Vulnerability and Social Functioning in Schizophrenia

GABRIELLA STÅLBERG
Abstract


This thesis offers a broad approach in elucidating biological risk factors, as well as psychological and social functioning in schizophrenia. The aims are as follows: (I) investigate the association between birth characteristics and schizophrenia, (II) study the association between levels of neurotransmitter neuropeptide Y (NPY) in cerebrospinal fluid (CSF), social function and longitudinal outcome in schizophrenia, (III) compare social functioning of patients with schizophrenia with their biological siblings and (IV) explore how siblings to patients with schizophrenia perceive the sibling relationship and their role.

Paper I was a cohort analysis of 11,360 same-sexed twins in which obstetric records were used. Low birth weight and small head circumference were associated with later development of schizophrenia. To some extent the results persisted in the within-pair analyses conducted on 82 pairs discordant for schizophrenia.

Fifty-six patients with schizophrenia were included in paper II. Levels of NPY in CSF correlated to social competence at index admission. For each standard deviation increase in baseline NPY, there was a concomitant increased risk of being unemployed, having moderate or severe symptoms or recent hospitalization at the 3-year follow-up.

In paper III, social functioning was investigated using the Swedish version of the videotaped test Assessment of Interpersonal Problem Solving Skills (AIPSS) in 70 participants (25 patients with schizophrenia, 20 siblings and 25 randomly selected controls). The patients presented severe deficits in social functioning. The siblings expressed subtle impairments in nonverbal language but did not generally differ from the controls.

To explore the siblings’ perspective on schizophrenia a qualitative study was conducted with interviews of 16 siblings in paper IV. A unifying major theme was an emotional sibling bond. Siblings developed several coping patterns, including avoidance, isolation, normalization, caregiving and grieving. A third major theme consisted of the fear of inheriting schizophrenia.

In conclusion, fetal growth, altered levels of NPY in CSF and subtle impairments in nonverbal social behavior might be important risk factors in schizophrenia. Patients with schizophrenia revealed extensive impaired social functioning, and from the siblings’ perspective, a brother or sister’s diagnosis of schizophrenia seems to have a profound psychological impact on the siblings.

Keywords: Coping, fetal growth, low birth weight, neuropeptides, outcome, problem solving skills, psychosis, risk factors, schizophrenia, siblings, social function, twins

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To Simon and Melker
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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<tbody>
<tr>
<td>AIPSS</td>
<td>Assessment of Interpersonal Problem Solving Skills</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal spinal fluid</td>
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<tr>
<td>CPRS</td>
<td>Comprehensive Psychopathological Rating Scale</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<tr>
<td>DUP</td>
<td>Duration of untreated psychosis</td>
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<tr>
<td>GEE</td>
<td>Generalized estimated equation</td>
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<tr>
<td>HPA</td>
<td>Hypothalamic-pituitary-adrenal</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>M</td>
<td>Mean</td>
</tr>
<tr>
<td>NOSIE-30</td>
<td>Nurses’ Observation Scale for Inpatient Evaluation</td>
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<tr>
<td>NPY</td>
<td>Neuropeptide Y</td>
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<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PANSS</td>
<td>Positive and Negative Syndrome Scale for Schizophrenia</td>
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<td>SD</td>
<td>Standard deviation</td>
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Introduction

Schizophrenia is a mental disorder characterized by impairments in social functioning, a disintegration of thought processes and inadequate or poor emotional responses. Significant social dysfunction is a diagnostic feature in the disorder and other principal symptoms include auditory hallucinations, paranoid or bizarre delusions, disorganized speech and thinking and cognitive deficits.\(^1\) The lifetime prevalence is about 1% and schizophrenia is among the world’s top 10 causes of long-term disability.\(^2,3\)

Vulnerability in schizophrenia

The etiology of schizophrenia is still unknown and its pathophysiology poorly understood. Genetics, early environment, neurobiology, psychological and social processes are suggested to be important contributory factors. One of the few areas of agreement between proponents of the biological and psychodynamic origins of schizophrenia is that many of the roots lie within the family.\(^4\) Familiality, however, can arise from common or shared environmental factors, as much as genetic causes. Furthermore, it has been apparent for almost two decades of a developmental component to schizophrenia.\(^5\)

Vulnerability models

The vulnerability-stress model

In 1977, Zubin and Spring introduced the term vulnerability to schizophrenia.\(^6\) Their vulnerability model proposes that each of us is endowed with a degree of vulnerability that will express itself in an episode of schizophrenia if under a certain amount of stress. According to this model, there are two major components of vulnerability, inborn with a genetic origin and the acquired, such as perinatal complications or family stress. Both endogenous events, such as biochemical mechanisms, and exogenous events, such as life events, are viewed as possible stressors. A highly vulnerable person reacts with psychosis at a lower level of stress compared with a person with a lower degree of vulnerability.
The vulnerability-stress model also suggests that relapses and hospitalizations can be prevented by lowering biological vulnerability or reducing stress.\(^7\) The targeting of these factors has played an important role in the development of psychosocial interventions for schizophrenia over the past three decades.\(^8\) In subsequent years several authors later have elaborated on the Zubin and Spring concept. These models mostly presume that schizophrenia-spectrum disorders do not necessarily have a hereditary origin.\(^9\) However, high heritability estimates indicate a strong genetic influence in schizophrenia and it has been difficult to generate data to substantiate this well-known stress-vulnerability model.\(^10\)

The neurodevelopmental model

The neurodevelopmental hypothesis posits that schizophrenia is the end stage of abnormal neurodevelopmental processes that began years before onset.\(^11,12\) Evidence from neuropathological, neuroimaging, neurochemical and epidemiological studies suggests that aberrations in the control of early brain development and environmental hazards produce the neuronal phenotype that manifests as schizophrenia.\(^13,14\) Current data, however, indicate that human neurodevelopment is not confined to the womb, but is a protracted process that continues in post-natal life well into adolescence and early adulthood.\(^15\) Moreover, more recent formulations incorporate the role of social factors (e.g., urban upbringing, social isolation and migration) and point to an interaction between the biological and psychological in a cascade of increasingly deviant development.\(^16-18\)

Stress

Because stress is a key feature of many etiological models of psychosis, it might be relevant to briefly conceptualize stress and describe its possible mediating mechanism in the development of schizophrenia. Early conceptualizations of stress defined it as a physiological reaction of an organism to a threatening stimulus. In short, the psychological stress response involves activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic branch of the autonomic nervous system.\(^19\) Although it is not the only neural system activated by stress exposure, psychopathologists have focused on the HPA axis because it has been linked with a number of mental disorders, including psychoses.\(^20\) Assuming that schizophrenia involves an abnormality in the dopamine system, the HPA axis has been proposed to act as a potentiating system by means on its effects on dopamine.\(^21\) Thus, of particular relevance to psychosis is the reciprocal interaction between the HPA axis and dopaminergic pathways.\(^22,23\)
In short, stress is also defined as a psychological concept in which cognitive appraisal of threatening stimuli occurs, resulting in the activation of a coping response. Within this context, coping has been defined as constantly changing cognitive and behavioral efforts to manage specific external or internal demands that are appraised as taxing or exceeding the individual’s resources.24

Risk factors

Whether schizophrenia develops depends not only on the person’s vulnerability but also on risk factors that increase the likelihood of developing schizophrenia and on protective factors that decrease the risk. Briefly, there are two main reasons for studying risk factors for psychotic disorders. First, there is the possibility of preventing the onset of full-blown psychosis by identification and treatment of individuals at risk for psychotic disorder. Second, to increase our understanding of the etiology of schizophrenia and to enable the development of new treatments.25

Early environmental risk factors

Prospective studies have shown that some factors in fetal life (such as hypoxia, maternal infection, maternal stress and maternal malnutrition) might account for a small proportion of the incidence of schizophrenia.26 Although maternal risk factors during the prenatal-perinatal period have received the most attention, older paternal age at conception has been linked to an approximately twofold increased risk for developing schizophrenia.27

To date, there is ample evidence for non-specific complications of pregnancy and delivery (generally known as “obstetric complications”), which may contribute to the vulnerability for schizophrenia.28,29 More specifically, a meta-analysis of prospective population-based studies found three groups of complications significantly associated with schizophrenia: complications of pregnancy (e.g., bleeding, diabetes, rhesus incompatibility and preeclampsia), abnormal fetal growth and development (e.g., low birth weight, congenital malformations and reduced head circumference) and complications of delivery (e.g., uterine atony, asphyxia and emergency cesarean section).30 The reported findings of an approximately doubled risk for individuals exposed to obstetric complications to develop schizophrenia are supported by three other meta-analyses.31-33 The mediating mechanism for obstetric complications as a risk factor is still unknown, but several studies suggest that hypoxic brain damage associated with prenatal underdevelopment might be a causal factor for subsequent schizophrenia.34,35

Delayed attainment of various developmental milestones and a range of premorbid impairments during childhood and adolescence have also been linked to an increased likelihood for future schizophrenia. According to a review by Tandon et al., specific cognitive impairments, poor academic
achievement, minor physical anomalies, soft neurological signs and poor social adjustment are promising examples of such early risk factors. However, whether such impairments represent early risk factors or are early signs of the mental disorder is still unclear.

**Neurobiological risk factors**

In general, there seem to be fewer studies on biological risk factors in schizophrenia compared with clinical, psychological or social risk factors. However, adolescents and young adults at genetic risk for schizophrenia have been found to have several structural brain abnormalities similar to those in patients with the disorder. A recent review reported regional as well as global brain volume reductions and gray matter deficits in relatives at risk. More precisely, high-risk subjects have been found to have statistically significantly reduced mean volumes of the left and right amygdala-hippocampus and thalamus than healthy controls. Some of the grey matter abnormalities linked to psychosis have been found to predate the onset of frank symptoms. These brain regions, however, are dynamically changing during normal maturation, meaning that any putative neurobiological markers identified at the earliest stages of the illness may be relatively unstable.

Historically, the prevailing theory of the neurochemical basis for schizophrenia is the dopamine hypothesis. Theories about the mechanism of dopamine in schizophrenia assert that symptoms of schizophrenia are caused by a disturbed hyper- or hypoactive dopaminergic system. A recent review noted that the need for more potential treatments with fewer side effects in schizophrenia has turned interest towards neuropeptides. One of these neuropeptides is neuropeptide Y (NPY), a 36-amino acid peptide widely distributed in the central, peripheral and enteric nervous system. NPY is a member of the pancreatic polypeptide family and its physiological effects are mediated by G protein coupled receptors, five of which have been cloned, Y₁, Y₂, Y₄, Y₅ and Y₆.

