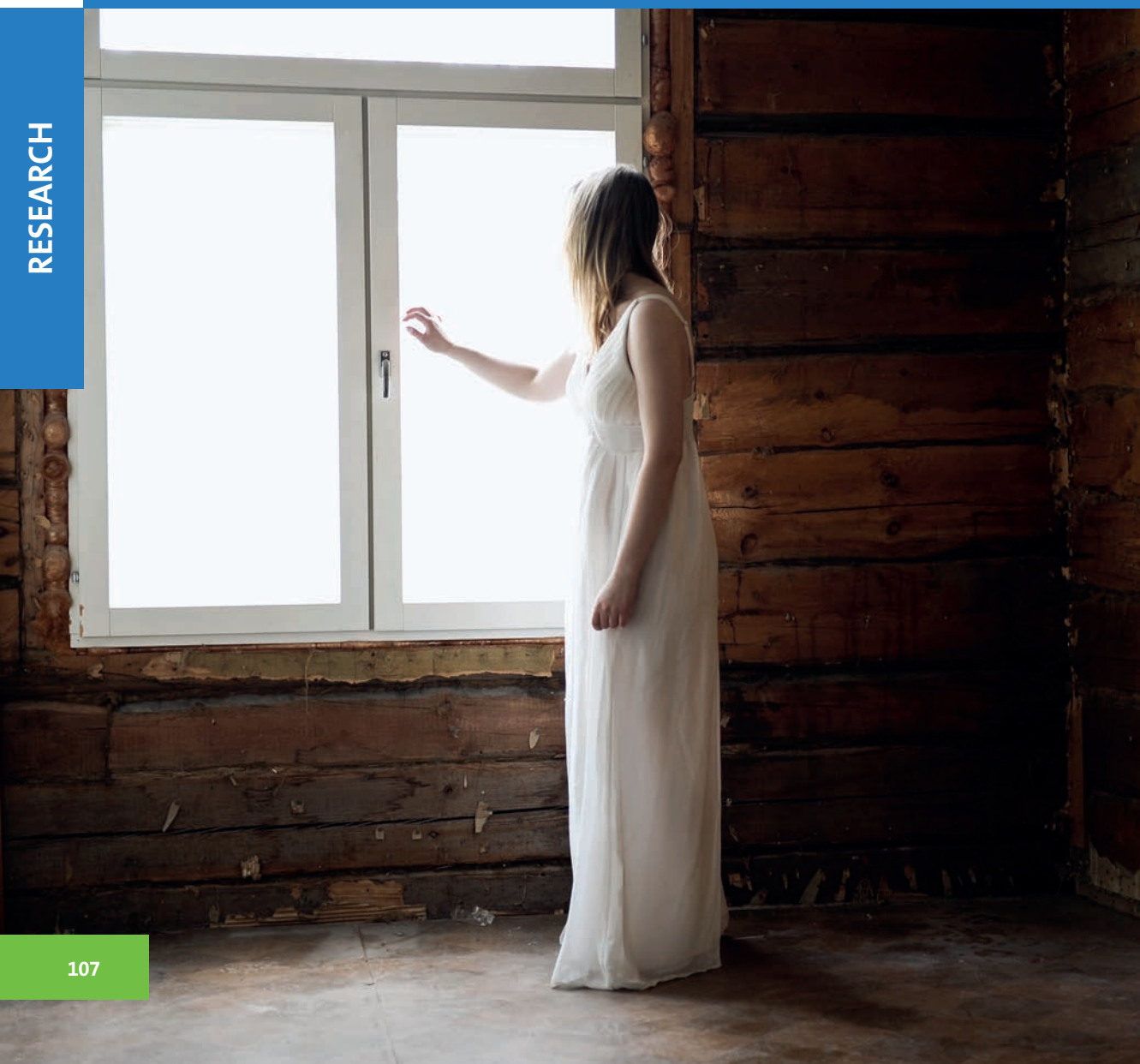
NATIONAL INSTITUTE FOR HEALTH AND WELFARE

Minna Torniainen

Cognitive Impairment in Schizophrenia: Related Risk Factors and Clinical Characteristics

RESEARCH



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RESEARCH 107

Minna Torniainen

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ACADEMIC DISSERTATION

To be publicly discussed with the permission of the Faculty of Behavioural Sciences, University of Helsinki, in room 302, Siltavuorenpenger 3A, on June 14th, 2013, at 12 noon.

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To friends and family

Abstract

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Schizophrenia is considered to be a neurodevelopmental disorder. Although the aetiology of schizophrenia remains largely unknown, it appears to result from several factors, including genetic vulnerability and environmental insults as well as their interactions. Schizophrenia is usually associated with broad cognitive impairment and related problems in psychosocial functioning. As in patients with schizophrenia, patients with schizoaffective disorder, a psychiatric disorder characterized by both symptoms of schizophrenia and prominent affective symptoms, also show cognitive impairment. Previous research has identified many risk factors for schizophrenia, such as obstetric complications and male sex. In addition, in Finland, internal genetic isolates with a high prevalence of schizophrenia have been identified. However, few studies have investigated the relationship between these risk factors for schizophrenia and cognitive functioning.

The aims of the thesis were to characterize cognitive functioning in schizophrenia and schizoaffective disorder and to examine whether clinical characteristics are related to cognitive impairment in these disorders. An additional aim was to investigate whether previously identified risk factors for schizophrenia (low and high birth weight, male sex, originating from an internal isolate) are associated with cognitive impairment in families with schizophrenia, and whether the illness or the degree of genetic loading for the illness modifies this relationship.

The present thesis is a part of the Genetic Epidemiology and Molecular Genetics of Schizophrenia in Finland project. Previously the project has focused on the genetic epidemiology of schizophrenia in Finland as a whole and within the genetic isolate, as well as on neuropsychological deficits in schizophrenia patients and their family members, and on the use of neuropsychological variables as endophenotypes in genetic analyses. Schizophrenia patients with a high genetic loading for schizophrenia were identified from nationwide health care registers. In the present thesis, groups of persons with schizophrenia (n = 218), persons with schizoaffective disorder (n = 62) and their unaffected first-degree relatives (n = 438) were investigated. The control group comprised 123 persons and, in the study focusing on the isolate, 112 persons. The participants were diagnosed on the basis of a diagnostic interview and case records from mental health care contacts. The participants underwent a battery of neuropsychological tests, assessing processing speed,

executive functions, attention, working memory, verbal learning and memory and verbal ability.

The schizophrenia group demonstrated broad cognitive impairment compared to the control group with large effect sizes. In schizoaffective disorder, broad cognitive impairment with effect sizes ranging from medium to large were detected. Differences in clinical characteristics accounted for the differences in cognitive functioning between the diagnostic groups. Irrespective of diagnosis, patients with severe negative symptoms and a high dose of antipsychotic medication had the most severe cognitive impairment. Both low and high birth weight were associated with more severe cognitive impairment than intermediate birth weight in persons with schizophrenia and their first-degree relatives. Sex differences in cognitive functions were mostly preserved in schizophrenia families when compared to controls despite large cognitive impairment in schizophrenia, and mild cognitive impairment in first-degree relatives. In persons with schizophrenia and their first-degree relatives, persons from the internal isolate had slightly better performance in some of the cognitive measures than persons from the rest of the country. However, no such differences were noticed in the controls.

In conclusion, persons with schizoaffective disorder demonstrated broad cognitive impairment, which was milder than in schizophrenia. The results suggest that symptom severity predicts the level of cognitive impairment in these disorders more accurately than categorical diagnosis does. The results also showed that the assessed schizophrenia risk factors may have distinct associations with cognitive functioning. Low and high birth weight were associated with slightly lower cognitive performance than intermediate birth weight in persons with schizophrenia and in their first-degree relatives. Despite sex differences in illness characteristics, sex did not affect the level of cognitive impairment in persons with schizophrenia or in their first-degree relatives. Originating from an internal isolate was associated with slightly higher cognitive performance than originating from the rest of Finland both in persons with schizophrenia and in their first-degree relatives, but not in the control group. This difference may reflect differences in the genetic aetiology of schizophrenia between the isolate and the rest of Finland.

Keywords: schizophrenia, schizoaffective disorder, cognitive functions, neuropsychology, birth weight, isolate, sex, gender

Tiivistelmä

Minna Torniainen. Cognitive Impairment in Schizophrenia: Related Risk Factors and Clinical Characteristics [Kognitiiviset häiriöt skitsofreniassa: yhteys sairauden riskitekijöihin ja kliinisiin piirteisiin]. Terveyden ja hyvinvoinnin laitos (THL). Tutkimus 107. 100 sivua. Helsinki, Finland 2013.
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Skitsofreniaa pidetään aivojen kehityksen häiriönä. Skitsofreniaan sairastumisen syitä ei tunneta, mutta sairastumisalttiuden taustalla on sekä geneettisiä että ympäristötekijöitä ja niiden yhteisvaikutuksia. Skitsofreniaan liittyy yleensä laaja-alaisia kognitiivisten toimintojen häiriöitä, jotka ovat yhteydessä myös psykososiaalisen toimintakyvyn ongelmiin. Myös skitsoaffektiivisessa häiriössä, jossa on sekä skitsofreniaoireita että huomattavia mielialaoireita, esiintyy kognitiivisten toimintojen häiriöitä. Aiemmissa tutkimuksissa on tunnistettu monia skitsofrenian riskitekijöitä kuten synnytykseen liittyvät komplikaatiot ja miessukupuoli. Lisäksi Suomessa on tunnistettu maan sisäisiä geneettisiä isolaatteja, joissa on korkea skitsofrenian esiintyvyys. Näiden skitsofrenian riskitekijöiden ja kognitiivisten toimintojen yhteyttä on tutkittu vain vähän. Tämän väitöskirjan tavoitteina oli luonnehtia kognitiivisia häiriöitä skitsofreniassa ja skitsoaffektiivisessa häiriössä sekä selvittää, ovatko näiden häiriöiden kliiniset piirteet yhteydessä kognitiivisten toimintojen häiriöihin. Lisäksi tavoitteena oli tutkia, ovatko aikaisemmin havaitut skitsofrenian riskitekijät (alhainen ja korkea syntymäpaino, miessukupuoli sekä maan sisäiseen isolaattiin kuuluminen) yhteydessä kognitiivisten toimintojen häiriöihin skitsofreniaperheissä ja modifioiko sairaus tai geneettinen alttius sairaudelle yhteyttä.

Tämä väitöskirja on osa ”Vakavien mielenterveyshäiriöiden geneettinen epidemiologia ja molekyyligeneettinen perusta” –projektia. Aikaisemmin projektissa on keskitytty tutkimaan skitsofrenian geneettistä epidemiologiaa sekä koko maan tasolla että maan sisäisessä isolaatissa. Lisäksi on tutkittu neuropsykologisia häiriöitä skitsofreniapotilailla ja heidän perheenjäsenillään sekä neuropsykologisten muuttujien käyttöä endofenotyyppeinä geneettisissä analyyseissä. Skitsofreniapotilaat, joilla on korkea geneettinen alttius skitsofrenialle, tunnistettiin valtakunnallisista terveydenhuollon rekistereistä. Tässä väitöskirjassa tutkittiin skitsofreniaryhmää (n = 218), skitsoaffektiivisesta häiriöstä kärsivien ryhmää (n = 62) ja heidän terveitä perheenjäseniä (n = 438). Verrokkiryhmään kuului 123 henkilöä ja isolaattiin keskittyvässä tutkimuksessa 112 henkilöä. Tutkimukseen osallistujien diagnoosit tehtiin diagnostisen haastattelun ja mielenterveysongelmiin liittyneiden hoitojen sairauskertomusten perusteella. Osallistujille tehtiin neuropsykologinen tutkimus, johon kuului prosessointinopeutta, toiminnanohjausta,

tarkkaavaisuutta, työmuistia, kielellistä oppimista sekä muistia ja kielellistä kyvykkyyttä arvioivia tehtäviä.

Skitsofreniaa sairastavilla oli laaja-alaisia kognitiivisten toimintojen häiriöitä, ja efektin koko oli suuri verrattaessa verrokkiryhmään. Myös skitsoaffektiivisessa häiriössä havaittiin laaja-alaisia kognitiivisia häiriöitä, joiden efektin koot vaihtelivat keskisuuresta suureen. Erot sairauden kliinisissä piirteissä selittivät erot diagnostisten ryhmien välillä kognitiivisissa toiminnoissa. Diagnoosista riippumatta potilailla, joilla oli vakavia negatiivisia oireita ja korkea psykoosilääkeannos, oli heikoin kognitiivinen toimintakyky. Sekä matala että korkea syntymäpaino liittyivät vakavampiin kognitiivisiin häiriöihin kuin keskimääräinen syntymäpaino niin skitsofreniapotilailla kuin heidän perheenjäsenilläänkin. Kognitiivisten toimintojen sukupuolierot skitsofreniaperheissä olivat suurimmaksi osaksi samanlaisia kuin kontrolliryhmässä huolimatta suurista kognitiivisista häiriöistä skitsofreniassa ja lievistä kognitiivisista heikentymistä perheenjäsenillä. Maan sisäisestä isolaatista kotoisin olevat skitsofreniapotilaat ja heidän perheenjäsenensä suoriutuivat hieman paremmin osassa kognitiivisista tehtävistä kuin muualta Suomesta kotoisin olevat potilaat ja perheenjäsenet. Samanlaista eroa ei kuitenkaan havaittu verrokkiryhmässä.

Tämän tutkimuksen tulosten perusteella skitsoaffektiiviseen häiriöön liittyy laaja-alaisia kognitiivisten toimintojen häiriöitä, jotka ovat lievempiä kuin skitsofreniassa. Oireiden vakavuus vaikutti kuitenkin ennustavan kognitiivisten häiriöiden tasoa paremmin kuin kategorinen diagnoosi. Tutkimuksessa ilmeni, että tutkituilla skitsofrenian riskitekijöillä saattaa olla erilainen yhteys kognitiiviseen toimintakykyyn. Matalaan ja korkeaan syntymäpainoon liittyi hieman matalampi kognitiivinen toimintakyky kuin keskimääräiseen syntymäpainoon sekä skitsofreniapotilailla että heidän perheenjäsenillään. Sukupuoli ei vaikuttanut kognitiivisten häiriöiden tasoon skitsofreniapotilailla tai heidän perheenjäsenillään huolimatta sukupuolieroista sairauden piirteissä. Maan sisäisestä geneettisestä isolaatista lähtöisin oleminen vaikutti liittyvän hieman parempaan kognitiiviseen toimintakykyyn osassa kognitiivisista tehtävistä kuin muualta maasta kotoisin oleminen sekä skitsofreniapotilailla että heidän perheenjäsenillään mutta ei kontrolliryhmässä. Ero saattaa heijastella skitsofrenian geneettisen etiologian eroja isolaatin ja muun Suomen välillä.

Avainsanat: skitsofrenia, skitsoaffektiivinen häiriö, kognitiiviset toiminnot, neuropsykologia, syntymäpaino, isolaatti, sukupuoli

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II Torniainen, M., Suvisaari, J., Partonen, T., Castaneda, A.E., Kuha, A., Perälä, J., Saarni, S., Lönnqvist, J. & Tuulio-Henriksson, A. (2011). Sex differences in cognition among persons with schizophrenia and healthy first-degree relatives. Psychiatry Res. 188, 7-12.

III Torniainen, M., Wegelius, A., Tuulio-Henriksson, A., Lönnqvist, J. & Suvisaari, J. (2013). Low and high birth weight are associated with cognitive impairment in persons with schizophrenia and their first-degree relatives. Psychol. Med. Published online before print January 19, 2013, doi: 10.1017/S0033291713000032.

