rearing dimensions and functioning on developing schizophrenia spectrum disorders among adoptees of affected mother with those without this genetic risk. The study showed that only in the adoptees with the genetic risk the disordered family rearing increased risk to these disorders in a 21 years follow-up (Tienari et al 2004). However, the concordance of schizophrenia among identical twins, sharing 100% of the genes, is less than 50%, which clearly shows the environmental importance and the lack of genetic determinism in schizophrenia. It has to be kept in mind that a disorder that clusters in families is not necessarily genetic (Gottesman and Shields 1982).

Identification of the genes that function behind the high heritability of schizophrenia is essential for understanding the biological background of the disorder and its etiology. The identification of genes is most probably inevitable also for structuring the environmental and epigenetic factors involved in the process of developing the illness (Harrison and Weinberger 2005). Gottesman and Shields wrote year 1967 that one should not be satisfied with a polygenic theory of schizophrenia for too long, if other viable theories emerge (Gottesman and Shields 1967). Congruently with the views of that time, it still seems evident that there is

not one single gene that would determine the person to develop schizophrenia. Instead, it is likely that effects of multiple genes acting additively or multiplicatively provide the best model. According to this model, no particular constellation of genes will be characteristic in all ill individuals (Harrison and Weinberger 2005), and a set of genes that combine to produce schizophrenia in one family may not be the same as those that cause it in another family (Tsuang 2001).

Several genome scans on schizophrenia have been conducted, and many of them have produced significant LOD scores on several chromosomal locations, but the discovery of genes predisposing to schizophrenia has thus far remained elusive (Lewis et al 2003). A successful search for the genes has partly been hindered by the diagnostic and symptomatic complexity of the disorder and on its diagnostic criteria that lean on a clinical rather than an etiological standpoint. Furthermore, schizophrenia is a common disorder, which results in common genetic liability variants, found with relatively high frequency in the general population. The genetic and environmental variables may all have a small effect that act in an additive fashion to produce a vulnerability to the disorder (Gottesman and Erlenmeyer-Kimling 2001).

Although the search for the genes of the disorder has not thus far been very successful, recent progress in genetics in general and psychiatric genetics have given new optimism for this effort (O'Donovan et al 2003; Harrison and Weinberger 2005). It has been argued that "it is time to move away from solely statistical arguments to directly test the importance of specific loci and genes" (Harrison and Weinberger 2005, p. 44). Several reviews published during the last couple of years describe a list of genes, which might warrant the title of schizophrenia genes (O'Donovan et al 2003; Owen et al 2004) (Table 2). The evidence for these particular genes seems statistically and neurobiologically possible (Harrison and Owen 2003).

**Table 2. Putative candidate genes of schizophrenia**

| Gene | Chromosome Locus | Replication |
|------|------------------|-------------|
| NRG1 (Neuregulin 1) | 8p12-p21 | Yes |
| DISC1 | 1q42 | Yes |
| DTNBP1 (Dysbindin) | 6p22 | Yes |
| G72 | 13q22-34 | Yes |
| DAAO (D-aminoacid oxidase) | 12q24 | No |
| RGS4 | 1q21-22 | Yes |
| PRODH (Proline dehydrogenase) | 22q11 | Failed |
| COMT (Cathecol-O-methyltransferase) | 22q11 | Yes |

In Finnish study samples, several chromosomal regions have shown linkage with schizophrenia. These include 1q, 2q, 5q, and 7q (Hovatta et al 1999, Ekelund et al 2000, Paunio et al 2001, Hennah et al 2003). The molecular genetic studies in Finland have included both dense maps in certain chromosomal regions and genomewide linkage studies. The linkage results originally received by Hovatta et al (1999) and Ekelund et al (2001) have been recently replicated in a large sample including the original one (Ekelund et al 2004). The region 1q42 of includes interesting candidate genes for schizophrenia, DISC1 and DISC2, which are disrupted by the breakpoint of a balanced (1;11)(q42;q14) translocation linked to schizophrenia, and have been associated with schizophrenia in Scottish studies, too (e.g. Millar et al 2000). Hennah et al (2003) found further evidence for the hypothesis that the DISC1 gene is involved in the etiology of schizophrenia, and implies a putative sex difference for the effect of the gene. In particular, DISC1, which has been found to express in proteins involved in neurodevelopment and neuronal migration, has shown interesting associations with cognitive functions (Hennah et al, submitted).

2.7.4 Epigenetic effects

Epigenetic mechanisms, defined as regulation of such genomic functions that are controlled by heritable but potentially reversible changes in the DNA that cause permanent change of function or form of a cell (Petronis 2004; Gottesman and Hanson 2005), have been suggested to have an impact on the complexity of both the clinical symptomatology and genetic epidemiology of schizophrenia. According to the epigenetic approach, the actual phenotype of an individual depends on the

interaction of many genes and the environmental influences on them, plus stochastic events, based on random variation (Gottesman and Hanson 2005).

Although there is no direct experimental evidence that epigenetic factors do actually impact the development of schizophrenia, it can be imagined that schizophrenia results from a chain of unfavorable epigenetic events that begin with a primary epigenetic defect, so called epimutation. These events may then cause no clinical problems during decades, although they may result in a variety of minor cytoarchitectural changes in the brain, which in turn are observed as subtle neuropsychological or neurological aberrations that can be observed in some children who later develop schizophrenia (Erlenmeyer-Kimling et al 2000; Petronis 2004). However, only some individuals with these epimutations will outrun the "threshold" and get the full-blown illness. Epigenetics is one mechanism that could explain why the genetically identical twins do not show concordance for example to schizophrenia (Gould and Manji 2004; Petronis 2004).

2.8 STRUCTURAL AND FUNCTIONAL BRAIN ABNORMALITIES IN SCHIZOPHRENIA

There is no doubt that schizophrenia is a brain disease (Harrison 1999). Along with ventricular enlargement (Gaser et al 2004), subtle but significant reductions in brain volume and weight have been observed (Lawrie and Abukmeil 1998; Harrison et al 2003). Abnormalities in gray and white matter (Cannon et al 2002a; Job et al 2002), hippocampal volume and shape (Nelson et al 1998; Harrison 2004; van Erp et al 2004), cortical thickness and folding (Kuperberg et al 2003; Harris et al 2004), gyrification (White et al 2003) and volume, particularly in the prefrontal cortical areas (Wiegand et al 2004), have been detected in prodromal, drug-naïve, first-episode patients, and chronic patients (Seidman et al 2002a; Faraone et al 2003; Salgado-Pineda et al 2003).

Functional MRI studies have indicated that in schizophrenia, there is aberrant activity and connectivity in the components of distributed circuits involving the prefrontal cortex (Ragland et al 2004), hippocampus (Jessen et al 2003) and certain subcortical structures (Eyler Zorrilla et al 2003). Significant hypoactivation has been found particularly in the right hemisphere, in the dorsolateral frontal and temporal regions and in the inferior parietal, and subcortically in the thalamus (Salgado-Pineda et al 2004).

However, thus far the neuropathological findings do not warrant to be considered diagnostically useful, or to explain the cause of the disorder (Harrison and Weinberger 2005). The disorder is characterized by small to moderate case-

control differences across measures of cerebral structure and function, whereas the differences in cognition and psychophysiological measures, such as verbal memory, or eye-tracking and event-related potentials, may be relatively large (Heinrichs 2004).

2.9 COGNITIVE DYSFUNCTIONS IN RELATIVES OF PATIENTS WITH SCHIZOPHRENIA

Studies on the cognitive functioning of the first-degree relatives of the schizophrenia patients have suggested that the dysfunction may be familial or genetic. In several studies, cognitive deficits in relatives of schizophrenia patients have been found to parallel those observed in the patients, although to a milder degree (Cannon et al 1994; Faraone et al 1995; Lyons et al 1995; Toomey et al 1998; Faraone et al 1999a; Seidman et al 1999; Gilvarry et al 2000; Seidman et al 2002b; Toulopoulou et al 2003). Twin studies have shown that the deficits correlate more strongly in discordant monozygotic than in discordant dizygotic twins (Goldberg et al 1990; Cannon et al 2000b). Dysfunction in cognition has also been observed to appear in subjects at high risk for schizophrenia, and particularly deficits in attention during childhood may predict schizophrenia in subjects with at least one affected parent (Erlenmeyer-Kimling et al 2000).

Relative risk of the impairment seems to be particularly elevated for verbal memory, psychomotor speed and working memory (Egan et al 2001a). A recent meta-analysis (Sitskoorn et al 2004) examined neuropsychological test data on 37 studies, comprising 1639 relatives of schizophrenia patients and 1380 comparison subjects. Reporting the results as Cohen´s effect sizes (Cohen 1988), it was concluded that the relatives of patients with schizophrenia show less cognitive efficiency than healthy controls on several cognitive measures. However, no single test did adequately discriminate relatives from controls, albeit the best effect sizes were found in verbal recall measures (d=0.54, 95% CI 0.43-0.66). This moderate effect size implies that substantial numbers of relatives perform within a normal range in the neuropsychological tests, and that cognitive deficiency can not be considered to characterize each relative of a patient with this disorder (Sitskoorn et al 2004). Still, on some measures the test performance of the relatives is more than half a standard deviation lower than that of healthy controls. Appels et al (2003) compared unaffected parent couples of schizophrenia patients with healthy control couples and found that the former performed significantly worse than the controls in measures that previously had been found to be most impaired in schizophrenia patients (Heinrichs and Zakzanis 1998). These measures included global verbal memory, motor skills, verbal attention and executive function (Appels et al 2003). This result is of

particular interest as the parents represent an age group (mean age 53.6 years) that already had passed the age at risk for schizophrenia.

Verbal and visuospatial memory deficits and attentional dysfunction have consistently been found in patients and their relatives (Faraone et al 1995; Park et al 1995; Faraone et al 1999a; Conklin et al 2000; Egan et al 2000). In a family study (Almasy et al 2000), marked heritabilities were observed for attention, spatial memory, spatial processing, and verbal reasoning. Impaired visuospatial working memory and recall errors in a verbal memory task have recently been linked to genetic loading for schizophrenia in a relatively large sample of twins in Finland (Cannon et al 2000b). Genetic influences in schizophrenia were associated with reduced semantic encoding of verbal information, but non-genetic influences further compromised the episodic memory system in patients with the full-blown schizophrenia phenotype. In another study on Finnish twins, van Erp et al (submitted) found that episodic memory processes were more impaired than non-episodic memory processes in patients with schizophrenia. Based on MRI-scans, these disturbances suggested hippocampal pathology and supported previous results in which reduced hippocampal volumes have been associated with genetic liability for schizophrenia (Lawrie et al 2001; Seidman et al 2002a).

In high-risk children of schizophrenic parents who later develop schizophrenia, several impairments in cognition have been observed prior to the illness onset. In addition to dysfunctional motor development (Jones et al 1994; Cannon et al 1999), these children tend to perform poorly in cognitive tests and gain lower IQ than high-risk children who do not get affected (Kremen et al 1998; Davidson et al 1999; Cannon et al 2000a; for a review see Niemi et al 2003).

2.10 STRUCTURAL AND FUNCTIONAL BRAIN ABNORMALITIES OF RELATIVES OF SCHIZOPHRENIA PATIENTS

Similar reductions in frontal and temporal regions of the brain as in schizophrenia patients, but in attenuated form, have been revealed in relatives of schizophrenia patients (Lawrie et al 2001; Cannon et al 2002a), thus suggesting shared genetic liability. Regional volume reductions related to a genetic liability to schizophrenia include those found in the thalamus and temporal and frontal lobes (McIntosh et al 2004). Some evidence also suggests that some volume reductions found in the medial temporal lobe might be related either to environmental factors (e.g., obstetric complications) or to the actual manifestation of the illness (McNeil et al 2000; Lawrie et al 2001). Schulze et al (2003) failed to find

evidence that hippocampal volume loss would be associated with familial liability to schizophrenia. Instead, they found association between hippocampal volume loss and obstetric complications. In a study by McIntosh et al (2004), reduced anterior thalamic gray matter was found in relatives of schizophrenia and bipolar patients, which suggests liability to psychosis in general.

Following from the observation that relatives of schizophrenia patients show deficits in attention, declarative memory, and certain electrophysiological measures such as sensorimotor gating and eye tracking, there may also be functional abnormalities in the functioning of prefrontal cortex and associated regions, including thalamus and hippocampus. Although only a few studies have studied this, the results have shown abnormalities expressed as exaggerated functioning in the prefrontal cortex (Callicott et al 2003), or reductions in this functioning (Keshavan et al 2002). A recent study (Thermenos et al 2004) supported the view that functioning of the thalamic nuclei was increased compared with control subjects during a working memory task. The exaggerated activation may reflect the reduced thalamic volume that has been observed in relatives with schizophrenia patients (Seidman et al 1999).

2.11   ENDOPHENOTYPES IN THE GENE SEARCH

2.11.1 The concept of endophenotype

Although it has become relatively simple to localize and characterize genes for monogenic disorders, the situation is quite different in complex psychiatric disorders, which are influenced by multiple genes and their interaction, and for which there is no laboratory test available for diagnosis. An alternative way to find susceptibility genes for complex disorders may be using traitlike variables associated with the disorder as phenotypes in genetic studies (Faraone et al 1995; Freedman et al 1999; Egan and Goldberg 2003). For this reason, there has arisen interest in examining traits that directly index the underlying pathology or liability to the disorders, and that can be observed both in patients and their relatives. Because some relatives of patients carry genes for the illness although the illness is not expressing in them, the abnormal brain functioning that is often observed in them is not secondary to the illness or to the effects of its treatment. Rather, it can be attributed to the effect that the illness genes have on the brain even in the absence of the full-blown illness (Faraone et al 1999b).

This effort to identify intermediate phenotypes, or endophenotypes, is driven by the idea that they involve the same biological pathways as the disorder but are closer to the relevant gene action than the categorical diagnoses, thus adding power to genetic studies. The endophenotypes are assumed to have a simpler genetic architecture than the disorder that they correspond (Freedman et al 1999), although many of them may be complex, too (Egan et al 2003).

The endophenotype refers to an internal phenotype that can be discovered by measurements, but is not seen without an "aided eye" (Gottesman and Shields 1982; Gottesman and Gould 2003). It is the intermediate factor between the phenotype and genotype. The endophenotypes may be any neurobiological measures related to the underlying molecular genetics of the illness, including biochemical, endocrinological, neurophysiological, neuroanatomical, or neuropsychological markers.

However, the endophenotypes should fulfill several criteria before they can be considered valuable: 1) the endophenotype is associated with illness in the population, 2) the endophenotype is significantly heritable, 3) the endophenotype is present in individuals with and without an active phase of the illness, 4) in families with the illness, also the unaffected relatives have the same endophenotypic trait, and 5) the endophenotype that is present in the affecteds, is more prevalent in the unaffecteds in the family than in general population (Gottesman and Gould 2003). The measurements that are used to evaluate the endophenotypic traits, e.g. neuropsychological tests, may not have a sensitivity or specificity of 100% for the disorder phenotype, i.e. the diagnosis – if it was, no additional gain in power would be received (Egan et al 2003).

In schizophrenia, several types of endophenotypes that fill the above listed criteria, have been suggested. These include eye-tracking abnormalities (Kathmann et al 2003), certain electrophysiological markers, such as event-related potentials measuring the P300 amplitude abnormalities (Blackwood et al 1991; Winterer et al 2003), neurochemical variations, for example pharmacological treatment response parameters (Garver et al 2000), or scores from negative and positive symptom scales (Wilcox et al 2002). Recently, neuroimaging phenotypes have produced interesting results (e.g. Cannon et al 2002a) about the genetic effects of schizophrenia on brain morphometry as measured with MRI, or from fMRI studies of the effect of COMT genotype on prefrontal functioning (Egan et al 2001b; Marcelis et al 2003).

2.11.2 Neuropsychological endophenotypes

The search for the schizophrenia endophenotypes "to inform genetic studies of psychiatric disorders is never as productive and exciting as in neuropsychological studies" (Egan and Goldberg 2003, p. 163). This is because the cognitive deficits observed in schizophrenia are, unlike those in other psychiatric disorders, trait-like core features of this illness that are closely related to clinical and functional outcome. Furthermore, the neurobiology of some of the cognitive functions, such as working memory and verbal memory, are increasingly well understood.