NPY is found to be involved in physiological processes and behaviors that are relevant to psychopathology (e.g., stress regulation, coping, learning, memory and cognition). There is also strong evidence showing that NPY has anxiolytic-like effects. The general consensus is that NPY tones down CNS activity by inhibiting the activity of pro-stress transmitters, thereby controlling anxiety responses and stress. Preclinical and clinical studies suggest that NPY dysregulation may occur in various psychiatric conditions, including schizophrenia, depression, anxiety, alcoholism and trauma-induced disorders.
Sibling studies

A reason for investigating siblings of patients with schizophrenia is to further explore the established notion that schizophrenia is familial as demonstrated by family, twin and adoption studies. A meta-analysis of twin studies established the heritability of schizophrenia to be about 81%, results suggested to be consistent with a view of schizophrenia as a complex trait resulting from genetic and environmental etiological influences. Family and twin studies can be a useful tool for investigating whether the pattern of risks rises and falls as a function of the genetic overlap rather than as a consequence of shared experience. Thus, schizophrenia is a disease demanding a multifactorial-polygenic model to answer the puzzling and complex question about transmission within families and across generations.

The principal focus for sibling studies in schizophrenia during the 1950s-1970s was possible vulnerability to the disorder and theories about familial transmission. The reported disturbed symptomatology in the affected families was mostly regarded as causing schizophrenia. With the evolving perspective of schizophrenia as a multi-etiological disorder, roughly beginning in the early 1980s, the focus on the families now shifted to family burden and potential family intervention programs. Noteworthy, although there is growing evidence for complex schizophrenia heredity and the prevalence for schizophrenia in biological siblings has been estimated to 9%, is the remarkable lack of studies about siblings’ perceptions and fears of possible schizophrenia heredity.

Social behavior in siblings

Social dysfunction might be a possible indicator of vulnerability to schizophrenia, but little is still known today about the capacity to solve social problems in biological relatives to patients with schizophrenia. Studies on mixed groups of relatives to patients with schizophrenia have shown that high-risk individuals seem to have an elevated risk for developing early interpersonal problems. Additionally, unaffected relatives have shown qualitatively similar abnormalities in social development and personality traits as the children and adolescents who subsequently developed schizophrenia. In one study with only siblings in the group of relatives unaffected siblings were found to display deviant social behavior similar to those present in their affected sibling at both age 4 and 7 years.

However, not many studies investigating social functioning in adult siblings to patients with schizophrenia are available. Those studies that are available seem to largely apply experimental designs of social perception reflected by perception and processing of emotions. In a study by Toomey et al. unaffected relatives (half of them siblings) to patients with schizophrenia showed poor perception of nonverbal social-emotional cues. When including only siblings, behavioral studies have reported subtle impairments in
facial affect perception as well as impaired emotion processing. Further, compared with healthy controls, siblings showed abnormal activation within brain areas involved in emotion processing. In another study of complex social information processing unaffected siblings rated faces as more trustworthy compared with healthy controls, albeit to a lesser degree than patients. These results suggest that deficits in social functioning are related to the genetic overlap in schizophrenia.

The sibling role
Because mental illness is, by its very nature, a familial experience, schizophrenia has a profound effect on the lives of both the patients and their family. Although siblings of patients with schizophrenia can provide important support for the patient, most studies in this field have largely excluded siblings. Many of the researchers that argue for more studies on the sibling role in schizophrenia emphasize the uniqueness in sibling relationships. Compared with the roles of parents or children, the sibling role has been suggested to be more free: referred to as “the voluntariness of the sibling tie”. The lack of norms for a standard sibling relationship might lead to a freedom of choice for the siblings that may be curtailed by family hardships such as having a mentally ill family member. Sibling ties have also been suggested to be actualized, intensified and deepened as key events in life are experienced.

Siblings’ experiences and coping
Despite the need for greater understanding of siblings’ experiences in schizophrenia, only recently have efforts been made to systematically describe the emotional impact of being a brother or sister of a patient suffering from schizophrenia. In a recent study siblings were found to report more intense negative feelings and shame, elevated levels of experienced burden and less closeness than controls who did not have a sibling with any illness. Similar findings of siblings’ feelings of guilt, shame, severe anxiety and sadness have been reported in studies based on in-depth interviews or psychotherapy with siblings. Other studies have found similar reactions in offsprings and parents, but there seem to be qualitative differences in evoked feelings and needs for support because of different family roles. Thus, it is still unclear whether siblings’ experiences are specific as compared with other family members. Some authors reason that the subjective experiences of siblings are quite similar to that of parents in affected families, whereas others suggest a specificity of siblings’ experiences. This possible specificity might more easily allow detachment and physical and mental escape. In another study based on focus group interviews with siblings of individuals with psychotic illness the siblings’ experiences were interpreted into an overall theme named “a lonely life journey bordered with struggle”.

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The patients’ psychotic breakdown can be a strong stressor for their family and evoke the need for support and strategies to manage the new situation. In a study by Gerace et al, siblings to patients with schizophrenia were found to cope by being collaborative, crisis-oriented or detached. Understanding that families were not to blame for schizophrenia was identified as the most helpful coping strategy for nearly three-fourths of siblings in a national study of siblings to patients with schizophrenia. These authors argue that education and support for siblings will become more important as they are faced with the responsibility of being possible future primary caregivers. There are also findings proposing that healthcare organizations need to re-evaluate current approaches for assisting individuals to cope with having a sibling with schizophrenia. However, siblings also describe potential strengths (e.g., being more empathic, assertive and creative) as a result of having grown up with schizophrenia in the family.

Social functioning in schizophrenia

Deficits in social functioning are among the core characteristics of schizophrenia. Persons with schizophrenia have been shown to have disabilities in social skills as well as in other domains of social functioning. Early impaired social functioning also appears to be a risk factor for psychosis, and social functioning measures have been shown to play a key role in the assessment of clinical outcomes in schizophrenia.

Concepts and measurements

Although the concept of social functioning has been poorly defined in the literature, several definitions have been proposed to conceptualize social functioning. In a review by Couture et al, the term social functioning is applied to self-reports or other reports of interpersonal behaviors, behavior in community settings, skills of independent living, ratings of social skills in laboratory settings and ratings of social problem solving skills. Accordingly, some researchers use the broader term “functional outcome” to encapsulate this conglomeration of domains.

In another review social functioning is suggested to represent a global construct that embraces the concepts social skills and social cognition. In the following section these three aspects of social functioning in schizophrenia will be elucidated because of their relevance to the present thesis, especially to paper II and III.

Global aspects of social functioning

Social functioning is a broad, multidimensional construct implying overall performance across several domains of everyday living (e.g., independent
living, employment, relationships and leisure time).\textsuperscript{100} Because of a broad range of existing operationalizations of this construct, terms such as “social functioning”, “community functioning” and “social competence” are often used interchangeably.

General measures of social functioning use self-report questionnaires, interviews or rating scales. Although inventories of global aspects of social behavior in schizophrenia have been widely used, there still is inconsistency in how to characterize and measure the included domains.\textsuperscript{96} Examples of specific measurements have been reported elsewhere.\textsuperscript{100}

Social problem solving skills
The concept of social skills refers to the cognitive, verbal and nonverbal behaviors needed for interpersonal interactions. The term skill is used to emphasize that social competence is based on a set of learned abilities rather than intrapsychic processes such as traits or needs.\textsuperscript{101} Further, social problem solving skills have been conceptualized as one of several components of social skills.\textsuperscript{102,8} Most conceptualizations of the social problem solving process are variants of the multistep model developed by D’Zurilla and Goldfried, who define problem solving as an overt or covert behavioral process.\textsuperscript{103} This process is assumed to (1) make available a variety of potentially effective response alternatives capable of dealing with the problematic situation and (2) increase the probability of selecting the most effective response from these alternatives.

This social skills model proposes that there are three components necessary for social competence: receiving skills, processing skills and sending skills.\textsuperscript{8} A socially skilled response is theorized to be the end result of a chain of behaviors with the first step involving the receiving of relevant interpersonal stimuli.\textsuperscript{104} The next step is flexible processing of the received stimuli leading to the generation and evaluation of possible responses. After one accurate response alternative is chosen, the chain ends with appropriate behavioral sending of this response.\textsuperscript{105} However, recent findings suggest a dissociation of the social problem solving processes.\textsuperscript{106}

The majority of social information processing tasks are paper and pencil tests that are easy to administer.\textsuperscript{100} A typical social problem solving task presents a hypothetical problem for the participant that, as a next step, is required to decide on and report an appropriate solution. However, delivering adequate verbal responses does not guarantee a corresponding appropriate behavior enacted in real life. Therefore, some researchers prefer measuring social problem solving skills in schizophrenia with role-play tests using videotaped problematic social interactions. These measures consist primarily of role-play tasks that allow direct observation of social behaviors.\textsuperscript{107} The problematic situations are chosen with regard to ecological validity in daily life and the person’s current rather than past functioning is
rated by its use of role-playing compared with self-report or third-party report. The psychometric properties of role-play tests have been questioned but there is new evidence suggesting their good psychometric properties.108

**Social cognition**

Definitions of social cognition are quite varied and range from the relatively brief to the more extended. A commonly applied definition in schizophrenia research is that social cognition refers to how people think about themselves and others in the social world.109 The social cognition construct focuses on how people process information in social contexts, including person perception, causal attributions concerning self and others and bringing social judgments to decision making.110-112

Because definitions of social cognition vary, attempts have been made to define terms commonly used in schizophrenia research. In an extensive analysis of research findings Green et al. propose that the term social cognition covers five areas: theory of mind, social perception, social knowledge, attributional bias and emotional processing.113 In a recent meta-analysis Savla et al. found clear empirical evidence for deficits across multiple social cognitive domains in schizophrenia.114

Theory of mind refers to the ability to infer one’s own and other people’s opinions, beliefs and intents, as well as to establish a connection between these mental states and a person’s behavior.115,116 Impairments in this ability to “mentalize” make it difficult to understand the true intentions and anticipate the actions of others. The increase of research over the past decade about theory of mind in schizophrenia has resulted in a proliferation in the number of tasks measuring this area of social cognition. Based on a review by Harrington et al., the tasks can be broadly grouped into two main categories according to the overarching construct being assessed: (1) false-belief and deception and (2) pragmatic speech comprehension.117 However, these authors argue that the tasks used to assess theory of mind ability tend to be primarily concerned with measuring the ability to infer other’s beliefs and intentions, and less with the ability to monitor one’s own beliefs and intentions.

Social perception, the proposed second area of social cognition is chiefly about the ability to identify social roles, societal rules and social context.118 In tasks measuring social perception individuals may be asked to identify interpersonal features in a situation such as mood, intimacy and status. Generally, social perception measures are of two categories: those focusing exclusively on affect perception and those assessing the perception of multiple social cues.100 Therefore, measurements of social perception consist mostly of performance-based tasks that more directly test the participants’ perceptual skills.
The next proposed area of social cognition is social knowledge, which refers to awareness of the roles, rules and goals characterizing social situations. This area also pertains to knowledge about what guides social interactions and is viewed as an initial step for adequate social competence. Social knowledge can be measured with paper and pencil tests.