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Abbreviations

CIDI	Composite International Diagnostic Interview
CPZE	Chlorpromazine equivalents
CVLT	California Verbal Learning Test
COGS	The Consortium on the Genetics of Schizophrenia
DSM	Diagnostic and Statistical Manual of Mental Disorders
DISC1	Disrupted in schizophrenia 1
DNA	Deoxyribonucleic acid
GAF	Global Assessment of Functioning
GEE	Generalized estimating equations
n	Number of participants
M	Mean
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MEAF	Mental Health in Early Adulthood
MIR137	MicroRNA 137
OPCRIT	Operational Criteria Checklist
PIF	Psychoses in Finland
RELN	Reelin
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SCID	Structured Clinical Interview for DSM-IV
SD	Standard deviation

WAIS-R	Wechsler Adult Intelligence Scale - Revised
WMS-R	Wechsler Memory Scale - Revised
ZNF804A	Zinc finger protein 804A

1 Introduction

Schizophrenia is a severe mental disorder, which is associated with deterioration in social and vocational functioning (American Psychiatric Association, 2000). The symptoms of schizophrenia can be divided into positive (e.g. hallucinations), disorganized (e.g. bizarre behaviour) and negative (e.g. lack of motivation) symptoms (Andreasen *et al.*, 1995). Mood symptoms in schizophrenia are also common, but if depressive or manic symptoms are present for "a substantial portion" of the time a schizoaffective disorder diagnosis is assigned (American Psychiatric Association, 2000). In addition to more common mood symptoms in schizoaffective disorder, persons with schizoaffective disorder have a more favourable outcome and less severe negative symptoms than persons with schizophrenia (Cheniaux *et al*., 2008).

Currently, schizophrenia is thought to result from both genetic vulnerability and environmental insults and their interaction (van Os *et al.*, 2008). These together affect neurodevelopment during prenatal period, childhood and early adulthood, causing neurodevelopmental impairment that may predispose to schizophrenia (van Os *et al*., 2008). Many factors that are associated with an increased risk for schizophrenia have been identified, such as male sex and obstetric complications (Matheson *et al.*, 2011). Schizophrenia prevalence also varies between regions, and in Finland, internal genetic isolates with a high prevalence of schizophrenia have been identified (Hovatta *et al.*, 1997).

Cognitive impairment is often severe and generalized in persons with schizophrenia and affects psychosocial functioning (Dickinson *et al.*, 2007, Fett *et al.*, 2011). The impairment is already present at the illness onset and thereafter tends to be persistent and relatively independent of symptom fluctuations (Hoff *et al.*, 2005). For these reasons, cognitive impairment is said to be the "core" of the disorder (Elvevåg & Goldberg, 2000). Many studies have also found cognitive impairment in schizoaffective disorder, but the results of studies comparing schizoaffective disorder with schizophrenia groups have been inconsistent (Bora *et al.*, 2009).

The aetiology of cognitive impairment in schizophrenia is largely unknown (Dickinson & Harvey, 2009). Some environmental schizophrenia risk factors have been associated with cognitive impairment in the general population (Saha *et al.*, 2009, Seidman *et al.*, 2000), but the association between cognitive impairment in people with schizophrenia and the risk factors of schizophrenia has not received much attention. Similar cognitive impairment, as in schizophrenia but milder, has

been detected in the unaffected first-degree relatives of the patients (Sitskoorn *et al.*, 2004a), suggesting that cognitive impairment in schizophrenia may be partly inherited (Tuulio-Henriksson *et al*., 2002). Genetic studies have suggested that the genetic aetiology may differ between schizophrenia with severe cognitive impairment and schizophrenia with relatively spared cognitive functions (Green *et al.*, 2012, Morar *et al.*, 2011, Wessman *et al.*, 2009).

The first aim of the present thesis was to characterize cognitive functioning in schizophrenia, schizoaffective disorder, their unaffected first-degree relatives and controls. The other aims were to examine if male sex, lower or higher than average birth weight, or belonging to a genetic isolate with a high schizophrenia prevalence of previously reported risk factors for schizophrenia, are related to cognitive impairment in schizophrenia families.

2 Review of the literature

2.1 Schizophrenia

Schizophrenia is a severe mental disorder. The prevalence of schizophrenia is approximately 1% in Finland (Perälä *et al*., 2007). Schizophrenia is a heterogeneous disorder and the clinical picture varies from one person to another. The diagnostic criteria for schizophrenia are shown in Table 1. The symptoms of schizophrenia can be divided into positive, disorganized and negative symptoms (Andreasen *et al.*, 1995, Andreasen & Olsen, 1982). Positive symptoms refer to hallucination and delusions and disorganized symptoms to disorganized speech, inappropriate affect and bizarre behaviour. Negative symptoms refer to affective flattening, alogia (poverty of speech), avolition (lack of motivation), anhedonia (inability to experience pleasure) and attentional impairment. Mood symptoms (mania and depression) and cognitive deficits are also suggested to be included as relevant symptom dimensions (van Os & Kapur, 2009), for example, in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, DSM-5 (www.dsm5.org).

Schizophrenia is associated with deterioration in everyday functioning (Viertiö *et al*., 2012). People with schizophrenia are often unable to work (Perälä *et al*., 2008) and may even be unable to live independently (Lauronen *et al*., 2007). Since the onset of the illness is often in late adolescence or in early adulthood (Angermeyer & Kuhn, 1988, Kirkbride *et al.*, 2012), schizophrenia also causes a huge financial burden to society (Gustavsson *et al*., 2011). However, many persons with schizophrenia are able to achieve symptomatic remission or good vocational and social functioning, and 10-20% of persons with schizophrenia may achieve full recovery from the illness after the first episode (Albert *et al.*, 2011, Harrison *et al.*, 2001, Jääskeläinen *et al.*, 2012). Schizophrenia is also associated with excess mortality from both suicide and natural causes (Kiviniemi *et al.*, 2010, Saha *et al.*, 2007, Suvisaari *et al.*, 2012a). Antipsychotic medication is in most cases effective in the treatment of positive symptoms, and psychosocial treatments are designed to alleviate negative symptoms and functional impairment (Dixon *et al.*, 2009, Grant *et al.*, 2012, Leucht *et al.*, 2009).

Table 1. DSM-IV criteria for schizophrenia (American Psychiatric Association, 2000).

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):

- delusions
- hallucinations
- disorganized speech
- grossly disorganized or catatonic behaviour
- negative symptoms

Note: 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 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 expected level of interpersonal, academic, or occupational achievement).

C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal (symptomatic of the onset) or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective and Mood Disorder exclusion: Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either no Major Depressive Episode, Manic Episode, or Mixed Episode 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 duration of 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).

2.2 Schizoaffective disorder and other schizophrenia spectrum psychoses

From the beginning of the twentieth century, psychoses have been divided into non-affective (e.g. schizophrenia) and affective psychoses (Kraepelian dichotomy; Greene, 2007). Of affective disorders, both unipolar depressive disorder and bipolar disorder may include psychotic symptoms. Some patients have both characteristic symptoms of schizophrenia and prominent mood symptoms. Consequently, a

diagnosis of schizoaffective disorder was introduced to characterize those patients whose symptoms seemed to resemble both schizophrenia and affective psychoses. In schizoaffective disorder, the person has depressive, manic or mixed episodes concurrent with psychotic symptoms, and a period with only delusions and hallucinations, without prominent affective symptoms, is also required (Table 2).

Table 2. DSM-IV criteria for schizoaffective disorder (American Psychiatric Association, 2000).

A. An uninterrupted period of illness during which, at some time, there is either a Major Depressive Episode, a Manic Episode, or a Mixed Episode concurrent with symptoms that meet Criterion A for Schizophrenia. Note: The Major Depressive Episode must include Criterion A1: depressed mood.
B. During the same period of illness, there have been delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms.
C. Symptoms that meet criteria for a mood episode are present for a substantial portion of the total duration of active and residual periods or the illness.
D. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

The division of psychoses according to the severity of affective symptoms has been challenged by difficulties in finding a point of rarity. Firstly, mood symptoms, especially depression, are common in non-affective psychoses, as well (Häfner *et al.*, 2008). Secondly, it has been difficult to separate schizoaffective disorder from schizophrenia and affective psychosis, and the longitudinal stability of the diagnosis has been low (Lake, 2007, Malhi *et al.*, 2008, Pope *et al.*, 1980), which has questioned the validity of the diagnosis of schizoaffective disorder. Despite the lack of clarity in the validity of the diagnosis, the diagnosis will be retained in the DSM-5 (www.dsm5.org). Thirdly, epidemiological studies have described common environmental risk factors for schizophrenia, schizoaffective disorder and affective psychotic disorders (Laursen *et al.*, 2007). Family studies have noticed that having a relative with schizophrenia, schizoaffective disorder or mood disorder increases the risk of any of these disorders (Cardno *et al.*, 2012, Laursen *et al.*, 2005, Lichtenstein *et al.*, 2009). However, having a relative with schizophrenia may especially increase the risk of schizophrenia and having a relative with mood disorder the risk of mood disorders (Laursen *et al.*, 2005, Lichtenstein *et al.*, 2009).

Comparison studies of schizophrenia and schizoaffective disorder have concluded that schizoaffective disorder has a more favourable outcome. Social and occupational functioning and premorbid adjustment are better in persons with schizoaffective disorder than in schizophrenia, whereas in schizophrenia, negative

symptoms are more severe (Bottlender *et al.*, 2010, Cheniaux *et al.*, 2008, Saracco-Alvarez *et al.*, 2009). Compared to affective psychoses, the outcome of schizoaffective disorder appears worse (Cheniaux *et al*., 2008).

In addition to schizophrenia and schizoaffective disorder, schizophrenia spectrum psychoses also include schizophreniform disorder, brief psychotic disorder, delusional disorder and psychotic disorder not otherwise specified (American Psychiatric Association, 2000). In schizophreniform disorder, the symptoms of schizophrenia are present for no more than six months, and in brief psychotic disorder, the symptoms are present for no more than a month. In delusional disorder, a person has long-lasting, non-bizarre delusions but may otherwise have normal functioning.

2.3 Cognitive functions

Cognitive functions are separable but interrelated processes of acquiring, processing, storing of and acting upon information (Lezak *et al.*, 2012). Cognitive functions include, for example, processing speed, executive functions, attention, working memory, verbal and visual learning and memory, verbal skills, visual functions and motor functions (Lezak *et al*., 2012). All these functions are multidimensional and can be divided further. Cognitive functions can be best assessed using standardized, widely recognized and validated neuropsychological test methods (Lezak *et al.*, 2012).

Processing speed refers to the speed of performing cognitive processes, which may affect performance on a variety of cognitive tasks, such as attention and working memory tasks (Lezak *et al.*, 2012, Salthouse, 1996). Executive functions were conceptualized by Jurado and Rosselli (2007) as "abilities of goal formation, planning, carrying out goal-directed plans, and effective performance". Further, the initiation of activity, the inhibition of irrelevant information, the shifting of mental set, the regulation of activity based on feedback from environment and the evaluation of own actions are all incorporated into executive functions (Jurado & Rosselli, 2007, Lezak *et al.*, 2012, Miyake *et al.*, 2000). Attention refers to the processes of the selecting of and attending to a limited amount of material for enhanced processing while filtering out other information (Chun *et al.*, 2011). Aspects of attention include the capacity or the span of attention, the ability to focus on a target, to inhibit the processing of irrelevant stimuli, to sustain the attention over a period, to shift attention to a new target and to divide attention between tasks (Lezak *et al.*, 2012, Mirsky *et al.*, 1991, Petersen & Posner, 2012).

The complex memory systems include the declarative memory for material that can be consciously recollected and non-declarative memory for material that cannot be consciously recollected, such as skills like riding a bicycle (Squire & Zola, 1996). The performance on declarative memory tasks depends on the effectiveness of encoding, learning and retrieving (Lezak *et al.*, 2012). Memory can be separated into short-term or working memory and long-term memory. Working memory can be defined as temporary maintenance and manipulation of a limited amount of information (Baddeley, 2012). According to the model by Baddeley (2012), working memory consists of the phonological loop for speech, the visuospatial sketchpad for visual and spatial material, the episodic buffer for binding information into integrated episodes, and the central executive, which is close to the executive functions concept. Long-term memory is responsible for storing information (Lezak *et al.*, 2012). Memory systems are also usually separated on the basis of sensory modality of the presented material (Lezak *et al.*, 2012).

Verbal skills can be divided to verbal expression, verbal comprehension and verbal academic skills (e.g. writing) (Lezak *et al.*, 2012). Impairment of verbal skills can manifest, for example, as problems in naming, fluency, comprehension and vocabulary (Lezak *et al.*, 2012). Visual functions include visual or visuospatial perception and visual construction, which requires linking perception with motor response (Lezak *et al.*, 2012). Motor functions include not only simple motor coordination but also encoding and executing motor representations (Lezak *et al.*, 2012).

2.4 Cognitive functioning in schizophrenia

Most of the persons with schizophrenia have severe and widespread cognitive impairment (Dickinson *et al*., 2007). According to meta-analyses, persons with schizophrenia perform on average one standard deviation below unaffected controls in cognitive measures (Dickinson *et al.*, 2007, Mesholam-Gately *et al.*, 2009). A large portion of variance in cognitive impairments has been shown to be attributable to the impairment of general cognitive ability (Dickinson *et al.*, 2008, Keefe *et al.*, 2006). An impairment in processing speed and verbal memory may be the largest against the broad cognitive impairment (Dickinson & Gold, 2008, Mesholam-Gately *et al.*, 2009). However, cognitive performance may be relatively spared in 20-30% of the patients with schizophrenia (Gonzalez-Blanch *et al.*, 2010, Kremen *et al.*, 2004, Palmer *et al.*, 1997, Wilk *et al.*, 2005).

Persons who later develop schizophrenia may have had in childhood small developmental abnormalities or weaknesses in motor functions, cognitive functions, school performance and social adjustment (Cannon *et al.*, 1999, Isohanni *et al.*, 2006,

Jones *et al.*, 1994, Reichenberg *et al.*, 2010, Seidman *et al.*, 2013, Sorensen *et al.*, 2010). Moderate cognitive impairment has been detected in persons who later develop schizophrenia in high risk samples (Giuliano *et al*., 2012). As the impairment is present before illness onset, it has been considered to be a risk factor for schizophrenia (Isohanni *et al.*, 2006, Maccabe, 2008). Around the onset of schizophrenia, cognitive functioning may deteriorate further (Woodberry *et al.*, 2008). In persons with first-episode psychosis, cognitive impairment is already full-blown, and after the illness onset the impairment appears to be fairly stable (Hoff *et al.*, 2005, Mesholam-Gately *et al.*, 2009, Szoke *et al.*, 2008). Similar but milder cognitive impairment has also been detected in healthy first-degree relatives (Sitskoorn *et al.*, 2004a).

Cognitive remediation is a psychosocial treatment form aiming to improve cognitive functioning in schizophrenia. Cognitive remediation refers to a variety of methods. Usually patients perform cognitive tasks with an increasing level of difficulty which can be delivered by face-to-face contact or computer assisted (Medalia & Choi, 2009). Cognitive remediation has been shown to at least modestly alleviate cognitive impairment (McGurk *et al.*, 2007, Wykes *et al.*, 2011). It has been shown to improve also community functioning, especially when combined with other psychiatric rehabilitation (McGurk *et al*., 2007).

Huge effort has been made into research of pharmacological treatment of cognitive functioning in schizophrenia (Harvey, 2009). Thus far, no consensus as to the effectiveness of currently available antipsychotic medications on cognitive functioning has been reached. Some studies have shown a small positive effect of antipsychotic medication on cognitive functioning, but it is unclear whether this reflects practice effect in doing similar or identical tasks within a short time interval (Davidson *et al.*, 2009, Goldberg *et al.*, 2007). Some naturalistic studies have shown the largest impairment in persons with the largest dose of antipsychotics and large medication dose has been associated with greater progressive brain changes (Elie *et al.*, 2010, Ho *et al.*, 2011). Newer atypical or second-generation antipsychotics may have a more favourable effect than conventional neuroleptic treatment on cognitive functioning, but the effect size has been small in meta-analyses (Mishara & Goldberg, 2004, Woodward *et al.*, 2005). The difference may also be related to extrapyramidal side effects caused by conventional neuroleptic treatment and its treatment with anticholinergics that may have an adverse effect on cognition (Leucht *et al.*, 2009, Ogino *et al.*, 2011). The research into new treatments to improve cognitive functioning in schizophrenia has been fuelled by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative (Buchanan *et al.*, 2011). The project has drawn attention to the goal and developed guidelines and the MATRICS Consensus Cognitive Battery for research into

treatment of cognition in schizophrenia (Buchanan *et al.*, 2005, Nuechterlein *et al.*, 2008).