It has been suggested that there may be several endophenotypes derived from neuropsychological test data (Egan et al 2001a). Results from twin and family studies have suggested that particularly visuospatial working memory functions, related to prefrontal neural systems (Park et al 1995; Cannon et al 2000b; Myles-Worsley et al 2002), but also verbal working memory functions (Conklin et al 2000), may be potentially valid endophenotypes to be included in genetic analyses. Moreover, the relative risk of impairment in siblings of schizophrenia patients is elevated in verbal learning and memory functions that rely on temporal brain systems, as well as in tests measuring executive functions (Egan et al 2001a). Data from studies assessing the relative risk of impairments have shown that these impairments exist in several, independent domains of cognitive functions also in relatives of schizophrenia patients, which at this point warrant including multiple test scores in genetic linkage analyses.

2.11.3 Quantitative trait loci and schizophrenia

Thus far, only a few studies have exploited the endophenotypes derived from neuropsychological test data in genetic analyses of schizophrenia. Gasperoni et al (2003) conducted QTL linkage and association analysis on Finnish twins including the region of chromosome 1q that had shown evidence for linkage to schizophrenia in two prior Finnish patient samples. The study exploited quantitative neuropsychological measures of liability. Analyses with a composite measure of liability yielded suggestive evidence for linkage at marker D1S2833 ($P = 0.04$). Follow-up analyses of the individual trait measures showed that the Visual Span subtest of the WMS-R (Wechsler 1987), an indicator of visual working memory function, was uniquely sensitive to marker D1S2833 ($P = 0.007$). Association analysis confirmed that allelic variation in D1S2833 is associated with variation in visual working memory performance as measured by the Visual Span subtest ($P = 0.003$). These data support the utility of this

approach and provide evidence for a susceptibility locus on chromosome 1q affecting working memory functioning.

The Weinberger group (for a review, see Weinberger et al 2001) has worked for years with the COMT gene at chromosome locus 22q11, and its association with neuropsychological test parameters of prefrontal function. They have repeatedly received associations with the Val108/158Met allele of the gene and Wisconsin Card Sorting Test and a N-back test (Egan et al 2001b; Goldberg et al 2003), but it is possible that the variation in COMT genotype is more strongly linked with these cognitive functions than with schizophrenia (Harrison and Weinberger 2005).

However, there is not yet evidence that the quantitative endophenotypes derived from neuropsychological test data, including test variables from attention, verbal memory and working memory, and executive functions, concluded by several studies as being potentially usable in genetic analyses, would indeed fulfill their promise. The present thesis provides one of the first studies for exploring this aim.

## 3    AIMS OF THE STUDY

The general aim of the present thesis was to identify neuropsychological endophenotypes in schizophrenia families from two samples collected in Finland: a genetic isolate in North Eastern Finland, and a sibpair family sample covering the whole geographical area of Finland. Further, the aim was to use these endophenotypes in genetic linkage analyses in searching for putative predisposing genes for schizophrenia.

The specific aims were:

Study I  *To estimate the heritability of various neuropsychological variables, and the number of quantitative trait loci (QTL) contributing to them in families with schizophrenia.* It was assumed that at least moderately heritable cognitive traits can be found. On the basis of earlier research on cognitive dysfunction in schizophrenia, particularly traits associating with working memory were expected to detect a restricted number of contributing loci.

Study II  *To compare performance in neuropsychological tests among the healthy family members coming from families with several affected siblings and families with only a single case.*  The goal of the study was to discover whether the unaffected subjects in families with several affected siblings perform worse in the neuropsychological tests than the unaffected subjects in families with only one affected sibling. It was expected that in families with several affected family members more cognitive impairments were found than in families with only one case.

Study III  *To study the effect of age at onset and neuropsychological functioning in patients with schizophrenia.*  It was expected that earlier age at onset is associated with impairments in neuropsychological functions. Furthermore, it was expected that the association between the impairments and early onset would be particularly emphasized in patients with several affected family members.

Study IV  *To link quantitative traits derived from the neuropsychological test data with genetic marker data over the whole genome.* It was expected that using quantitative traits, the significant LOD scores found previously in a genome scan of the present study population would at least remain significant or become more focused.

Study V *To search for family clusters with similar neuropsychological test performance among families with at least two family members suffering from schizophrenia.* A family-based cluster analysis was conducted on the neuropsychological test performance of the affected and unaffected family members. It was expected that at least a cluster with impaired performance and a well performing family cluster would be detected.

# 4     SUBJECTS AND METHODS

## 4.1   THE STUDY PROJECT

The present study is a part of the collaborative project "The Genetic Epidemiology and Molecular Genetics of Schizophrenia in Finland" run by the Department of Mental Health and Alcohol Research and the Department of Molecular Medicine at the National Public Health Institute, Helsinki, Finland. The general aims of the project were to characterize the epidemiology, particularly genetic epidemiology, of schizophrenia in Finland, to understand why the disorder occurs in some families but not in others, to investigate genetic and environmental risk factors of schizophrenia, and to identify genes predisposing to schizophrenia. The principal investigators were professor Jouko Lönnqvist and professor Leena Peltonen-Palotie. The study protocol was accepted by the Ethics committee of the National Public Health Institute, and by the Ministry of Social Affairs and Health.

## 4.2   SUBJECTS

From a cohort of all people born in Finland during 1940 to 1976 inclusive, we identified 33,731 individuals with a diagnosis of schizophrenia using the data derived from three nation-wide computerized health care registers for 1969 to 1998 inclusive. The Hospital Discharge Register covers all the public and private hospitals in Finland, a Nordic country with the population of approximately 5 million. For each stay, hospital identification code, admission and discharge dates, primary diagnosis and up to three subsidiary diagnoses are recorded. The discharge diagnoses for each admission are made by the attending physician. The diagnoses in the register were coded according to ICD-8 before 1987, DSM-III-R for 1987 to 1995, and ICD-10 since 1996.

The Free Medicine Register and the Pension Register index primary diagnoses for state-subsidized outpatient medications, and beginning and ending dates and primary diagnoses justifying disability pensions, respectively. Eligibility for a medication subsidy or pension must be documented by the treating physician and reviewed by another independent physician specialized for this procedure. All Finnish citizens have free access to inpatient and outpatient health care and are entitled to a state-subsidized outpatient medication and to a state-funded disability pension. More than 90% of individuals with psychotic disorders in Finland come into contact with the health care system in at least one of those ways.

The Population Register contains data on place of birth, residence, marital status, census data, and first-degree relatives for each Finnish citizen. Personal identification numbers which code the date of birth and sex are unique for each individual. By linking these numbers of the affected subjects to the data on their family members derived from the national population register centre, we were able to construct pedigrees.

Two samples of subjects with schizophrenia were collected for this population-based genetic study. The first sample consisted of families with at least two siblings with schizophrenia and their first-degree relatives from the whole geographical area of Finland (AF).  The second sample comprised patients and their relatives from families with at least one member with schizophrenia from an isolated region in the northern part of the country (IS). This isolated subpopulation originated from 40 families at the end of the 17th century, and precise details of subsequent births, deaths, marriages, and moves elsewhere have been recorded and preserved by the Finnish Church (Varilo et al 2000). In this area, the age-corrected lifetime risk of schizophrenia of 3.2% contrasts with the national average of 1.1% (Hovatta et al 1999). To increase homogeneity, the sample was restricted to persons with at least one parent born in the isolate area, which was enabled by the available genealogical data. Parenthood and sibship were ascertained by genetic analyses. The genealogical search has been reported in detail previously (Hovatta et al 1999; Varilo et al 2000).

In both samples, each affected individual was contacted only after the receipt of permission from the treating physician most familiar with the subject to begin the informed consent process. Only after the affected subject had given a written informed consent, the remaining family members were contacted. The collection of blood samples followed the recommendations given in the Declaration of Helsinki and its amendments.

All available case note records were collected for those with a diagnosis of psychosis in any of the three abovementioned registers. Two psychiatrists, blind to the family structure and register diagnosis, assessed independently the best-estimate lifetime diagnoses for each case, according to the classification of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, American Psychiatric Association 1994). One of the assessors also filled out the Operational Criteria (OPCRIT, or OCCPI; McGuffin et al 1991) checklist. Disagreements on the assessment of research diagnoses on the lifetime basis were reviewed by a third assessor, and a consensus was made.

The affected subjects were grouped into six diagnostic liability classes: class 1 included schizophrenia, class 2 added schizoaffective disorder, class 3 added schizophreniform and delusional disorders, brief reactive psychosis, psychotic disorder not otherwise specified (NOS), and paranoid, schizoid, and schizotypal personality disorders, class 4 added affective disorders with psychotic symptoms, class 5 added psychotic disorders due to substance use or general medical conditions. Class 0 included all non-psychotic mental disorders.

All schizophrenia patients were under antipsychotic medication, and in other patient groups, antipsychotic medication, antidepressives and anxiolytes were common.

Altogether 975 subjects from 292 families were interviewed using the Structured Clinical Interview for DSM-IV (SCID) (First et al 1997), and a neuropsychological test battery was administered. Altogether 68 subjects (44 from the isolate) were excluded from the analyses of the present thesis. The reasons for exclusion were 1) high age (80 and above), 2) neurological conditions, severe medical comorbidity, or current alcohol or substance use disorders, 3) mental retardation, 4) acute psychosis with consequent untestability. Table 3 shows the distribution of the abovementioned liability classes of the remaining 907 subjects separately for the two subsamples, and for gender.

**Table 3. Distribution of the liability classes in the study project samples**

|  | Isolate (IS) N=625 | | All Finland (AF) N=282 | |
|---|---|---|---|---|
|  | Females | Males | Females | Males |
|  | 299 | 326 | 136 | 146 |
| Mean age (SD) | 50.7 (11.8) | 48.7 (11.5) | 50.8 (11.8) | 48.2 (10.2) |
| Liability class (%) |  |  |  |  |
| 1 | 56 (18.6) | 122 (37.1) | 44 (32.4) | 46 (31.5) |
| 2 | 14 (4.7) | 21 (6.4) | 8 (5.9) | 9 (6.2) |
| 3 | 15 (5.0) | 21 (6.4) | 3 (2.2) | 8 (5.5) |
| 4 | 33 (11.0) | 12 (3.6) | 3 (2.2) | 10 (6.8) |
| 0 | 71 (23.6) | 51 (15.5) | 24 (17.6) | 26 (17.8) |
| Healthy | 110 (36.5) | 99 (30.1) | 54 (39.7) | 47 (32.2) |

All subjects from the families gave a written informed consent for the study protocol comprising a diagnostic research interview and neuropsychological testing. Both patients and their family members were interviewed using the Structured Clinical Interview for DSM-IV (SCID-I for axis I disorders and SCID-II for axis II disorders). All the interviewers were trained in a similar manner for the use of these instruments. The final consensus diagnoses were based on the data collected from the records, the OPCRIT process, and the SCID interview.

For each of the five studies comprising the present thesis, different inclusion and exclusion criteria were applied when subsamples derived from the described project were exploited.

4.2.1 Subjects in the Study I

The Study I comprised 264 subjects from 131 of the 397 families identified from the isolated region in the northeastern part of Finland. The Study I was conducted when subjects from 131 families had been unselectively processed in the still ongoing study. Both parents of 85 (65%) families were born in the isolated region, and in 116 (89%) families, both parents were born within the larger region defined by the border municipalities. In the remaining families, one parent was born in the core region, and the other elsewhere in the northern or central Finland.

Based on the consensus process and interview, 137 subjects (44 females, mean age 48.5, SD 7.6, and 93 males, mean age 45.6, SD 7.6) had schizophrenia or schizoaffective disorder, 34 subjects (17 females, mean age 46.8, SD 6.9, and 17 males, mean age 45.8, SD 5.6) had other mental disorder, including other psychotic (except current alcohol induced psychoses) and non-psychotic disorders (except mental retardation), and 93 subjects (53 females, mean age 48.0, SD 7.3, and 40 males, mean age 46.1, SD 8.2) had no mental disorder.

4.2.2 Subjects in the Study II

The Study II included only subjects who did not receive any psychiatric diagnosis in the consensus process. The subjects were drawn from the families studied in the isolate sample, and divided into singleton and multiplex groups based on the following criteria.

A singleton family included 1) only one sibling with a consensus diagnosis of schizophrenia (schizoaffective disorder and schizophreniform disorder not included), and the patient is interviewed and neuropsychologically tested, 2) at least one interviewed and tested sibling without any DSM-IV diagnosis as assessed by the SCID, 3) no first-degree relatives with any psychotic disorder.

A multiplex family included 1) at least one sibling with a consensus diagnosis of schizophrenia, and at least one sibling with schizophrenia (schizoaffective disorder and schizophreniform disorder not included), or another nonaffective psychosis, all interviewed and neuropsychologically tested, 2) at least one interviewed and tested sibling without any DSM-IV diagnosis as assessed by the SCID.

The final sample of the Study II comprised 31 healthy siblings from 27 singleton families, and 67 healthy siblings from 49 multiplex families. In the singleton families, the proband was suffering from schizophrenia. In the multiplex families, at least one sibling had schizophrenia, and at least another with this diagnosis or another non-affective psychotic disorder. No diagnosis of mental disorder, lifetime or current, was assigned to the siblings included in the study, based on the SCID interview and information from the registers, and none was taking psychopharmacological medication. None of the singleton families had a parent with a psychotic disorder. In 18 multiplex families, one parent had a psychotic disorder, and in three families, both parents were affected. In the multiplex group there were significantly more females than in the singleton group ($chi^2$=6.6, p=0.01). Age, education years, or estimated intelligence quotient (IQ) did not differ between the groups (Study II: Table 1, page 624). The number of siblings in the family of origin differed significantly between the study groups. The mean number of siblings was 5.5 (SD 2.7) in the singleton group, and 7.7 (SD 2.8) in the multiplex (t=-3.4, p=0.01). In 41% of the singleton group, there were 2-4 siblings in the family, in 41% 5-8, and in 18% nine or more. The respective figures in the multiplex group were 17%, 47% and 36%.

4.2.3 Subjects in the Study III

The Study III included patients suffering from schizophrenia, drawn from the isolate sample and all Finland sample. From 275 families, altogether 411 patients and 561 family members were interviewed using the Structured Clinical Interview for DSM-IV (SCID) (First et al 1997), and the neuropsychological test battery was administered.

From the Study III, we excluded 41 patients, who had a schizophrenia spectrum diagnosis in the registers but who were assigned a lifetime consensus diagnosis of bipolar disorder, and 11 patients who received a consensus diagnosis of a nonpsychotic disorder instead of psychotic schizophrenia spectrum disorders. Furthermore, we excluded 52 patients with schizoaffective disorder and 20 patients with schizophreniform disorder. This left us with 287 patients with schizophrenia. Of them, 35 either did not give a valid test performance or were untestable (acute psychotic state, severe medical comorbidity). Of nine patients, reliable information of the age of onset was not received, and four patients were excluded because of very early age of onset (7-12 years).

The Study III thus comprised 237 subjects with the diagnosis of schizophrenia from 208 families. Of the patients, 81 were women and 156 were men (p<0.001), thus reflecting a slight overrepresentation of males (66% vs. 58% in the registers). The age of women (mean 45.4, SD 8.4) and that of men (mean 45.0, SD 7.5) were similar. The course of the illness was chronic in 71% of women and 74% of men (data derived from the OCCPI).

Table 1 of the Study III (page 216) shows the demographic data of the study sample. Information of the age of onset was derived from the case notes as one of the OCCPI-items. The case notes were comprehensive and covered the inpatient and outpatient phases of the whole illness history of the patients. The age of onset was defined as the earliest age at which medical advice was sought for occurrence of psychiatric symptoms, or at which the symptoms began to cause subjective distress or impair functioning. The mean age of onset in the final sample was 23.2 years (SD=5.7) with no difference between women (mean 23.0, SD 5.7) and men (mean 23.3, SD 5.7).

4.2.4 Subjects in the Study IV

The sample of the Study IV was obtained by linking the data derived from neuropsychological tests with the genotypes of genome-wide polymorphic microsatellite markers. There were 168 nuclear families with at least two individuals having both the detailed phenotypic investigation and molecular genetic data. The sample thus comprised 598 individuals with valid neuropsychological test data. Of them, 179 had a diagnosis of schizophrenia (mean age 45.8, SD 8.3; 65 females and 114 males). Furthermore, 419 subjects were siblings or parents (mean age 52.4, SD 11.9; 218 females and 201 males), including both subjects with other psychiatric diagnoses than schizophrenia, plus

subjects to whom no diagnosis was assigned. However, in this study, the phenotype was not based on the categorical diagnosis but on the continuous variables that the cognitive tests provided.