The term attributional bias refers to explanations people generate to the causes of positive and negative events in their lives. The majority of work in schizophrenia has focused on attributional style in individuals with paranoia or persecutory delusions and their tendency to blame others rather than situations for negative events (e.g., personalizing bias). In this area of social cognition assessments are often made by self-report questionnaire or transcribed social interactions.

The last suggested area of social cognition, emotional processing, is mainly related to the ability to recognize and use emotions. Of four proposed abilities, two have been thoroughly investigated in schizophrenia research: identifying emotions via facial expressions and affective prosody and understanding emotions when people use ironic expressions.

Relation between laboratory and real-life social functioning

Studies investigating the relation between community based or real-life measures of social functioning and role-play test performance have generally found only modest correlations. One explanation for this weak link is that laboratory-based measures typically assess social competence or social skill ability, whereas community functioning-based instruments measure the degree to which an individual actually engages in social activities in real life.

Reported qualitative differences between global aspects of social functioning and role-play tests are also suggested to depend on community functioning that belongs to a macro social domain and social problem solving skills that belong to a micro social domain. These domains might be either independent of one another or at opposite ends of a continuum. In line with this view is the statement that the global construct social functioning includes the more molecular concepts of social skills and social cognition. Thus, these constructs are suggested to represent different levels of social behavior.

There are also findings demonstrating that community functioning but not role-test play performance was significantly associated with social cognition. It may be that the relation between social cognition and functional outcome depends on the specific domains of each construct examined. However, there are findings indicating that social cognition among individuals with schizophrenia, but not in non-clinical controls, significantly contributed unique variance to interpersonal skills. Further, areas of the social cognition construct have been related to the first two steps of the three-stage
model of social information processing. Receiving skills are proposed to be comparable with social perception and processing skills with social cognition.\textsuperscript{7,8} However, only a few studies have shown a linkage between performance on social cognitive tasks and real-life social behavior.\textsuperscript{129,130} Moreover, social competence has been suggested to refer to sending skills (e.g., the verbal and nonverbal communication skills that allow successful execution of interpersonal interactions).\textsuperscript{131,132} Altogether, these findings underline the importance of conceptualizing social functioning as a multidimensional construct in schizophrenia research.

Other possible correlates
Factors contributing to social dysfunction in schizophrenia have not yet been well delineated, although the functional outcome of schizophrenia seems to be affected by multiple factors. Two of the most studied are cognitive function and clinical symptoms, but both personality (e.g., schizotypy) and attachment appear to contribute variance to domains of social functioning.\textsuperscript{133-135} However, divergent results suggest that most socio-demographic and clinical factors apparently do not have a significant impact on social functioning.\textsuperscript{136}

Psychiatric symptoms
Negative symptoms and certain cognitive deficits have been found to be important predictors of social functioning.\textsuperscript{136} Concerning the impact of psychiatric symptoms, it appears that patients with a high level of negative symptoms exhibit more impairments of social problem solving skills.\textsuperscript{122,137,138} Although positive symptoms may play a role, associations between negative symptoms and social deficits receive stronger support in the literature.\textsuperscript{139} Thus, symptomatology seems to influence, but not fully explain, social impairments in schizophrenia and there is still inconsistency about the relation between symptoms and social functioning. Such discrepancy might reflect the heterogeneity of the scales used to measure symptoms in different studies. Moreover, it is not always clear whether the correlations between negative symptoms and social functioning are due to associations between separate constructs or the redundancy of assessment.\textsuperscript{140}

Cognitive functions
During the past decades, intensive research has transpired on cognitive aspects of schizophrenia and their impact on social functioning. In a review by Green et al. neurocognition is suggested to explain generally 20-60\% of the variance in functional outcome in schizophrenia.\textsuperscript{141} More specifically, there is evidence of associations between attention, vigilance, verbal ability, verbal memory, verbal fluency, visuo-spatial ability and executive functioning and global aspects of social functioning as well as role-play assessments of
social skills. However, other findings of associations between social problem solving measured with role-play tests and psycho-motor speed, verbal learning, semantic fluency and cognitive flexibility have been reported.106

Despite many contributions about social functioning in schizophrenia, traditional cognitive models have been criticized for not providing a complete picture of the impact of the disorder.94 One main limitation with non-social cognitive models is their focus on processes relatively devoid of social context and thereby omitting the social-cognitive processes often discussed in normative samples.110

Furthermore, the complex relation between cognitive function, psychiatric symptoms and social functioning remains unclear. Although neurocognition and negative symptoms are both predictors of functional outcome, negative symptoms have been reported to at least partially mediate the association between neurocognition and outcome.142 Other findings suggest that negative symptoms mediate the influence of social cognition on functional outcome in schizophrenia.143 In a study controlling for emotion perception the association between neurocognition and social problem solving was weakened, suggesting a mediating role of the emotion perception dimension of social cognition.144 There also results indicating that 25% of work-related social skills could be explained by social cognition and non-social cognition.145 However, results indicate that social cognition is a better predictor of community functioning in schizophrenia than either general cognition or negative symptoms together.146 Thus, the associations seem to be complex and both non-social and social cognitive processes have to be taken into consideration for a more complete understanding of the impact of cognitive functions on social functioning in schizophrenia.

Longitudinal outcome

Despite advancement in treatments and managements, the long-term outcome of schizophrenia is heterogeneous, including both full remission and severe chronic states.147-149 These studies suggest that about one third of the persons with schizophrenia present a deteriorating course, with most showing a stable or fluctuating course and some actually improving. A recent cohort study of people with first episode psychosis found that 14% met the criteria for symptomatic and psychosocial recovery at a 10-year follow-up.150

Most noteworthy is the lack of longitudinal research in schizophrenia despite the fact that longitudinal study of change can provide greater understanding about the course of this disorder and subsequent interventions. Significant heterogeneity exists in clinical presentation, longitudinal course and treatment response within those affected by schizophrenia. Therefore, reported outcome figures in schizophrenia are highly dependent on several methodological issues, among them sample characteristics, attrition and outcome measures.151
Prediction of outcome

Prediction can be described as the formal study of the association between measurable sample characteristics and outcome. The core reasons for identification of predictors are benefits in clinical practice (such as possible prevention) and modifiable treatment targets. In addition, increased knowledge about specific predictors might provide a better understanding of the underlying pathophysiology of schizophrenia.

In an early review by McGlashan many important predictors for schizophrenia were identified: genetics, premorbid functioning, illness onset, psychopathological signs and symptoms and course of illness up to index admission. These findings are partly supported in a recent review reporting that pronounced negative symptoms in the early stages of illness predict a poor long-term outcome. A possible central role of negative symptoms in the process of recovery in schizophrenia has been suggested in another study as well. Other identified predictors for poor outcome were male gender, cognitive impairment, low education level, social isolation, repeated hospitalizations, a longer duration of untreated psychosis (DUP) and a higher score on the Strauss-Carpenter scale. In another review insight, early treatment response and DUP appeared to be particularly important predictors of long-term outcome. Several other studies have shown the predictive value of cognitive impairment and negative symptoms for poor social functioning. However, there is still little information on the individual prognosis in schizophrenia.
Aims

The overall aim of this thesis was to explore both biological risk factors and psychological and social functioning in schizophrenia. The thesis comprises four studies that focus on the role of several possible contributory factors.

The specific aims were:

1. To investigate the associations between birth weight, other birth characteristics and schizophrenia, and to determine whether the association between fetal growth and subsequent development of schizophrenia is mediated by familial factors.

2. To study the association between levels of NPY in cerebrospinal fluid (CSF), social function and clinical characteristics in schizophrenia, as well as to explore whether NPY levels can predict outcome in schizophrenia 3 years after index admission.

3. To introduce a Swedish version of the video-based vignette test AIPSS and compare social functioning in patients with schizophrenia with their biological siblings.

4. To explore how siblings to patients with schizophrenia perceive the sibling relationship and their role as siblings.
Methods

This thesis uses both quantitative and qualitative research methods. The four papers are based on data from a birth size project in the Swedish Twin Registry at the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, and two research projects about schizophrenia at Uppsala University Hospital, Ulleråker. An overview of the aims, samples and study designs is presented in Table 1.

Table 1. Overview of papers I – IV

<table>
<thead>
<tr>
<th>Paper</th>
<th>Specific aim</th>
<th>Subjects</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>To investigate whether the association between fetal growth and subsequent development of schizophrenia is mediated by familial factors</td>
<td>Same-sexed twin pairs born 1926 onwards and alive in 2000 (n=11,360 twins)</td>
<td>Cohort and case-control study</td>
</tr>
<tr>
<td>II</td>
<td>To study the associations between levels of NPY in CSF, social function, clinical variables and longitudinal outcome in schizophrenia</td>
<td>Patients with schizophrenia (n=56)</td>
<td>Cross-sectional and longitudinal study</td>
</tr>
<tr>
<td>III</td>
<td>To compare social problem solving skills of patients with schizophrenia with their biological siblings and with non-psychiatric controls</td>
<td>Patients with schizophrenia (n=25) Siblings to patients with schizophrenia (n=20) Non-psychiatric controls (n=25)</td>
<td>Cross-sectional and case-control study</td>
</tr>
<tr>
<td>IV</td>
<td>To develop an analysis of the psychological aspects of having a sibling with schizophrenia</td>
<td>Siblings to patients with schizophrenia (n=16)</td>
<td>Qualitative study</td>
</tr>
</tbody>
</table>
Paper I
Participants
In paper I, all same-sexed twins born from 1926 with a main diagnosis of schizophrenia and their co-twin were identified by linkage between the Swedish Twin Registry, the Swedish Hospital Discharge Registry and the Cause of Death Registry. The first step in the sampling procedure was identification of 302 eligible cases with schizophrenia (all were alive in 2000). Thereafter, the doctors responsible for each patient were contacted and asked permission to contact the twins (Figure 1). Eight of the contacted cases could not be interviewed because of severe psychotic symptoms or lack of informed consent. The sampling resulted in access to delivery records for 90 twins diagnosed with schizophrenia.

Figure 1. Flow chart for inclusion of twins with schizophrenia in paper I
The analyses in paper I were performed in two steps. The first step was a cohort analysis of unaffected, unrelated twins, where 11,360 same-sexed twins born between 1926 and 1958 whose birth records had been retrieved in an ongoing project in the Swedish Twin Registry were included. Among them, 88 cases were twins with schizophrenia. The second step was a within-pair analysis with unaffected co-twins as controls. Eighty-two same-sexed twin pairs discordant for schizophrenia born between 1927 and 1974 were included. Thus, four twin-pairs concordant for schizophrenia were excluded. The unaffected co-twins were without a history of schizophrenia at the time the cases were diagnosed.