2.4.1 Correlation of cognitive impairment with clinical characteristics of schizophrenia

Cognitive impairment has a strong impact on the everyday functioning of persons with schizophrenia (Fett *et al.*, 2011, Ventura *et al.*, 2009). The impairment has been associated with decreased ability to live independently, poor social skills and weakened ability to work (Bowie *et al.*, 2008, Green *et al.*, 2000, Shamsi *et al.*, 2011). The relationship of cognitive functions with everyday functioning may not be merely direct, but may be mediated, for example, by social or functional skills (Bowie *et al*., 2008).

Cognitive impairment in schizophrenia associates with negative symptoms of the illness, whereas positive symptoms show less correlation with the impairment (Dominguez *et al.*, 2009, Ventura *et al.*, 2009, Ventura *et al.*, 2010). Despite consistently observed correlations, negative symptoms and cognitive functions have been suggested to be separable with possibly separate aetiologies (Bell & Mishara, 2006, Foussias & Remington, 2010). Furter, disorganized symptoms appear to be associated with cognitive impairment (Ventura *et al*., 2010). The relationship of affective symptoms with cognitive functioning in schizophrenia is less consistent (Bozikas *et al.*, 2004, Brebion *et al.*, 2005, Dominguez *et al.*, 2009, Gladsjo *et al.*, 2004, Rieckmann *et al.*, 2005, Simonsen *et al.*, 2011, Stip & Mancini-Marie, 2004). Early illness onset and poor insight are also associated with cognitive impairment (Orfei *et al.*, 2010, Rajji *et al.*, 2009).

2.5 Cognitive functioning in schizoaffective disorder

Cognitive functioning is impaired in schizoaffective disorder compared to controls (Bora *et al.*, 2010, Torrent *et al.*, 2007). Compared to schizophrenia, persons with schizoaffective disorder have on average a milder impairment of certain cognitive functions, such as verbal memory and processing speed (Fiszdon *et al.*, 2007, Heinrichs *et al.*, 2008). In a meta-analysis, the effect size of difference was small (Bora *et al*., 2009). All studies have not detected differences in cognitive functioning between schizophrenia and schizoaffective disorder (Bilder *et al.*, 2000, Evans *et al.*, 1999, Simonsen *et al.*, 2011). These results have been used to justify combining subjects with schizoaffective disorder and schizophrenia in the same group in research projects (Evans *et al*., 1999). The inconsistencies in earlier studies

comparing cognitive functioning in schizophrenia and schizoaffective disorder may have resulted from small sample sizes (Bilder *et al.*, 2000, Reichenberg *et al.*, 2009, Simonsen *et al.*, 2011). Furter, in affective psychoses cognition appears impaired, but the impairment is smaller than in schizophrenia or in schizoaffective disorder (Bora *et al.*, 2009, 2010, Krabbendam *et al.*, 2005). The profile of impairment has been suggested to be similar to schizophrenia and differ only in magnitude (Reichenberg *et al*., 2009).

2.6 Brain abnormalities in schizophrenia

Schizophrenia is related to widespread deviations in the brain on many levels (for review, see Keshavan *et al.*, 2008), which is compatible with broad cognitive impairment. The volume of grey matter, especially in frontotemporal areas, has been reduced (Ellison-Wright & Bullmore, 2010, Ellison-Wright *et al.*, 2008, Haijma *et al.*, 2012). Further, abnormalities in white matter tracks have been detected, suggesting disrupted connectivity between brain regions (Bora *et al.*, 2011, Ellison-Wright & Bullmore, 2009). Besides structural findings, brain function has been aberrant both during task performance and at rest (e.g. hypofrontality and reduced gamma oscillations) (Brown & Thompson, 2010, Kühn & Gallinat, 2011, Minzenberg *et al.*, 2009, Uhlhaas & Singer, 2010). Abnormalities in multiple neurotransmitter systems (e.g. dopamine, glutamate, γ-amino butyric acid and acetylcholine systems) have also been shown (Gonzalez-Burgos *et al.*, 2010, Howes & Kapur, 2009, Kantrowitz & Javitt, 2012, Sarter *et al.*, 2012). Most of these abnormalities have been linked with cognitive impairment (Bustillo *et al.*, 2011, Minzenberg *et al.*, 2009, Perez-Iglesias *et al.*, 2010, Sarter *et al.*, 2012, Sullivan *et al.*, 1996).

2.7 Aetiology of schizophrenia

Despite intensive research during the last decades, the aetiology of schizophrenia remains largely unknown. The diversity in schizophrenia symptomatology suggests that the aetiology of the disorder is multifactorial. A strong aetiological theory has been the theory of schizophrenia as a neurodevelopmental disorder (Rapoport *et al.*, 2012). Deviations already in prenatal brain development may result from a combination of genetic vulnerability and prenatal environment (Bayer *et al.*, 1999, Mittal *et al.*, 2008, van Os *et al.*, 2008). Aberrant neurodevelopment may emerge as developmental delays or abnormalities in childhood in a proportion of the persons who will receive a schizophrenia diagnosis (Isohanni *et al.*, 2006, Jones *et al.*, 1994, Seidman *et al.*, 2013, Sorensen *et al.*, 2010). Schizophrenia symptoms typically manifest during late adolescence or early adulthood, and therefore brain

development during this age period may be crucial in schizophrenia aetiology. Synaptic pruning, reorganization of inhibitory interneuron control of cortical networks and increase in neuronal myelination occur during adolescence and early adulthood, and have been implicated in the pathophysiology of schizophrenia (Insel, 2010, Rapoport *et al.*, 2012). After illness onset, brain changes still progress, which may be related to possible neurodegenerative processes occurring in schizophrenia (Andreasen *et al.*, 2011, Arango *et al.*, 2012, Church *et al.*, 2002, Olabi *et al.*, 2011).

2.7.1 Biological and psychosocial risk factors for schizophrenia and their relationship to cognitive impairment

Many biological and psychosocial risk factors for schizophrenia have been identified, which may affect development during prenatal period, childhood or early adulthood. The risk factors may have a stronger effect on persons with high genetic loading for schizophrenia than on persons with low genetic loading (van Os *et al*., 2008). Most often reported psychosocial risk factors include urban environment, childhood adversity (e.g. maltreatment or bullying) and migration (Bendall *et al.*, 2008, Cantor-Graae & Selten, 2005, March *et al.*, 2008, Matheson *et al.*, 2012, McGrath *et al.*, 2004, Vassos *et al.*, 2012). Biological risk factors include male sex, increased paternal age at birth, cannabis use, traumatic brain injury and pregnancy and delivery complications, such as maternal infections, nutritional deficiency and hypoxia (Aleman *et al.*, 2003, Cannon *et al.*, 2002, Miller *et al.*, 2011, Molloy *et al.*, 2011, Moore *et al.*, 2007, Suvisaari *et al.*, 2012b).

In the general population, most of the identified biological and psychosocial risk factors, such as paternal age, season of birth, childhood trauma, some infections, low socioeconomic status and pregnancy complications, have been related to impairment of cognitive functioning (Jefferis *et al.*, 2002, Kannan & Pletnikov, 2012, Lawlor *et al.*, 2006, Nolin & Ethier, 2007, Saha *et al.*, 2009, Seidman *et al.*, 2000). Few studies have addressed the relationship of cognitive impairment and risk factors in schizophrenia. Childhood trauma (e.g. physical abuse or neglect) and infections have in previous studies been associated with pronounced cognitive impairment in persons with schizophrenia (Aas *et al.*, 2012, Dickerson *et al.*, 2012, Kannan & Pletnikov, 2012, Lysaker *et al.*, 2001). Cannabis use is associated with impaired cognitive functioning in the general population and increased risk for schizophrenia (Meier *et al.*, 2012, Moore *et al.*, 2007). However, in a recent meta-analysis, patients with schizophrenia and with lifetime cannabis use had less severe cognitive impairment than patients without cannabis use, which was suggested to result from a subgroup of patients with relatively spared cognitive functions who have developed schizophrenia only due to cannabis use (Yucel *et al*., 2012). More research is required on which components of the illness the risk factors affect.

2.7.1.1 Sex differences in schizophrenia

The most consistently reported sex differences in schizophrenia are earlier age of illness onset and more severe negative symptoms in men with schizophrenia than in women with schizophrenia (Eranti *et al.*, 2013, Galderisi *et al.*, 2012, Häfner, 2003, Thorup *et al.*, 2007). Schizophrenia may be more prevalent among men (Aleman *et al.*, 2003, McGrath *et al.*, 2004), and schizoaffective disorder in women (Bardenstein & McGlashan, 1990, Laursen *et al.*, 2007, Perälä *et al.*, 2007). In schizophrenia, as well as in the general population, women have more affective symptoms than men (Kuehner, 2003, Maric *et al.*, 2003). Men with schizophrenia may have more disorganized symptoms and poorer premorbid functioning and short-term outcome than women with schizophrenia (Galderisi *et al.*, 2012, Grossman *et al.*, 2008, Morgan *et al.*, 2008a). Disorganized schizophrenia, the most severe DSM-IV subtype of schizophrenia, is more common in men than in women (Suvisaari *et al.*, 2009b). Studies dividing schizophrenia patients into subgroups have suggested that men might be more vulnerable to a subtype with early illness onset, obstetric complications, negative symptoms, poor premorbid functioning, poor outcome and structural brain changes, whereas women would be more vulnerable to a subtype with affective symptoms and better outcome (Castle *et al.*, 1995, Huang *et al.*, 2011, Roy *et al.*, 2001). Many studies have found gender-specific structural or functional brain abnormalities (Goldstein *et al.*, 2002b, Takayanagi *et al.*, 2010, Walder *et al.*, 2007), but for now these results have been inconclusive (Wright *et al*., 2000).

The most commonly stated hypothesis to explain sex differences in schizophrenia has been the hypothesis that oestrogen provides relative protection against the illness. According to this hypothesis, women are more vulnerable to psychotic symptoms when the level of oestrogen is low (Markham, 2012, Seeman & Lang, 1990). For example, as described above, in premenopausal women schizophrenia is less common and they have a more benign course of illness. Around the menopause, women have the second peak in the incidence and outcome is worse than before menopause, which may be related to decreasing levels of oestrogen (Goldstein *et al.*, 2002a, Häfner *et al.*, 1998, Häfner *et al.*, 1993). In addition, women have increased vulnerability for psychosis following childbirth when oestrogen levels fall (puerperal psychosis) (Boyce & Barriball, 2010, Valdimarsdottir *et al.*, 2009). Sex steroid hormones also influence prenatal and pubertal brain development and the male brain is possibly more vulnerable to insults during pregnancy, due to for example, later prenatal maturation (Markham, 2012, Seeman & Lang, 1990).

Sex steroid hormones have both organizational effects on brain development and acute and non-permanent activational effects on brain function (Schulz *et al.*, 2009).

The influence of sex steroid hormones on the brain is reflected in sex differences in cognitive functions in the general population. Sex differences in general cognitive ability are negligible, but there are differences in more narrow abilities (Colom *et al.*, 2000, van der Sluis *et al.*, 2006). In the general population, women outperform men in many verbal skills, such as verbal fluency, reading and verbal memory, whereas men outperform women in spatial skills, mathematical skills and reaction time (Burton *et al.*, 2005, Der & Deary, 2006, Jorm *et al.*, 2004, Logan & Johnston, 2009, Lynn & Irwing, 2008, Voyer *et al.*, 1995). Mostly, sex differences in cognitive functions are small, but moderate sex differences appear in mental rotation with a male advantage, and in processing speed with a female advantage (Burns & Nettelbeck, 2005, Camarata & Woodcock, 2006, Voyer *et al.*, 1995).

In schizophrenia, studies into sex differences in cognitive functions have reached variable findings. Some often cited studies have concluded that cognitive impairment is exacerbated in men with schizophrenia (Goldstein *et al.*, 1998, Seidman *et al.*, 1997, Vaskinn *et al.*, 2011), which would also be in accordance with studies finding earlier age of onset and more severe negative symptoms in men with schizophrenia, as well as with the hypothesis of men being more vulnerable to neurodevelopmental adversities than women. However, other studies have found more severe cognitive impairment in women with schizophrenia (Lewine *et al.*, 1996, Roesch-Ely *et al.*, 2009). Many studies have also found that normal sex differences in cognitive functions are preserved in persons with schizophrenia (Bozikas *et al.*, 2010, Gur *et al.*, 2001, Halari *et al.*, 2006, Hoff *et al.*, 1998). In addition, a few authors have proposed that sex differences in cognition are diminished in schizophrenia (for review see Mendrek, 2007).

Many earlier studies have limitations, which may explain the variability of results concerning sex differences in cognitive functions in schizophrenia, such as, lack of a control group to which detected differences can be compared (Goldberg *et al.*, 1995, Sota & Heinrichs, 2003) or a too small sample size for studying sex differences (Goldstein *et al.*, 1998, Seidman *et al.*, 1997). In addition, because possible differences in the outcome of the illness and in treatment contact, samples collected from treatment facilities may not be suitable for assessing sex differences (Longenecker *et al.*, 2010, Walker & Lewine, 1993). Especially in samples collected from hospitals, women with the most severe illness may be over-represented.

Few studies have addressed sex differences in healthy first-degree relatives of schizophrenia patients. The results suggest that male relatives may have more paranoid-like schizotypal traits (Kremen *et al.*, 1998). One study suggested that male relatives may have more structural brain abnormalities than female relatives (Fan *et al.*, 2008). Studies into sex differences in cognitive impairment in first-degree

relatives have reached mixed results: some studies have found more pronounced impairment in men (Hans *et al.*, 1999, Sitskoorn *et al.*, 2004b) and one study found more pronounced impairment in women (Kremen *et al*., 1997). A few studies have found normal sex differences in first-degree relatives (Byrne *et al.*, 1999, Myles-Worsley *et al.*, 2007a).

2.7.1.2 Birth weight

The growth of a foetus is controlled by genes, hormones and supply of nutrition. Many adverse factors (e.g. placental pathology or infections) affecting the foetus may affect its growth (Ergaz *et al.*, 2005, Fineberg *et al.*, 2012, Godfrey & Barker, 2001, Rapoport *et al.*, 2005). Therefore, birth weight can be seen as a proxy variable for fetal environment and adverse factors influencing the growth (Cannon *et al.*, 2002). The factors influencing growth may also affect neurodevelopment and increase the risk of neurodevelopmental disorders.

Persons with a birth weight of less than 2500 g are usually referred to as having low birth weight and persons with a birth weight of more than 4000 g or 4500 g as having high birth weight or being macrosomic. Low birth weight may result from preterm birth or slow intrauterine growth. Risk factors for low birth weight include inadequate nutrition, multiple pregnancy, smoking, placental pathology and intrauterine infections (Ergaz *et al*., 2005). Low birth weight has been associated with impaired perinatal and postnatal health and increased mortality risk (Ergaz *et al*., 2005). In adulthood, persons with low birth weight have an increased risk for coronary heart disease, diabetes and hypertension (Andersen *et al.*, 2010, de Lauzon-Guillain *et al.*, 2010, Gamborg *et al.*, 2007). Low birth weight may also increase the risk of attention deficit hyperactivity disorder, autism and depression (Costello *et al.*, 2007, Mick *et al.*, 2002, Schendel & Bhasin, 2008). Very low birth weight (birth weight < 1500 g) or extremely low birth weight (birth weight < 1000 g) are associated with greater mortality, medical complications and greater deficits in neurodevelopment than higher birth weight (Aarnoudse-Moens *et al.*, 2009, Eichenwald & Stark, 2008, Lemons *et al.*, 2001). Very and extremely low birth weight are rare (Vuori & Gissler, 2012) and they are not discussed further in this thesis.