One hundred and ten families (65%) came from the internal isolate (IS) in northeastern Finland. Although many individual nuclear families of the IS sample can be linked to larger pedigrees (Hovatta et al 1999; Paunio et al 2001), due to incompleteness of the data with a significant amount of missing information, analysis of only IS core families was considered to be the most appropriate approach for the current study. The remainder of the families lived elsewhere in Finland (AF). The correct family structures were confirmed by Mendelian inheritance analysis of various multiallelic markers within the families (Paunio et al 2001).

The twin pairs, whose neuropsychological test data were used as control data, were originally recruited to represent a control sample without any mental disorder in a study examining the inheritance of neuropsychological dysfunction (Cannon et al 2000b), and structural abnormalities of the brain (Cannon et al 2002a) in twins discordant for schizophrenia. For the Study IV, every other MZ twin and DZ co-twin was randomly selected, and the sample thus comprised 56 individuals (26 females) with well corresponding mean of age and sex distribution to those in the family sample.

4.2.5 Subjects of the Study V

Of those multiply affected families from the whole geographical area of Finland, who already had given the blood samples, a subsample was targeted for collection of more detailed phenotypic information. This sample was selected randomly based on the data from the registers and the OPCRIT process.

A total of 281 subjects from 54 families fulfilled the inclusion criteria for the Study V, and the families thus included at least two siblings with schizophrenia, schizoaffective disorder or schizophreniform disorder, and at least two siblings without these disorders. Altogether 16 patients were excluded because of being too psychotic (n=6), having a current substance use diagnosis (n=6), or being mentally retarded (n=4). Of the family members to whom no psychiatric diagnosis was assigned for their lifetime, 6 were excluded because of high age, or for a defect in vision or hearing. The final sample thus comprised 165 subjects with a psychiatric diagnosis and 94 unaffected family members from 54 families.

Of the 165 subjects with a diagnosis, altogether 82 subjects had schizophrenia, while 13 subjects suffered from schizoaffective disorder, 10 from schizophreniform disorder and 12 from bipolar disorder. A nonpsychotic disorder was assigned to 48 individuals. The 94 unaffected subjects did not get any current or lifetime psychiatric diagnosis. In 51 families, at least one of the patients included in the analysis suffered from pure schizophrenia. In the remaining three families, at least one subject with schizoaffective or schizophreniform disorder was included.

All families from which the subjects for the Study V were drawn, represent familial schizophrenia, as in each of them there were at least one sibling with a diagnosis of pure schizophrenia, plus at least one other sibling with schizophrenia, schizoaffective disorder or schizophreniform disorder.

4.3  THE NEUROPSYCHOLOGICAL TEST PROCEDURES

The neuropsychological tests were administered to the subjects in fixed order. The battery included two blocks. If the subject was unable to complete the whole battery in one day, the second block was administered next day. The subjects were tested in the local field-work offices, or at their homes, or in some cases in hospital.  All examiners were psychologists or advanced psychiatric nurses experienced with severely ill psychiatric patients. They received extensive training with the test battery before the study began, and sessions with feedback and supervision were organized regularly thereafter. All scoring was done by experienced psychologists.

The Digit Span subtest of the WMS-R (Wechsler, 1987) was used to assess auditory attention (forward condition) and verbal working memory (backward condition).The Digit Span test is an auditory task in which the examiner reads out numbers at one per second. The forward task requires the participant to repeat the numbers verbatim. In the backward task, the numbers need to be repeated in reverse order. The number series increases one at a time until the participant fails two trials consecutively of the same series length. According to Finnish normative data, the test-retest reliability coefficients of the Span subtest have varied from .74 to .82, depending on age.

The Visual Span subtest of the WMS-R (Wechsler, 1987) was used to assess visual attention (forward condition) and visual working memory (backward condition).  In the Visual Span Forward subtest, the examiner points at squares

printed on a sheet, and the subject then has to point at the same squares in the same order. In the Visual Span Backward subtest, the subject has to point at the squares in reverse order. As in the verbal span task, the number of stimuli increases by one, until a failure occurs in two tests of equal length. According to Finnish normative data, the test-retest reliability coefficients of the Visual Span subtest have varied from .72 to .80, depending on age.

Verbal learning and memory were assessed with the California Verbal Learning Test (CVLT) (Delis et al 1987), which examines recall and recognition of word lists over a number of trials. First, the subject is presented with a list of 16 words (four words in four semantic categories). The examiner reads aloud the list five times, and the subject is then asked to repeat all the recalled words in a free order. An interference list of 16 new words is then presented, after which the subject is immediately asked to recall the words from the original list, first freely and then with cues from the four categories used in the list (fruits, clothes, spices, and tools). After an interval of 20 to 30 minutes both free and cued recall, and recognition of the original list are assessed. This procedure yields several parameters for use as independent variables: levels of total recall and recognition, semantic and serial learning strategies, degree of distractibility, retention of information, and recall errors.

The Studies I-V report the following variables induced from the CVLT: total recall, semantic clustering, learning from the beginning of the list (primacy) and from the end of the list (recency), recall errors (perseverations and intrusions), delayed recall, and recognition (discriminability). No reliability data for Finnish subjects exists, but the split-half reliability of the CVLT is .77 to .86, according to the manual of the test (Delis et al 1987).

Four subtests of the Wechsler Adult Intelligence Test – Revised (WAIS-R) (Wechsler 1981) were used. Verbal abilities were measured with the Vocabulary and Similarities subtests. Vocabulary is considered as one of the best single measure of general ability, and it is usually well preserved in different neurological conditions (Lezak et al 2004). The subject is asked to explain the meaning of a list of words. The Similarities subtest is a task of abstraction and concept formation. The subject has to find a shared meaning for a pair of words, and the best scores are given for forming the most general concepts. These two tasks are included in the Verbal Scale of the WAIS-R. The Block Design and the Digit Symbol subtests belong to the Performance Scale. Both tasks have a motor component as the trials are timed. The former subtest is a measure of visuospatial reasoning and abstraction. The subject constructs shapes with cubes, following a

picture as a model. The latter subtest measures psychomotor performance, the task being to fill in as many blank spaces as possible in 90 seconds with symbols paired to numbers. The key for pairing each number with a symbol is printed above the trial rows. According to Finnish normative data, the test-retest reliabilities for Vocabulary, Similarities, Block Design and Digit Symbol have been .89-.95, .69-.88, .78-.83, and .82-.86, respectively, depending on age.

The Span tasks from the WMS-R (Wechsler 1987), the WAIS-R (Wechsler 1981) tasks, and the CVLT (Delis et al 1987) were included in the studies I-III and V. In addition, the Study V included the Logical Memory story A, of the WMS-R (Wechsler 1987), immediate and delayed, which was used to assess recall and retention in a story format. Furthermore, in the study V, visual memory was measured by the Visual Reproduction subtest of the WMS-R (Wechsler 1987) immediate and delayed. In Finnish normative data, the test-retest reliabilities of these subtests have varied with age from 0.84 to 0.91, and 0.31 to 0.34, respectively. The Study V included also the Controlled Oral Word Association Test (COWAT) (Benton and Hamsher 1989), which was used to assess verbal fluency. The quantity of words the subject produces in one minute, both with words beginning with a designated letter (S,K), and within a category (animals), was assessed. No reliability data for Finnish subjects are availabe.

Study IV included the WMS-R Span tasks, the CVLT, and the Stroop (Golden 1978). From the Stroop, the interference score was computed and used as a measure of executive function. For the Stroop, no reliability data are available for Finnish subjects. Because standardized scores were not available for all neuropsychological tests, raw scores from the tests were used in all Studies. Table 4 lists the variables used in the Studies I-V.

**Table 4. Test variables included in the Studies I-V**

| | I | II | III | IV | V |
|---|---|---|---|---|---|
| **Intelligence** | | | | | |
| WAIS-R (Wechsler 1981) | | | | | |
| Vocabulary | x | x | x | | x |
| Similarities | x | x | x | | x |
| Block Design | x | x | x | | x |
| Digit Symbol | x | x | x | | x |
| **Attention** | | | | | |
| WMS-R (Wechsler 1987) | | | | | |
| Digit Span forward | x | x | x | x | x |
| Visual Span forward | x | x | x | x | x |
| **Working memory** | | | | | |
| WMS-R (Wechsler 1987) | | | | | |
| Visual Span backward | x | x | x | x | x |
| Visual Span backward | x | x | x | x | x |
| **Verbal memory functions** | | | | | |
| CVLT (Delis et al 1987) | | | | | |
| Total recall | x | x | x | x | x |
| Semantic clustering | x | x | x | x | x |
| Intrusions | x | x | x | x | |
| Perseverations | x | x | x | x | |
| Delayed memory | x | | | x | |
| Primacy | x | x | x | | |
| Recency | x | x | x | | |
| Recognition | x | x | x | x | x |
| WMS-R (Wechsler 1987) | | | | | |
| Logical Memory | | | | x | |
| Visual Reproduction | | | | x | |
| **Executive functioning** | | | | | |
| Stroop (Golden 1978) | | | | | |
| Interference | | | x | | |
| COWAT (Benton and Hamsher 1989) | | | | | |
| Letters S and K | | | | x | |
| Animals | | | | x | |

4.4  STATISTICAL ANALYSES

In all difference testing analyses, the probability level $p < 0.05$ indicated statistical significance. These analyses were performed using the S-Plus statistical software, version 3.4 (S-Plus 1996).

4.4.1 Statistical analyses in the Study I

In the Study I, polygenic heritability, the proportion of variance due to the polygenic effect, was estimated using the Solar algorithm (Almasy and Blangero 1998). Heritability refers to the proportion of variance for e.g. a disorder that is estimated to be attributable to genetic factors.

The number of trait loci and their effects, and the effects of covariates on the ncognitive traits were estimated using oligogenic segregation analysis. Reversible jump Markov Chain Monte Carlo (MCMC) methods implemented in the Loki computer program (Heath 1997) were applied. Loki analyses quantitative traits observed on large pedigrees, however, the Study I exploited data from nuclear families only. The method allows for variation in the number of QTLs and in their linkage status. In the Study I, the raw scores from the neuropsychological tests were considered as the phenotypes, instead of the dichotomous affected vs. unaffected diagnosis.

The assumed model relates the phenotypes *(y)* to an additive function of covariate and genotype effects. The model for each trait is as follows: $y = \mu + X\beta + \sum_{i=1}^{k} Q_i \alpha_i + e,$ where $\mu$ is the overall population mean, $\beta$ *(m x 1)* is the vector of the covariate effects, $\alpha_i$ *(2 x 1)* is the vector of the effects for the $i^{th}$ QTL, e *(n x 1)* is the vector of the normally distributed residual effects, $k$ is the number of QTLs in the model, and *X (n x m)* and $Q_i$ *(n x 2)* are incidence matrices for the covariates in all individuals and QTL effects, respectively. The MCMC analysis produces a sample from the posterior distribution of all unknown parameters in the model ($\mu, \beta, k, Q_i, \alpha_i, e$). Prior distributions of parameters were generally normal, except that the prior for $k$ was uniform between zero and sixteen, and independent normal priors ($N(0,\tau)$) were assigned for two components of $\alpha_i$.

In the QTL models, the proportion of variance due to QTLs is reported. This is comparable to the polygenic heritability, but does not include the residual polygenic part of the variance, which remains after accounting for the QTLs. The estimation involves a stochastic element, and no single model is identified to the exclusion of another. Instead, it produces a series of models. 10,500 iterations for

each trait were run, omitting the first 500. The convergence of the iterations was checked graphically. The 95% credibility limits and posterior means of the parameters from empirical posterior distribution produced by the MCMC algorithm were obtained.

Age, sex, and verbal ability as measured with the WAIS-R Vocabulary subtest, were used as covariates in the analyses.

4.4.2 Statistical analyses in the Study II

The significance of the differences in neuropsychological functioning between the unaffected subjects from families with one schizophrenia patient or with two or more patients was tested using linear mixed effects models. To control for intrafamilial correlation, as some subjects came from the same family, family was included as the random effect. Belonging to a singleton or multiplex family, number of siblings in the family, and sex, were included as fixed effects. The significance of the fixed effects was determined using a Wald-type test of fixed effect parameter estimates (t-statistics).

For comparing the test results with the normative Finnish data, the raw scores were transformed to age-corrected standard scores using available Finnish normative data tables for WMS-R (Wechsler 1996) and WAIS-R (Wechsler 1992). The differences of the standardized test scores from the national norm means were tested using one-sample t-test, with the national norm mean as the test value. These data were available for the WMS-R (Wechsler 1987) and for the WAIS-R (Wechsler 1981). In the WMS-R span tasks, the mean for the standard score distribution is 0, and the standard deviation is 1. In the WAIS-R, the respective figures are 10 and 3. The effect sizes comparing standardized test scores with the normative mean were calculated using Cohen´s d (Cohen 1988). The analyses were made separately for the singleton and multiplex siblings. Furthermore, the effect sizes comparing the standardized scores of the singleton and multiplex groups were calculated. For the CVLT, normative data were not available.

4.4.3 Statistical analyses in the Study III

The associations between age of onset and the neuropsychological test variables were examined using linear mixed effect models. Age of onset was treated in the models as a continuous variable, ranging from 13 to 44 years. Family was included as a random effect, as the subjects came in part from the same families. Age (years), sex, course of the illness (chronic vs. episodic), and age of onset (years)

were included as the fixed effects. Furthermore, the number of affected members in the family was included in the models as a fixed effect in order to detect whether the familial loading, as measured with the number of first-degree relatives with a psychotic disorder, modifies the effect of the age of onset on the cognitive functions. The information of the illness of the first-degree relatives was obtained from the registers. Furthermore, additional models with all test variables with the abovementioned random and fixed effects plus duration of the illness (tertiles from age of onset subtracted from the age at testing in years) were run.

4.4.4 Statistical analyses in the Study IV

SOLAR, an oligogenic variance-component linkage method incorporating the variance component program FISHER, was applied for the quantitative trait locus (QTL) linkage analysis for the Study IV (Lange et al 1988). Preliminary statistical analyses of the neuropsychological features, including descriptive statistics as well as bivariate correlation analysis, were performed using SPSS software (SPSS Inc, Chicago, USA). As variance-component based analysis may be vulnerable to deviation from multivariate normality and, in particular, to high levels of kurtosis in the trait distribution, transformations towards normality were applied for perseverations, intrusions, and executive function; semantic clustering, and for recognition memory.

All genetic analyses included an ascertainment correction in which individuals with schizophrenia were labeled as the proband. The mean of the control sample using the twin data was applied as a constraint, and age and gender terms were included as covariates. The primary interest of the study was to analyze the complete study sample (Com). However, owing to the potential difference in the genetic background of the 110 families collected from an internal isolate representing a more restricted gene pool, separate analyses were also run for the IS families and AF families.

4.4.5 Statistical analyses in the Study V

4.4.5.1 Cluster analysis

The variables used in the Study V cluster analysis included 17 neuropsychological test variables together with the age and the sex of the subjects. With a total of $M = 19$ variables and $N = 259$ subjects, the data formed an $M \times N$ matrix $x = (x_{ik})$, where $x_{ik}$ is the value of the $i^{th}$ variable for the $k^{th}$ subject.

The clusters were obtained by treating families as single objects whose dissimilarity was measured by the pairwise test performance differences between the family members. The families were clustered using a complete-linkage clustering algorithm. Each variable was normalized by subtracting the mean value and dividing by the standard deviation. The normalization was done to ensure that each variable contributes equally to the clustering procedure. In the sense of this distance measure, two clusters were close when all subjects in both clusters showed close to similar test performance.

The clustering followed three steps. In the first step, the initial clusters were defined by the families. In the second step, the two clusters with the smallest inter-cluster distance were merged into one larger cluster. Then, the steps 2 and 3 were repeated until a desired number of clusters remained. Figure 1 of the Study V, page 4/12, demonstrates this procedure.

4.4.5.2 Visualization of clusters

The Study V introduces a visualization technique that helps in identifying candidate clusters and also gives an overall picture of the main differences between the produced clusters as measured by all variables simultaneously. The method gives information about the dynamics of the clustering process and the characteristics of the candidate clusters. The Figure 2 in the Study V (on page 5/12) presents the data matrix as what is called the "color histogram" with the rows corresponding the variables and the columns correspond the subjects. The values of the neuropsychological tests and other variables are visualized using color coding.