Measurements

Prospectively filed obstetric records were retrieved from an ongoing birth size project in the Swedish Twin Registry. This population-based registry is updated by linkage to the Hospital Discharge Registry and the Cause of Death Registry. The Swedish Twin Registry, held by Karolinska Institutet, includes information on twins born in Sweden from 1886. In 1972, the cohort of same-sexed twins born 1926 to 1958 was approached and both members of 14,000 twin pairs completed a questionnaire. The Hospital Discharge Registry has a nationwide coverage of psychiatric diagnoses from 1973 and includes data on individual hospital discharges from inpatient care in Sweden. The Causes of Death Registry, held by the National Board of Health and Welfare, includes date of death and main and contributory cause of death.

The information retrieved from the obstetric records was: maternal age, maternal complications during pregnancy, birth year, birth order, birth place (at home or hospital), gestational age (completed gestational weeks calculated on the last menstrual period), sex of the child, birth weight, head circumference and complications of the infant in the neonatal period.

A diagnosis of schizophrenia was set as the outcome measure. Validation of the discharge diagnosis of schizophrenia has reported few false positive cases. Low birth weight, small head circumference, preterm delivery and congenital debility were established as risk factors. Measures of low birth weight were divided into three categories according to the birth weight distribution in the cohort: ≤1999, 2000-2299 and ≥2300 grams, including 10%, 15%, and 75% of the cohort, respectively. Small head circumference was defined as ≤31.5 cm and preterm delivery as delivery before 37 weeks of gestation. Categories of small head circumference and preterm delivery were chosen to approximate the lowest quartile. Signs of asphyxia at birth, weakness after delivery and the need for a child to remain under care after birth were noted with the diagnosis ‘congenital debility’. Congenital debility was used as a proxy for the Apgar score, the current standardized assessment of asphyxia.
As indicators of fetal growth restriction, the birth weight ratio and the head circumference ratio were used. The birth weight ratio was defined as the ratio of the observed to the expected birth weight for gestational age and sex. The head circumference ratio was created in the same manner and the small head circumference ratio was chosen to approximate the lowest quartile.

Statistical analysis

In the cohort analysis the associations between fetal growth, indicators of fetal growth restriction and schizophrenia were performed using logistic regression. The Generalized Estimation Equation (GEE) models were used to take into account the dependence within twin pairs. GEE provides a correlation structure within an observation. As a second step, within-pair analyses were calculated with conditional logistic regression. All statistical analyses based on logistic regression models were performed using the SAS System version 8.2.

Paper II

Participants

In paper II, patients with schizophrenia were consecutively recruited between 1980 and 1990 from a ward for young patients with psychosis at the Uppsala University Hospital. For the present study, we only included 56 patients whose NPY had been measured in CSF. Thirty-four patients were first-episode psychosis and had never been on psychotropic drugs. The remaining 22 patients were known to have a schizophrenic disorder. The original cohort, consisting of 120 patients with schizophrenia, has been described by Lindström. Before antipsychotic treatment was initiated, CSF-sampling and various clinical assessments were conducted. All participants were antipsychotic medication free at a minimum of two weeks before the lumbar puncture and the spinal tap was performed under standardized conditions. The patients’ psychiatric symptoms were rated at index admission. Finally, the patients were longitudinally assessed with outcome ratings 3 years after index admission.

Measurements

The levels of NPY in the CSF were determined by radioimmunoassay according to standardized methods. Social function at index admission was assessed with the Nurses’ Observation Scale for Inpatient Evaluation (NOSIE-30), a 30-item ward behavior rating scale using a 0 – 4 frequency of
occurrence format for each item.\textsuperscript{169} Ratings for two of six factors were used in our study: Social Competence and Social Interest.

Assessments of psychiatric symptoms were made with the Comprehensive Psychopathological Rating Scale (CPRS).\textsuperscript{170} CPRS is an interview-based rating instrument consisting of 65 scaled items covering a broad range of psychiatric signs and symptoms. Each item is scored from 0 (no symptoms) to 3 (severe symptoms), yielding a scale with seven steps (0, 0.5, 1.0 etc.). Five of the 33 items were summarized to cover negative psychotic symptoms: indecision, lack for appropriate affect, withdrawal, reduced speech and slowness of movement. Three items were summarized to represent excitation: hostility, overactivity and agitation.

The longitudinal 3-year outcome was assessed with the Strauss-Carpenter Outcome Scale, a five-point Likert scale covering four major dimensions of outcome: duration of nonhospitalization, social contacts, useful employment and symptoms.\textsuperscript{171}

\textbf{Statistical analysis}

Spearman’s rank-order correlations (\(r_s\)) were calculated to investigate the association between level of NPY and social function and psychiatric symptoms at baseline. Differences in levels of NPY between patients with or without school problems and history of alcohol abuse were calculated with the two-tailed probability \(t\)-test for independent samples. The association between levels of NPY at baseline and outcome at the 3-year follow-up was investigated with binary logistic regression analyses. Level of NPY was set as the independent variable and the dichotomized items from Strauss-Carpenter Outcome Scale as the dependent variables. Statistical analyses were performed using SPSS Statistics version 21.

\textbf{Paper III}

\textbf{Participants}

In paper III, 25 outpatients were recruited at the Psychiatric Center, Uppsala University Hospital, Ulleråker between 1998 and 2002 within the frame of a project investigating the situation of adult siblings and adaptive function in schizophrenia. Eighteen of 20 eligible patients accepted that their sibling could be asked to take part in the study. Of the 20 participating biological siblings, 18 were recruited by their ill sibling, one via another sibling and one via a psychoeducational program at the psychiatric clinic. Nine siblings had a history of psychiatric treatment and 15 sibling pairs participated in the study. The patients were assessed on two occasions within a one-week interval and all siblings performed the tests on the same occasion.
The controls were a representative community sample of 25 persons recruited from 962 randomly selected individuals identified by Statistics Sweden in a catchment area of Uppsala University Hospital (Figure 2). These individuals were included based on age and sex of the patients. In all, 200 persons were contacted and asked to participate. Exclusion criteria were earlier treatment in child and adolescent psychiatry, contact with inpatient adult psychiatric care or ongoing psychopharmacological treatment. The controls performed all tests on the same occasion. Three persons were excluded after the tests were completed because of new information about their mental health.

Figure 2. Sampling flow chart for inclusion of non-psychiatric controls in paper III

Measurements

In paper III, social functioning was assessed with a Swedish version of the role-play test Assessment of Interpersonal Problem Solving Skills (AIPSS).\textsuperscript{172,173} In this study an earlier preliminary Swedish version of the AIPSS, made at the Psychiatric Center, Uppsala University Hospital in 1993 was revised and improved by the first author. The AIPSS is a manual-based videotaped vignette test that implies a problem solving model of social skills with the following components: receiving skills (Identification and Description), processing skills (Processing) and sending skills (Content, Performance and Overall sending).\textsuperscript{103,104} The test consists of 13 short videotaped interactions. When watching the vignettes, participants are instructed to identify themselves with one of the actors. After each scene, they are asked
the following questions: Is there a problem in the scene? Can you describe the problem (receiving skills)? What would you do about the problem if you were in the same situation (processing skills)? The final step is to role-play the chosen solution of the problem (sending skills). Each participant was videotaped and scored afterwards using a manual. Possible scores for receiving and processing skills are 0, 1 and 2. The scoring for sending skills is a three-point scale (0, 1 and 2) with 0.5 increments. Data in the present study were reduced to percentage scores according to guidelines in the manual of Donahoe.172

The participants’ psychiatric symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) for Schizophrenia.174 PANSS is a 30-item, 7-point rating instrument. The raters were blind to other measures in the study.

Statistical analysis
The Wilcoxon rank sum test was performed to test the hypothesis of no difference in the AIPSS distribution between the three groups. To adjust for possible differences in education and psychiatric symptoms nonparametric analysis of covariance was calculated by applying the Wilcoxon rank sum test on the AIPSS-Z. Z is the predicted value from a linear regression; Z-values were computed by standard least square. Analyses of within-sibling differences in the AIPSS were performed with the Wilcoxon signed-rank test. Kendall’s tau (τ) was calculated to measure interrater reliability, correlations between the scales of the AIPSS and the correlations between the AIPSS and psychiatric symptoms. All statistical analyses were done by SAS System version 8.2.

Interrater reliability
The interrater reliability for the AIPSS was determined for approximately 20% of the videotapes from each study group. According to the manual, two raters agree if their ratings are within 0.5 points of each other. Enforcing this criterion, the interrater agreement was 94%. The agreements were highest on the scales Identification, Processing and Overall sending skills (τ > 0.80). The interrater correlations (τ) were from 0.65 to 0.74 for Description, Content and Performance.

Correlations (τ) between the six scales in the AIPSS were also measured and ranged from 0.21 to 0.85 (p < 0.05).
Paper IV

Participants
The 16 participants in paper IV were siblings to 14 of the patients in paper III. Seven of the siblings had earlier contact with psychiatric care and it was most common to be younger than the ill sibling. All 16 interviews were conducted by the first author: 11 at the research clinic, three via telephone and two in the participants’ home.

Interviews
Paper IV involved face-to-face semi-structured interviews guided by the interview guide Adult Sibling Response to Chronic Mental Illness by Gerace et al. The original version, consisting of 25 questions, was translated from English to Swedish and abridged to 15 questions related to the aim of the study. The interviews were eliciting the participants’ perspective on their siblings’ psychiatric illness, the perceived impact of the illness on self and the family system and the participants’ perceived role in illness management. The in-person interviews were audiotaped and then transcribed.

Interview analysis
The data analysis in paper IV was guided by a variant of the inductive methodological school of grounded theory. In this constant comparative method the theory created is derived from systematically gathered data analyzed through the research process. Because the data collection in our study was performed with the use of an interview guide, the analysis could not strictly be conducted according to grounded theory procedures. Instead, the following procedure was used: (1) each interview was openly coded, (2) codes from all interviews were studied and different themes were identified and (3) the major themes were explored by seeking elaboration and clarification from the interview texts.

Interrater reliability
To evaluate the coherence and reliability of quotations and themes two psychologists independently read the transcribed interviews and identified themes. The interrater agreement for the themes was 92%. For the major theme of coping patterns, the evaluation was taken a step further. One of the psychologists categorized the interviews according to the five coping patterns identified for the siblings by the other psychologist. The two psychologists made exactly the same linking for each sibling to one of the five coping patterns in 94% of the siblings.
Results

Fetal growth and schizophrenia (paper I)

In paper I, the cohort analysis of 11,360 same-sexed twins showed that children with low birth weight and children with small head circumference had an increased risk for later development of schizophrenia (Table 2). After adjustment for gestational age and sex (e.g., birth weight ratio and head circumference ratio), the odds of developing schizophrenia still increased, although not statistically significantly.