Risk factors for high birth weight include maternal diabetes, maternal overweight, high birth weight of previous babies, male foetus, multiparity and postmaturity (Heiskanen *et al.*, 2006). High birth weight is associated with an elevated risk for obstetric complications (Jolly *et al.*, 2003, Stotland *et al.*, 2004). In addition, persons with high birth weight have an increased risk, for example, for autoimmune diseases and diabetes (Caughey & Michels, 2009, Harder *et al.*, 2009). For now, less is

known about the association of high birth weight with psychiatric illnesses. Some studies have, however, linked high birth weight with autism, depression and externalizing problems in the young (Leonard *et al.*, 2008, Van Lieshout & Boyle, 2011).

Studies on the effects of birth weight on cognitive functioning have largely concentrated on low birth weight. Many studies have noticed slight impairment in cognitive functioning and an increase in the probability of various neurodevelopmental disabilities in persons with low birth weight (Bergvall *et al.*, 2006, Boulet *et al.*, 2011, Power *et al.*, 2006, Strauss, 2000). In addition, many studies have noticed that the association is not restricted to low birth weight, but an increase in birth weight improves cognitive functioning in persons with normal birth weight and some have even observed a similar association in persons with high birth weight (Rahu *et al.*, 2010, Shenkin *et al.*, 2004). Lately, however, some studies have concluded that high birth weight may associate with slight impairment of cognitive functioning (Eide *et al.*, 2007, Shenkin *et al.*, 2004, Silva *et al.*, 2006).

Low birth weight has long been associated with increased schizophrenia risk (Abel *et al.*, 2010, Wahlbeck *et al.*, 2001). Besides low birth weight, other factors related to fetal growth retardation, such as being small for gestational age and small head circumference, increase the risk of schizophrenia (Cannon *et al.*, 2002, Dalman *et al.*, 1999). Recent studies have also noticed that high birth weight may increase the risk of schizophrenia (Moilanen *et al.*, 2010, Wegelius *et al.*, 2011). The influence of birth weight on clinical features of schizophrenia remains poorly understood. In a few studies, low birth weight has been associated with early onset of the illness, poor premorbid social functioning and decreased cognitive functioning in schizophrenia (Freedman *et al.*, 2012, Hultman *et al.*, 1999, Rifkin *et al.*, 1994). Recently, Wegelius *et al*. have described an association between both extremes of birth weight, and an increase in the severity of disorganized and negative symptoms, in the same sample as is used in this thesis (Wegelius *et al.*, 2012). In turn, both disorganized and negative symptoms are associated with pronounced cognitive impairment (Dominguez *et al.*, 2009, Ventura *et al.*, 2009, Ventura *et al.*, 2010).

A few studies have implicated that a high genetic risk for schizophrenia may increase the effects of obstetric complications (Cannon, 2002, Cannon *et al.*, 1993, Fineberg *et al.*, 2012, Forsyth *et al.*, 2012, Freedman *et al.*, 2012). Cannon *et al*. (2002) observed that fetal hypoxia is associated with greater structural brain abnormalities in people with schizophrenia than in their unaffected siblings, and in controls with low genetic risk for schizophrenia the effect was smallest. In addition, a study with a small sample size found that low birth weight had a stronger effect on

cognitive functions in persons with schizophrenia than in controls (Freedman *et al*., 2012).

2.7.2 Genetic risk factors for schizophrenia and their relationship to cognitive impairment

Family and twin studies have shown schizophrenia to be highly heritable. Heritability estimates have been high, up to 80% (Lichtenstein *et al.*, 2009, Sullivan *et al.*, 2003). Early genetic research into schizophrenia using linkage analysis in families with schizophrenia and candidate genes identified many genes but findings in most of these genes have not been convincingly replicated (Collins *et al.*, 2012). Lately genome-wide association studies have identified many common risk variants with small effects (O'Donovan *et al.*, 2008, Ripke *et al.*, 2011, Stefansson *et al.*, 2009). Genes that have been associated with schizophrenia include: *microRNA 137* (*MIR137*), *Zinc finger protein 804A* (*ZNF804A*), *Neurogranin* (*NRGN*), *Transcription factor 4* (*TCF4*), *Calcium channel, voltage-dependent, L type, alpha 1C subunit* (*CACNA1C*), *Disrupted in schizophrenia 1* (*DISC1*) and *Reelin* (*RELN*) (Ayalew *et al.*, 2012, O'Donovan *et al.*, 2008, Ripke *et al.*, 2011, Shifman *et al.*, 2008, Stefansson *et al.*, 2009). Some relatively uncommon copy number variations, such as deletions in 22q11 (Karayiorgou *et al*., 1995) and in *Neurexin 1* (*NRXN1*) (Kirov *et al*., 2009), with larger effect sizes have been identified (Malhotra & Sebat, 2012, Rees *et al.*, 2011, The International Schizophrenia Consortium, 2008). Inherited vulnerability may not be specific to schizophrenia, but schizophrenia may also be genetically related to other psychiatric disorders, such as bipolar disorder, and to neurodevelopmental disorders, such as mental retardation or autism (Carroll & Owen, 2009, Lichtenstein *et al.*, 2009, Morgan *et al.*, 2008b). Environment may modify gene expression and the association of genes with phenotype (Jaenisch & Bird, 2003, Szyf *et al.*, 2008). Therefore, new information about the aetiology of schizophrenia may be elicited from studies into gene-environment interactions and epigenetics (for review, see Gebicke-Haerter, 2012, van Os *et al.*, 2008).

Complexity in the definition of illness phenotype and heterogeneity within the illness group may complicate genetic research into schizophrenia. For these reasons, intermediate phenotypes, also called endophenotypes, have been advocated. An endophenotype is a measurable trait that is supposed to be more proximal to the biological aetiology and genotype than the phenotype or illness itself (Tuulio-Henriksson *et al.*, 2009). Gottesman and Gould (2003) have suggested that endophenotypes should be associated with the illness in population, be heritable, be independent of illness state, co-segregate with illness within families and be more often noticed in healthy first-degree relatives than in the general population. Cognitive functions have been widely used as endophenotypes in genetic research

into schizophrenia (Allen *et al.*, 2009, Gottesman & Gould, 2003, Gur *et al.*, 2007, Paunio *et al.*, 2004). Besides cognitive functioning, structural and functional brain abnormalities (e.g. ventricular size or P50 event-related potential) and motor impairments (e.g. smooth pursuit eye movements) are considered as endophenotypes (Allen *et al.*, 2009, Greenwood *et al.*, 2012).

Genetic aetiology of schizophrenia may differ between patients with severe cognitive impairment and patients with relatively spared cognitive functions. Risk alleles in, for example, *RELN*, *DISC1*, *Neuregulin 1* (*NRG1*), *Dysbindin* (*DTNBP1*) and *MIR137* associate with impairment of cognitive functioning, whereas other genes, such as *Neuregulin 3* (*NRG3*) and *ZNF804A*, have been associated with the subgroup with relatively spared cognitive functions (Chen *et al.*, 2012, Green *et al.*, 2012, Greenwood *et al.*, 2011, Jablensky *et al.*, 2011, Morar *et al.*, 2011, Walters *et al.*, 2010, Wessman *et al.*, 2009).

2.7.2.1 Isolates in the research into schizophrenia

The advantages of isolates in genetic research are increased genetic and environmental homogeneity (Peltonen *et al.*, 2000). Some disease risk alleles may be enriched in an isolate and the number of potential alleles may be decreased. Isolates have been successfully used in the genetic research into Mendelian diseases. Lately, they have also been used in the research of polygenic or complex disorders.

In schizophrenia research, many isolates have been utilized (DeLisi *et al.*, 2002, Hovatta *et al.*, 1999, Myles-Worsley *et al.*, 1999, Myles-Worsley *et al.*, 2007b, Paunio *et al.*, 2009, Åberg *et al.*, 2008). The Finnish internal isolate investigated in this study was founded in 17th century by 34 families. The population growth has been fast. Until World War II, the population of the isolate has remained isolated. Due to the small number of founders and fast recent growth, linkage disequilibrium (meaning non-random association of alleles in near loci) is increased and the population is genetically homogeneous compared to other Finns and to other isolates in the world (Jakkula *et al.*, 2008, Service *et al.*, 2006, Varilo *et al.*, 2003). Other advantages of the isolate are records dating back to the founding of the municipality, good municipal health care and high participation rate in research.

Figure 1. Finnish isolate

The lifetime risk of schizophrenia within the isolate is high (3.2%) compared to the rest of Finland or other countries (Hovatta *et al.*, 1997, McGrath *et al.*, 2008, Saha *et al.*, 2005). In the isolate, the families with schizophrenia have showed a high degree of inbreeding (Hovatta *et al*., 1999), and the estimated kinship coefficient, a measure of relatedness that represents the probability that two alleles, one sampled at random from each individual, are identical by descent, is 1.43 times higher than expected (Paunio *et al*., 2009). Some differences between the isolate and the rest of the country have been found in susceptibility loci and in the frequency of risk alleles (Hennah *et al.*, 2003, Paunio *et al.*, 2001, Paunio *et al.*, 2004, Wedenoja *et al.*, 2008, Wedenoja *et al.*, 2010, Wessman *et al.*, 2009). For example, an intragenic short tandem repeat allele in the *Reelin* gene, which has been associated with moderate cognitive impairment, is almost absent within the isolate, but can be found in the rest of Finland (Wedenoja *et al.*, 2008, Wedenoja *et al.*, 2010). Comparison of symptoms between schizophrenia patients from the isolate and the rest of Finland has shown that patients from the isolate have less positive symptoms than persons from the rest of Finland (Arajärvi *et al.*, 2004, Arajärvi *et al.*, 2006). If cognitive functions are more proximal to the biological aetiology of schizophrenia, as the theory of endophenotypes suggests, the differences between the isolate and the rest of Finland in the genetic aetiology of schizophrenia might be reflected as differences in cognitive functioning, too.

3 Aims of the study

The first aim of the thesis was to characterize cognitive functioning in people with schizophrenia or schizoaffective disorder, their unaffected first-degree relatives and controls. The second aim was to explore if male sex, lower or higher than average birth weight or belonging to a genetic isolate, with high schizophrenia prevalence of previously reported risk factors for schizophrenia, are related to cognitive impairment in schizophrenia families and if the relationship is modified by the illness or high genetic loading for the illness.

The specific aims of the study were:

1. To compare cognitive functioning in schizophrenia, in schizoaffective disorder and in unaffected controls. In addition, the association between clinical characteristics and cognitive functions in these illnesses was examined. Accordant with earlier studies, the hypotheses were that persons with schizoaffective disorder perform better than persons with schizophrenia and worse than controls in cognitive tasks. Based on earlier studies, a correlation of negative symptoms, age of onset and functional level with cognitive functioning was also expected, which may explain differences between persons with schizophrenia and schizoaffective disorder.

2. To compare the effects of sex on cognitive functioning in persons with schizophrenia, their first-degree relatives and controls. Based on earlier studies, the expectation was either that men would have more severe cognitive impairment than women, or that sex differences in cognition would be preserved. More severe impairment in men than women with schizophrenia would fit well with the hypothesis of men being more vulnerable to adversities affecting neurodevelopment and with findings of more negative symptoms and earlier age of onset in men than in women with schizophrenia. Preserved sex differences in cognitive functions in schizophrenia would accord with many studies finding preserved sex differences in schizophrenia.

3. To explore the effects of birth weight on cognitive functioning in persons with schizophrenia and their unaffected first-degree relatives. Based on the earlier results in the study project that low and high birth weight are associated with increased schizophrenia risk and the severity of negative and disorganized symptoms (Wegelius *et al.,* 2011; Wegelius *et al.,* 2012), it was expected that both low and high birth weight would impair cognitive functioning and that the effect may differ between persons with schizophrenia and their first-degree relatives.

4. To investigate if persons with schizophrenia, their first-degree relatives and controls from the Finnish genetic isolate differ from the rest of the country in cognitive functioning. The aim was then to study whether the possible differences could be explained by some factors, such as illness characteristics, genetic loading for schizophrenia or the earlier reported differences in the frequency of the intragenic *Reelin* short tandem repeat allele, previously associated with cognitive impairment. Finally, it was investigated if the possible differences are also reflected in the occurrence of mental retardation in the families. The assumption was that high prevalence of schizophrenia may result from the accumulation of some, genetic or environmental, risk factors for schizophrenia in the isolate. Since many schizophrenia risk factors have in earlier studies been associated with impaired cognitive functioning, the accumulation of risk factors might also appear as pronounced cognitive impairment within the isolate.

4 Method

4.1 Project description

The present thesis is a part of the Genetic Epidemiology and Molecular Genetics of Schizophrenia in Finland project. The study protocol was accepted by the Ministry of Social Affairs and Health and by the ethics committees of the National Public Health Institute (since January 1, 2009, the National Institute for Health and Welfare) and the Hospital District of Helsinki and Uusimaa. The principal investigators of the project were Professors Jouko Lönnqvist and Leena Peltonen-Palotie. Numerous peer-reviewed articles in international journals (Arajärvi *et al.*, 2004, Ekelund *et al.*, 2000, Hennah *et al.*, 2009, Hovatta *et al.*, 1998, Hovatta *et al.*, 1999, Paunio *et al.*, 2004, Tuulio-Henriksson *et al.*, 2003, Wedenoja *et al.*, 2008) and doctoral theses (Arajärvi, 2006, Ekelund, 2001, Hennah, 2005, Hovatta, 1998, Tuulio-Henriksson, 2005, Wedenoja, 2010) have been published from the project.

The project has largely focused on the genetic aetiology of schizophrenia. In addition to genetic studies in general, variables from the neuropsychological test methods have been successfully used as endophenotypes in many studies (Hennah *et al.*, 2005, Palo *et al.*, 2007, Paunio *et al.*, 2004, Tomppo *et al.*, 2009, Wedenoja *et al.*, 2008). Major genetic findings of the project have been the association of *DISC1* and other genes in the *DISC1* pathway, such as *Nuclear distribution gene E homolog 1* (*NDE1*), with schizophrenia and cognitive functioning, and the association of *Dysbindin* with psychotic disorders with generalized cognitive deficits (Hennah *et al.*, 2007, Hennah *et al.*, 2005, Hennah *et al.*, 2003, Wessman *et al.*, 2009). In addition, a genome-wide linkage of a locus on chromosome 7q22 with schizophrenia (Ekelund *et al.*, 2000) resulted in the detection that short tandem repeats within the *Reelin* gene are associated with schizophrenia symptoms and cognitive functioning (Wedenoja *et al.*, 2008, Wedenoja *et al.*, 2010). An internal isolate has been utilized in genetic studies and the place of origin has been shown to influence the genetic aetiology of the illness (Hovatta *et al.*, 1999, Paunio *et al.*, 2009). In addition, differences in the prevalence of schizophrenia and some small differences in the clinical characteristics of schizophrenia between the internal isolate and the rest of Finland have been detected (Arajärvi *et al.*, 2004, Arajärvi *et al.*, 2006, Hovatta *et al.*, 1997). Neuropsychological deficits in schizophrenia patients and their family members have also been characterized in the project (Tuulio-Henriksson, 2005, Tuulio-Henriksson *et al.*, 2009). The findings have suggested that

neuropsychological impairment is heritable in families with schizophrenia and mild impairment is also present in unaffected first-degree relatives of the patients (Kuha *et al.*, 2007, Tuulio-Henriksson *et al.*, 2003, Tuulio-Henriksson *et al.*, 2002). Studies into schizophrenia epidemiology have suggested that high birth weight may increase the risk of schizophrenia and both low and high birth weight may increase the symptoms of schizophrenia (Wegelius *et al.*, 2012, Wegelius *et al.*, 2011).

4.2 Participants

4.2.1 Schizophrenia family samples

The participants were identified from three nationwide health care registers in Finland: the Finnish Hospital Discharge Register, the Pension Register and the Medication Reimbursement Register. The persons born between years 1940 and 1976 with a schizophrenia, schizoaffective disorder or schizophreniform disorder diagnosis made between 1969 and 1998 were identified in the 1990s (n = 33731). The first-degree relatives of the identified persons were searched from the National Population Register.