The lower part of Figure 2 of the Study V (page 5/12) visualizes the actual clustering process using the dendrogram. The history (vertical direction) of the mergings is shown from the beginning (one family in each cluster) to the end (all families in one cluster). By simultaneously exploring the two images, a reasonable value for the number of clusters can be found and the characteristics of the cluster solution visualized in a useful manner. It is also helpful to monitor the inter-cluster distance measure for possible large jumps which indicate that two distant clusters are being merged (Figure 3, Study V, page 6/12).

4.4.5.3  Difference testing between the clusters

Further, after the cluster analysis, the proposed family clusters were examined for differences on demographic and neuropsychological measures. In addition, the patients included in the clusters were examined for the differences in clinical variables as evaluated by the OPCRIT (premorbid social adaptation, response to neuroleptic treatment, chronicity, age of onset) of the disorder. In comparing the demographic and clinical variables, the Chi-square test, or t-test, both two-tailed, were applied. The differences in the quantitative neuropsychological measures were analyzed using the linear mixed effects model, which takes into account the dependence between the subjects, who, a priori, came from the same families. Thus, family was included as a random effect in all models with age and sex as the fixed effects. In addition, post hoc models were conducted with education years as an added fixed effect, a known confounder for cognitive functions.

# 5    RESULTS

## 5.1    HERITABILITY OF COGNITIVE FUNCTIONS AND THE NUMBER OF THEIR RESPECTIVE LOCI (STUDY I)

### 5.1.1 Heritability

In the polygenic model with age, sex and verbal ability as covariates, significant heritability was obtained for the following neurocognitive traits: verbal working memory ($h^2$=0.42, p<0.003), semantic clustering ($h^2$=0.28, p<0.03), recall errors (intrusions) ($h^2$=0.66, p<0.001), recognition (discriminability) ($h^2$=0.49, p<0.01), and visuospatial ability ($h^2$=0.48, p<0.04). Visual working memory and concept formation showed a trend of significance ($h^2$=0.36, p<0.06 and ($h^2$=0.38, p<0.06, respectively). Verbal ability, with age and sex as the only covariates, showed significant heritability ($h^2$=0.62, p<0.0006) (Study I, Table I, page 486).

### 5.1.2 Number of QTLs

The posterior probabilities for one or more loci, and the number of loci contributing to a trait are shown in Table III of the Study I (page 487). The neurocognitive variables with a mean number of loci very close to one, together with a high posterior probability for at least one locus, were verbal working memory and visual working memory. High probabilities for at least one locus, and the mean number of contributing loci less than two, were found in concept formation, intrusions, perseverated responses, and visuospatial ability. Semantic clustering had a high probability for at least one locus, and slightly over two loci contributed to it. The traits, which provided little evidence for genetic contribution (posterior probability for at least one locus less than 50%) were attention, verbal memory, and visuomotor speed.

The measures with a high posterior probability for one locus were assessing verbal working memory (73%) and visual working memory (70%). The ability to use semantic clustering while learning was contributed by only one locus with a posterior probability of 99%. Verbal concept formation and visuospatial ability, as measured with the WAIS-R subtests Similarities and Block Design, respectively, supported genetic contribution for a one gene locus, with corresponding posterior probabilities for one locus of 97% and 84%.

One or two loci with posterior probabilities for one locus around 90% contributed to forgetting what had already been produced in the word list test (perseverations), and also to the function of producing words that did not exist on the list (intrusions). Two loci with a posterior probability 100% for at least one locus contributed to recalling words from the end of the word list (recency), implying poor working memory and impairment in learning ability.

The posterior probability for no quantitative trait loci contributing to attention measures was around 50%. In addition, declarative verbal memory (total words recalled from the list over five trials), and an ineffective learning strategy (primacy) did show very small genetic contributions. Psychomotor speed revealed the largest probability of negative genetic contribution (72% for no locus).

## 5.2 EFFECT OF FAMILIAL LOADING ON THE COGNITIVE FUNCTIONS AMONG RELATIVES OF SCHIZOPHRENIA PATIENTS (STUDY II)

In the linear models with family as a random effect, a significant difference between the singleton and multiplex families was found in the backward visual span, assumed to measure immediate visual memory and components of visuospatial working memory: the healthy subjects of the multiply affected families performed worse than those of the singleton families (t=-2.06, p=0.04). No other significant differences were detected in the linear models (Study II, Table 2, page 625).

The possible sex by group interactions were examined, and significant interactions were found in one variable (primacy in the CVLT). The follow-up analyses by sex revealed that females in the multiplex group scored significantly higher than females in the singleton group in remembering words from the beginning of a word list (primacy) (t=-2.2, p=0.04). For males, no significant singleton-multiplex differences were found. We then repeated all linear mixed effects model analyses separately for each sex, but the results remained similar. The effect of family size was nonsignificant in all models.

In comparisons of the standardized scores of the span tests with the available Finnish normative data, healthy siblings from the multiplex families were found to perform significantly worse than the norm mean in all WMS-R forward and backward span tests Although the healthy siblings from the singleton families scored below the norm mean in all span tests, the difference was not significant. In the singleton group, the effect sizes comparing standardized test scores with

the normative mean were small in all span test variables (d<0.3). In the multiplex group, the effect sizes were moderate in the forward and backward visual span (d=0.5 and d=0.6, respectively), but small in the verbal span tasks (d<0.3). The between group effect size was moderate for the backward visual span (d=0.5), and small for all other variables.

In the subtests from the WAIS-R, both groups scored above the norm mean in the Digit Symbol subtest, and the siblings from the multiplex families scored better than the norm mean in the Vocabulary subtest (Study II, Table 3, page 626). However, only small effect sizes (d<0.5) were received from the WAIS-R tests as compared with the normative mean.

## 5.3 EFFECT OF AGE OF ONSET ON COGNITIVE FUNCTIONS IN SCHIZOPHRENIA (STUDY III)

### 5.3.1 Effect of age of onset

In the linear mixed effect models, lower scores on four cognitive functions were significantly associated with earlier age of onset (Study III, Table 2, page 217). These functions were verbal learning and memory (total recall from trials 1 to 5 in the CVLT) (coefficient for the effect of how much each increasing year in the age of onset changes the value of the test score =0.483, SD=0.14, p=0.002), using semantic clusters as a learning strategy (effect coefficient=0.023, SD=0.01, p=0.02), recognition memory (effect coefficient =0.256, SD=0.15, p=0.05), and making errors during recall (intrusions) (effect coefficient = -0.033, SD=0.01, p=0.007).

### 5.3.2 Fixed effect contributions

Course of the illness (chronic vs. episodic) contributed to the measured four intelligence functions (all p-values < 0.03). Chronicity also showed a significant negative effect on verbal learning and memory (effect coefficient =-6.245, SD=1.8, p=<0.001), semantic clustering (effect coefficient =-0.287, SD=0.11, p=0.02), delayed verbal memory (effect coefficient =-1.723, SD=0.48, p=<0.001), recognition memory (effect coefficient =-5.300, SD=1.62, p=0.002), and making intrusions (effect coefficient =0.348, SD=0.14, p=<0.02), but it did not eliminate the effect of age of onset on these variables. Including duration of the illness into the models did not change the results, and this variable did not contribute significantly to any of the measured cognitive functions. The number of affected first-degree relatives in the family showed a significant negative effect

on visual working memory (effect coefficient =-0.27, SD=0.13, p=0.04) and on verbal ability (effect coefficient =-1.80, SD=0.83, p=0.04), and on psychomotor speed (effect coefficient =-1.31, SD=0.61, p=0.03).

## 5.4 GENOMEWIDE QTL-ANALYSIS OF COGNITIVE TRAIT COMPONENTS IN SCHIZOPHRENIA (STUDY IV)

Prior to conducting the linkage analyses, we performed preliminary statistical analyses on the variables derived from the neuropsychological test data, including estimation of heritability of the cognitive traits, calculation of the descriptive statistics, and the correlations between the traits. Significant heritability estimates were received for all traits (data not shown). Furthermore, the mean performance of the study sample was inferior to that of the control sample (Study IV, Table 1, page 1694). The affected probands generally performed worse than their relatives, and the mean performance of the latter was also below that of the general population (data not shown). Correlations between the transformed traits were sought by bivariate correlation analysis of all individuals of the study sample. The strongest correlation was observed among the different indices of memory function: verbal learning and semantic clustering (0.66; p= 0.000001), verbal learning and delayed memory (0.69; p=0.000001), and semantic clustering and delayed memory (0.59; p=0.000001) (Study IV, Table 2, page 1695).

### 5.4.1 Genomewide Search

In the genome-wide search for QTLs for the neurocognitive functions, our primary interest was the analysis of the complete study sample (Com). However, owing to the potential differences in the genetic backgrounds of families collected from an internal isolate, representing a more restricted gene pool, we also analyzed separately the families from the internal isolate (IS) and from the rest of the country (AF).

Several quantitative parameters of verbal learning and memory were found to be linked to chromosome 4q13-25 within a 30-cM region. The best individual two-point and multipoint LOD score values, as presented by SOLAR (Z and Zmp, respectively), for the complete study sample (Com) were obtained for delayed memory to 4q21 (Z = 3.01 to D4S2361; Zmp = 3.84) (Study IV, Table 3, page 1696). Both families from the internal isolate and elsewhere from Finland apparently contributed to these findings, despite slight variations in the relative LOD score values even with nearby locating markers (Study IV, Table 3, pages

1696-1697). Based on variance-component analysis, variation on 4q would account for 33%, 33% and 32% of the variation in delayed memory, semantic clustering and verbal learning, with a residual additive genetic component of 12%, 17% and 20%, and a random environmental contribution of 38%, 33% and 26%, respectively.

Among the measures for attention and working memory, the best evidence of linkage was obtained with visual working memory to chromosome 2q36. A suggestive evidence for linkage was found in the complete study sample at D2S1363 and was contributed to by both AF and IS families (Study IV, Table 3, page 1696). According to variance-component analysis, variation in the 2q would account for 21% of the variation in visual working memory, with a residual additive genetic component of 15% and a random environmental contribution of 49%.

Some evidence of linkage also emerged for executive function on chromosome 9p22, for recognition memory on 10p13 and for visual attention on 15q22 in the complete study sample (Study IV, Table 3, page 1696). Families from the IS sample contributed most to the evidence of the linkage signal on 10p13 and 15q22, and from the AF sample to the signal on 9p22, respectively. In IS families, semantic clustering showed some evidence of linkage to chromosome 1q42, and in the AF families measure of intrusions was suggestively linked to 1q32 (Study IV, Table 4, pages 1697-1698). A genomewide maximum LOD score of 3.05 was obtained in the AF families for delayed memory to D8S1113 on 8q12.

Compared with the QTL analysis, application of the clinical diagnosis greatly reduced the linkage signal in the loci putatively revealed in the present study (Study IV, Table 3, page 1696), reflecting the capacity of the quantitative traits to extract maximal information from the study sample.

5.4.2 Genomewide p-values

In order to assess the relative significance of the most important findings of the current study, we permutated some of the neuropsychological functions and recalculated the data for genome-wide scans using the permutated phenotypes. All adjustments, including adaptation of age and gender as covariates, were identical to those used in the original data analysis. The phenotype permutation was confined to the family members having both phenotype and genotype data.

In 1000 permutated genome scans with visual working memory, we found maximum two-point LOD scores $\geq 2.80$ 93 times, which resulted in an empiric p-

value of 0.093. For functions related to verbal learning and memory, a maximum two-point LOD score $\geq 2.96$ was found 26 times for verbal learning (p = 0.026), a LOD score $\geq 2.86$ 143 times for sematic clustering (p= 0.143), and a LOD score $\geq 3.01$ 31 times for delayed memory (p=0.031). Thus, verbal learning and delayed memory were the functions providing statistically the most significant evidence of linkage in terms of the empiric p-value in the current study.

5.5 COGNITIVE CLUSTERS AMONG FAMILIES REPRESENTING FAMILIAL SCHIZOPHRENIA (STUDY V)

5.5.1 The cluster solution

Three clusters of families were successfully identified from the study sample. The first cluster comprised 94 subjects from 17 families, the second cluster 50 subjects from 12 families, and the third cluster 115 and 25. Adding more neuropsychological test variables or leaving out the sex or the age of the subjects had little effect on the solution.

The data image (Study V, Figure 2, page 5/12) indicated that the overall performance of the subjects was higher in the first cluster than in the second, and that the performance in the third cluster was between the other two. The three clusters were therefore identified as consisting of subjects that were relatively well-performing, impaired and intermediate, respectively. A three cluster solution is supported by the homogeneity of the within-cluster test performance patterns of the proposed groups (Study V, Figure 2, page 5/12). As shown by the dendrogram in the lower part of the figure, the two-cluster solution would combine the impaired and the intermediate clusters, and the four-cluster result would divide the well-performing cluster into two subclusters one of which is very small, consisting only of six families. Stopping the merging process even earlier does not appear to suggest any interesting alternative cluster solutions. Note also the jump in the distance function of Figure 3 (Study V, page 6/12) after three clusters.

5.5.2 Demographic and clinical characteristics

The three clusters did not differ by age or sex distribution. The well performing cluster had significantly more years of education than the two others (p <0.001 in contrasts versus both other clusters). Overall, the clusters did not differ in clinical characteristics, except that the well-performing cluster showed better premorbid adaptation than the intermediate cluster (p = 0.04). The age of onset did not differ

between the clusters (mean 25.9, SD 7.8, mean 24.7, SD 7.6, mean 23.7, SD 7.6 in clusters 1, 2, and 3, respectively, all p-values > 0.20). The impaired cluster did not include any patients with schizoaffective disorder, bipolar disorder or other affective psychotic disorders, while in the well-performing and intermediate clusters, these diagnoses were assigned to 14% and 11% of the subjects, respectively. About 36% of family members in all three clusters were unaffected.

5.5.3 Neuropsychological variables

The impaired cluster scored lowest in all measured neuropsychological variables, and the intermediate cluster showed consistently worse performance than the well-performing one. The differences between the family clusters in the neuropsychological variables were tested by the within-family linear mixed effect models (Study V, Table 4, page 9/13). In these models, the impaired cluster was found to achieve significantly lower scores than both other clusters in almost all traits. The only variable not reaching statistical significance in differentiating any of the clusters was auditory attention.

5.5.4 Effect of education

As the clusters differed significantly from each other in education years, we conducted post hoc linear mixed effects models with family as the fixed effect, and age, sex and education years as the random effects (data not shown). This did not eliminate the significant differences in cognitive functioning between the well-performing and the impaired cluster. In contrasts between the well-performing and intermediate cluster, all other differences remained significant, except in the scores of Visual immediate recall, Digit Symbol, and Verbal fluency, which lost their significance. Between the intermediate and the impaired cluster, scores in Vocabulary and Digit Symbol were no longer significantly different after controlling for education years.

# 6    DISCUSSION

The main aim of the present thesis was to explore whether quantitative traits derived from neuropsychological test data could be successfully used in a genomewide QTL-analysis of schizophrenia patients and their family members. Before coming to this aim, the cognitive test variables, collected from two population based samples with familial schizophrenia, were examined as to their heritability, and the number of their contributing loci was estimated. Furthermore, their association with familial loading in unaffected relatives, and the contribution of this loading on the effect of age at onset on the cognitive functions was examined. A genomewide linkage analysis including the neuropsychological test variables that were considered the most valid endophenotypes was then conducted. For further genetic studies that would benefit from using more homogeneous family data, a family-based cluster analysis was done in order to identify schizophrenia families with similar neuropsychological test performance among the affected and unaffected family members.

6.1  ARE COGNITIVE DYSFUNCTIONS HERITABLE IN SCHIZOPHRENIA?

In the Study I, a sample of genealogically well-defined and genetically homogeneous families with schizophrenia was used to estimate the heritabilities of cognitive traits, and to detect the number of QTLs contributing to these traits. Significant additive heritability estimates were detected in several cognitive functions that reflect the encoding stage during verbal learning. The significantly heritable functions were using semantic clusters while recalling words from a word list, providing words that were not in the list (intrusive recall errors), recognition memory, verbal working memory, and verbal ability. In addition, the heritability estimate of visual working memory was marginally significant. Impairment in the functions during the encoding phase affects on maintenance and retrieval of information, which in turn may cause poor recognition memory and producing recall errors. Slowed encoding affects working memory and impairs the activation of mental representations essential for efficient working memory.