Table 2. Associations between birth weight, head circumference, fetal growth restriction and risk for schizophrenia

<table>
<thead>
<tr>
<th>Birth weight</th>
<th>Very low</th>
<th>1.7</th>
<th>0.9-3.1</th>
<th>1.4</th>
<th>0.8-2.7</th>
<th>1.3</th>
<th>0.7-2.6</th>
<th>1.5</th>
<th>0.6-3.7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderately low</td>
<td>1.8</td>
<td>1.1-3.0</td>
<td>1.1</td>
<td>0.6-2.0</td>
<td>1.0</td>
<td>0.6-1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Head circumference</th>
<th>Small</th>
<th>1.6</th>
<th>1.0-2.5</th>
<th>1.4</th>
<th>0.9-2.2</th>
<th>1.3</th>
<th>0.8-2.1</th>
<th>1.7</th>
<th>0.6-4.6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Birth weight (grams): very low ≤ 1999, moderately low 2000-2299, normal ≥ 2300; head circumference (cm): small ≤ 31.5, normal ≥ 32.0
b Birth weight ratio: very low 10%, moderately low 15%, normal 75% of the cohort; head circumference ratio: small 25%, normal 75% of the cohort
c Adjusted for congenital debility
d Birth weight (grams): low ≤ 2299, normal ≥ 2300; head circumference: small ≤ 31.5, normal ≥ 32.0

The results from the within-pair analysis of 82 individuals with schizophrenia and their co-twins without schizophrenia are summarized in Table 2. Although not statistically significant, the increased risk for schizophrenia for
twins with low birth weight and twins with small head circumference held when taking unmeasured familial factors into account (e.g., genetic or shared environmental factors).

The only infant complication in the neonatal period that differed significantly between twins with and without schizophrenia was congenital debility ($\chi^2 = 4.76, p = 0.03$). The results from the analysis with external unrelated controls revealed a doubled risk for twins with debility for developing schizophrenia compared with twins without debility (odds ratio [OR] 1.87, 95% confidence interval [CI] 0.99-3.53). When adjusting for gestational age, the risk decreased, but was still elevated (OR 1.55, CI 0.80-2.98). This increase, however, was not statistically significant. When adjusting for debility in the cohort analysis, the risk estimates decreased (Table 2). The increased risk for schizophrenia associated with debility remained in the within-pair analysis, though not statistically significant (OR 2.00, CI 0.18-22.05).

NPY and social functioning in schizophrenia (paper II)

In paper II, studying the associations between NPY levels in CSF, social function and clinical variables at index admission resulted in one significant relation. NPY was cross-sectionally correlated to Social Competence ($r_s = 0.37, p < 0.05$). NPY levels at baseline were not correlated to the other measurements of social function: Social Interest ($r_s = 0.17, p = 0.31$), frequency of social contacts ($r_s = -0.21, p = 0.13$) or school problems ($t (51) = -0.38, p = 0.70$). The results for Social Competence and Social Interest are depicted in Figure 3. Concerning clinical variables, NPY was not cross-sectionally correlated to negative symptoms ($r_s = -0.02, p = 0.92$), excitation ($r_s = 0.17, p = 0.21$) or alcohol abuse ($t (53) = 0.89, p = 0.38$).

Figure 3. Correlations between NPY level, Social Competence and Social Interest for 38 patients with schizophrenia at index admission
The longitudinal analysis at the 3-year follow-up showed that, for each standard deviation increase in baseline NPY, there was an increased risk of being unemployed, having moderate or severe symptoms or being hospitalized at least 6 months the previous year at the 3-year follow up (Figure 4). After adjustments for employment status and symptoms the associations were strengthened. Because the majority of the patients had not been hospitalized during the past year before index admission, no adjustments were made for the outcome measure hospitalized ≥ 6 months. Although the estimate is imprecise, baseline NPY levels were not associated with frequency of social contacts at the 3-year follow-up (Figure 4).

Figure 4. Association between levels of NPY at baseline and dichotomized poor outcome adjusted for the baseline levels of the longitudinal outcomes as measured with the Strauss-Carpenter Outcome Scale. * No adjustments were made because the majority of the patients were first-episode psychosis and had not been hospitalized during the past year before index admission.
Impaired social problem solving in schizophrenia (paper III)

According to the AIPSS, severe deficits in social functioning in patients that were not shared with their biological siblings were observed in paper III. The performance in the AIPSS and level of psychiatric symptoms according to the PANSS for the patients, siblings and controls are listed in Table 3. In general, patients had the lowest scores in the AIPSS, siblings had medium scores and controls had the highest scores. The level of psychiatric symptoms was significantly higher in patients than in siblings and controls ($p < 0.001$). Even the siblings had a higher level of symptoms than the controls ($p < 0.001$).

### Table 3. AIPSS scores and psychiatric symptoms according to PANSS$^a$

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=25)</th>
<th>Siblings (n=20)</th>
<th>Controls (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td><strong>AIPSS scales</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identification</td>
<td>84.9</td>
<td>9.0</td>
<td>91.1</td>
</tr>
<tr>
<td>Description</td>
<td>86.2</td>
<td>15.1</td>
<td>95.3</td>
</tr>
<tr>
<td>Processing</td>
<td>54.4</td>
<td>17.6</td>
<td>71.1</td>
</tr>
<tr>
<td>Content</td>
<td>52.2</td>
<td>11.9</td>
<td>77.2</td>
</tr>
<tr>
<td>Performance</td>
<td>58.4</td>
<td>13.6</td>
<td>84.3</td>
</tr>
<tr>
<td>Overall sending</td>
<td>53.9</td>
<td>12.8</td>
<td>81.0</td>
</tr>
<tr>
<td><strong>PANSS items</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>12.2</td>
<td>3.6</td>
<td>8.8</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>15.0</td>
<td>5.2</td>
<td>8.3</td>
</tr>
<tr>
<td>Total sum</td>
<td>53.6</td>
<td>11.0</td>
<td>36.7</td>
</tr>
</tbody>
</table>

$^a$AIPSS = Assessment of Interpersonal Problem Solving skills, PANSS = Positive and Negative Syndrome Scale for Schizophrenia

Comparisons of the AIPSS scores between patients, siblings and controls are displayed in Table 4. In comparison with siblings, patients achieved statistically significantly lower scores on all scales of the AIPSS (i.e. to identify, describe, process and act out solutions to interpersonal problems) after adjusting for the highest attained education level. Patients, in comparison with controls, performed significantly lower in all scales, except in the Identification scale.
After adjustment for education level, siblings significantly performed higher than patients in all aspects of social problem solving but did not perform significantly lower than controls, except in Performance \( (p < 0.05) \). Performance includes nonverbal aspects (e.g., eye contact, voice volume and appropriate affect) of social problem solving. Separate analyses of differences in the AIPSS within 15 sibling pairs did not significantly change the results (data not shown).

Table 4. Comparisons of the AIPSS scores between patients, siblings and controls adjusted for education level, positive symptoms and negative symptoms

<table>
<thead>
<tr>
<th>Scales</th>
<th>Education level</th>
<th>Positive symptoms</th>
<th>Negative symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>0.04</td>
<td>0.15</td>
<td>0.28</td>
</tr>
<tr>
<td>Description</td>
<td>0.03</td>
<td>&lt;0.01</td>
<td>0.14</td>
</tr>
<tr>
<td>Processing</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.24</td>
</tr>
<tr>
<td>Content</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.39</td>
</tr>
<tr>
<td>Performance</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>Overall sending</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.25</td>
</tr>
</tbody>
</table>

a P/S = comparisons between patients and siblings, P/C = comparisons between patients and controls, S/C = comparisons between siblings and controls

The significant differences in receiving skills (identification of a social dilemma and description of a goal) and processing skills (deriving a verbal solution) between patients and siblings and patients and controls were no longer apparent when adjustments were applied for positive and negative symptoms (Table 4). The pattern was more pronounced concerning negative symptoms. Generally, patients’ low performance in sending skills (Content, Performance and Overall skills) in relation to siblings and controls persisted, but siblings’ poor nonverbal language was largely attributed to subtle symptoms.
Siblings’ perspective in schizophrenia (paper IV)

In paper IV, the systematic organization and interpretation of the textual material resulted in three major themes: (1) sibling bond, (2) coping patterns and (3) fear of possible schizophrenia heredity (Figure 5).

![Figure 5. A tentative conceptual model of major themes in paper IV](image)

The sibling bond has a central position in the analysis and the siblings’ stories are loaded with affectionate experiences in their description of the sibling relationship (Figure 5). The main feelings expressed are love, sorrow, anger, envy, guilt and shame. The feelings are often intertwined with each other and can make coping of situations easier or harder. For example, sibling love was described as alleviating the circumstance of having a mentally ill brother or sister. Complex feelings of guilt and shame seem to make the situation most difficult to handle. For many of the siblings, shame was described as being linked to stigma.

The second major theme is the siblings’ coping patterns (Figure 5). Five coping patterns were expressed: avoidance, isolation, normalization, caregiving and grieving. Avoidance is described as a strategy applied to achieve cognitive and physical avoidance. Isolation was found to involve the psychological dampening of bad experiences in an effort to create distance between oneself and the many stressful situations going on because of having a mentally disordered sibling. Normalization largely includes making comparisons between the ill sibling’s present state and somebody else’s or the sibling’s earlier mental condition. Caregiving is described as a way to deal with
feelings of inadequacy and guilt according to emotional and practical engagement in the ill sibling’s daily living. Finally, grieving is about processing empathic feelings of the ill sibling’s experienced burden of having schizophrenia and a loss of an earlier sibling relationship.

The third theme is fear of possible schizophrenia heredity (Figure 5). Five of the siblings had a mentally disordered parent and 10 had a family history of psychiatric disorders. Thus, they share a heavy disposition to psychiatric disorder. In addition, we found that an earlier family history of mental disorders had an impact on beliefs about etiology of schizophrenia. Siblings with a relative suffering from a mental disorder tended to be more aware of the possible heredity of schizophrenia than siblings without a psychiatric family history. The other two sub-dimensions, the fear of becoming mentally ill and reflections about “bad genes”, were also tainted by an earlier history of psychiatric illness. The siblings that had grown up with a mentally disordered parent made the most direct statements concerning fear of becoming mentally ill themselves. These siblings also expressed complex reflections about who brought in the “bad genes” in the family and the desire to protect the ill parent from feelings of guilt. Another aspect about this sub-dimension is the siblings’ concerns about passing the mental disorder on to their children, i.e. the risk of being a carrier of “bad genes”.
General discussion

The present thesis provided a broad approach in elucidating biological risk factors, as well as psychological and social functioning in schizophrenia. Papers I - IV included data from several domains: (1) population-based registers, (2) telephone interviews, (2) medical records, (3) CSF samples, (4) clinical data from interviews, (5) standardized rating scales, (6) role-play test and (7) semi-structured qualitative interviews.

Main findings

Interpretation of the major findings in papers I – IV is summarized within three thematic headings: risk and protective factors in schizophrenia, the meaning of social impairment in schizophrenia and coping with the risk of being a carrier of “bad genes”.