Two samples with presumably high genetic loading for schizophrenia spectrum illness from the identified families were compiled: the isolate and the rest of Finland sample (Figure 2). The rest of Finland sample consisted of parents and siblings from families with at least two siblings with schizophrenia, schizoaffective disorder or schizophreniform disorder from the whole geographical area of Finland. The isolate sample comprised families with at least one member with schizophrenia from an isolated region in the north-eastern part of the country with an exceptionally high lifetime risk of schizophrenia (3.2%) (Hovatta *et al*., 1997). From the majority of families, only siblings and parents were invited to participate in the study.

The proband identified from the registers was contacted through the treating physician, who was the most familiar to the proband. After receiving permission from the proband to contact other family members, they were invited to participate. After a complete description of the study to the subjects, written informed consent was obtained from all participants.

All participants gave blood samples, and medical records from all treatment contacts were collected from participants with any mental health care contacts. In addition, all families from the isolate and a random sample of families from the rest of Finland sample were asked to participate in a clinical assessment that consisted of a structured clinical interview with the Structured Clinical Interview for DSM-IV

(SCID-I and SCID-II), assessment of symptom severity with the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) and neuropsychological testing.

Altogether, 1016 persons were interviewed and administered a neuropsychological test battery in the project. Of the persons who had participated in neuropsychological testing, 280 persons received a schizophrenia diagnosis, 76 persons a schizoaffective disorder diagnosis and 565 did not receive a diagnosis of psychotic disorder or bipolar disorder. The exclusion criteria in studies assessing cognitive functioning were: over 70 years of age, severe neurological disorder, mental retardation, or severe somatic illness, current alcohol or substance use disorder, and untestability due to, for example, severe disorganized symptoms with difficult attentional problems. In addition, the included relatives were not allowed to have any current psychiatric disorder.

The final sample consisted of 218 persons with schizophrenia, 62 persons with schizoaffective disorder and 438 healthy relatives. Of these, 145 (66%) persons with schizophrenia, 43 (69%) persons with schizoaffective disorder and 304 (69%) healthy first-degree relatives originated from the isolate. Of the persons with schizoaffective disorder, ten had depressive type and 52 had bipolar type.

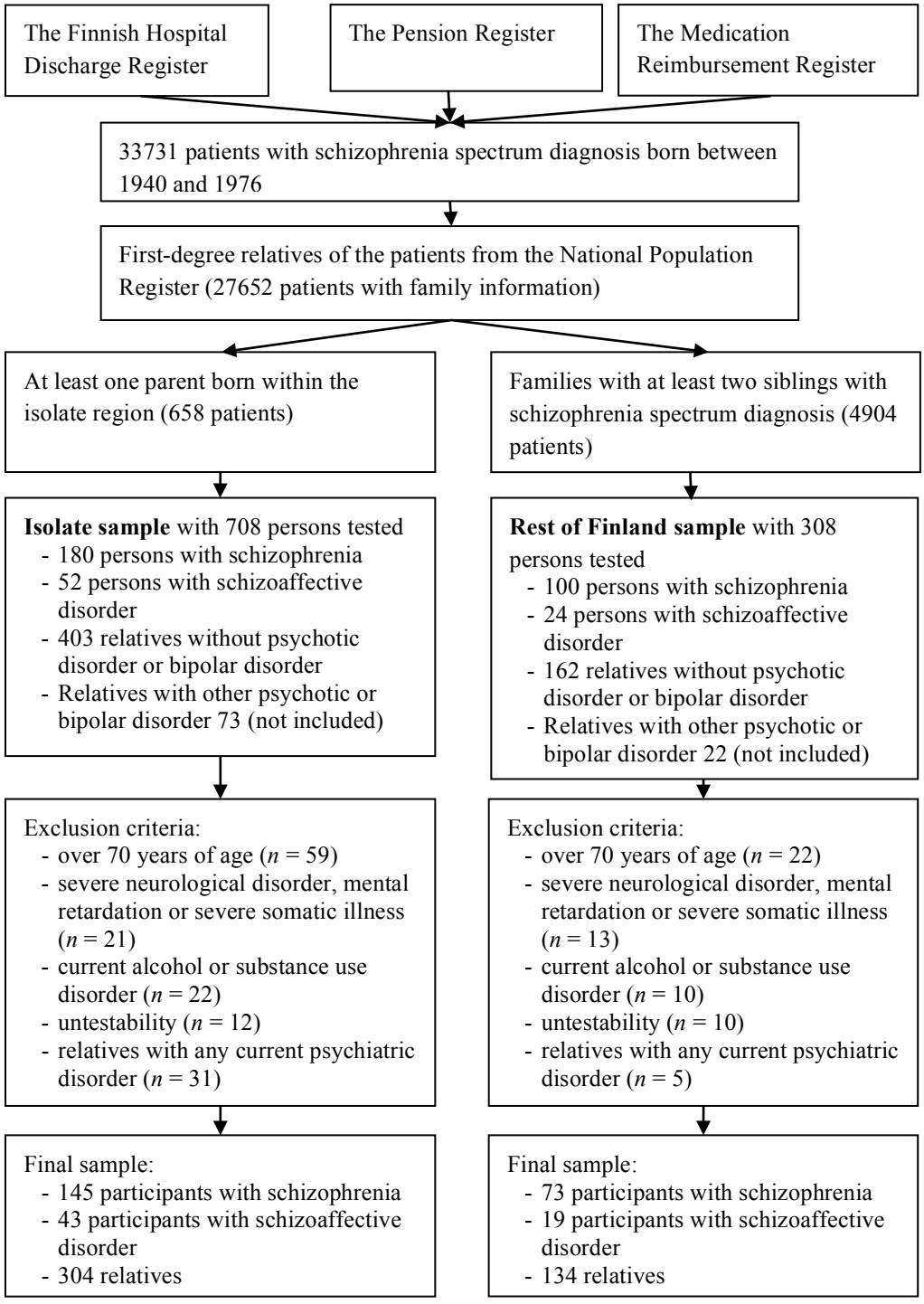

Figure 2. Collection of schizophrenia family samples

4.2.2 Control sample

The control sample consisted of people who had participated in the mental health substudies of the Health 2000 study. The Health 2000 study sample was selected using a 2-stage stratified cluster sampling from the Finnish population (Aromaa & Koskinen, 2004). The fieldwork for the Health 2000 study was carried out during years 2000-2001. The adult sample consisted of 8028 participants aged 30 years or over at the point of selection and the young adult sample of 1894 persons aged 18 - 29 years (Aromaa & Koskinen, 2004). A comprehensive health examination including the Composite International Diagnostic Interview (CIDI) (Wittchen *et al.*, 1998) was administered to the adult sample, while a more narrow health interview was conducted in the young adult sample.

In the Psychoses in Finland (PIF) substudy, the adult sample was screened for possible psychotic disorder using information from the CIDI interview, self-reported diagnoses, health examination and health care registers (Perälä *et al.*, 2007, Tuulio-Henriksson *et al.*, 2011). Screen positives and a nationwide random sample of screen negatives were invited for a SCID interview and neuropsychological assessment. In addition, to obtain a control group from the isolate region, all consenting screen negatives from the isolate region were invited to participate in the study. In the Mental Health in Early Adulthood (MEAF) substudy, the Health 2000 young adult sample was screened for multiple psychiatric disorders using several screening scales and health care registers. Screen positives and a random sample of screen negatives were invited for a SCID interview and neuropsychological assessment (Castaneda *et al.*, 2008, Suvisaari *et al.*, 2009a).

The control group was formed from the screen negatives in the PIF study. In Studies I and II, in order to obtain a control group that would match the schizophrenia family samples in age, a random sample of 39 participants from the screen negatives of the MEAF study was included, of whom one person originated from the isolate. In Study IV, 28 participants from the MEAF study with genotyping information were included in the control group. The assessment procedure and exclusion criteria were similar as in the schizophrenia family samples. In addition, controls were excluded if they reported having a first-degree relative with psychotic disorder or bipolar disorder. The control group comprised 123 participants in Studies I and II and of 112 participants in Study IV of whom 32 (29 %) were born within the isolate.

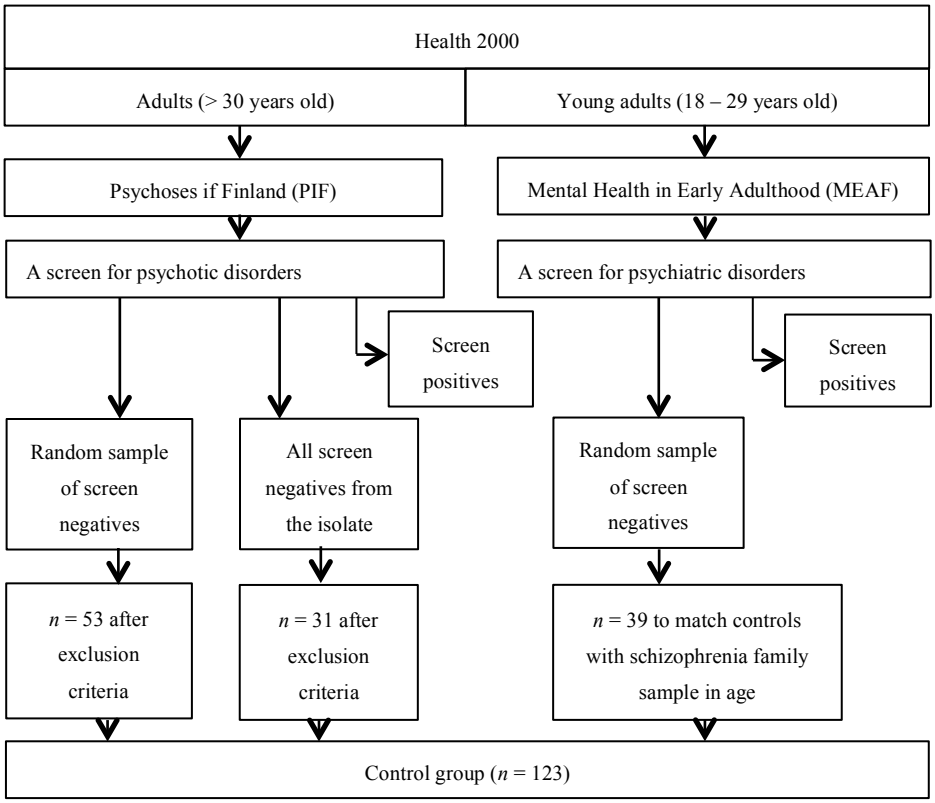

Figure 3. Formation of the control group in Studies I and II

4.3 Assessment methods

4.3.1 Diagnostic and clinical evaluation

The participants were interviewed with the Structured Clinical Interview for DSM-IV Axis I Diagnosis (SCID-CV; First *et al*., 1996). The DSM-IV diagnoses were made on the basis of the interview and case records from all lifetime inpatient and outpatient psychiatric treatments. Two psychiatrists assigned the diagnoses independently, and in case of disagreement, a third psychiatrist assessed diagnoses and a consensus diagnosis was reached.

Positive and negative symptoms were assessed in the interview with the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and with the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1982), respectively. Level of psychological, social and occupational functioning was evaluated with the Global Assessment of Functioning (GAF; American Psychiatric Association, 2000).

The Operational Criteria (OPCRIT) checklist (McGuffin *et al*., 1991) was filled based on case records. Age at illness onset was defined as the earliest age in which medical advice was sought for psychiatric reasons or in which symptoms began to cause subjective distress or impair functioning and was recorded in the OPCRIT. OPCRIT items were also used for analysing premorbid social and work adjustment and affective symptoms. Manic and depressive symptoms (Study I) were defined as the number of DSM-IV symptoms during the most severe episode. The method is based on earlier studies that have used a similar approach to reach a continuous depression and mania score (Regeer *et al.*, 2006, van Rossum *et al.*, 2011).

The use of medication was inquired in the interview. The dose of antipsychotics was converted to chlorpromazine equivalents (CPZE) according to the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations (Lehman *et al*., 2004). If an antipsychotic was not mentioned in the PORT recommendations, the conversion was based on the instructions from the Finnish Psychiatric Association (Isohanni *et al.*, 2007) or from the pharmaceutical industry.

4.3.2 Neuropsychological test administration

Most of the participants were assessed in local work offices (e.g. in health care centres) or in participants' home. The participants were interviewed and tested by psychologists or psychiatric nurses, who received intensive training in the use of the methods. Experienced psychologists scored all tests. The test battery administered to the control group did not include all tests given to the participants from the families with schizophrenia (Table 3). Within groups, the tests were administered in a fixed order.

Verbal ability was evaluated with the Vocabulary subtest from the Wechsler Adult Intelligence Scale - Revised (WAIS-R; Wechsler, 1981). The correlation of the subtest with full scale intelligence quotient is approximately 0.90 (Wechsler, 1992). Verbal ability and concept formation were analysed with the Similarities subtest of the WAIS-R (Wechsler, 1981). Visuospatial reasoning was assessed with the Block Design from the WAIS-R (Wechsler, 1981).

Table 3. Description of neuropsychological tests. All tests were performed in the family sample but only a part in the control group (marked with ×).

Test	Description	Performed in the control group
Verbal ability and Visuospatial Reasoning		
WAIS-R Vocabulary	Explaining the meaning of words	×
WAIS-R Similarities	Stating how two words are alike	
WAIS-R Block Design	Assembling displayed patterns from blocks as fast as possible	
Processing speed and executive functions		
WAIS-R Digit Symbol	Drawing corresponding symbols under digits according to a key provided as fast as possible in 90 seconds	×
Trail Making part A	Drawing a line to connect numbers in circles in an ascending order as fast as possible	×
Trail Making part B	Drawing a line to connect numbered and lettered circles alternating between two sequences and in an ascending order as fast as possible	×
Stroop colour task	Naming the colour of inks as fast as possible	
Stroop colour-word task	Naming the ink colour independent of written words as fast as possible	
Attention and working memory		
WMS-R Digit Span Forward	Immediate recall of digit series increasing in length	×
WMS-R Digit Span Backward	Immediate recall of digit series in reverse order increasing in length	×
WMS-R Visual Span Forward	Immediate recall of spatial location patterns increasing in length	×
WMS-R Visual Span Backward	Immediate recall of spatial location patterns in reverse order increasing in length	×
Verbal learning		
CVLT Immediate recall	Learning and recall of a list of 16 words on five trials	×
CLVT Short delay recall	Recall of the original list after a recall of an interference list	×
CVLT Long delay recall	Recall of the original list after a delay of 20 to 30 minutes	×

Processing speed and executive functions were tapped with three tests. Digit symbol subtest from the WAIS-R (Wechsler, 1981) evaluated processing speed. Trail Making Test parts A and B (Reitan & Wolfson, 1985) were used to assess processing speed and cognitive flexibility, respectively. Speed of processing and selective attention were evaluated with the Stroop (Golden, 1978, MacLeod, 1991). The times to complete the Trail Making Test and the Stroop tasks were recorded. The interference score was calculated from the Stroop performance according to the instruction by Golden (Golden, 1978).

$$\text{Interference score} = \text{Colour-Word Task} - \frac{Color\ Task * Word\ Task}{Color\ Task + Word\ Task}$$

Verbal attention span and verbal working memory were assessed with the Digit Span forward and backward of the Wechsler Memory Scale - Revised (WMS-R), respectively, and visual attention span and visual working memory with the Visual Span forward and backward of the WMS-R (Wechsler, 1987), respectively. Verbal learning and memory were measured with the California Verbal Learning Test (CVLT; Delis *et al.*, 1987). Of the CVLT, immediate recall (sum of trials 1-5), short delay recall, long delay recall and the ratio of semantic clustering were used in the present study.

4.3.3 Collection of birth weights

From the schizophrenia families, birth weights and the type of delivery (hospital vs. home with professional assistance vs. home without professional assistance) were collected from obstetric and health-care records. Birth weight information was available for 142 (65%) persons in the schizophrenia group and 277 (63%) persons in the relatives group.