Results in the Study I suggested that dysfunctional encoding was heritable in the studied families with schizophrenia. However, the outcome of verbal learning as measured by the total score of the recalled words in the word list test, showed only suggestive additive heritability in the present study sample, and the number of its contributing loci was dispersed. Still, verbal memory is among the most impaired functions in schizophrenia (Saykin et al 1991;

Heinrichs and Zakzanis 1998; Heinrichs 2004), and impairments are observed in the relatives of schizophrenia patients, too (Faraone et al 1995; Faraone et al 1999a; Egan et al 2001a).

Functions that related to working memory showed the most restricted number of loci, when these were estimated on a theoretical basis. These functions are assumed to reflect frontal lobe functioning and their connections to subcortical areas (Stuss and Benson 1987; Lezak et al 2004). The result suggested that genetic linkage analyses could benefit particularly from using the quantitative data derived from working memory test scores.

The Study I showed that the cognitive traits relating to working memory and such verbal memory functions that associate with the primary encoding phase of learning, are at least modestly heritable in schizophrenia families and could be valuable endophenotypic traits in genetic analyses. Of particular interest would be the traits measuring working memory functions, as they were contributed by a very restricted number of loci in the theoretical estimation of their number.

6.2   COGNITIVE FUNCTIONING IN THE HEALTHY RELATIVES OF SCHIZOPHRENIA PATIENTS: EFFECT OF FAMILIAL LOADING

In the Study II, only the unaffected relatives of the schizophrenia patients were included in the analysis. The subjects were divided into two groups according to the number of first-degree relatives with schizophrenia. The singleton group included healthy relatives with only one family member with schizophrenia, and the multiplex group included those with at least one relative with schizophrenia plus at least another with schizophrenia or other non-affective psychosis. The aim was to study whether individuals from multiplex families perform worse than individuals from singleton families on the cognitive tests. This difference would indicate the effect of familial loading. Only visual working memory showed such an association.

In the study by Faraone et al (2000), relatives from singleton families scored worse than controls in immediate verbal memory, while controls outperformed the relatives from multiplex families in estimated intelligence, logical memory, and immediate visual reproductions. The relatives from multiplex families were worse than those from the singleton families in logical memory and immediate visual memory. The Study II did not find differences between the groups in verbal long-term memory, as the Faraone et al (2000) study did. They used the Logical Memory subtest from WMS-R, while we used the CVLT. The latter is

more than the former a measure of using strategies in verbal learning and memory rather than a measure of pure verbal memory, which may explain the different results.

However, results of the study accord partly with the finding in the Faraone et al (2000) study, in which females from multiply affected families were more impaired than females from the singleton families in verbal memory. In the present study, females from multiply affected families were found to use more primacy in learning word lists than females in the singleton families. High score in this type of serial clustering may indicate an uneffective learning strategy, which usually results in poor performance in other verbal memory tests (Delis et al 1987). It is also interesting to note, that in the Faraone et al (2000) study the second largest difference between the groups was detected in the immediate visual reproductions, whereas the delayed score was not significantly different. This may well represent visual working memory impairments in the multiplex group, which is in accordance with our results.

Lacking a control group, the results of the Study II could only be compared with the mean of national normative data. It was observed that attention and working memory scores were lower than the norms in both groups, but significantly so only among the siblings from multiply affected families. As the study focused specifically on a sample of healthy siblings with no confounding effects of clinical psychiatric symptomatology or medication on neuropsychological performance, all subjects were free from any DSM-IV axis I or axis II psychiatric diagnosis. However, lack of completed diagnoses does not mean that certain psychiatric symptoms could not have been present. The results further supported the validity of the working memory functions, and visual working memory in particular, as valuable endophenotypic traits to be included in genetic linkage studies.

6.3   VERBAL MEMORY DYSFUNCTION ASSOCIATES WITH EARLIER AGE OF ONSET OF SCHIZOPHRENIA

Among 237 patients with schizophrenia, the effect of age of onset on cognitive functions was examined. In verbal memory as measured with the total score of recalled words in the CVLT (Delis et al 1987), in using semantic clusters as a learning strategy, in producing intrusive recall errors, and in recognition memory, worse performance associated with earlier age of onset.

The results of the Study III were in line with previous studies. Verbal memory impairment has consistently been found to associate with earlier onset (Jeste et al

1998; Hambrecht et al 2002; Turetsky et al 2002). Impairments in verbal learning and memory tasks, found to be relatively most impaired in schizophrenia (Saykin et al 1991; Heinrichs and Zakzanis 1998; Heinrichs 2004), are probably present in the initial phase of the disorder. These functions also associate with the most complicated functional consequences of schizophrenia (Green 1996), and should be taken into account in the neuropsychological evaluation and efforts at remediation in patients with early-onset disorder.

Furthermore, familial loading, as measured by the number of affected first-degree relatives, was included in additional models as a possible mediating factor for the effect of age of onset on cognitive functions, but the finding was negative. However, scores in visual working memory and verbal IQ were worse when there were more affected first-degree relatives in the family, irrespective of the age of onset. This result provides further support for the evidence of genetic influence on visual working memory dysfunction in families with schizophrenia.

## 6.4 COGNITIVE TRAITS APPLIED IN A GENOMEWIDE QTL-ANALYSIS

The Study IV applied those quantitative cognitive traits that had previously been suggested as valuable endophenotypic variables in a genomewide QTL-based linkage analysis. The heritabilities of the included traits were found to be significant when reanalyzed in the process of the Study IV (data not shown). All included variables had also been found to associate with the vulnerability of the disorder in previous studies (Park et al 1995; Faraone et al 1999a; Cannon et al 2000b; Egan et al 2000; Myles-Worsley and Park 2002).

Analyses were run separately for the isolate (IS) and all Finland (AF) samples, and for the combined (Com) sample including both. The main interest was in the combined sample, in which the strongest evidence of linkage was obtained for verbal learning and memory functions as measured by the CVLT (Delis et al 1987). The finding that verbal learning and semantic clustering were linked to the same chromosomal region was not surprising, since these traits correlate with each other. Previously, Egan et al (2001a) have detected that siblings of schizophrenia patients have a significant relative risk for impaired performance in verbal learning.

The LOD score on chromosome locus 4q21, marker D4S2361, was 2.87 for semantic clustering, for delayed verbal memory 3.01, and 2.96 for verbal learning. The importance of this region was emphasized by the fact that evidence of linkage was found for other traits related to verbal learning strategies within a

30cM region on 4q13-25. This region has also shown linkage in previous genetic analyses based on clinical diagnosis (Hovatta et al 1999).

Visual working memory has been suggested as a valid quantitative trait in schizophrenia in many studies (Park et al 1995; Cannon et al 2000b; Myles-Worsley and Park 2002), and results from the Studies I-III further supported this view. It has also been used successfully in the first actual QTL-analysis on chromosome 1q32 with cognitive test data among Finnish twins (Gasperoni et al 2003). In the Studies II and III, it showed familial associations both in the unaffected family members and in the patients. In the genomewide linkage analysis of the Study IV, suggestive evidence for visual working memory was detected at chromosome 2q35-36, which is close to a locus detected in a previous linkage study comprising families from the isolate sample and with the diagnosis as the phenotype (Paunio et al 2001). No locus on the chromosome 1 showed linkage in the study IV, which may be caused by the genomewide approach not including all the essential markers.

In the Study IV, which is the first published genomewide QTL-study on neuropsychological test variables used as endophenotypic traits, the linkage information was greatly accentuated by applying these traits as compared with using the clinical dichotomical diagnosis. The results not only confirm and extend previous linkage findings, but also demonstrate the benefit of using trait components instead of clinical diagnoses in genomewide hunt for genes involved in susceptibility to schizophrenia.

6.5   COGNITIVE FUNCTIONING AS A BASIS FOR CLUSTERING FAMILIES WITH SCHIZOPHRENIA

The Study V included 54 families from the whole geographical area of Finland. In all families, there were at least two siblings with schizophrenia, schizoaffective psychosis or schizophreniform disorder, and their unaffected family members. In addition, some family members with affective psychotic disorders were included. The study aimed at identifying families with convergent neuropsychological test performance, including such test variables that in previous studies have been considered potential endophenotypic components in schizophrenia. The rationale for this effort was to allow selecting phenotypically more homogeneous groups of families for subsequent genetic analyses. For this aim, 17 neuropsychological test variables, plus age and sex were incorporated in a visually aided clustering algorithm. This process identified three clusters of families. The first cluster included 17 families with well-performing subjects, the cluster two comprised an

impaired cluster with 12 families, and the third was intermediate with a less clear performance profile in 25 families. The clusters did not differ from each other in age, sex distribution, and, regarding the affected subjects, in the age of onset. The well-performing cluster was better educated than the other two, but covariating with education did not change the main results in comparing the cognitive test differences between the clusters.

The three cluster solution was supported by the homogeneity of the within-group test performance pattern, and a visual exploration of the merging distance process (see Figures 2 and 3 in the Study V, pages 4/12 and 5/12).

The diagnostic distribution among the patients was interesting, as all the patients in the impaired cluster suffered from schizophrenia, and no family members with affective psychotic disorders ended up into this cluster. It can thus be considered to represent a subsample of core schizophrenia with the most impaired cognitive functioning. This cluster included the same proportion of unaffected subjects as the two other clusters, and by the logic of the clustering algorithm, also the unaffected subjects performed poorly in this cluster.

The Study V is the first one in which whole families with schizophrenia has been included in a clustering analysis. Previously, clusters comprising solely patients with schizophrenia have revealed similar groupings and the same number of clusters as ours (Sautter et al 1995; Hill et al 2002; Turetsky et al 2002). The results of the Study V will be exploited in further genomewide analyses, as well as associating them with candidate gene data derived from the present study sample.

6.6 METHODOLOGICAL LIMITATIONS

Several limitations have to be noted. The study sample derived from a geographical isolate may limit the generalizability of the results of all Studies I-V. In the Studies II and III, in which familial loading was operationalized as the number of first-degree relatives with psychotic disorders, the genetic isolate design allows considering only horizontal loading effects, as there may have been vertical genetic connections between the families. This is particularly the case in the Study II, in which only the isolated sample from the northeastern part of Finland was included in the analyses. This study also suffered from the lack of a control group. Furthermore, although the subjects for the study project were randomly selected and carefully diagnosed, they mainly came from families with multiple members with schizophrenia spectrum disorders, which represent only

the fifth part of all schizophrenia cases. Thus the results may apply only when familial schizophrenia is concerned.

Furthermore, the subjects in all studies I-V were rather aged, with the mean age generally over 45 years. Thus some of the dysfunctions observed may have reflected normal deterioration of cognitive function with increased age. However, age was controlled for in each study. The possible medication effects among the affected subjects was not controlled for in any of the studies comprising the present thesis. Many patients were on both typical and atypical neuroleptics, both of which may have enhancing or impairing effects on cognition. Furthermore, the use of anxiolytics and anticholinergics was common. In literature, no consent exists whether medication should be added as a confounding factor in the analyses, and the choice was made here not to take medication effects into account.

Concerning the used neuropsychological tests, which were all well known and internationally used methods, and allow comparison between studies, some concerns arise. This is particularly the case with the measures for attention, and the task that was used to assess visual working memory. The forward verbal or visual span tasks as measures of attention (Lezak et al 2004) may not have been sufficiently powerful for assessing this trait. Performance in specifically forward condition span tasks is suggested not to depend on the function of the prefrontal cortex (for a review, see D´Esposito and Postle, 1999). Generally, attention has been measured in many studies using versions of Continuous Performance Tests, which assess sustained attention (vigilance), or summary measures like Attention Deviance Index (Erlenmayer-Kimling and Cornblatt 1992; Cornblatt and Keilp 1994; Cornblatt et al 1999; Erlenmayer-Kimling 2000). It is possible that such measures would have given more interesting results concerning the genetic effects of attention in the present studies, too.

The majority of studies on the visuospatial working memory in schizophrenia has employed the delayed response task (DRT) (e.g. Park et al 1995; Myles-Worsley and Park 2002), while only a few have used the visual span task as was done in the present studies (Cannon et al 2000b; Gasperoni et al 2003). The visual span subtest of the WMS-R (Wechsler 1987) is a complex task involving immediate memory, maintenance, memory of sequence, and a motor response, including volition to initiate the response. In addition, the task requires encoding-related processes (Glahn et al 2003), and storage processes of working memory (D'Esposito and Postle 1999). The motor planning to give the response may demand working memory as well (Saper et al 2000). Thus, the span test may be

reflecting interactions between subsystems or processes of working memory (Fischer 2001). However, the results of the present thesis showed that the backward visual span, which may require more central working memory (Chey et al 2002) was associated with genetic effects among the unaffected subjects (Study II), in the patients (Study III), and in combined samples (Studies I, IV and V).

Furthermore, the test battery that was applied in the present thesis, did not include certain important measures that have shown genetic associations and could have produced valid endophenotypic variables. These include the Wisconsin Card Sorting Test (WCST, Heaton et al 1981), a measure of executive functioning, that has been succesfully used in the studies of the associations of the prefrontal cortex functioning and the COMT gene (e.g. Egan et al 2001b), although recently these results have not been replicated (Rosa et al 2004). Furthermore, certain novel computerized test paradigms, for example the n-back test assessing working memory functions, were not included. However, all the included test measures covered those areas of functioning that have been found impaired in schizophrenia, i.e. attention, memory, and executive functioning.

Although the heritability issue and the familial and genetic effects were approached from many angles, the fundamental criterion of an endophenotype - the heritability - was estimated when only a part of the targeted sample of families was collected. Thus, the heritability of neuropsychological test variables was estimated among 264 subjects, 171 affected and 93 unaffected, from 131 families living at the Kuusamo isolate. If a larger sample would have been included, the heritability estimates would most probably have been higher. Moreover, it is possible that controlling for verbal ability in the heritability analyses of the Study I reduced the particularly the verbal memory estimates. Indeed, when the heritabilities were estimated again for the Study IV, with age and sex as the only covariates, markedly enhanced estimates were received (data not shown). This was particularly the case with verbal learning as measured by the CVLT total score in trials 1-5.

It is not very well known how heritable the cognitive functions are among the general population. Heritability estimates associated with cognitive functions may reflect true biological factors, but their association with schizophrenia is not necessarily evidenced. Relatives share environments as well as genes. It is possible that other modeling with factors of bias potential (e.g. shared deviant rearing environment, assortative mating, or gene-environmental interaction) would have given different results and in part explain those features that were assumed to be genetically inherited in the Study I.

6.7 GENERAL DISCUSSION AND IMPLICATIONS FOR FURTHER RESEARCH

The cognitive functions that were included in the studies comprising the present thesis proved at least modestly heritable among a representative population sample of families with schizophrenia.

The present study showed that particularly the cognitive traits associated with verbal learning and memory increased markedly the LOD scores of linkage compared with the use of categorical diagnosis. Although not very strong familial effects contributing to this trait were detected in the Studies I-III, it is unquestionably one of the most impaired cognitive functions in schizophrenia, and is also observed in non-psychotic relatives of the patients. The importance of the results is emphasized by the previous evidence of linkage, using the same study population, to the same region using the clinical diagnosis as the phenotype (Paunio et al 2001). However, the LOD scores received here were still moderate, suggesting that the traits assumed to be endophenotypes of schizophrenia proved out not to be highly sensitive at least on the markers included in the genomewide scan. Moreover, their specificity to schizophrenia remains unknown. Studies on the genetic factors of cognitive functions in other psychiatric family samples, and in the general population would be highly required for receiving reference data for further studies like the present one.

Visual working memory was the variable that consistently showed familial and genetic effects in samples of both unaffected family members and patients with schizophrenia in the Studies I-III. However, the results in the present genomewide linkage analysis with data from 449 markers still left open questions of the validity of this cognitive endophenotype. Further hypothesis driven analyses, utilizing both the knowledge of the neurobiological basis of this function and denser marker data are warranted.