Risk and protective factors in schizophrenia

There is an intricate interplay between protective and vulnerability factors associated with social functioning, psychotic symptoms and occupational functioning in schizophrenia. Furthermore, both potential risk factors and protective factors have been suggested to be either personal or environmental.

In paper I, we found that low birth weight, small head circumference or fetal growth restriction, as well as early signs of weakness (e.g., congenital debility) might be possible risk factors for the later development of schizophrenia. Generally, these findings are in line with studies suggesting that low birth weight and hypoxia-related complications are among the specific obstetric complications most consistently associated with schizophrenia. Furthermore, the results from the cohort study were partly supported by the analyses within twin pairs discordant for schizophrenia, indicating that the association between fetal growth and the risk of schizophrenia is independent of familial factors. The divergent results in other studies on twins discordant for schizophrenia might be due to recall bias as these twin studies mostly use retrospective interviews with mothers or other relatives to obtain data rather than hospital records. Another explanation for these differences across studies is different cutoffs regarding birth weight. We believe that lack of statistical
power to measure small and interactive effects and lack of detailed information about the prenatal period are major problems with current approaches: aspects that might explain why most of our findings were not significant despite increased point estimates.\textsuperscript{30}

The mediating mechanism between obstetric complications and schizophrenia is still unknown. However, studies suggest that hypoxic brain damage associated with prenatal underdevelopment might be a contributing factor for later schizophrenia.\textsuperscript{34,35} Further, perinatal complications are one of several possible acquired components of vulnerability according to the vulnerability-stress model.\textsuperscript{6} Our finding that fetal growth seems to be associated with risk of schizophrenia independently of familial factors suggests that these specific obstetric complications belong to one of the two proposed major components of vulnerability, namely the acquired environmental component as opposed to the other major component with a genetic origin.

The findings of the neurotransmitter NPY having anxiolytic and antistress effects\textsuperscript{51} makes it possible to interpret the main findings in paper II within the framework of the vulnerability-stress model. To sum up, we found that baseline levels of NPY in the CSF of patients with schizophrenia can apparently predict longitudinal outcome in schizophrenia. NPY was also associated with Social Competence at baseline. Considering the suggested vulnerability models by Häfner\textsuperscript{179} and Goldstein,\textsuperscript{180} our findings generally indicate that an imbalance in NPY levels in CSF might be one of several risk factors associated with some aspects of longitudinal outcome in schizophrenia. More specifically, for each standard deviation increase in baseline NPY, there was an increased risk for poor longitudinal outcome for employment status, psychiatric symptoms or hospitalization. This finding is consistent with one study on NPY levels in CSF in schizophrenia, suggesting that high NPY levels might be an indicator of vulnerability.\textsuperscript{183} However, other cross-sectional studies have reported no differences in NPY levels in patients with schizophrenia compared with non-psychiatric controls.\textsuperscript{168,184} These contradictory results could be due to methodological differences between studies, particularly study design, small sample sizes, sample characteristics and NPY measurements. However, with the applied longitudinal design in paper II, NPY levels can be found to have a predictive value in schizophrenia although within normal ranges.

Furthermore, because of the difficulty to find other studies on the relation between NPY and social functioning in schizophrenia, we have to turn to experimental studies for further understanding of our findings. Cross-sectional experimental studies showing an association between alterations in NPY activity and changes in social behavior in mice can be suggested to support our findings.\textsuperscript{185} However, there is uncertainty in the translatability of measured social behavior in mice and the measures of social functioning in patients with schizophrenia in paper II. Moreover, because of the lack of studies investigating the association between NPY levels in CSF and social
functioning in normative samples, we need to compare our findings with results showing altered NPY levels being related to changed capacity to cope with stress in normative samples. Although it is well known that patients with psychosis are more vulnerable to stress, reliable interpretations have to be preceded by confirmation if the measures of social functioning in paper II actually are connected to stress. Further, alterations in NPY levels in schizophrenia might have other functional effects compared with non-psychiatric controls. In other words, for a better understanding of whether NPY is a risk factor for poor functional outcome in schizophrenia, additional research is needed to determine the specific mechanisms for this neurotransmitter in schizophrenia and the relation to social functioning.

In paper III, we found indications that poor subtle nonverbal aspects of social problem solving could be a possible indicator of vulnerability in schizophrenia mediated by a subclinical level of psychiatric symptoms. The performance part of the role-play test seems to put heavier demand on the slightly reduced cognitive processing capacity in siblings compared with the other skills measured in AIPSS. Previous findings of subtle neurocognitive impairments in siblings to patients with schizophrenia support this interpretation. Moreover, after adjustments for education level, the siblings showed a significantly lower capacity to act out solutions leading to effective social problem solving. Hypothetically, education level might therefore be a protective factor for developing nonverbal poor social functioning in schizophrenia. However, a possible association between social functioning, academic status and neurocognition in schizophrenia needs to be further elucidated.

As shown in paper IV, the siblings’ need to manage the situation of having a brother or sister with schizophrenia led to five coping patterns. These coping patterns might be personal protectors for the siblings; however, at present, we can only speculate as to whether the efficiency of a certain coping strategy makes siblings more vulnerable to develop various symptoms or whether it can protect the siblings’ psychological and physical health from negative effects. Thus, the causal chain and the intricate play between risk and protective factors in patients with schizophrenia and their siblings are not yet fully understood.

The meaning of social impairment in schizophrenia
Deficits in social functioning are among the most distinctive characteristics of schizophrenia. In paper III, patients with schizophrenia were found to have severe deficits in social functioning as measured with the AIPSS. This finding is in accordance with both previous studies and recent studies comparing patients’ social problem solving capacity with non-psychiatric controls using the AIPSS. Moreover, in our paper it seems as though the patients have specific deficits in the more complex social
problem solving tasks demanded in good sending skills. These findings are also supported by other studies. Contrary to our findings, one study that used our Swedish version of the AIPSS with dubbed-over Norwegian voices found lower intercorrelations between the scales of the AIPSS. However, results are available supporting our findings of a proposed serial nature of AIPSS. The divergent findings might be explained by sample characteristics or the use of a dubbed version of the AIPSS. Furthermore, we propose that more work is needed to clarify the three-stage process of social skills. Reciprocal influences might be involved as well as the documented sequential nature of AIPSS.

Another relevant issue to consider when interpreting the main findings in paper III is whether the sending dimension of social skills is an independent social deficit component in schizophrenia. According to one study, this social functioning concept is of equal importance for effective community functioning as for the more explored concept of social cognition. Because we had a cross-sectional design, it is not clear whether this is the case for our patients. However, challenging situations involving social interactions occur regularly in our everyday life. Because of the impact social functioning deficits are likely to have in schizophrenia, it might be relevant to consider a possible relation between these nonverbal difficulties and the patients poor social functioning in paper II. However, this interpretation is just speculative in that we did not compare the patients’ social functioning in paper II with a control group.

Our findings indicate that psychiatric symptoms, especially negative symptoms, are associated with initial judgment and description of a situation with a social interactive problem. These findings are consistent with other studies suggesting that social functioning is related to psychiatric symptoms in schizophrenia, especially negative symptoms. However, the patients’ difficulties to actively act out solutions in role-play seem to be independent of either positive or negative symptoms. This finding is difficult to interpret because of a lack of comparable studies. Further, there are findings suggesting that, despite substantial associations between social functioning role-play performance with cognitive variables, social skills and cognition seem to some extent to function as independent predictors of vocational functioning. There are also findings showing that AIPSS is associated with general intellectual ability, whereas other findings suggest specific neurocognitive abilities to be more relevant, with sending skills having the strongest associations with neurocognition. Considering the previously stated complex interaction between psychiatric symptoms, neurocognition and social functioning, the unclear relation between different constructs of social functioning, the lack of cognitive variables in paper III and education level being too crude to be a proxy for cognitive functioning, it is premature to conclude that sending skills are an independent component in schizophrenia.
To date, no other studies exist using the AIPSS for comparisons between patients with schizophrenia and their siblings. To gain a fuller understanding of our findings regarding the siblings’ subtle impairments in nonverbal language (e.g., made eye contact, voice volume, gestures and facial affect), we compared our results with studies on emotional processing deficits in siblings. Several studies have shown that siblings to patients with schizophrenia have facial emotion recognition deficits, show subtle affect perception deficits, and express similar dysfunctions in processing facial expressions as their probands with a psychotic disorder. Assuming that the nonverbal part of sending skills demands good emotion processing capacity, the nonverbal language may be the component of the AIPSS most capable of capturing some of the deficits reported in other studies. However, the results in paper III suggest that we cannot exclude a possible mediation by psychiatric symptoms on a subclinical level.

Coping with the risk of being a carrier of “bad genes”

The main finding in paper III is that having a brother or sister with schizophrenia disorder deeply affects the siblings emotionally and psychologically. The major themes that emerged from the qualitative analysis were sibling bond, coping patterns and fear of the possibility of inheriting schizophrenia. The siblings self-reported experiences of strong feelings evoked in relation to descriptions of the sibling relationship are supported by other studies. Although the sibling relationship is unique in that it is long-lasting and involve common social, genetic and cultural heritage, some studies report similar emotional reactions in parents. However, the tradition of investigating the experiences in mixed groups of relatives prevents evaluating the specificity of the siblings’ experiences. Further, some of the participating siblings in our study had a mentally ill parent. This circumstance might have contributed to a possible confounding: a young child is probably more affected by a caregiver suffering from a mental disorder than a sibling. The possible impact of double family roles is seldom discussed in most studies on relatives to patients with schizophrenia. To minimize confounding in our study it would have been preferable to have included specific questions exploring this potential dilemma. Moreover, to our knowledge few studies have compared adult siblings to patients with schizophrenia with adult siblings with a physical disease or other psychiatric disabilities. Thus, the specificity of the sibling bond in schizophrenia remains unclear.

The five coping patterns found in paper IV are both similar and different compared with other studies. In one study the coping pattern care giving has similar characteristics as “collaborative participation” while the coping patterns avoidance and isolation seem similar to a “detached approach”. However, in another study reporting eight coping skills for siblings, coping with avoidance was described as “constructive escape” and isolation as
“internalization of emotions or unhealthy escapes”. Differences in conceptualizations of coping and the central position of the preexisting sibling bond in our paper might have contributed to these discrepancies.

Moreover, the finding of high levels of interpersonal problem solving skills in siblings in paper III might be interpreted as personal strengths developed in the siblings by having a family member with schizophrenia requiring sensitive and clear communication strategies. Better individual social problem solving skills might have influenced the choice of coping pattern. Unfortunately, we do not have any data on these possible associations or the efficiency of the coping patterns in paper IV, which limits further interpretations.