4.3.4 Genotyping

In Study IV, previously genotyped *RELN* intragenic short tandem AATA repeat located in *RELN* intron 27 was used (Wedenoja *et al.*, 2008, Wedenoja *et al.*, 2010). This short tandem repeat, termed RELNSAT6, was selected due to its previously reported effect on cognition and lower frequency within than outside the internal isolate (Wedenoja *et al.*, 2008, Wedenoja *et al.*, 2010). For genotyping, the flanking DNA sequences for RELNSAT6 were derived from the UCSC Genome Browser (Kent *et al.*, 2002), and PCR primers were designed with the Primer3 software (Rozen & Skaletsky, 2000). Genotyping was performed in single-plex reactions in 96-well plates by using the ABI3730xl DNA analyser platform (Applied Biosystems, Foster City, California). The total reaction volume was 15 µl including 10 ng of genomic DNA. Two water controls and two duplicated DNA samples in

each plate served as quality controls. Genotype calling was performed automatically with ABI GeneMapper 4.0 software and verified manually. The RELNSAT6 short tandem repeat passed the quality control criteria of genotyping success rate ≥ 95%, HWE *p* value ≥ 0.01 (calculated from unrelated individuals by using PEDSTATS 0.6.10 (Wigginton & Abecasis, 2005)), and the number of Mendelian errors < 5 in PedCheck 1.1 (O'Connell & Weeks, 1998). All genotypes for individuals with ≥ 3 Mendelian errors or genotyping success rate < 90% were removed from analysis.

4.3.5 Statistical analyses

To control for within-family correlation in cognitive performance (Davis *et al.*, 2009, Lee *et al.*, 2012) and to estimate unbiased population averaged regression coefficients, statistical analyses of cognitive functioning were performed with generalized estimating equations (GEE) (Zeger & Liang, 1986). The raw scores of the neuropsychological tests were used in the statistical analyses. Statistical analyses were conducted with Intercooled Stata 9.2 for Windows (StataCorp, 2007). *P*-values under 0.05 were considered statistically significant. All GEE analyses were adjusted for sex and age. The effect sizes were assessed with Cohen's *d* on the basis of means and standard deviations (Cohen, 1988). Effect sizes of ⩾ 0.20, ⩾ 0.50 and ⩾ 0.80 reflected small, medium and large, respectively.

Study I

To compare cognitive functioning in schizophrenia, in schizoaffective disorder and in unaffected controls, the cognitive performance of the schizophrenia group and the schizoaffective disorder group was first compared to the control group with the GEE models. Then, the schizophrenia and the schizoaffective disorder groups were compared to each other with the Wald test for evaluating linear hypotheses after model estimation. To examine if clinical characteristics are associated with cognitive performance and if clinical characteristics explain the group differences in cognitive performance, illness characteristics were included in the GEE models as covariates, and the control group was excluded. The used clinical characteristics were: SANS sum scores, SAPS sum scores, number of depressive symptoms (that had been present in the most severe depressive episode), number of manic symptoms (that had been present in the most severe manic episode), GAF, age of illness onset, poor premorbid social adjustment (yes / no), poor premorbid work adjustment (yes / no), use of antidepressants (yes / no), use of mood stabilizers (yes / no), CPZE and any lifetime substance use disorder (yes / no). The final predictor variables were selected using backward selection, in which the least significant variables were removed from the analysis one by one.

Study II

Sex differences in the schizophrenia, the first-degree relatives and the control groups were analysed with the GEE models. To compare the sex differences in cognitive functioning in the schizophrenia and healthy relatives groups to the control group, sex × group interaction was used. The Wald test for evaluating linear hypotheses after model estimation was used in the testing of the group differences and sex × group interaction between the schizophrenia and the relatives groups. In addition, sex differences in illness characteristics in the schizophrenia group were assessed with the GEE models.

Study III

When assessing the effects of birth weight on cognitive functioning in the schizophrenia and the relatives groups, birth weight was entered in the GEE models as a continuous variable in kilograms. Squared birth weight was entered to assess nonlinear effects. If squared birth weight term was statistically significant, the association of birth weight with cognitive functioning was considered to be curvilinear, which means that at some value of birth weight, the association of birth weight with cognitive functioning changes from positive to negative or vice versa. Squared birth weight × group interaction and birth weight × group interaction were used to assess if the effect of birth weight on cognitive functioning is different in the schizophrenia and relatives groups. The factors that might have an effect on cognitive functions based on the results of Studies I and IV were controlled for (GAF score, number of affected siblings per family, place of birth meaning isolate vs. rest of Finland, age and sex). Besides these, the type of delivery (hospital vs. home with professional assistance vs. home without professional assistance) was added as a covariate, to control for its potential role in the association of birth weight with cognitive functioning (because people born at home may have suffered from more complications).

Study IV

To investigate if persons with schizophrenia, their first-degree relatives and controls from the Finnish genetic isolate differ from the rest of the country in cognitive functioning, GEE models comparing the isolate and the rest of Finland samples were conducted in each group separately. Firstly, the schizophrenia patients from the isolate were compared with the patients from the rest of the country with GEE models and by calculating effect sizes with Cohen's *d*. In GEE model 1 only age and sex were controlled for. In GEE model 2, illness characteristics that may have an impact on cognitive functioning on the basis of Study I (positive symptoms,

negative symptoms, dose of antipsychotic medication and GAF) were controlled for. The number of affected siblings was controlled for to investigate whether genetic loading for the illness explained differences between the isolate and the rest of the country. In GEE model 3, the presence of the longest RELNSAT6 allele was controlled for. The same analyses were repeated in the relatives and control groups, but in GEE model 2 the number of affected siblings and GAF in the relatives group and GAF in the control group were controlled for.

5 Results

5.1 Demographic and clinical characteristics

Sociodemographic characteristics of the groups are presented in Table 4. Men were over-represented in the schizophrenia group, but in the other groups the proportion of men and women was close to equal. Education was highest in the control group and lowest in the patient groups. Further, the level of global functioning (GAF) was highest in the control group and lowest in the patient groups. Persons with schizoaffective disorder had a higher level of functioning than persons with schizophrenia. With regard to clinical characteristics (Table 5), the persons with schizophrenia had more negative symptoms and higher antipsychotic medication dose than the persons in the schizoaffective group, but in other characteristics the groups did not differ.

Table 4. Sociodemographic characteristics of the study groups

Variables	Schizophrenia	Schizoaffective disorder	Relatives	Controls [a]
Sex, Female / Male	76 / 142	31 / 31	144 / 133	62 / 61
Age, M (SD)	46 (8)	45 (6)	46 (8)	45 (13)
Range	26-66	28-55	24-67	27-70
Education (years), M (SD)	10 (2)	11 (2)	12 (3)	13 (4)
GAF, M (SD)	37 (11)	47 (15)	78 (12)	84 (9)
Range	20-90	27-90	36-98	50-95

Note: [a] The control group used in Studies I and II. The smaller control group used in the Study IV did not differ in sociodemographic characteristics from the one used in Studies I and II, and therefore only the characteristics of the larger group are demonstrated.

Table 5. Clinical characteristics of the schizophrenia and the schizoaffective groups and the results of GEE models comparing the patient groups

Variables	Schizophrenia	Schizoaffective disorder	Coefficient	*p*
Age of onset, M (SD)	23 (6)	24 (7)	0.91	0.33
Range	11-48	12-44		
Negative symptoms, M (SD)	54 (22)	36 (19)	-16.9	< 0.001
Positive symptoms, M (SD)	44 (21)	42 (19)	-1.9	0.49
Medication use				
Antipsychotics, *n* (%)	204 (95)	54 (95)	0.01	0.77
CPZE, M (SD)	570 (557)	410 (385)	-162	0.009

Note: CPZE = chlorpromazine equivalents

5.2 Cognitive performance in schizophrenia and schizoaffective disorder (Study I)

Cognitive performance was worse in the schizophrenia and schizoaffective groups than in the control group in all the variables measured (Figure 4 and Study I, Tables 3 and 4, page 319). The effect size of difference was large between the schizophrenia group and the control group in all the variables and medium to large between the schizoaffective group and the control group. Persons in the schizoaffective group outperformed persons in the schizophrenia group in the Vocabulary, the Digit Symbol, the Trail Making part A, the Visual Span backward and immediate recall, short delay recall and long delay recall in the CVLT (Study I, Tables 3 and 4, page 319). The schizophrenia and schizoaffective groups did not differ in the Trail Making Test part B, in the Digit Span or in the Visual Span Forward. The effect sizes ranged between small and medium.

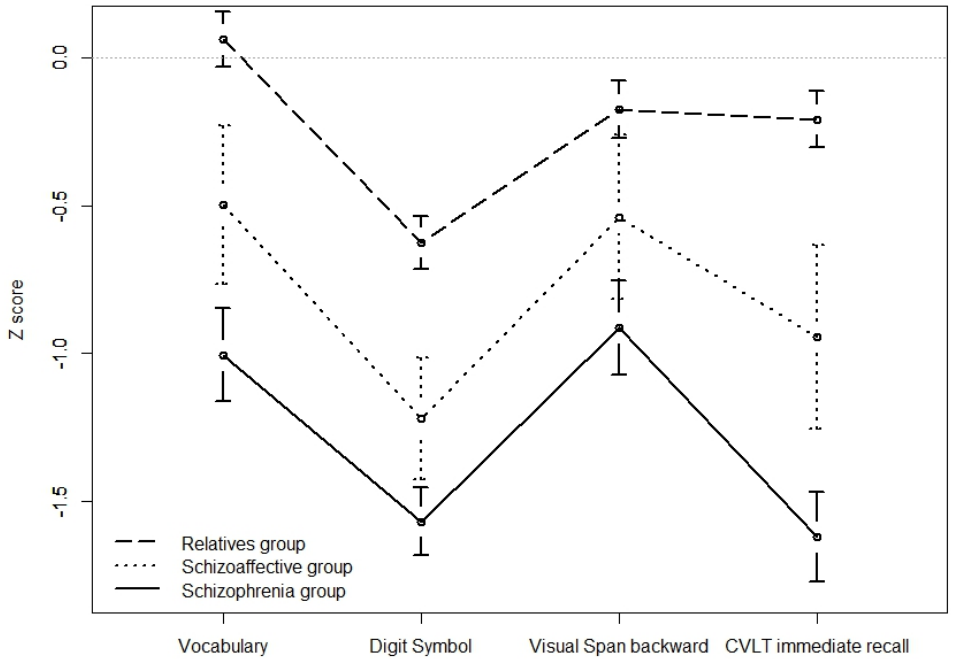

Figure 4. Mean performance and 95% confidence intervals of relatives, schizoaffective and schizophrenia groups in the Vocabulary, the Digit Symbol, the Visual Span backward and the CVLT immediate recall tests as Z-scores. Values were standardized based on control group performance.

When clinical characteristics were included in the models to examine if clinical characteristics were associated with cognitive performance and if clinical

characteristics explained the group differences in cognitive performance, severe negative symptoms were related to impairment in all investigated variables except the Trail Making part B, and high antipsychotic medication dose was related to impairment in the Vocabulary, in the Trail Making Test part B and in all included variables of the CVLT (Study I, Table 4, page 319). In addition, positive symptoms were related to impaired performance in the Digit Span backward and age of onset at trend level to the Visual Span backward. After controlling for clinical characteristics, schizophrenia and schizoaffective groups did not differ significantly. The number of depressive symptoms, the number of manic symptoms, use of antidepressants, the use of mood stabilizers, GAF, premorbid social adjustment, premorbid work adjustment and any lifetime substance use disorder did not have a statistically significant effect on cognitive functioning.

5.3 Sex differences in cognitive functions (Study II)

When investigating sex differences in cognitive functions, women outperformed men in the Digit Symbol, the Trail Making part B, and in short delay recall, long delay recall and recognition in the CVLT in all groups (Figure 5 and Study II, Tables 3 and 4, page 10). Men outperformed women in the Visual Span forward and backward (Figure 5 and Study II, Tables 3 and 4, page 10). Comparison of sex differences between the groups produced statistically significant sex × group interaction between the schizophrenia and the relatives groups in immediate recall and semantic clustering in the CVLT (Figure 5 and Study II, Table 4, page 10). In the relatives group, women outperformed men but, in the schizophrenia group, sex difference was smaller. The relatives performed worse than controls in the Digit Symbol and in the Trail Making part A and B (Study II, Tables 3 and 4, page 10).

Of clinical characteristics, men with schizophrenia had more severe negative symptoms and lived less frequently independently than women (Study IV, Table 2, page 9). Men and women with schizophrenia did not differ in positive symptoms, course of illness, age of onset, GAF or in medication use.

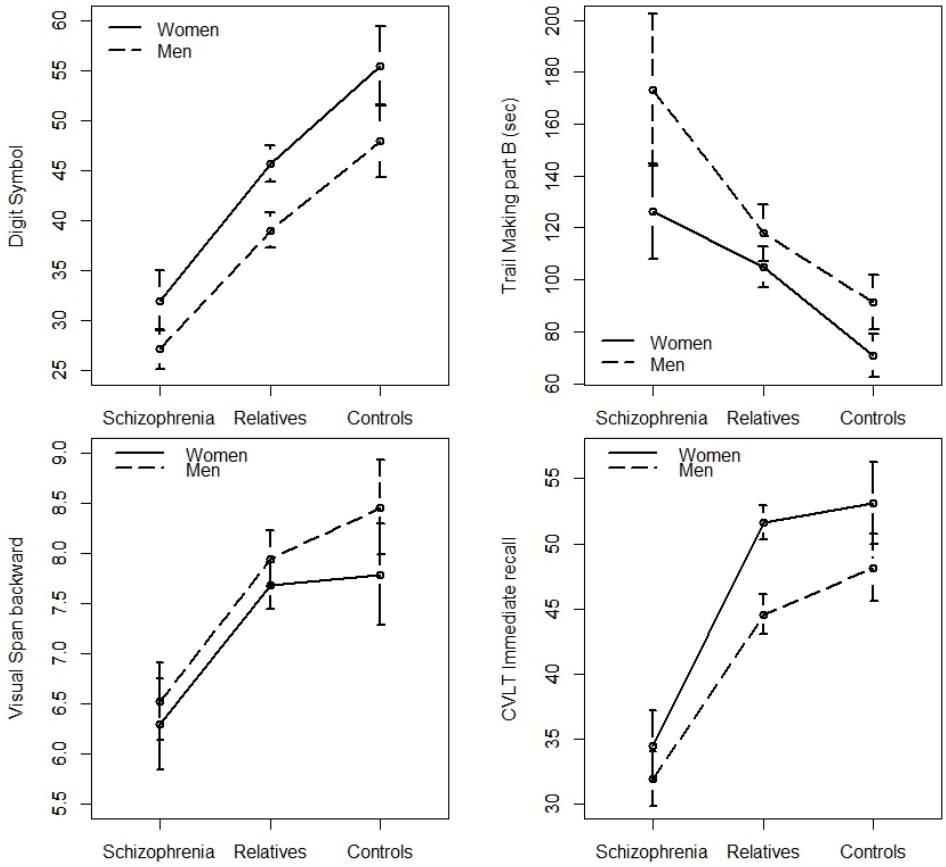

Figure 5. Mean performance and 95% confidence intervals of men and women in the schizophrenia, the relatives and the control groups in the Digit Symbol, Trail Making part B, Visual Span backward and immediate recall in the CVLT. Short time in the Trail Making part B indicated good performance.

5.4 The effects of birth weight on cognitive functioning (Study III)

The association of birth weight and cognitive performance was statistically significant and followed a curvilinear trajectory in the Block Design test, the Digit Symbol test, the Trail Making test part A and B, the Digit Span backward and the Visual Span backward when controlling for the type of delivery (hospital vs. home with professional assistance vs. home without professional assistance), GAF score, number of affected siblings per family, place of birth (isolate vs. rest of Finland), age and sex (Figure 6 and Study III, Table 2, page 5). Both low and high birth

weights were associated with lower cognitive performance. Birth weight of approximately 3500-4000 g was associated with the highest performance. Place of birth was also associated with cognitive performance. Compared to delivery in a hospital, delivery at home without professional assistance associated with lower performance in the Digit Span forward (β = -0.7, p = 0.03) and the Digit Span backward (β = -0.6, p = 0.05) and with professional assistance associated with lower performance in the Trail Making part B (β = -0.002, p = 0.02). The group × birth weight interactions were nonsignificant.