Kéri and Janka (2004) have presented a critical approach on the use of cognitive dysfunctions as endophenotypes of schizophrenia. Identifying altogether 82 relevant papers in a detailed review, they investigated the reliability and frequency of cognitive impairments in individuals with schizophrenia and their biological relatives. Kéri and Janka brought up the important fact that although a wide range of cognitive dysfunctions are present in patients as well as in their relatives, there exists a substantial proportion of patients and relatives with preserved cognition (Kéri and Janka 2004). Furthermore, Heinrichs (2004) in his important paper, states that although group differences suggest adequate temporal stability for many

biobehavioral measures, individual patients often fluctuate between impaired and unimpaired performance over time. Not all patients demonstrate trait-like performance, perhaps due to the nonspecific influence that may be transitory in nature (Heinrichs 2004). Kéri and Janka (2004) concluded that at present, cognitive dysfunctions can not be considered highly sensitive and specific endophenotypes. Indeed, there is evidence that e.g. executive dysfunction is observed both in schizophrenia and bipolar disorder. However, according to the review by Kéri and Janka (2004), elementary visual processing, verbal episodic memory, and spatial working memory seem to be among the most promising endophenotypic functions. The results of the present thesis, including the last two variables from this list, proved their promise at least on a modest level.

Further QTL linkage studies with denser marker data, probably looking at one chromosome at a time, or association studies on the promising candidate genes of schzophrenia, are highly warranted. The preliminary QTL analysis, conducted by Gasperoni et al (2003) is one example of such a study. Our study group has conducted a hypothesis based association analysis using certain cognitive traits and the DISC1 gene and its associated haplotypes (Hennah et al, submitted), and even the two SNPs comprising one of the most interesting haplotype (Tuulio-Henriksson et al 2004) with interesting results of these associations.

Furthermore, future will show whether the cluster analysis aiming at detecting more homogeneous subgroups of families with schizophrenia will be fruitful in genomewise linkage analyses and candidate gene association analyses. A refined definition of the phenotype of schizophrenia may also be attained by including both neuropsychological and other clinical data simultaneously into clustering paradigms.

Although the results of the present study do not produce direct clinical implications, they clearly show the importance of the clinical neuropsychological assessment of a schizophrenia patient. In fact, the last two decades during which the cognitive deficits in schizophrenia have been considered as one type of core symptoms of the disorder, implicate a neuropsychological assessment to a patient with schizophrenia should be a routine in clinical practice. Although this assessment may not be of help for the diagnosis, it has important contributions to understanding the course of cognitive impairment, as well as its relationship with the functional consequences of the disorder. For patients with early onset, and for the first-episode patients, this is of particular importance.

The studies comprising the present thesis stand for basic schizophrenia research aiming at giving tools for the research on the biological processes that lay behind the vulnerability to the disorder. Further studies on the neurobiology of the cognitive dysfunctions that have been shown to be familial, and possibly genetic, may lead to elucidating the genetic background of schizophrenia. Studies on the cognitive dysfunction in schizophrenia may help in understanding better the environmental and individual possibilities for preventing the psychosocial problems that still today are reality for too many patients with this disorder.

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# 8    REFERENCES

Addington J, Addington D, Maticka-Tyndale E. Cognitive functioning and positive and negative symptoms in schizophrenia. Schizophrenia Research 1991; 4:123-134.

Addington J, Brooks BL, Addington D. Cognitive functioning in first episode psychosis: initial presentation. Schizophrenia Research 2003; 62:59-64.

Albus M, Hubmann W, Wahlheim C, Sobizack N, Franz U, Mohr F. Contrasts in neuropsychological test profile between patients with first-episode schizophrenia and first-episode affective disorders. Acta Psychiatrica Scandinavica 1996; 94:87-93.

Aleman A, Hijman R, de Haan EHF, Kahn RS. Memory impairment in schizophrenia: a meta-analysis. American Journal of Psychiatry 1999; 159:1358-1366.

Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees.
American Journal of Human Genetics 1998; 62:1198-1211.

Almasy L, Blangero J, Gur RC, Gur RE. Heritability of neurocognitive correlates of schizophrenia. American Journal of Medical Genetics 2000; 96:508. Abstract.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association, 1994.

Andreasen NC. Schizophrenia: the fundamental questions. Brain Research Reviews 2000; 31:106-112.

Andreasen NC.  Understanding the causes of schizophrenia. New England Journal of Medicine 1999; 340:645-647.

Appels MC, Sitskoorn MM, Westers P, Lems E, Kahn RS. Cognitive dysfunctions in parents of schizophrenic patients parallel the deficits found in patients. Schizophrenia Research 2003; 63:285-293.

Baddeley A. The fractionation of working memory. Proceedings of the National Academy of Sciences of the United States of America 1996; 93:13468-13472.

Baddeley A. Working memory. Science 1992; 255:556-559.

Battle YL, Martin BC, Dorfman JH, Miller LS. Seasonality and infectious disease in schizophrenia: the birth hypothesis revisited. Journal of Psychiatric Research 1999; 33:501-509.

Benton AL, Hamsher K. Multilingual Aphasia Examination Manual. Iowa City: University of Iowa, 1989.

Bilder RM, Goldman RS, Robinson D, Reiter G, Bell L, Bates JA, Pappadopulos E, Willson DF, Alvir JM, Woerner MG, Geisler S, Kane JM, Lieberman JA. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. American Journal of Psychiatry 2000; 157:549-559.

Blackwood DH, StClair DM, Muir WJ, Duffy JC. Auditory P300 and eye tracking dysfunction in schizophrenic pedigrees. Archives of General Psychiatry 1991; 48:899-909.

Brébion G, Amador X, Smith MJ, Gorman JM. Memory impairment and schizophrenia: the role of processing speed. Schizophrenia Research 1998; 30:31-39.

Brown AS, Cohen P, Harkavy-Friedman J, Babulas V, Malaspina D, Gorman JM, Susser ES. Prenatal rubella, premorbid abnormalities, and adult schizophrenia. Biological Psychiatry 2001; 49:473-486.

Brown AS, Susser ES. In utero infection and adult schizophrenia. Mental Retardation and Developmental Disabilities Research Reviews 2002; 8:51-57.

Brown S. Excess mortality of schizophrenia: a meta-analysis. British Journal of Psychiatry 1997; 171:502-508.

Cadenhead KS, Perry W, Shafer K, Braff KS. Cognitive functions in schizotypal personality disorder. Schizophrenia Research 1999; 37:123-132.

Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. American Journal of Psychiatry 2003; 160:2209-2215.

Cannon M, Jones P, Huttunen M, Tanskanen A, Huttunen T, Rabe-Hesketh S, Murray R. School performance in Finnish children and later development of schizophrenia. Archives of General Psychiatry 1999; 56:67-74.

Cannon TD, Bearden CE, Hollister JM, Rosso IM, Sanchez LE, Hadley T. Childhood cognitive functioning in schizophrenia patients and their unaffected siblings: a prospective cohort study. Schizophrenia Bulletin 2000a; 26:379-393.

Cannon TD, Huttunen MO, Lönnqvist J, Tuulio-Henriksson A, Pirkola T, Glahn D, Finkelstein J, Hietanen M, Kaprio J, Koskenvuo M. The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia. American Journal of Human Genetics 2000b; 67:369-382.

Cannon TD, Kaprio J, Lönnqvist J, Huttunen M, Koskenvuo M. The genetic epidemiology of schizophrenia in a Finnish twin cohort. A population-based modeling study. Archives of General Psychiatry 1998; 55:67-74.

Cannon TD, Thompson PM, van Erp TG, Toga AW, Poutanen VP, Huttunen M, Lönnqvist J, Standerskjöld-Nordenstam CG, Narr KL, Khaledy M, Zoumalan CI, Dail R, Kaprio J. Cortex mapping reveals regionally specific patterns of genetic and disease-specific gray-matter deficits in twins discordant for schizophrenia. Proceedings of the National Academy of Sciences of the United States of America 2002a; 99:3228-3233.

Cannon TD, van Erp TG, Rosso IM, Huttunen M, Lönnqvist J, Pirkola T, Salonen O, Valanne L, Poutanen VP, Standertskjöld-Nordenstam CG. Fetal hypoxia and structural brain abnormalities in schizophrenic patients, their siblings, and controls. Archives of General Psychiatry 2002b; 59:35-41.

Cannon TD, Zorrilla LE, Shtasel D, Gur RE, Gur RC, Marco EJ, Moberg P, Price RA. Neuropsychological functioning in siblings discordant for schizophrenia and healthy volunteers. Archives of General Psychiatry 1994; 51:651-661.

Cardno AG, Marshall EJ, Coid B, Macdonald AM, Ribchester TR, Davies NJ, Venturi P, Jones LA, Lewis SW, Sham PC, Gottesman II, Farmer AE, McGuffin P, Reveley AM, Murray RM. Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. Archives of General Psychiatry 1999; 56:162-168.

Censits DM, Ragland JD, Gur RC, Gur RE. Neuropsychological evidence supporting a neurodevelopmental model of schizophrenia: a longitudinal study. Schizophrenia Research 1997; 24:289-298.

Chan RC, Chen EY, Cheung EF, Cheung HK. Executive dysfunctions in schizophrenia. Relationships to clinical manifestation. European Archives of Psychiatry and Clinical Neurosciences 2004; 254:256-62.

Chey J, Lee J, Yong-Sik K, Suk-Man K, Young-Min S. Spatial working memory span, delayed response and executive function in schizophrenia. Psychiatry Research 2002; 110:259-271

Cirillo MA, Seidman LJ. Verbal declarative memory dysfunction in schizophrenia: From clinical assessment to genetics and brain mechanisms. Neuropsychology Review 2003; 13:43-77.

Cohen J. Statistical power analysis for the behavioral sciences, 2nd ed. Hillsdale, New Jersey: Lawrence Earlbaum, 1988.

Conklin HM, Curtis CE, Katsanis J, Iacono WG. Verbal working memory impairment in schizophrenia patients and their first-degree relatives: evidence from the digit span task. American Journal of Psychiatry 2000; 157:275-277.

Conklin HM, Calkins ME, Anderson CW, Dinzeo TJ, Iacono WG. Recognition memory for faces in schizophrenia patients and their first-degree relatives. Neuropsychologia 2003; 40:2314-2324.

Cornblatt BA, Keilp JG. Impaired attention, genetics, and the pathophysiology of schizophrenia. Schizophrenia Bulletin 1994; 20:31-46.

Cornblatt BA, Malhotra AK. Impaired attention as an endophenotype for molecular genetic studies of schizophrenia. American Journal of Medical Genetics 2001; 105:11-15.

Cornblatt B, Obuchowski M, Schnur D, O´Brien JD. Attention and clinical symptoms in schizophrenia. Psychiatric Quarterly 1997; 68:343-359.

Cornblatt B, Obuchowski M, Roberts S, Pollack S, Erlenmeyer-Kimling L. Cognitive and behavioral precursors of schizophrenia. Development and Psychopathology 1999; 11:487-508.

Davidson M, Harvey PD, Powchik P, Parrella M, White L, Knobler HY, Losonczy MF, Keefe RS, Katz S, Frecska E. Severity of symptoms in chronically institutionalized geriatric schizophrenic patients. American Journal of Psychiatry 1995; 152:197-207.

Davidson M, Reichenberg A, Rabinowitz J, Weiser M, Kaplan Z, Mark M. Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. American Journal of Psychiatry 1999; 156:1328-1335.

Davies G, Welham J, Chant D, Torrey EF, McGrath J. A systematic review and meta-analysis of Northern Hemisphere season of birth studies in schizophrenia. Schizophrenia Bulletin 2003; 29:587-593.

Delis DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test. Manual. Research Edition. The Psychological Corporation. San Antonio: Harcourt Brace & Company, 1987.

D'Esposito M, Postle BR. The dependence of span and delayed response performance on prefrontal cortex. Neuropsychologia 1999; 37:1303-1315.

Dickerson FB, Sommerville J, Origoni AE, Ringel NB, Parente F. Outpatients with schizophrenia and bipolar I disorder: Do they differ in their cognitive and social functioning? Psychiatry Research 2001; 102:21-27.

Egan MF, Goldberg TE. Intermediate cognitive phenotypes associated with schizophrenia. Methods in Molecular Medicine 2003; 77:163-197.

Egan MF, Goldberg TE, Gscheidle T, Weirich M, Bigelow LB, Weinberger DR. Relative risk of attention deficits in siblings of patients with schizophrenia. American Journal of Psychiatry 2000; 157:1309-1316.

Egan MF, Goldberg TE, Gscheidle T, Weirich M, Rawlings R, Hyde TM, Bigelow L, Weinberger DR. Relative risk for cognitive impairments in siblings of patients with schizophrenia. Biological Psychiatry 2001a; 50:98-107.

Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR. Effect of COMT Val108/158Met genotype on frontal lobe functioning and risk for schizophrenia. Proceedings of the National Academy of Sciences of the United States of America 2001b; 98:6917-6922

Egan MF, Leboyer M, Weinberger DR. Intermediate phenotypes in genetic studies of schizophrenia. In SR Hirsch and DR Weinberger (Eds.) Schizophrenia. Massachusetts: Blackwell Science, Inc., 2003.

Ekelund J, Hennah W, Hiekkalinna T, Parker A, Meyer J, Lönnqvist J, Peltonen L. Replication of 1q42 linkage in Finnish schizophrenia pedigrees. Molecular Psychiatry 2004; 9:1037-1041.

Ekelund J, Hovatta I, Parker A, Paunio T, Varilo T, Martin R, Suhonen J, Ellonen P, Chan G, Sinsheimer JS, Sobel E, Juvonen H, Arajarvi R, Partonen T, Suvisaari J, Lonnqvist J, Meyer J, Peltonen L. Chromosome 1 loci in Finnish schizophrenia families. Human Molecular Genetics 2001; 10:1611-1617.

Ekelund J, Lichtermann D, Hovatta I, Ellonen P, Suvisaari J, Terwilliger JD, Juvonen H, Varilo T, Arajärvi R, Kokko-Sahin ML, Lönnqvist J, Peltonen L. Genome-wide scan for schizophrenia in the Finnish population: evidence for a locus on chromosome 7q22. Human Molecular Genetics 2000; 9:1049-1057.

Elliott R, McKenna PJ, Robbins TW, Sahakian BJ. Neuropsychological evidence for frontostriatal dysfunction in schizophrenia. Psychological Medicine 1995; 25:619-630.

Elvevåg B, Goldberg TE. Cognitive impairment in schizophrenia is the core of the disorder. Critical Reviews in Neurobiology 2000; 14:1-21.

Erlenmeyer-Kimling L. Neurobehavioral deficits in offspring of schizophrenic parents: liability indicators and predictors of illness. American Journal of Medical Genetics 2000; 97:65-71.

Erlenmeyer-Kimling L, Cornblatt BA. A summary of attentional findings in the New York High-Risk Project. Journal of Psychiatric Research 1992; 26:405-426.

Erlenmeyer-Kimling L, Rock D, Roberts SA, Janal M, Kestenbaum C, Cornblatt B, Adamo UH, Gottesman II. Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York High-Risk Project. American Journal of Psychiatry 2000; 157:1416-1422.

Eyler Zorrilla LT, Jeste DV, Paulus M, Brown GG. Functional abnormalities of medial temporal cortex during novel picture learning among patients with chronic schizophrenia. Schizophrenia Research 2003; 59:187-198.

Faraone SV, Seidman LJ, Kremen WS, Kennedy D, Makris N, Caviness VS, Goldstein J, Tsuang MT. Structural brain abnormalities among relatives of patients with schizophrenia: implications for linkage studies. Schizophrenia Research 2003; 60:125-140.

Faraone SV, Seidman LJ, Kremen WS, Pepple JR, Lyons MJ, Tsuang MT. Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: a diagnostic efficiency analysis. Journal of Abnormal Psychology 1995; 104:286-304.

Faraone SV, Seidman LJ, Kremen WS, Toomey R, Pepple JR, Tsuang MT. Neuropsychologic functioning among the nonpsychotic relatives of schizophrenic patients: the effect of genetic loading. Biological Psychiatry 2000; 48:120-126.

Faraone SV, Seidman LJ, Kremen WS, Toomey R, Pepple JR, Tsuang MT. Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: a 4-year follow-up study. Journal of Abnormal Psychology 1999a; 108:176-181.

Faraone SV, Tsuang MT, Tsuang DW. Genetics of Mental Disorders. A Guide for Students, Clinicians, and Researchers. New York: The Guildford Press, 1999b.

First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders – Clinician Version (SCID-CV). Washington, DC: American Psychiatric Press, 1997.

Fischer MH. Probing spatial working memory with the Corsi Block task. Brain and Cognition 2001; 45:143-154.

