Family matters

The impact of family history on phenomenology and IQ in patients with schizophrenia and their relatives

Kim Verweij

The studies described in this thesis were performed at the Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Center Utrecht, The Netherlands.

The studies which were part of the GROUP-project were supported by a grant from ZonMw.

Printed on FSC certified paper.

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The impact of family history on phenomenology and IQ in patients with schizophrenia and their relatives

Familie is van belang

De invloed van familiaire belasting op fenomenologie en IQ in patiënten met schizofrenie en hun familieleden

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 13 februari 2014 des ochtends te 10.30 uur

door

Kim Hendrika Wilhelmina Verweij

geboren op 2 november 1979 te Linschoten

Promotoren:	Prof. dr. R.S. Kahn Prof. dr. E.M. Derks
Co-promotor:	Dr. W. Cahn

One percent inspiration and ninety-nine percent perspiration

Thomas A. Edison

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General introduction

Schizophrenia

Schizophrenia is a severe and complex psychiatric disorder, characterized by abnormalities in the perception of reality and a disturbance of thought processes and feelings. The core signs and symptoms of schizophrenia are subdivided in positive and negative symptoms. Positive symptoms reflect an excess or distortion of normal functions and include hallucinations, delusions and disorganized thinking, speech and behavior. Negative symptoms refer to a reduction or loss of normal functions and consist of reduced interest and drive, affective flattening and poverty of speech [1]. Besides these core symptoms, schizophrenia is characterized by a decline in cognitive and overall functioning. Patients with schizophrenia show a heterogeneous phenotype and clinical presentation differs from one patient to another, due to variation in symptoms, severity, course and outcome of the illness. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) provides several diagnostic subtypes to characterize patients with schizophrenia such as the paranoid, disorganized and catatonic type. Schizophrenia generally manifests during early adulthood and the lifetime prevalence varies between 0.3-0.7% [2]. The incidence of schizophrenia is significantly higher in males than in females with a male/female rate ratio of 1.4 [3]. Moreover, men have an earlier age of onset [4] and a higher risk for a more severe form of illness [5] compared to woman.

Risk factors

Although the exact aetiology of schizophrenia remains unknown, multiple familial/genetic and environmental factors influence the development and expression of schizophrenia. The most well studied environmental factors associated with an increased risk to develop schizophrenia are obstetric complications, psychosocial stress, urbanicity and cannabis use [6]. A range of genes has been proposed to be implicated in the development of psychotic disorders such as the genes coding for catechol-O-methyl transferase (COMT) [7], brainderived neurotrophic factor (BDNF) [8] and neuregulin (NRG1) [9]. Another genetic risk factor includes de novo Copy Number Variants (CNVs) as CNV deletions at 1q21.1, 15q11.2 and 15q13.3 are associated with schizophrenia [10]. However, the strongest risk factor that has been identified is familial risk. Not only is the risk to develop schizophrenia elevated in individuals who have an affected relative, this risk also increases with the level of genetic relatedness to the patient [11]. For example, first-degree relatives such as siblings share about 50% of their genes and show a risk of 9% to develop schizophrenia while third-degree relatives such as cousins share about 12.5% of their genes and show a risk of 2% (see **Figure 1.1**). Despite the strong heritable component and all other identified risk factors, the biological pathways and the interaction between risk factors remain largely unknown making it difficult to predict the development of schizophrenia.

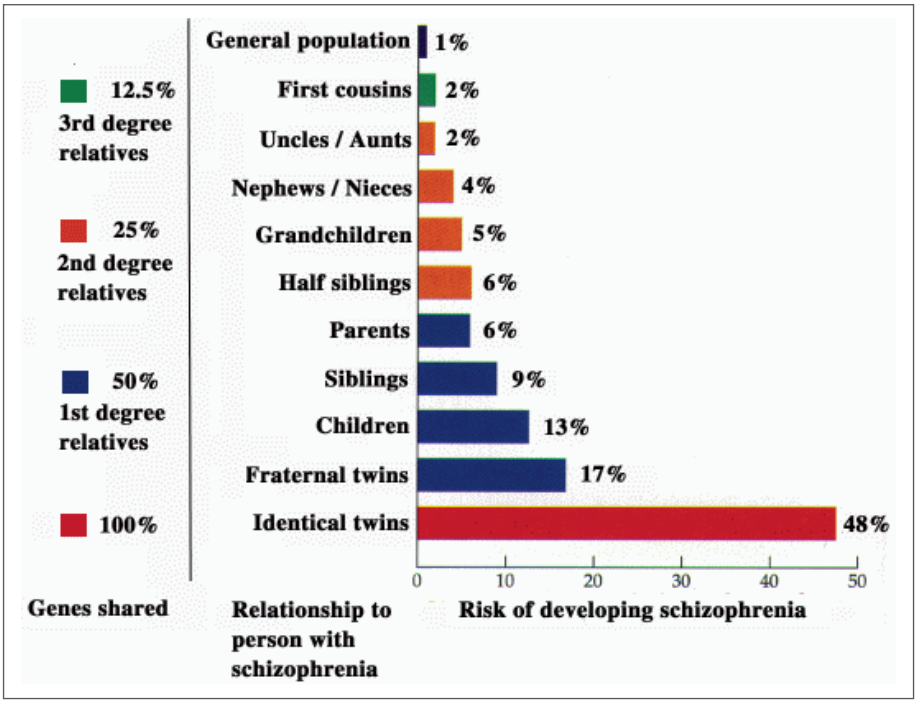

Figure 1.1 | Lifetime risk of developing schizophrenia, source: Gottesman, 1991

Family studies

The familial risk in schizophrenia leaded to the emergence of family studies. Family studies all describe the familiarity of schizophrenia, but the focus can be very different. The most important family studies for this thesis are those investigating endophenotypes and familial loading and therefore will be further discussed.