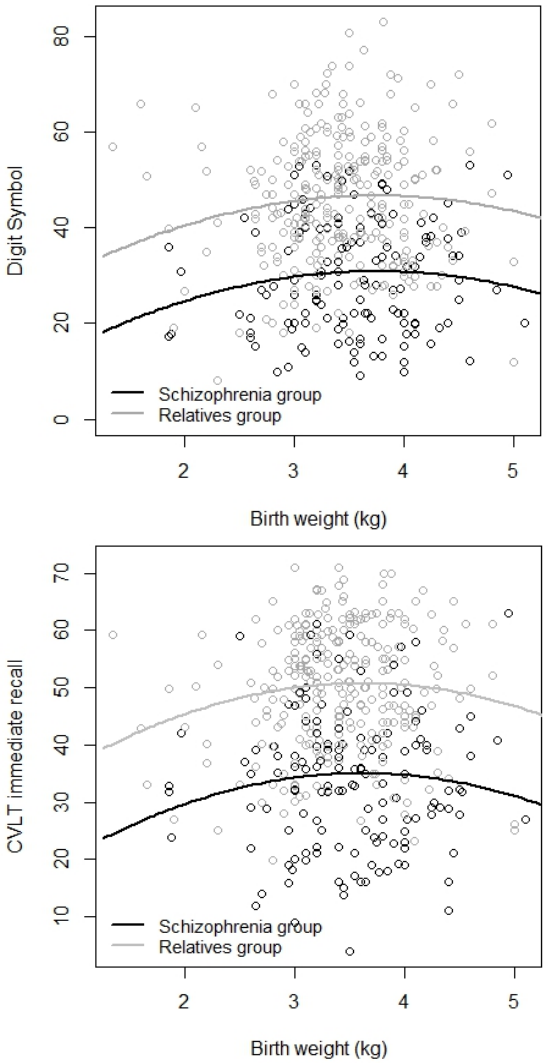

Figure 6. Scatter plots and regression lines on the basis of GEE models of the effects of birth weight on the performance in the Digit Symbol task and in the CVLT immediate recall

5.5 Cognitive performance in the isolate and the rest of Finland (Study IV)

The comparison of the isolate and the rest of Finland samples in cognitive functioning showed that in the schizophrenia groups, patients from the isolate outperformed patients from the rest of the country in the Vocabulary, the Trail Making part B and the CVLT immediate recall (Figure 7 and Study IV, Table 3, page 4). Controlling for clinical characteristics (positive symptoms, negative symptoms, dose of antipsychotic medication, GAF and the number of affected siblings) strengthened the findings, and differences in the Digit Symbol and the Stroop Colour-Word task also became statistically significant. When the patients from the isolate and the rest of Finland were compared by illness characteristics, persons from the isolate had higher dose of antipsychotic medication. In other illness characteristics, the patients from the two samples did not differ (Study IV, Table 2, page 3). Controlling for *RELN* risk allele did not change the results from the analyses with only age and sex as covariates.

In the relatives groups, the persons from the isolate outperformed the persons from the rest of Finland in the Stroop Colour task, the Stroop Colour-Word task and in all used CVLT variables (Figure 7 and Study IV, Table 4, page 4). When the number of affected siblings and GAF score were controlled for, the differences in the Vocabulary, the Stroop Interference and the Digit Span backward were also statistically significant. The *Reelin* risk allele controlled for, the differences remained significant in the Stroop Colour task and in the all used CVLT variables. In the control group, the isolate and the rest of Finland did not differ significantly and this finding did not change when GAF or *RELN* risk allele were controlled for (Figure 7 and Study IV, Table 5, page 5). Despite differences in the level of cognitive impairment in the schizophrenia families, the number of families with mental retardation was similar in the samples (8% in the isolate vs. 11% in the rest of Finland, $\beta = 0.33$, $p = 0.49$).

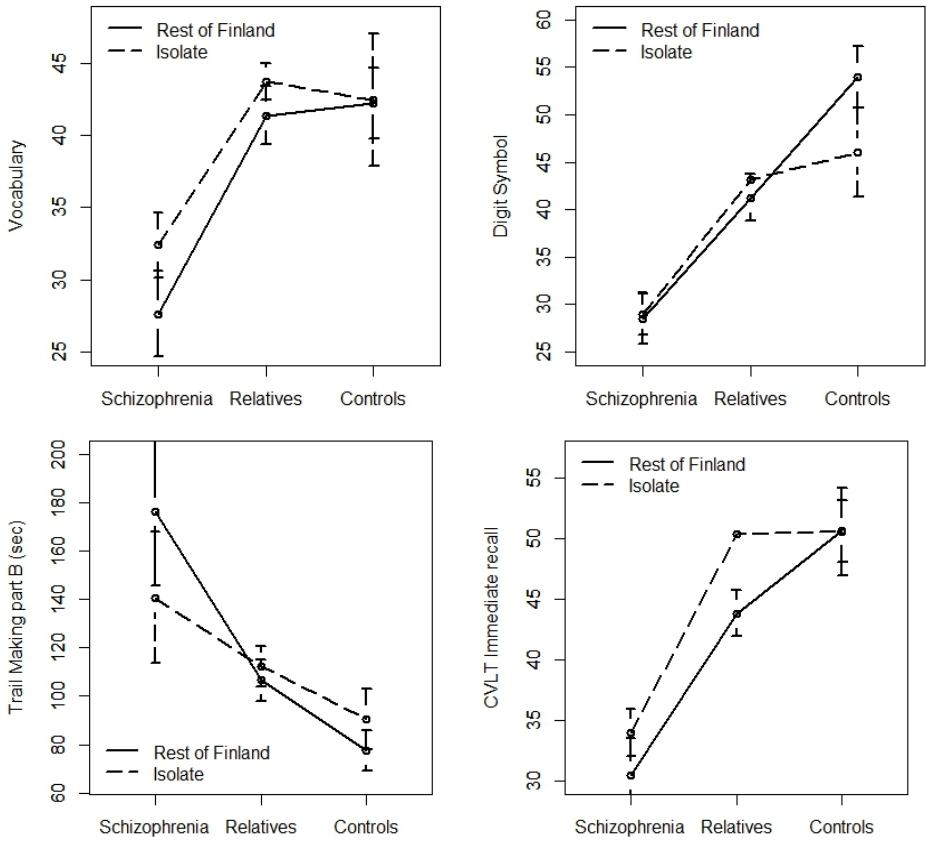

Figure 7. Means and 95% confidence intervals in the Vocabulary, the Digit Symbol, the Trail Making part B and the CVLT immediate recall. Persons from the isolate outperformed persons from the rest of Finland sample in most of the variables in the schizophrenia and the relatives groups, but the same effect was not detected in the control group. Short time in the Trail Making part B indicated good performance.

6 Discussion

The general aim of this thesis was to characterize cognitive impairment in people with schizophrenia, schizoaffective disorder and their unaffected first-degree relatives, and to explore if some of the previously reported schizophrenia risk factors are also related to cognitive impairment. First, cognitive impairment in schizophrenia and schizoaffective disorder was compared, and the association between clinical characteristics and cognitive functions was studied in these illnesses. Next, the relationship of birth weight and male sex, both previously reported risk factors of schizophrenia, with cognitive impairment in schizophrenia was explored. Then, differences in cognitive functions between families with schizophrenia from the Finnish internal isolate, which is genetically more homogeneous than the Finnish general population and has high schizophrenia prevalence, and families with schizophrenia from the rest of Finland were investigated. A large population-based schizophrenia family sample with high genetic loading for schizophrenia spectrum disorders and a population-based control sample comprised the study population of the thesis.

Persons with schizoaffective disorder exhibited broad cognitive impairment, with effect sizes varying between moderate to large, but the impairment was milder than in schizophrenia. The noticed differences were mostly accounted for by differences in the severity of negative symptoms and antipsychotic medication dose. The schizophrenia risk factors had distinct associations with cognitive functioning. Low and high birth weight were associated with slightly lower cognitive performance than intermediate birth weight, and originating from the isolate with better cognitive performance than originating from the rest of Finland both in persons with schizophrenia and their first-degree relatives. Men with schizophrenia did not have more severe cognitive impairment than women, but sex differences in cognitive functions were preserved both in persons with schizophrenia and their first-degree relatives.

6.1 Cognitive impairment in schizophrenia and schizoaffective disorder (Study I)

Cognitive impairment was large in schizophrenia, which is in agreement with previous studies (Dickinson *et al*., 2007). In schizoaffective disorder, cognitive impairment was observed to be broad and the effect sizes of differences were from medium to large when compared to unaffected controls, which is in line with the results of a recent meta-analysis (Bora *et al*., 2009). The impairment was milder in schizoaffective disorder than in schizophrenia in verbal ability, processing speed,

visual working memory and verbal learning. The effect sizes of the differences between people with schizophrenia and schizoaffective disorder varied between small and medium, which is in the same range as in previous studies (Bora *et al*., 2009).

When illness characteristics were controlled for (negative symptoms, antipsychotic medication dose, positive symptoms and age of onset), the statistically significant differences in cognitive functions between schizophrenia and schizoaffective disorder disappeared. This result is consistent with the suggestion that symptom dimensions explain more variance in cognitive functioning as well as in clinical characteristics and outcome than the diagnoses (Lewandowski *et al.*, 2011, Peralta & Cuesta, 2008, Rosenman *et al.*, 2003). Many authors agree that the symptoms of psychosis should be viewed as a continuum (van Os & Kapur, 2009). Schizophrenia spectrum disorders may differ mainly in the severity of illness characteristics rather than being qualitatively distinct entities.

Negative symptoms and antipsychotic dose were observed to be crucial in predicting cognitive functioning. In previous research, the association of negative symptoms with cognitive impairment has been a robust finding (Dominguez *et al.*, 2009, Harvey *et al.*, 2006, Hawkins *et al.*, 1997). However, cognitive functions and negative symptoms have been suggested to be separable dimensions (Bell & Mishara, 2006, Foussias & Remington, 2010). The dimensions may correlate because they may have partly similar or related aetiology or because the definition of negative symptoms includes symptoms that may affect cognitive performance or may also be a component of cognitive functions (e.g. motivational or attentional impairment) (Foussias & Remington, 2010, Harvey *et al.*, 2006). Further, some naturalistic studies have found that large medication dose is related to impaired cognition and increased brain tissue loss (Bornstein *et al.*, 1990, Elie *et al.*, 2010, Ho *et al.*, 2011, Hori *et al.*, 2006). The effect may also be related to extrapyramidal side effects related to high medication dose and to the treatment of those side effects with anticholinergics (Leucht *et al.*, 2009, Ogino *et al.*, 2011). Interestingly, mood symptoms did not have a statistically significant effect on cognitive impairment, despite their significance in diagnostic process. Earlier studies support the conclusion that mood symptoms are not related to cognitive impairment in schizophrenia spectrum disorders (Dominguez *et al.*, 2009, Simonsen *et al.*, 2011).

6.2 Effects of sex on cognitive impairment (Study II)

In the general population, women outperform men in processing speed and in some of the verbal skills, whereas men may outperform women in spatial skills (Burton *et*

al., 2005, Jorm *et al.*, 2004, Lynn & Irwing, 2008, Voyer *et al.*, 1995). Accordingly, in this study, women outperformed men in processing speed, in set-shifting and in verbal learning and memory, whereas men outperformed women in visual working memory in all groups.

Sex differences appeared to be mostly preserved in schizophrenia. Only in verbal learning and in the use of semantic clustering as a learning strategy, sex differences apparent in the relatives group were reduced in the schizophrenia group. Some often cited studies have suggested that men with schizophrenia have larger cognitive impairment than women with schizophrenia, but this view is challenged by the fact that studies reporting more severe cognitive impairment in women with schizophrenia also exist (Goldstein *et al.*, 1998, Lewine *et al.*, 1996, Roesch-Ely *et al.*, 2009, Seidman *et al.*, 1997). The findings are mostly concordant with the hypothesis of preserved sex differences in cognitive functioning in persons with schizophrenia. Preserved sex differences in unaffected first-degree relatives is also consistent with the conclusion. Support for this conclusion comes from studies finding preserved sex differences in cognitive functions in schizophrenia (Bozikas *et al.*, 2010, Gur *et al.*, 2001, Halari *et al.*, 2006, Hoff *et al.*, 1998). The reduced sex differences in verbal learning and in the use of semantic clustering in the persons with schizophrenia could also be interpreted as a support for the hypothesis of diminished sex differences in schizophrenia (Mendrek, 2007, Shipman *et al.*, 2009). The finding could also result from multiple testing or reflect other factors, such as, floor effect, because both men and women used semantic clustering very poorly.

Men had more negative symptoms, concordant with earlier studies (Galderisi *et al.*, 2012, Thorup *et al.*, 2007), and lived less frequently independently than women. Negative symptoms are correlated with cognitive impairment (Dominguez *et al.*, 2009). Nevertheless, earlier studies suggest that cognitive impairment and negative symptoms are separable constructs and they may have at least partly separate aetiologies (Harvey *et al.*, 2006). Sex may have a different effect on the aetiology of negative symptoms and cognitive functions in schizophrenia.

In many other psychiatric disorders and in developmental disorders, large sex differences have been detected. Depression and anxiety disorders are more common in women than in men, and substance disorders and developmental disorders, such as autism, are more common in men than in women (Idring *et al.*, 2012, Seedat *et al.*, 2009). Culture may especially influence sex differences in depression and substance disorders (Seedat *et al.*, 2009), but in schizophrenia sex differences may be more biological.

There may be separate mechanisms how sex influences the risk of schizophrenia and related phenotypic features at different time points. The hypothesis that female sex protects against schizophrenia is supported by the findings of men having higher risk of schizophrenia, earlier age of illness onset, more severe negative symptoms and possibly, in the general population, more prevalent subclinical psychotic experiences and negative symptoms than women (Aleman *et al.*, 2003, Eranti *et al.*, 2013, Miettunen & Jääskeläinen, 2010, Thorup *et al.*, 2007, van Os *et al.*, 2009). If female sex raised the threshold of having the symptoms of schizophrenia, despite risk factors and neurodevelopmental deviations, women should have more pronounced cognitive impairment in the groups of persons with schizophrenia and their first-degree relatives. This view is supported by the observation that women have less psychotic symptoms when oestrogen level is high (Markham, 2012). In contrast, if female sex protected only from neurodevelopmental deviations causing schizophrenia and cognitive impairment, women with schizophrenia should have better preserved cognitive functions than men with schizophrenia. Earlier studies have shown that men may have an increased risk for other neurodevelopmental disorders and be more vulnerable to neurodevelopmental insults (Markham, 2012, Spinillo *et al.*, 2009, Suren *et al.*, 2012). These mechanisms are not mutually exclusive and the finding of preserved cognitive functions may imply that both of these possible mechanisms for the protective role of female sex may take place, or that the effects are so small that a very large sample size would be required to detect the effect.

6.3 Effects of birth weight on cognitive impairment (Study III)

Previous studies from the same sample as in this study found that the risk of schizophrenia and, of schizophrenia symptom dimensions, the severity of negative and disorganized symptoms were increased in persons with either low or high birth weight (Wegelius *et al.*, 2012, Wegelius *et al.*, 2011). In agreement with this, lower performance in persons with low or high birth weight were noticed in visuospatial reasoning, processing speed, set-shifting, and verbal and visual working memory, while persons with the birth weight of 3500-4000 g had the best cognitive performance. However, the effect of birth weight on cognitive functioning was small.

The findings of this study are in accordance with general population studies. Many studies have shown that low birth weight is associated with many adversities, such as slightly impaired cognitive functioning (Bergvall *et al.*, 2006, Boulet *et al.*, 2011). Although research has mostly concentrated on the effects of low birth weight, some studies have detected that cognitive functioning as well as other neurodevelopmental and health outcomes may be impaired in persons with high birth weight (Leonard *et al.*, 2008, Shenkin *et al.*, 2004, Van Lieshout & Boyle, 2011).