Fleck DE, Sax KW, Strakowski SM. Reaction time measures of sustained attention differentiate bipolar disorder from schizophrenia. Schizophrenia Research 2001; 52:251-259.

Freedman R. Schizophrenia. New England Journal of Medicine 2003; 349:1738-1749.

Freedman R, Adler LE, Leonard S. Alternative phenotypes for the complex genetics of schizophrenia. Biological Psychiatry 1999; 45:551-558.

Fucetola R, Seidman LJ, Kremen WS, Faraone SV, Goldstein JM, Tsuang MT. Age and neuropsychologic function in schizophrenia: a decline in executive abilities beyond that observed in healthy volunteers. Biological Psychiatry 2000; 48:137-146.

Fuller RLM, Schultz SK, Andreasen NC. The symptoms of schizophrenia. In SR Hirsch and DR Weinberger (Eds.) Schizophrenia. Massachusetts: Blackwell Science, Inc., 2003.

Garver DL, Holcomb JA, Christensen JD. Heterogeneity of response to antipsychotics from multiple disorders in the schizophrenia spectrum. Journal of Clinical Psychiatry 2000; 61:964-972.

Gaser C, Nenadic I, Buchsbaum BR, Hazlett EA, Buchsbaum MS. Ventricular enlargement in schizophrenia related to volume reduction of the thalamus, striatum, and superior temporal cortex. American Journal of Psychiatry 2004; 161:154-156.

Gasperoni TL, Ekelund J, Huttunen M, Palmer CG, Tuulio-Henriksson A, Lönnqvist J, Kaprio J, Peltonen L, Cannon TD. Genetic linkage and association between chromosome 1q and working memory function in schizophrenia. American Journal of Medical Genetics 2003; 116B:8-16.

Gilvarry C, Takei N, Russell A, Rushe T, Hemsley D, Murray RM. Premorbid IQ in patients with functional psychosis and their first-degree relatives. Schizophrenia Research 2000; 41:417-29.

Glahn DC, Therman S, Manninen M, Huttunen M, Kaprio J, Lönnqvist J, Cannon TD. Spatial working memory as an endophenotype for schizophrenia. Biological Psychiatry 2003; 53:624-626.

Gold JM, Carpenter C, Randolph C, Goldberg TE, Weinberger DR. Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. Archives of General Psychiatry 1997; 54:159-165.

Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, Goldman D, Weinberger DR. Executive subprocesses in working memory:

relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. Archives of General Psychiatry 2003; 60:889-896.

Goldberg TE, Ragland JD, Torrey EF, Gold JM, Bigelow LB, Weinberger DR. Neuropsychological assessment of monozygotic twins discordant for schizophrenia. Archives of General Psychiatry 1990; 47:1066-1072.

Golden C. Stroop Color and Word Test: Manual for Clinical and Experimental Uses. Chicago: Stoelting, 1978.

Goldman-Rakic PS. The physiological approach: functional architecture of working memory and disorganized cognition in schizophrenia. Biological Psychiatry 1999; 46: 650-661.

Goldman-Rakic PS, Selemon LD. functional and anatomical aspects of prefrontal pathology in schizophrenia. Schizophrenia Bulletin 1997; 23:437-458.

Goldstein G, Shemansky WJ, Allen DN. Cognitive function in schizoaffective disorder and clinical subtypes of schizophrenia. Archives of Clinical Neuropsychology 2005; 20:153-159.

Gottesman II, Erlenmeyer-Kimling L. Family and twin strategies as a head start in defining prodromes and endophenotypes for hypothetical early-interventions in schizophrenia. Schizophrenia Research 2001; 51:93-102.

Gottesman II, Gould TD. The endophenotypic concept in psychiatry: Etymology and strategic intentions. American Journal of Psychiatry 2003; 160:636-645.

Gottesman II, Hanson DR. Human Development: Biological and Genetic Processes. Annual Reviews in Psychology 2005; 56:263-286.

Gottesman II, Shields J. A polygenic theory of schizophrenia. Proceedings of the National Academy of Sciences of the United States of America 1967; 1:199-205.

Gottesman II, Shields J. Schizophrenia. The Epigenetic Puzzle. Cambridge: Cambridge University Press, 1982.

Gould TD, Manji HK. The molecular medicine revolution and psychiatry: bridging the gap between basic neuroscience research and clinical psychiatry. Journal of Clinical Psychiatry 2004; 65:598-604.

Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? American Journal of Psychiatry 1996; 153:321-330.

Green MF, Kern PS, Braff DL, Minz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophrenia Bulletin 2000; 19:797-804.

Hambrecht M, Lammertink M, Klosterkotter J, Matuschek E, Pukrop R. Subjective and objective neuropsychological abnormalities in a psychosis prodrome clinic. British Journal of Psychiatry 2002; 181(S43): 30-37.

Harris JM, Whalley H, Yates S, Miller P, Johnstone EC, Lawrie SM. Abnormal cortical folding in high-risk individuals: a predictor of the development of schizophrenia? Biological Psychiatry 2004; 56:182-189.

Harrison PJ. The hippocampus in schizophrenia: a review of the neuropathological evidence and its pathophysiological implications. Psychopharmacology 2004; 174:151-62.

Harrison PJ. The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain 1999; 122:593-624.

Harrison PJ, Freemantle N, Geddes JR. Meta-analysis of brain weight in schizophrenia. Schizophrenia Research 2003; 64:25-34.

Harrison PJ, Owen MJ. Genes for schizophrenia? Recent findings and their pathophysiological implications. Lancet 2003; 361:417-419.

Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Molecular Psychiatry 2005; 10:40-68.

Haukka J, Suvisaari J, Varilo T, Lönnqvist J. Regional variation in the incidence of schizophrenia in Finland: a study of birth cohorts born from 1950 to 1969. Psychological Medicine 2001; 31:1045-53.

Heath SC. Markov Chain Monte Carlo segregation and linkage analysis for oligogenic models. American Journal of Human Genetics 1997; 61:758-760.

Heaton RK. Wisconsin Card Sorting Test. Odessa: Psychological Assessement Resources, 1981.

Heaton RK, Gladsjo JA, Palmer BW, Kuck J, Marcotte TD, Jeste DV. Stability and course of neuropsychological deficits in schizophrenia. Archives of General Psychiatry 2001; 58:24-32.

Heinrichs RW. In Search of Madness. Schizophrenia and Neuroscience. New York: Oxford University Press, 2001.

Heinrichs RW. Meta-analysis and the science of schizophrenia: variant evidence or evidence of variants? Neuroscience and Biobehavioral Reviews 2004; 28:379-394.

Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 1998; 12:426-445.

Hennah W, Tuulio-Henriksson A, Paunio T, Ekelund J, Varilo T, Partonen T, Cannon TD, Lönnqvist J, Peltonen L. A haplotype from the DISC1 gene associates with visual working memory. Submitted.

Hennah W, Varilo T, Kestilä M, Paunio T, Arajärvi R, Haukka J, Parker A, Martin R, Levitzky S, Partonen T, Meyer J, Lönnqvist J, Peltonen L, Ekelund J. Haplotype transmission analysis provides evidence of association for DISC1 to schizophrenia and suggests sex-dependent effects. Human Molecular Genetics 2003; 12:3151-3159.

Hijman R, Hulshoff Pol HE, Sitskoorn MM, Kahn RS. Global intellectual impairment does not accelerate with age in patients with schizophrenia: a cross-sectional analysis. Schizophrenia Bulletin 2003; 29:509-517.

Hill SK, Ragland DJ, Gur RC, Gur RE. Neuropsychological profiles delineate distinct profiles of schizophrenia, an interaction between memory and executive function, and uneven distribution of clinical subtypes. Journal of Clinical and Experimental Neuropsychology 2002; 24:765-780.

Hoff AL, Shukla S, Aronson T, Cook B, Ollo C, Baruch S, Jandorf L, Schwartz J. Failure to differentiate bipolar disorder from schizophrenia on measures of neuropsychological function. Schizophrenia Research 1990; 3:253-260.

Hollister JM, Laing P, Mednick SA. Rhesus incompatibility as a risk factor for schizophrenia in male adults. Archives of General Psychiatry 1996; 53:19-24.

Hovatta I, Varilo T, Suvisaari J, Terwilliger JD, Ollikainen V, Arajärvi R, Juvonen H, Kokko-Sahin ML, Väisänen L, Mannila H, Lönnqvist J, Peltonen L. A genomewide screen for schizophrenia genes in an isolated Finnish subpopulation, suggesting multiple susceptibility loci. American Journal of Human Genetics 1999; 65:1114-1124.

Hughes C, Kumari V, Soni W, Das M, Binneman B, Drozd S, O´Neill S, Mathev V, Sharma T. Longitudinal study of symptoms and cognitive function in chronic schizophrenia. Schizophrenia Research 2003; 59:137-146.

Hultman CM, Ohman A, Cnattingius S, Wieselgren IM, Lindstrom LH. Prenatal and neonatal risk factors for schizophrenia. British Journal of Psychiatry 1997; 170:128-33.

Hyde TM, Nawroz S, Goldberg TE, Bigelow LB, Strong D, Ostrem JL, Weinberger DR, Kleinman JE. Is there cognitive decline in schizophrenia? A cross-sectional study. British Journal of Psychiatry 1994; 164:494-500.

Häfner H, an der Heiden W. Course and outcome of schizophrenia. In SR Hirsch and DR Weinberger (Eds.) Schizophrenia. Massachusetts: Blackwell Science, Inc., 2003.

Häfner H, Löffler W, Maurer K, Hambrecht M, van der Heiden W. Depression, negative symptoms, social stagnation and social decline in the early course of schizophrenia. Acta Psychiatrica Scandinavica 1999; 100:105-118.

Jessen F, Scheef L, Germeshausen L, Tawo Y, Kockler M, Kuhn KU, Maier W, Schild HH, Heun R. Reduced hippocampal activation during encoding and recognition of words in schizophrenia patients. American Journal of Psychiatry 2003; 160:1305-1312.

Jeste DV, McAdams LA, Palmer BW, Braff D, Jernigan TL, Paulsen JS, Stout JC, Symonds LL, Bailey A, Heaton RK. Relationship of neuropsychological and MRI measures to age of onset of schizophrenia. Acta Psychiatrica Scandinavica 1998; 98:156-164.

Job DE, Whalley HC, McConnell S, Glabus M, Johnstone EC, Lawrie SM. Structural gray matter differences between first-episode schizophrenics and normal controls using voxel-based morphometry. Neuroimage 2002; 17:880-889.

Johnson J, Tuulio-Henriksson A, Pirkola T, Huttunen MO, Lönnqvist J, Kaprio J, Cannon TD. Do schizotypal symptoms mediate the relationship between genetic risk for schizophrenia and impaired neuropsychological performance in co-twins of schizophrenic patients? Biological Psychiatry 2003; 54:1200-1204.

Jones P, Rodgers B, Murray R, Marmot M. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet 1994; 344:1398-402.

Kathmann N, Hochrein A, Uwer R, Bondy B. Deficits in gain of smooth pursuit eye movements in schizophrenia and affective disorder patients and their unaffected relatives. American Journal of Psychiatry 2003; 160:696-702.

Keefe RS. The contribution of neuropsychology to psychiatry. American Journal of Psychiatry 1995; 152:6-15.

Keefe RS, Eesley CE, Poe MP. Defining a cognitive function decrement in schizophrenia. Biological Psychiatry 2005; 57:688-691.

Keefe RS, Seidman LJ, Christensen BK, Hamer RM, Sharma T, Sitskoorn MM, Lewine RR, Yurgelun-Todd DA, Gur RC, Tohen M, Tollefson GD, Sanger TM, Lieberman JA.   Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. American Journal of Psychiatry 2004; 161:985-995.

Keefe RS; Silva SG, Perkins DO, Lieberman JA. The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. Schizophrenia Bulletin 1999; 25:201-222.

Kenny JT, Meltzer HY. Attention and higher cortical functions in schizophrenia. Journal of Neuropsychiatry 1991; 3:269-275.

Keri S, Janka Z. Critical evaluation of cognitive dysfunctions as endophenotypes of schizophrenia. Acta Psychiatrica Scandinavica 2004; 110:83-91.

Keshavan MS, Diwadkar VA, Spencer SM, Harenski KA, Luna B, Sweeney JA. A preliminary functional magnetic resonance imaging study in offspring of schizophrenic parents. Progress in neuro-psychopharmacology & biological psychiatry 2002; 26:1143-1149.

Kieseppä T, Tuulio-Henriksson A, Haukka J, van Erp T, Glahn D, Cannon TD, Partonen T, Kaprio J, Lönnqvist J. Memory and verbal learning functions in twins with bipolar-I disorder, and the role of information processing speed. Psychological Medicine 2005; 35:205-215.

Klosterkotter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F. Diagnosing schizophrenia in the initial prodromal phase. Archives of General Psychiatry 2001; 58:158-164.

Kremen WS, Buka SL, Seidman LJ, Goldstein JM, Koren D, Tsuang MT. IQ decline during childhood and adult psychotic symptoms in a community sample: a 19-year longitudinal study. American Journal of Psychiatry 1998; 155:672-677.

Kremen WS, Seidman LJ, Faraone SV, Toomey R, Tsuang MT. The paradox of normal neuropsychological function in schizophrenia. Journal of Abnormal Psychology 2000; 109:743-752.

Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F, Goff D, West WC, Williams SC, van der Kouwe AJ, Salat DH, Dale AM, Fischl B. Regionally localized thinning of the cerebral coretx in schizophrenia. Archives of General Psychiatry 2003; 60:878-888.

Kurtz M. Neurocognitive impairment across the lifespan in schizophrenia: an update. Schizophrenia Research 2005; 74:15-26.

Lange K, Weeks D, Boehnke M. Programs for Pedigree Analysis: Mendel, Fisher, and dGene. Genetic Epidemiology 1988; 5:471-472.

Lawrie SM, Abukmeil SS. Brain abnormality in schizophrenia - a systematic and quantitative review of volumetric magnetic resonance imaging studies. British Journal of Psychiatry 1998; 172:110-120.

Lawrie SM, Byrne M, Miller P, Hodges A, Clafferty RA, Cunningham Owens DG, Johnstone EC. Neurodevelopmental indices and the development of

psychotic symptoms in subjects at high risk of schizophrenia. British Journal of Psychiatry 2001; 178:524-530.

Lencz T, Conblatt B, Bilder RM. Neurodevelopmental models of schizophrenia: Pathophysiologic synthesis and directions for intervention research. Psychopharmacology Bulletin 2001; 35:95-125.

Lewis CM, Levinson DF, Wise LH, DeLisi LE, Straub RE, Hovatta I, Williams NM, Schwab SG, Pulver AE, Faraone SV, Brzustowicz LM, Kaufmann CA, Garver DL, Gurling HM, Lindholm E, Coon H, Moises HW, Byerley W, Shaw SH, Mesen A, Sherrington R, O'Neill FA, Walsh D, Kendler KS, Ekelund J, Paunio T, Lönnqvist J, Peltonen L, O'Donovan MC, Owen MJ, Wildenauer DB, Maier W, Nestadt G, Blouin JL, Antonarakis SE, Mowry BJ, Silverman JM, Crowe RR, Cloninger CR, Tsuang MT, Malaspina D, Harkavy-Friedman JM, Svrakic DM, Bassett AS, Holcomb J, Kalsi G, McQuillin A, Brynjolfson J, Sigmundsson T, Petursson H, Jazin E, Zoega T, Helgason T. Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Schizophrenia. American Journal of Human Genetics 2003; 73:34-48.

Lewis DA, Levitt P. Schizophrenia as a disorder of neurodevelopment. Annual Review of Neuroscience 2002; 25:409-432.

Lezak MD, Howieson DB, Loring DW. Neuropsychological Assessment. 4th ed. New York: Oxford University Press, 2004.

Lyons MJ, Toomey R, Seidman LJ, Kremen WS, Faraone SV, Tsuang MT. Verbal learning and memory in relatives of schizophrenics: preliminary findings. Biological Psychiatry 1995; 37:750-753.

Malaspina D, Harkavy-Friedman JM, Svrakic DM, Bassett AS, Holcomb J, Kalsi G, McQuillin A, Brynjolfson J, Sigmundsson T, Petursson H, Jazin E, Zoega T, Helgason T. Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Schizophrenia. American Journal of Human Genetics 2003; 73:34-48.