The heavy family history of psychiatric problems in the sibling sample in paper IV and the strong fear of schizophrenia heredity interwoven in the siblings’ responses might have also influenced the coping patterns. Although there is growing evidence for complex schizophrenia heredity and extensive genetic schizophrenia research, no studies have investigated siblings’ perceptions and fears of being genetically susceptible to schizophrenia. Studies dealing with this issue have focused on the unaffected siblings’ strengths rather than their fear of susceptibility to mental disorders. Although this is an important field, our findings indicate that siblings’ fear of becoming mentally ill themselves or being a carrier of “bad genes” is underestimated. One explanation for the lack of studies on siblings’ risk perception might be that the uncertainty of the complex issue of schizophrenia heredity makes this area particularly difficult to study, both ethically and psychologically.

Methodological considerations

The wide array of methods used in this thesis (register-based cohort, twin, clinical psychiatric, longitudinal, sibling, psychological psychometric and qualitative study methodologies) has served as an important educational aim. Within each of these methods, there are several methodological issues that need to be acknowledged.

Applied methods

Epidemiological twin studies

In epidemiology, cohort studies are generally regarded as the most powerful and persuasive of the observational studies. Cohort studies involve measuring the occurrence of disease within one or more cohorts and are well suited for investigations of rare outcomes such as schizophrenia. However, this requires sufficient size of the cohort because in many studies only a tiny minority of those at risk for the disease actually develop the disease. To
overcome this problem, case-control studies can be used because of the possibility to collect similar information but more efficiently by the use of sampling.\textsuperscript{194}

In paper I, a register-based cohort and a case-control studies with unaffected co-twins as controls were performed in a population of twins from the Swedish Twin Register.\textsuperscript{160} The cohort study design was chosen with reference to an available large cohort of twin-pairs and the case-control twin-study design allowed further exploration to determine whether the associations could be explained by familial factors (e.g., genetic or shared environmental). Generally, a limitation in register-based studies is restriction to the information about outcomes and potential confounders already included in the registers. In our case, the careful collecting of data in the Twin Register and a long tradition in Swedish health care to record information on hospital and home deliveries in obstetric records probably minimized this potential limitation. However, because of the linkage between the Swedish Twin Register and the Hospital Discharge Register,\textsuperscript{161} we had to rely on the diagnosis of schizophrenia made by the treating psychiatrist. Although the Swedish diagnostic procedures of schizophrenia are considered valid,\textsuperscript{163,195,196} some misclassification bias might be present with patients incorrectly assigned to the control group. This and a concordant twin pair being treated as discordant in the analysis would have resulted in an underestimation of the true risks.

A possible selection bias should be considered in paper I because of several vulnerable steps in the recruitment of the 302 identified cases from the twin cohort. The first step was the difficulty of contacting the treating physician. This is a case of systematic error that is difficult to avoid because of the inherent ethical reasons involved when contacting patients for participation without clinical consideration. Next, although most physicians allowed us to contact the patients, it is relevant to consider why the physicians did not allow us to contact other patients (n=7). A systematic gathering of information about the physicians’ reason for not letting us contact the seven patients would have been preferable so comparisons could have been made between the patients included and those excluded from the study. The final step -- patients not found or who declined to participate -- caused the greatest loss of cases. In the telephone interviews reasons for not wanting to participate included the general desire to avoid the health care system, not defining themselves as psychiatrically ill or feeling upset or offended by being contacted. An additional eight patients could not be interviewed because of difficulties in understanding the aim of the study or because of being too affected by psychotic symptoms. Thus, informed consent was not possible to obtain. The high loss to follow-up of these cases or those who did not want to participate might have influenced the results through loss of power and precision. Furthermore, if we lost cases with low birth weight, underestimation of the point estimates could occur, or the opposite, in the
event the loss of cases had a high birth weight. These risks could have been minimized if data from the birth records could have been retrieved without informed consent from the participants’ mothers. This is an important ethical dilemma needing further consideration.

To ascribe the correct birth weight to the twins, the twins who later developed schizophrenia were asked for the birth order in the telephone interview. The higher risk estimates for schizophrenia in the analyses restricted to pairs whose birth order was confirmed in written documents might also indicate misclassification and possible underestimation of the true risk.

A major strength with the applied co-twin control design in paper I concerns the possibility to control for the confounding of familial factors. Comparisons of disordered discordant twins in the case-control study allowed us to determine whether shared (e.g., genetic or shared environment) or individual factors were involved. Another strength with the twin methodology is that it permits further study of whether there are genetic or shared environmental factors that contribute to familial mediation by subdividing the twin sample into monozygotic and dizygotic twin pairs. In paper I, however, this division was not possible because of the small sample size. This problem is quite common in twin-studies because discrimination between and quantifying of the genetic and shared-environmental effects demand great statistical power or technology. Fortunately, this was not an issue in paper I because fetal growth seemed to be associated with risk of schizophrenia independently of familial factors.

Clinical psychiatric studies
A common challenge in schizophrenia research is the recruitment procedure. First, many patients struggling with this severe mental disorder have psychiatric symptoms or cognitive deficits that can hinder recruitment because of ethical reasons. Second, if recruited, difficulties (e.g., withdrawal, apathy, paranoid thoughts or cognitive impairments) can make it hard to fulfill the actual investigation. One way to approach this problem is to include all patients residing on the ward as was done in paper II. However, a prerequisite for such an approach is a supportive health care environment with motivated health care personnel that can support and motivate the participating patients as well as perform reliable assessments. In addition, the approach to recruit all patients fulfilling the inclusion criteria in the same catchment area, increases the possibility of attaining a representative sample (this point is discussed in greater detail in the following section). Unfortunately, in paper II the sample size is rather small, which limits any analysis of confounding, mediation and true effects.

Another methodological issue is the choice of rating scales. Although symptom rating scales are found to be valid and have good psychometric properties, careful consideration regarding the complexity to measure variables in persons with psychotic symptoms is warranted. In paper II, we
created a “summarized variable” (excitation) from variables assumed to represent the expression of anxiety in psychotic patients. However, it has not been validated but the summarized variable negative symptoms has previously been used.

In attempts to identify neurobiological risk factors in schizophrenia (e.g., imbalanced neurotransmitter NPY levels in CSF in paper II) it is not always certain what the biomarker represents. However, because of the heterogeneity of the disorder and the developing brain, finding stable biomarkers in schizophrenia is difficult. As recently reviewed by Lacrosse, the investigation of the potential role of neuropeptides in schizophrenia is promising, although not as well investigated compared to other transmitters. When performing clinical studies in an emerging field (as in paper II), comparing findings has to be performed with experimental preclinical studies. This raises the question about the comparability of behavioral variables between humans and mice and rats. Comparisons with studies on normative samples also have limitations because we still do not know whether the biochemical mechanism of NPY is specific to samples of patients with schizophrenia. Inclusion of a control group in paper II might have been a strategy to bypass this issue. However, although important, this was not within the scope of the present study.

**Longitudinal outcome studies**

Generally, longitudinal studies are required to detect possible predictors of outcome. Another advantage with the longitudinal design is the possibility to look at the directions of the associations and identify possible mediators. Characterization of the samples and applied outcome measures are two of the major methodological issues in longitudinal outcome studies. A methodological strength of paper II is the inclusion of a well-characterized sample with all patients being diagnosed with schizophrenia according to DSM-III and free of antipsychotic medication at baseline. Another strength is that the sample only comprised patients with schizophrenia (and not affective or brief psychosis), which enhances the possibility to compare our findings with those previously reported.

It has been argued that much of the long-term outcome variance can be accounted for by sample characteristics of differences. One way to deal with these methodological obstacles is to perform outcome studies of first-episode schizophrenia. Thus, the first-episode strategy provides a valuable method for homogenizing variability that is due to illness course in schizophrenia. In our paper, although the majority of the patients were first-episode psychosis, we cannot exclude a potential bias of the results because of a mixed patient group of both first-episode and multi-episode patients with schizophrenia. Even though we had a mixed sample, we were still able to detect a signal.
Until recently, outcome studies in schizophrenia lacked standardized measures. Traditional longitudinal research predominantly investigates recovery in symptoms, neurocognition and social functioning. Recent additions to outcome measurement include measures in domains of psychopathology, level of functioning (e.g., cognitive, social and occupational) and quality of life. The multi-dimensional Strauss-Carpenter Outcome Scale used as outcome measure in paper II is widely used, quick and easy to administer. However, by using dichotomized variables, we may have inadvertently decreased variance in the description of outcome. The main reason for dichotomizing the data was to be able to perform adjustments with covariates: in this case baseline levels of the longitudinal outcome. Moreover, the outcome dimension of moderate or severe symptoms is only defined in quantitative terms. However, positive and negative symptoms rated with the PANSS have been found to have a strong to moderate association with cross-sectionally measured social and occupational functional outcomes assessed with the Strauss-Carpenter Outcome Scale.

Sibling studies
As noted previously in this thesis, an important reason for studying siblings to individuals with schizophrenia is to investigate the established notion that schizophrenia is familial. Yet, drawing generalizable conclusions about possible vulnerability indicators and schizophrenia heredity require, among other things, representative samples of adequate size.

In paper III, a cross-sectional case-control design was applied to compare social problem skills between patients with schizophrenia, their biological siblings and non-psychiatric controls. Except for two persons, all the sibling participants were recruited by their sister or brother with a disorder. Because we only included those siblings who we were allowed to contact through their ill brother or sister, there might have been sampling bias towards inclusion of siblings with good social capacity and close contact with their brother or sister. As revealed in paper IV, however, there was a rather wide range in frequency of contact between the siblings. With the reservation of not having measured this aspect for all siblings in paper III, this observation suggests a representative sample of siblings to patients with schizophrenia. Moreover, by including siblings with psychiatric symptoms, the representativeness might have been further increased. However, because of the lack of normative studies for being “an unaffected sibling”, these arguments are somewhat speculative in nature. There might also have been information bias in the siblings’ report of symptoms due to the combination of wanting to appear mentally healthy and the reported fear of heredity as described in paper IV.

Performing this kind of cross-sectional study, a sample of 20 siblings (paper III) is rather small. The sample was restricted even further (to 15 sibling-pairs) when we analyzed within-sibling differences to study possible
vulnerability in social skills. Thus, conclusions drawn about possible social functioning vulnerability markers found in this study must be viewed with caution. To confirm the findings replications with larger samples are needed.

A major methodological strength in paper III is the case-control design that allowed comparisons with randomly selected controls matched for age and sex. The inclusion of a normative control group increases the possibility for other Scandinavian studies to use our Swedish version of the AIPSS. It is, however, relevant to consider the definition of “non-psychiatric controls”. The exclusion criteria in paper III were defined for common praxis, and the results showing that the controls had the highest scores, the siblings medium scores and the patients the lowest scores, is in accord with other sibling studies investigating social behavior in these three groups as mirrored by emotional processing. At the recruitment phase, however, we had to rely on the participants’ information about earlier and current contact with psychiatric care. This aspect, in combination with the exclusion of three controls because of added information about psychiatric contacts, is a limitation that needs to be dealt with by the complementary collection of more objective data (e.g., occupational status and medical records). This must be done in line with ethical issues.