Intermediate birth weight appears optimal in relation to neurodevelopment and cognitive functioning. Adverse effects causing intrauterine growth restrictions (e.g. inadequate supply of nutrition, placental pathology or infections) may cause adaptations, for example, in endocrine and metabolic processes, referred to as "fetal programming" (Barker, 1995, Fowden *et al.*, 2006). These effects may impair brain growth and affect cognitive functioning (Morgane *et al.*, 1993). Similarly, persons with high birth weight may have had a suboptimal intrauterine environment, which may affect neurodevelopment, but little is known about the mechanisms explaining the association between high birth weight and cognitive functioning (Van Lieshout & Boyle, 2011). Possibly, adaptations to a suboptimal environment caused, for example, by abnormal metabolic environment or levels of hormones may occur in the same way as in low birth weight (Freeman, 2010). Maternal obesity or diabetes, which are risk factors for high birth weight, may also increase, for example, the level of pro-inflammatory cytokines and oxidative stress (Challier *et al.*, 2008, Freeman, 2010). High birth weight is also associated with birth complications, the risk of prolonged second stage of labour is increased and Caesarean section is more often needed (Henriksen, 2008, Koskela, 1965). These factors may be especially problematic if the child is born outside a hospital, or in a local hospital where personnel are rarely required to perform Ceasarean sections, a situation that was common in rural areas at the time the study population was born. In addition, the association between birth weight and cognitive functioning may partly be explained by genetic effects or by family socioeconomic status (Bergvall *et al.*, 2006, Power *et al.*, 2006).

The probands of the schizophrenia family sample were born during years 1940-1976. In 1940, Finland was still an agricultural country and rather undeveloped especially in the countryside, but after that living standards and health care have developed rapidly (Palmgren, 1964). Likewise, maternal health care and the management of delivery have improved. In 1940, only 30% of the deliveries occurred at hospitals, but in 1960 it was 90% (Hemminki, 1983, Suomen virallinen tilasto XI, 1955). Nowadays, most of the deliveries occur in large, specialized maternity units (Hemminki, 1983). Since 1940, perinatal and infant mortality have dropped (Hemminki, 1983, Piekkala *et al.*, 1985, The official statistics of Finland XI: 62, 1962). Still, during years 1811-1870, infant mortality rate was 19%, during years 1950-1951 4% and during years 1991-1995 infant mortality rate was only 0.5% (Pitkänen *et al.*, 2000). These changes may have implications for applying the results to the present. The survival of low birth weight infants has increased (Heinonen *et al.*, 1988), which may increase the significance of low birth weight on cognitive functioning. Further, the effects of high birth weight on cognitive functioning may have changed. The prevalence of overweight in the general

population and the proportion of infants with high birth weight have increased (Kinnunen *et al.*, 2003, Lahti-Koski *et al.*, 2010), but on the other hand, modern specialized maternity units are prepared for handling complications associated with the delivery of a high birth weight infant. In addition, the antenatal care of pregnant women in maternity centres has improved, which enables better management of conditions causing low or high birth weight (Hemminki, 1983, The official statistics of Finland XI: 62, 1962).

6.4 Cognitive functioning in persons from the isolate and the rest of Finland (Study IV)

In comparing the Finnish genetic isolate to the rest of Finland in cognitive functioning, persons with schizophrenia from the isolate were noticed to perform slightly better than persons with schizophrenia from the rest of Finland in verbal learning, verbal ability and cognitive flexibility. Similar effect was detected in the unaffected first-degree relatives: the persons from the isolate outperformed the persons from the rest of Finland in verbal learning and in processing speed. However, the controls from the isolate did not differ from the controls from the rest of the country.

The clinical characteristics of schizophrenia appeared mostly similar in both samples, but persons from the isolate had higher antipsychotic dose and, in a previous study with larger sample size (Arajärvi *et al.*, 2004, Arajärvi *et al.*, 2006), less severe positive symptoms. However, differences in clinical characteristics or in the number of affected siblings in families did not explain the differences between the samples. *RELN* risk allele (the longest RELNSAT6 allele) has been shown to be associated with severe cognitive impairment in schizophrenia families and to be relatively absent from the isolate (Wedenoja *et al.*, 2008, Wedenoja *et al.*, 2010). However, the differences in the frequency of the allele did not explain the noticed differences between the samples. Lastly, the number of families with a sibling with mental retardation was studied as an indicator of the proportion of families where there could be a rare inherited variant, for example a copy number variation, predisposing to both schizophrenia and mental retardation. The proportion of families with mental retardation was noticed to be equal within the isolate and in the rest of Finland. The proportions were relatively high, which is accordant with studies reporting co-segregation of schizophrenia and mental retardation (Greenwood *et al.*, 2004, Morgan *et al.*, 2008b).

Higher prevalence of schizophrenia and slightly better preserved cognitive functions in schizophrenia families within the isolate compared to the rest of Finland suggest that some risk factors for schizophrenia, that do not expose for severe cognitive

impairment, may be enriched within the isolate. The lack of differences between the control groups from the isolate and the rest of the country may suggest that the difference is not some general genetic or environmental difference between the regions. Many earlier identified environmental risk factors for schizophrenia are related to slightly impaired cognitive functioning (Jefferis *et al.*, 2002, Lawlor *et al.*, 2006, Nolin & Ethier, 2007, Saha *et al.*, 2009, Seidman *et al.*, 2000), which might suggest that environmental risk factors are not the basis of the difference in cognitive functioning. Earlier studies have discovered that risk alleles for schizophrenia may affect cognitive functioning differently. Some risk alleles, such as *Neuregulin 3* (*NRG3*) and *ZNF804A*, may predispose to schizophrenia with relatively spared cognitive functioning, whereas several others are related to severe cognitive impairment (Chen *et al.*, 2012, Green *et al.*, 2012, Greenwood *et al.*, 2011, Jablensky *et al.*, 2011, Morar *et al.*, 2011, Walters *et al.*, 2010, Wessman *et al.*, 2009). Accordingly, the difference between the schizophrenia families within the isolate and outside the isolate may result from the enrichment of genetic risk factors for schizophrenia with relatively spared cognitive function in the isolate.

6.5 Methodological considerations

The purpose of the study project was to collect two samples with high genetic loading for schizophrenia in order to investigate the genetic epidemiology and aetiology of the disorder. From the isolate, the purpose was to identify and assess all available families with schizophrenia at the recruiting time period. Most of the families with schizophrenia within the isolate are related, and there are multiple links between the families of the isolate (Hovatta *et al.*, 1999). When an extensive genealogical study was done of 48 families with schizophrenia, a common founder couple born around 1650 was found for 39 families (Hovatta *et al*., 1999). Because of this, and because of the threefold risk of schizophrenia in the isolate compared with the rest of Finland (Hovatta *et al*., 1997), the patients with schizophrenia from the isolate are considered as representing familial schizophrenia. From the rest of Finland, families with high genetic loading for schizophrenia were assessed, which was defined as families with at least two siblings with schizophrenia. High familial loading for the illness is not expected to have a strong effect on the results in cognitive functioning, because in earlier studies, familial loading has had no or only minimal effect on cognitive functioning and illness characteristics (Birkett *et al.*, 2008, Esterberg *et al.*, 2010, Roy & Crowe, 1994, Tuulio-Henriksson *et al.*, 2003).

Of the families from the isolate, 60% had only one sibling with schizophrenia spectrum illness. Because the familial loading for schizophrenia differed between the isolate and the rest of Finland schizophrenia family samples, the number of affected siblings in the families was controlled for when assessing the differences

between the isolate and the rest of Finland samples in cognitive functioning (Study IV). In addition, it was confirmed that the inclusion of only the families with at least two affected siblings does not affect the results. Therefore, the differences between the family samples should not result from differences in familial loading for the illness.

Sex differences in age of onset do not appear in persons with high genetic loading for schizophrenia (Esterberg *et al.*, 2010, Suvisaari *et al.*, 1998), such as in this study sample. This finding has led to the suggestion that genetic loading for schizophrenia attenuate the protective effect of female sex (Albus *et al.*, 1994, Könnecke *et al.*, 2000). In contrast to the assumption by Esterberg *et al*. (2010) of lack of sex differences in negative symptoms in persons with high genetic loading for schizophrenia, in this study, men with schizophrenia had more severe negative symptoms than women. This sex difference with strong support of preserved sex differences in cognitive functions in earlier studies may suggest that the lack of sex differences in samples with high familial loading could be limited to the age of onset, even though familial loading may also possibly decrease sex differences in other illness characteristics.

The sample size in the control group was smaller than in the schizophrenia group or in the relatives group. The small sample size may hinder the observation of the differences between the isolate and the rest of Finland in cognitive functioning (Study IV). If the effect size of differences in the schizophrenia families is small to medium, the study did not have good statistical power to detect differences when *p*-values under 0.05 are considered statistically significant. However, the means in the control samples did not show a similar trend as in the schizophrenia family samples. The trend appeared to be mostly that the controls from the isolate performed slightly lower than the controls from the rest of Finland, which is opposite to the differences in the patient and the relatives groups. Therefore, there was no reason to assume that also controls born within isolate would perform better than controls from the rest of Finland.

After the other exclusion criteria, 20 (8%) persons with schizophrenia out of 238 were untestable, for example due to severe disorganized symptoms. In the schizoaffective group, only 1 out of 63 persons was untestable. The persons who were untestable may, on average, have larger cognitive impairment than persons who could be tested. If all persons could have been tested, the differences between schizophrenia and schizoaffective groups could possibly have been somewhat larger than how they turned out to be (Study I). Of patients with schizophrenia, from the isolate 7% were untestable and 11% from the rest of Finland. The small, statistically nonsignificant difference in the proportion of the untestable persons was in the same

direction as the finding of more severe cognitive impairment in the rest of Finland than in the isolate (Study IV). Of women with schizophrenia, 6% were untestable, whereas 10% of men with schizophrenia. The difference is small, and if all the persons could have been assessed, the conclusion of preserved sex differences would probably not change (Study II).

The exclusion of the persons with the most severe acute symptoms may affect the correlations between cognitive functioning and schizophrenia symptoms (Study I). Another limitation, which may affect the correlations of symptoms and cognitive functioning, was that the measures of mood symptoms were based on the number of the symptoms during the most severe mood episode and not on the current severity of the symptoms.

The strengths of this study include a control group representative of the Finnish population. In addition, the schizophrenia family sample was identified from nationwide health care registers. The method enables better representativeness than if the samples were collected from a treatment facility, such as a hospital. This way patients with good outcome and without a current treatment contact could also be included.

Birth weight data were not collected for the control group. Therefore, it was not possible to investigate whether the effect of birth weight on cognitive functioning was larger in the schizophrenia family sample than in the control group without familial loading for schizophrenia (Study III). Birth weight data were collected from obstetric records, which improves the reliability compared to relying on maternal recall.

The neuropsychological test methods that were used in the data collection are among those that have been commonly used in international schizophrenia research. Previous meta-analyses have shown that these test methods are sensitive to cognitive impairment related to schizophrenia (Dickinson *et al.*, 2007, Mesholam-Gately *et al.*, 2009), although not specific in this application. The MATRICS project defined speed of processing, verbal learning, visual learning, working memory, reasoning and problem solving, attention/vigilance and social cognition as the most relevant cognitive domains in schizophrenia, and The Consortium on the Genetics of Schizophrenia (COGS) used measures of sustained attention, verbal memory, working memory, abstraction and mental flexibility, face memory, spatial memory, spatial processing, sensorimotor dexterity and emotion processing in their cognitive assessment battery (Gur *et al.*, 2007, Nuechterlein *et al.*, 2008). The neuropsychological battery administered in the schizophrenia family samples covered most of the basic cognitive functions. Sustained attention and visual or

spatial learning tasks are sensitive to cognitive impairment in schizophrenia and have been included both in the MATRICS battery and in the COGS battery, and therefore might have been worthwhile to assess. Motor performance and perception are among the basic neuropsychological function; however, these functions have not appeared as sensitive as the used tests for the assessment of cognitive impairment in schizophrenia (Dickinson *et al*., 2007). In addition, social cognition deficits in schizophrenia have lately been recognized (Savla *et al.*, 2012), but the test battery in the present thesis study did not include tests assessing social cognition. Due to limitations in resources, it was not possible to perform the similar comprehensive neuropsychological assessment for the control group that was used in the family sample.

6.6 Conclusions and future implications

As in schizophrenia, cognitive impairment also appeared broad and severe in schizoaffective disorder. Although the impairment appeared milder in schizoaffective disorder than in schizophrenia, the diagnostic groups cannot be separated on the basis of cognitive functioning, because the distributions of cognitive impairment in schizophrenia and schizoaffective disorder were largely overlapping. Differences in negative symptoms and medication dose explained most of the differences in the level of cognitive impairment. The result suggested that schizophrenia and schizoaffective disorder are not essentially qualitatively distinct, but only have some differences in the severity of symptoms. Future studies are required to clarify if the assessment of mood symptoms (Boks *et al.*, 2007), cognitive impairment (Hoti *et al.*, 2004) or negative symptoms (Carpenter *et al.*, 1988, Kirkpatrick & Galderisi, 2008) can be used in dividing psychotic disorders into groups that might be less heterogeneous than at present relative to aetiology and treatment needs, or if the dimensional representation of psychosis (Peralta & Cuesta, 2008) can meet these needs.

Since many persons with schizoaffective disorder had severe, broad cognitive impairment, the assessment and treatment of cognitive impairment in schizoaffective disorder is similarly important as it is in schizophrenia. Persons with schizoaffective disorder may benefit from cognitive remediation in the same way as persons with schizophrenia (Anaya *et al.*, 2012, Wykes *et al.*, 2011). The association of large antipsychotic medication dose with cognitive impairment in schizophrenia gives further support for the proposition that lowest effective dose should be used in the long-term treatment of schizophrenia (Buchanan *et al.*, 2010).

Of the previously established schizophrenia risk factors, both low and high birth weight were associated with exacerbated cognitive impairment in persons with schizophrenia and their first-degree relatives. The illness did not change the relationship between birth weight and cognitive functioning in persons with high genetic loading for schizophrenia. Previous studies have detected a similar association in general population samples (Shenkin *et al.*, 2004) suggesting that the association is not restricted only to persons with high genetic loading for schizophrenia.

The effect of birth weight on cognitive functioning was only small, and therefore information on birth weight does not have clinical significance in the assessment and treatment of individuals with schizophrenia. Even though the effect is small at the individual level, at the population level the prevention of adverse factors causing low or high birth weight may be worthwhile. Research on specific mechanisms how birth weight is associated with cognitive functioning and increased schizophrenia risk may inform about some of the aetiological factors underlying schizophrenia and cognitive impairment in schizophrenia. The exacerbation of cognitive impairment in persons with low or high birth weight may result from suboptimal intrauterine environment or complications, which are related to both low and high birth weight.

Although schizophrenia is more common in men than in women and some of the schizophrenia symptoms are more severe in men than in women (McGrath *et al.*, 2004, Thorup *et al.*, 2007), cognitive impairment was not more severe in men than in women with schizophrenia. Sex differences in cognitive functions in persons with schizophrenia and their first-degree relatives were similar as in the control group. Even though sex did not affect the level of cognitive impairment, the possible protective role of some factor related to female sex (e.g. oestrogen) and especially the mechanism of how the protection may be delivered deserves further studies.

Within the Finnish internal isolate, schizophrenia risk is high compared to the rest of Finland (Hovatta *et al*., 1997). However, schizophrenia patients and their first-degree relatives from the isolate slightly outperformed the patients and the relatives from the rest of Finland in cognitive functioning. A similar difference was not noticed in the unrelated control groups. The result suggests that some, possibly genetic, schizophrenia risk factors that do not expose to severe cognitive impairment may be enriched within the isolate. The suggested differences in the aetiology of schizophrenia support the use of population isolates in the genetic research into schizophrenia.

The association of schizophrenia risk factors with cognitive impairment has thus far been little studied. Many risk factors may impair cognitive functioning, but the

severity of cognitive impairment that the risk factors cause may vary. The schizophrenia risk factors assessed in the present thesis had different effects on cognitive functioning. Low and high birth weight were associated with more severe cognitive impairment than intermediate birth weight, originating from the internal genetic isolate with better cognitive functioning in schizophrenia families than originating from the rest of Finland, and sex was not associated with the level of cognitive impairment. More research on the relationship between cognitive impairment and schizophrenia risk factors is required, in order to elucidate the aetiology of cognitive impairment in schizophrenia and to support the development of treatments to alleviate cognitive impairment in schizophrenia.

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