Marcelis M, Navarro-Mateu F, Murray R, Selten JP, Van Os J. Urbanization and psychosis: a study of 1942-1978 birth cohorts in The Netherlands. Psychological Medicine 1998; 28:871-879.

Marcelis M, Suckling J, Woodruff P, Hofman P, Bullmore E, van Os J. Searching for a structural endophenotype in psychosis using computational morphometry. Psychiatry Research 2003; 122:153-167.

Matsui M, Sumiyoshi T, Kato K, Yoneyama E, Kurachi M. Neuropsychological profile in patients with schizotypal personality disorder or schizophrenia. Psychological Reports 2004; 94:387-397.

McGrath J, Chapple B, Wright M. Working memory in schizophrenia and mania: correlation with symptoms during the acute and subacute phases. Acta Psychiatrica Scandinavica 2001; 103:181-188.

McGuffin P, Farmer A, Harvey I. A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. Archives of General Psychiatry 1991; 48:764-770.

McIntosh AM, Job DE, Moorhead TW, Harrison LK, Forrester K, Lawrie SM, Johnstone EC. Voxel-based morphometry of patients with schizophrenia or bipolar disorder and their unaffected relatives. Biological Psychiatry 2004; 56:544-552.

McNeil TF, Cantor-Graae E, Weinberger DR. Relationship of obstetric complications and differences in size of brain structures in monozygotic twin pairs discordant for schizophrenia. American Journal of Psychiatry 2000; 157:203-212.

Mednick SA, Machon RA; Huttunen MO, Bonett D. Adult schizophrenia following prenatal exposure to influenza epidemic. Archives of General Psychiatry 1988; 45:189-192.

Millar JK, Wilson-Annan JC, Anderson S, Christie S, Taylor MS, Semple CA, Devon RS, Clair DM, Muir WJ, Blackwood DH, Porteous DJ. Disruption of two novel genes by a translocation co-segregating with schizophrenia. Human Molecular Genetics 2000; 9:1415-1423.

Mishara AL, Goldberg TE. A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: Opening a closed book. Biological Psychiatry 2004; 55:1013-1022.

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

Mojtabai R, Bromet EJ, Harvey PD, Carlson GA, Craig TJ, Fennig S. Neuropsychological differences between first-admission schizophrenia and psychotic affective disorders. American Journal of Psychiatry 2000; 157:1453-1460.

Mueser KT, McGurk SR. Schizophrenia. Lancet 2004; 363:2063-2072.

Myles-Worsley M, Park S. Spatial working memory deficits in schizophrenia patients and their first degree relatives from Palau, Micronesia. American Journal of Medical Genetics 2002; 114:609-615.

Nelson MD, Saykin AJ, Flashman LA, Riordan HJ. Hippocampal volume reduction in schizophrenia as asessed by magnetic resonance imaging: a meta-analytic study. Archives of General Psychiatry 1998; 55:433-440.

Niemi LT, Suvisaari JM, Tuulio-Henriksson A, Lönnqvist JK. Childhood developmental abnormalities in schizophrenia: evidence from high-risk studies. Schizophrenia Research 2003; 60:239-258.

Okada A. Deficits of spatial working memory in chronic schizophrenia. Schizophrenia Research 2002; 53:75-82.

O'Donovan MC, Williams NM, Owen MJ. Recent advances in the genetics of schizophrenia. Human Molecular Genetics, 2003; 12 Spec No 2:R125-33.

O'Leary DS, Flaum M, Kesler ML, Flashman LA, Arndt S, Andreasen NC. Cognitive correlates of the negative, disorganized, and psychotic symptom dimensions of schizophrenia. Journal of Neuropsychiatry and Clinical Neurosciences 2000; 12:4-15.

Owen MJ, Williams NM, O'Donovan MC. The molecular genetics of schizophrenia: new findings promise new insights. Molecular Psychiatry 2004; 9:14-27.

Park S, Holzman PS. Schizophrenics show spatial working memory deficits. Archives of General Psychiatry 1992; 49:975-982.

Park S, Holzman PS, Goldman-Rakic PS. Spatial working memory deficits in the relatives of schizophrenic patients. Archives of General Psychiatry 1995; 52:821-828.

Paunio T, Ekelund J, Varilo T, Parker A, Hovatta I, Turunen JA, Rinard K, Foti A, Terwilliger JD, Juvonen H, Suvisaari J, Arajärvi R, Suokas J, Partonen T, Lönnqvist J, Meyer J, Peltonen L. Genome-wide scan in a nationwide study sample of schizophrenia families in Finland reveals susceptibility loci on chromosomes 2q and 5q. Human Molecular Genetics 2001; 10:3037-3048.

Petronis A. The origin of schizophrenia: genetic thesis, epigenetic antithesis, and resolving synthesis. Biological Psychiatry 2004; 55:965-970.

Ragland JD, Gur RC, Valdez J, Turetsky BI, Elliott M, Kohler C, Siegel S, Kanes S, Gur RE. Event-related fMRI of frontotemporal activity during word encoding and recognition in schizophrenia. American Journal of Psychiatry 2004; 161:1004-1015.

Riley EM, McGovern D, Mockler D, Doku VC, OCeallaigh S, Fannon DG, Tennakoon L, Santamaria M, Soni W, Morris RG, Sharma T. Neuropsychological functioning in first-episode psychosis – evidence of specific deficits. Schizophrenia Research 2000; 43:47-55.

Rosa A, Peralta V, Cuesta MJ, Zarzuela A, Serrano F, Martinez-Larrea A, Fañanas L. New evidence of association between COMT gene and prefrontal neurocognitive function in healthy individuals from sibling pairs discordant for psychosis. American Journal of Psychiatry 2004; 161:1110-1112.

Rossi A, Arduini L, Daneluzzo E, Bustini M, Prosperini P, Stratta P. Cognitive function in euthymic bipolar patients, stabilized schizophrenic patients, and healthy controls. Journal of Psychiatric Research 2000; 34:333-339.

Rund BR, Melle I, Friis S, Larsen TK, Midboe LJ, Opjordsmoen S, Simonsen E, Vaglum P, McGlashan T. Neurocognitive dysfunction in first-episode psychosis: correlates with symptoms, premorbid adjustment, and duration of untreated psychosis. American Journal of Psychiatry 2004; 161:466-472.

Salgado-Pineda P, Baeza I, Perez-Gomez M, Vendrell P, Junque C, Bargallo N, Bernardo M. Sustained attention impairment correlates to gray matter decreases

in first episode neuroleptic-naive schizophrenic patients. Neuroimage 2003; 19:365-375.

Salgado-Pineda P, Junque C, Vendrell P, Baeza I, Bargallo N, Falcon C, Bernardo M. Decreased cerebral activation during CPT performance: structural and functional deficits in schizophrenic patients. Neuroimage 2004; 21:840-847.

Salthouse TA. The processing-speed theory of adult age differences in cognition. Psychological Review 1996; 103:403-428.

Saper CB, Iversen S, Frackowiak R. Integration of sensory and motor function: the association areas of the cerebral cortex and the cognitive capabilities of the brain. In Kandel ER, Schwartz JH, Jessell TM, editors. Principles of neural science. 4th ed. New York: McGraw-Hill Co, Inc., 2000.

Sautter FJ, McDermott BE, Cornwell J, Johnson J, Borges A, Wilson AF, Vasterling JJ, Foundas AL. A preliminary study of the neuropsychological heterogeneity of familial schizophrenia. Schizophrenia Research 1995; 18:1-7.

Saykin AJ, Gur RC, Gur RE, Mozley PD, Mozley LH, Resnick SM, Kester DB, Stafiniak P. Neuropsychological function in schizophrenia. Selective impairment in memory and learning. Archives of General Psychiatry 1991; 48:618-624.

Saykin AJ, Shtasel DL, Gur RE, Kester DB, Mozley LH, Stafiniak P, Gur RC. Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. Archives of General Psychiatry 1994; 51:124-131.

Schultz SK, Andreasen NC. Schizophrenia. Lancet 1999; 353:1425-1430.

Schulze K, McDonald C, Frangou S, Sham P, Grech A, Toulopoulou T, Walshe M, Sharma T, Sigmundsson T, Taylor M, Murray RM. Hippocampal volume in familial and nonfamilial schizophrenic probands and their unaffected relatives. Biological Psychiatry 2003; 53:562-570.

Seidman LJ, Faraone SV, Goldstein JM, Goodman JM, Kremen WS, Toomey R, Tourville J, Kennedy D, Makris N, Caviness VS, Tsuang MT. Thalamic and amygdala-hippocampal volume reductions in first-degree relatives of patients with schizophrenia: an MRI-based morphometric analysis. Biological Psychiatry 1999; 46:941-954.

Seidman LJ, Faraone SV, Goldstein JM, Kremen WS, Horton NJ, Makris N, Toomey R, Kennedy D, Caviness VS, Tsuang MT. Left hippocampal volume as a vulnerability indicator for schizophrenia: a magnetic resonance imaging morphometric study of nonpsychotic first-degree relatives. Archives of General Psychiatry 2002a; 59:839-849.

Seidman LJ, Kremen WS, Koren D, Faraone SV, Goldstein JM, Tsuang MT. A comparative profile analysis of neuropsychological functioning in patients with schizophrenia and bipolar psychoses. Schizophrenia Research 2002b; 53:31-44.

Seidman LJ, Stone WS, Jones R, Harrison RH, Mirsky AF. Comparative effects of schizophrenia and temporal lobe epilepsy on memory. Journal of the International Neuropsychological Society 1998; 4:342-352.

Serper MR, Davidson M, Harvey PD. Attentional predictors of clinical change during neuroleptic treatment. Schizophrenia Research 1994; 13:65-71.

Sitskoorn MM, Aleman A, Ebisch SJ, Appels MC, Kahn RS. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. Schizophrenia Research 2004; 71:285-295.

Sponheim SR, Steele VR, McGuire KA. Verbal memory processes in schizophrenia patients and biological relatives of schizophrenia patients: intact implicit memory, impaired explicit recollection. Schizophrenia Research 2004; 71:339-348.

Stuss DT, Benson DF. The Frontal Lobes. New York: Raven Press, 1987.

Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait. Evidence from a meta-analysis of twin studies. Archives of General Psychiatry 2003; 60:1187-1192.

Susser ES, Lin SP. Schizophrenia after prenatal exposure to Dutch hunger winter of 1944-45. Archives of General Psychiatry 1992; 49:983-988.

Suvisaari JM, Haukka JK, Lönnqvist JK. No association between season of birth of patients with schizophrenia and risk of schizophrenia among their siblings. Schizophrenia Research 2004; 66:1-6.

Suvisaari J, Haukka J, Tanskanen A, Hovi T, Lönnqvist J. Association between prenatal exposure to poliovirus infection and adult schizophrenia. American Journal of Psychiatry 1999; 156:1100-1102.

Tamminga CA. Neuroscience and schizophrenia. Biological Psychiatry 1999; 46:301-302.

Thermenos HW, Seidman LJ, Breiter H, Goldstein JM, Goodman JM, Poldrack R, Faraone SV, Tsuang MT. Functional magnetic resonance imaging during auditory verbal working memory in nonpsychotic relatives of persons with schizophrenia: a pilot study. Biological Psychiatry 2004; 55:490-500.

Tienari P, Wynne LC, Sorri A, Lahti I, Läksy K, Moring J, Naarala M, Nieminen P, Wahlberg KE. Genotype-environment interaction in schizophrenia-spectrum disorder. Long-term follow-up study of Finnish adoptees. British Journal of Psychiatry 2004; 184:216-222.

Toomey R, Faraone SV, Seidman LJ, Kremen WS, Pepple JR, Tsuang MT. Association of neuropsychological vulnerability markers in relatives of schizophrenic patients. Schizophrenia Research 1998; 31:89-98.

Toulopoulou T, Rabe-Hesketh S, King H, Murray RM, Morris RG. Episodic memory in schizophrenic patients and their relatives. Schizophrenia Research 2003; 63:261-271.

Townsend LA, Malla AK, Norman RM. Cognitive functioning in stabilized first-episode psychosis patients. Psychiatry Research 2001; 104:119-131.

Tsuang MT. Defining alternative phenotypes for genetic studies: what can we learn from studies of schizophrenia? American Journal of Medical Genetics 2001; 105:8-10.

Turetsky BI, Moberg PJ, Mozley LH, Moelter ST, Agrin RN, Gur RC, Gur RE. Memory-delineated subtypes of schizophrenia: relationship to clinical, euroanatomical, and neurophysiological measures. Neuropsychology 2002; 16:481-490.

Tuulio-Henriksson A, Hennah W, Paunio T, Ekelund J, Partonen T, Peltonen L, Lönnqvist J. Evidence of association between cognitive functioning and DISC1. American Journal of Medical Genetics 2004; 130B:60. Abstract.

Van Erp TGM, Saleh PA, Huttunen M, Lönnqvist J, Kaprio J, Salonen O, Valanne L, Poutanen V-P, Standertskjöld-Nordenstam C-G, Cannon TD. Hippocampal volumes in schizophrenic twins. Archives of General Psychiatry 2004; 61:346-353.

Van Erp TGM, Therman S, Pirkola T, Tuulio-Henriksson A, Glahn DC, Bachman P, Huttunen MO, Lönnqvist J, Hietanen M, Kaprio J, Koskenvuo M, Cannon TD. Verbal encoding and recollection in schizophrenic twins. Submitted.

Varilo T, Laan M, Hovatta I, Wiebe V, Terwilliger JD, Peltonen L. Linkage disequilibrium in isolated populations: Finland and a young sub-population of Kuusamo. European Journal of Human Genetics 2000; 8:604-612.

Wahlberg KE, Wynne LC, Oja H, Keskitalo P, Pykäläinen L, Lahti I, Moring J, Naarala M, Sorri A, Seitamaa M, Läksy K, Kolassa J, Tienari P. Gene-environment interaction in vulnerability to schizophrenia: findings from the Finnish Adoptive Family Study of Schizophrenia. American Journal of Psychiatry 1997; 154:355-362.

Wechsler D. Wechsler Adult Intelligence Scale – Revised (WAIS-R), Manual. The Psychological Corporation. Cleveland: Harcourt Brace Jovanovich, Inc., 1981.

Wechsler D. Wechsler Memory Scale – Revised (WMS-R), Manual. The Psychological Corporation. San Antonio: Harcourt Brace Jovanovich, Inc., 1987.

Wechsler D. *WAIS-R Käsikirja* (in Finnish). Helsinki: Psykologien Kustannus, 1992.

Wechsler D. *WMS-R Käsikirja* (in Finnish). Helsinki: Psykologien Kustannus, 1996.

Weickert TW, Goldberg TE, Marenco S, Bigelow LB, Egan MF, Weinberger DR. Comparison of cognitive performances during a placebo period and an atypical antipsychotic treatment period in schizophrenia: critical examination of confounds. Neuropsychopharmacology 2003; 28:1491-500.

Weinberger DR. From neuropathology to neurodevelopment. Lancet 1995; 346:552-557.

Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Archives of General Psychiatry 1987; 44:660-669.

Weinberger DR, Egan MF, Bertolino A, Callicott JH, Mattay VS, Lipska BK, Berman KF, Goldberg TE. Prefrontal neurons and the genetics of schizophrenia. Biological Psychiatry 2001; 50:825-844.

White T, Andreasen NC, Nopoulos P, Magnotta V. Gyrification abnormalities in childhood- and adolescent-onset schizophrenia. Biological Psychiatry 2003, 54:418-426.

Wiegand LC, Warfield SK, Levitt JJ, Hirayasu Y, Salisbury DF, Heckers S, Dickey CC, Kikinis R, Jolesz FA, McCarley RW, Shenton ME. Prefrontal cortical thickness in first-episode psychosis: a magnetic resonance imaging study. Biological Psychiatry 2004; 55:131-140.

Wilcox MA, Faraone SV, Su J, Van Eerdewegh P, Tsuang MT. Genome scan of three quantitative traits in schizophrenia pedigrees. Biological Psychiatry 2002; 52:847-854.

Winterer G, Egan MF, Raedler T, Sanchez C, Jones DW, Coppola R, Weinberger DR. P300 and genetic risk for schizophrenia. Archives of General Psychiatry 2003; 60:1158-1167.

Zihl J, Gron G, Brunnauer A. Cognitive deficits in schizophrenia and affective disorders: evidence for a final common pathway disorder. Acta Psychiatrica Scandinavica 1998; 97:351-357.