**Psychological psychometric studies**

To assess the participants’ current level of social skills rather than past functioning a Swedish version of the role-play test AIPSS was developed for paper III. In developing a psychological test instrument several methodological aspects have to be considered (e.g., validity and reliability). In this study, however, we had to rely on the documented psychometric properties of the American original version of the AIPSS. We argue in paper III that the similar results for the patients in our study and those in the original version indicate psychometric adequacy. What is more certain is that our version of the AIPSS has roughly similar psychometric properties to those of the original version. Reasons for these similarities can be related to care taken to translate the manual and record the video scenes. Despite this limitation, a general advantage with role-play assessment is not having to deal with the variety of influences that come with the quick and easily administered self-report questionnaires.

The fact that the AIPSS was developed decades ago puts into question its ecological validity. Several of the situations in the AIPSS contain out-of-date scenes that today’s younger patients might have difficult identifying with (e.g., waiting in line to use a paid phone when another person jumps to the front of the queue). Moreover, although the manual provides guidelines for the scoring of answers that seem to be applicable to our Swedish culture, the influence of the raters’ interpretations should not be ignored. Nevertheless, the intrarater reliability was high (94%). These figures, however, rely on
application of the criteria that two raters agree if their ratings are within 0.5 points of each other.

Moreover, the lack of a psychiatric control group sets limits on determination of whether our findings are specific to schizophrenia. This methodological issue has also been discussed in other studies. For instance, Bellack raised the question about what conclusions can be drawn in applying the AIPSS, either specific or general, because of the absence of a psychiatric control group during the creation of the test instrument.107 Despite these limitations, role-play tests seem to capture an interactional aspect of social behavior that is more ecologically valid to how people actually solve interpersonal problems than responses measured by self-report or third-party interviews.

**Qualitative studies**

Another major reason for investigating siblings to patients with schizophrenia is to explore their experiences, work that is often neglected in family research within this field. It is frequently asserted that qualitative methods are suitable in areas of research with limited knowledge about the subject matter. Qualitative methods are also used in the exploration of meanings of social phenomena as experienced by the individuals themselves in their natural context.206 In paper IV, the siblings’ responses contained abundantly more information than was asked for in the semi-structured interview guide by Gerace et al. that formed the base for our inductive reasoning.86 Therefore, a qualitative method inspired by grounded theory was chosen to facilitate the emergence of the siblings’ whole experiences and gain a deeper understanding of the findings as compared with qualitative descriptions.207 Because the interviews were based on previously investigated main themes as formulated in the interview guide, we could not strictly apply the constant comparative strategies according to grounded theory.175 Instead, the siblings’ feelings, thoughts and behaviors were examined in an interview study based on the conventional sociological qualitative method of a close and repeated reading of the material.176

In qualitative research the concepts credibility, transferability, dependability and conformability have been used to describe various aspects of trustworthiness.208,209 In paper IV, the presentation of representative quotations from the transcribed text that were related to each of the major themes and their dimensions is one way to enhance credibility. To facilitate the transferability of the findings, we gave clear descriptions of the selection and characteristics of the participants (siblings), the data collection procedure and a transparent description of the three steps in the interview analysis.206 Because transferability refers to the extent to which findings can be transferred to other contexts, the high concordance in major themes found in paper IV might also have enhanced this aspect of trustworthiness. The concept dependability emphasizes the need for the researcher to account for the ever-
changing context within which research occurs. In paper IV, the use of the same phrases in introducing the interview to those individuals that who agreed to participate together with a thorough description of the setting might have minimized the problem of dependability. Still, we cannot exclude the possible influence of preexisting assumptions because the interviewer had met the siblings earlier when performing the role-play tests used in paper III. The clear descriptions when presenting the siblings’ narratives as compared with the authors’ interpretations facilitated judgments of conformability. Concerning the interpretations, another way to facilitate judgments of conformability was the continuous dialogue between the first author, who performed the interviews, the second author, who had experience with the method applied, and the third author, who had a long history of clinical experience with patients with schizophrenia.

In general, research on siblings’ experiences has mostly been quantitative using questions not always specifically designed to capture the sibling role or non-systematic descriptions from psychotherapeutic approaches. However, during the past decade an increasing number of qualitative sibling studies with systematic approaches have appeared in the literature. A major strength with the applied qualitative approach in study IV is that it generates new “theory free” psychological knowledge about siblings’ perspectives in schizophrenia.

Representativeness

Finding a representative sample demands knowledge about what is ”real”, which is a difficult issue in schizophrenia because of its heterogeneity. There are arguments for schizophrenia including several or different psychiatric diseases whose clinical manifestations are similar. Thus, we might have to consider the possibility that there is “no one schizophrenia”.

The samples in paper I can be considered representative because of the cohort design with large sample size and the use of valid registers. However, the generalizability of twin studies of schizophrenia to the general population has been questioned. On the contrary, there are findings suggesting that the incidence of schizophrenia in twins does not differ from that in singletons. Clearly, this issue needs further study.

In paper II, the recruitment of all patients in the same catchment area increases the generalizability of the findings. Further, the well characterized sample with both first- and multiple-episode patients having a diagnosis of schizophrenia after at least 5 years is worthy of consideration. Our sample is probably representative of schizophrenia but not necessarily for other psychoses such as affective or brief.

In comparison with paper II, paper III applied a more traditional recruitment procedure by asking health care personnel to ask patients they thought could be suitable to participate. This recruiting approach could have resulted
in a non-representative sample in social functioning because it is more likely that the personnel would prefer to recruit a socially skilled person rather than someone with poor social skills. However, the results were similar to those in the original version of the AIPSS, which demonstrates sufficient representativeness.

Confounding and mediation

Confounding is a statistical dilemma in cross-sectional and longitudinal studies. Although it is preferable to control for possible confounders and mediating pathways, this was not possible in paper II and III because of too small sample sizes. In contrast, because of the relatively large sample sizes, the twin cohort and case-control study performed in paper I allowed control for multiple covariates. Although we had small sample sizes in paper II, the rather exhaustive assessment procedure of the baseline state of the outcome variables as measured with the Strauss-Carpenter Outcome Scale permitted adjustment to ascertain the associations between NPY levels at baseline and poor outcome after 3 years. Thus, the associations were not merely confounded by a cross-sectional correlation at baseline.

A central mediator in paper III might be the participants’ neuropsychological functioning. Because we lacked cognitive data, educational years were used as a crude proxy for cognitive functioning. Research suggests that emotion perception is a mediator between neurocognition and functional outcome in schizophrenia as assessed with the AIPSS. 144 However, the cross-sectional design does not allow the disentanglement of direction of effects and possible mediation or confounding. Another confounding effect could be the antipsychotic medication. However, at least new-generation antipsychotics do not produce substantial changes in social problem solving capacity in schizophrenia. 214

Ethical considerations

In general, patients with a mental disorder can be regarded as a vulnerable group, especially patients with severe mental disorders such as schizophrenia. Including patients with severe mental disorders requires that relevant ethical considerations are enforced throughout the research process.

One important ethical consideration in paper I is, paradoxically, the procedure of asking the patients for permission to contact their mothers. Before contacting the patients, an informative letter about the aim of the study and interview procedures was sent shortly before phoning them. Included in the letter was also information about wanting to contact their mothers for permission to order the twins’ birth records. We were later informed by some patients that the letter generated negative thoughts related to
psychiatric history as well as to strained family relationships or raised fears about being contacted by a stranger. Therefore, it might have been more ethical to contact the mothers directly to minimize any emotional distress to the patients. This benefit, however, has to be balanced with the risk of making the patients feel that they are being deceived.

The use of lumbar puncture in a hospital setting in paper II challenges several ethical boundaries. Recruitment of patients in relation to their need of in-patient psychiatric care calls for awareness of an imbalance of power. To minimize any inconvenience in connection with the lumbar puncture the procedure was performed by specially trained professionals. In general, the patients expressed thoughts about “finally getting a real examination”. This generally positive attitude towards psychiatric research among patients with schizophrenia has been reported elsewhere.215

A main ethical consideration in paper III is asking the patients’ to contact their sibling without knowing about actual family relationships and the risk of triggering undesirable or negative experiences. Because most patients with siblings wanted us to contact their sibling, this did not seem to be an important issue in the present study. However, this ethical issue should be kept in mind when recruiting relatives via the patients.

The interviews with siblings of patients with schizophrenia in paper IV could lead to feelings of sadness and worry that could be hard for the siblings to handle. Because of this possibility, the interviewer has to be clear about the frames for the interview and if needed recommend who to contact for further psychological support. However, many of the siblings interviewed expressed positive experiences of having been listened to, sometimes for the first time even though their brother or sister had been ill for a long time.

Clinical implications and future directions

The population attributable risk of schizophrenia due to obstetrical complications is low. Thus, optimizing prenatal care probably would have little impact on the incidence of schizophrenia. The associations between fetal growth and higher risk for schizophrenia in paper I are more interesting from an etiological, than a preventive, perspective. A possible next step could be further investigation of familial mediation in larger samples.

We still have too little knowledge about the role of NPY in schizophrenia to have clinical implications, and further etiological studies are needed, preferably with longitudinal comparisons between patients with schizophrenia and normative samples in social functioning and by considering the impact of stress as well.
There are recent advances in social skills training for schizophrenia\(^7\)\(^{217}\) and AIPSS has been shown to be a useful outcome measure for the effects of cognitive treatment\(^2\)\(^{218}\). If AIPSS would be used in clinical practice, some of the scenes need to be revised and modernized. The indications of nonverbal language being a possible risk factor could be further elucidated in experimental studies considering the association between this dimension of social behavior and tests of emotion processing.

Possible implications of the findings in paper IV can be psychoeducation interventions focusing on the siblings’ needs that are formed by the uniqueness of the sibling bond. The siblings’ reported fear of becoming mentally ill in paper IV indicates a need for genetic counseling\(^2\)\(^{221}\). Finally, today’s community-focused psychiatric care with the aim of striving for independent living may increase the importance of the sibling relationship in schizophrenia. Because of a possible transactional aspect of coping and the still unknown specificity of the sibling bond, as a next step it would be beneficial to explore the affected siblings’ experiences of the sibling relationship.
Conclusions

1. Low birth weight and small head circumference are associated with increased risk for schizophrenia, an association that is probably independent of familial factors.

2. NPY levels in CSF are related to social competence and associated with longitudinal outcome of employment, psychotic symptoms and hospitalization in schizophrenia.

3. Patients with schizophrenia, who were tested with a Swedish version of AIPSS, were found to have severe impairments in social functioning. In addition, their siblings expressed subtle deficits in nonverbal language but did not generally differ from controls.

4. Our data indicated a strong emotional sibling bond in schizophrenia and a fear of possible schizophrenia heredity. Further, siblings to patients with schizophrenia developed several coping patterns, including avoidance, isolation, normalization, care giving and grieving.
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