Endophenotypes

Schizophrenia is a complex psychiatric disorder and endophenotypes may help to resolve a little of the aetiological puzzle since endophenotypes represent simpler clues to genetic underpinnings than the disease syndrome itself [12]. An endophenotype is a trait with a highly genetic component but not directly tied to the illness itself and may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive or neuropsychological in nature. Moreover, one of the criteria for an endophenotype is that a trait that is found in patients is also found in unaffected relatives at a higher rate compared to the general population [13]. Therefore, non-psychotic siblings provide good populations to study endophenotypes, given that siblings share on average 50% of their genes with the patient but not the clinical phenotype (psychosis). Candidate endophenotypes include intelligence [14], sustained

attention deficits [15], schizotypy [16] and movement disorders [17] among others since these are found in patients with schizophrenia as well as unaffected relatives as compared to healthy controls. So comparing patients with schizophrenia, their unaffected relatives and healthy controls can help to identify endophenotypes of schizophrenia.

Familial loading

In an attempt to describe the familiarity of schizophrenia, an often used classification is sporadic and familial schizophrenia. Patients with a familial form of schizophrenia have one or more relatives also affected with psychosis while sporadic patients are the only patient with schizophrenia in their family. There are different ways to define the familial and sporadic categories. A dichotomy can be used in which patients with a positive family history for psychosis are classified as familial and patients with a negative family history as sporadic. However, this dichotomy does not take account of family size and age structure. For example, patients with brothers and sisters younger than 18 years old can not definitely be classified as sporadic because it is not certain whether these brothers and sisters will develop schizophrenia when they grow older. Therefore Verdoux and colleagues [18] developed an algorithm that does comprise age and family size into the calculation of familial loading. First, the algorithm calculates the risk to develop schizophrenia for every relative in a family dependent on the age and illness status (affected or unaffected) of that relative (see **Figure 1.2a and 1.2b**). Then, the risk scores of all family members are multiplied and the logarithm is taken. This final score forms a probability score which indicates whether there is greater support for the patient to be sporadic or familial. This probability score is often referred to as the familial loading for schizophrenia.

$$\frac{0.1 \cdot \left(\frac{x-15}{50-15}\right)}{0.005 \cdot \left(\frac{x-15}{50-15}\right)} = 20$$

Figure 1.2a | The likelihood ratio if a relative of age x is affected

$$\frac{1-0.1 \cdot \left(\frac{x-15}{50-15}\right)}{1-0.005 \cdot \left(\frac{x-15}{50-15}\right)}$$

Figure 1.2b | The likelihood ratio if a relative of age x is unaffected

Some studies indicate that patients with familial schizophrenia have a poor outcome [19,20], lower age of onset [21] and impaired cognitive functioning [22] compared to sporadic patients. However, other studies conclude that there are few robust (neurocognitive) differences between schizophrenia patients with and without relatives affected by psychosis [23,24]. The fact that there are few differences between sporadic and familiar patients might be explained by the finding of a recent study that in complex, genetically heterogeneous disorders such as schizophrenia, the majority of the patients is expected to be sporadic [25].

Schizotypy

Psychotic experiences at the subclinical level, alternatively labeled as schizotypy, psychosis-proneness or psychosis-like symptoms, are more prevalent in relatives of patients with schizophrenia compared to healthy controls [26]. The concept of schizotypy was described decades ago by Meehl [27]. Like schizophrenia, schizotypy is multidimensional and heterogeneous. The architecture resembles that of schizophrenia and consists of three dimensions: positive, negative and disorganized schizotypy [28]. Since patients and their relatives share genetic and environmental influences, it has been hypothesized that specific symptom domains cluster within families. For example, when a patient with schizophrenia mainly experiences positive symptoms, it is expected that the relatives experience positive and not negative or disorganized symptoms of schizotypy. So far, studies analyzing associations between psychotic symptoms in patients and corresponding schizotypal traits in first-degree relatives are not convincing. However, this could (partly) be due to methodological issues since this type of patient-relative association may be difficult to interpret, as it may be attenuated by disease-specific environmental (e.g., medication use in patients) or genetic (e.g., risk genes that are present in the patient, but not in the unaffected relative) factors [29].

Schizophrenia and overlap with other psychiatric disorders

Besides schizotypy or schizotypal personality disorder, a variety of other psychiatric disorders are often present in relatives of patients with schizophrenia [30]. High rates of axis I disorders such as attention deficit hyperactivity disorder (ADHD), mood disorder and anxiety disorder have been shown in offspring and siblings from patients with schizophrenia [31–33]. Moreover, recent findings indicate that genetic risk factors for schizophrenia are partly shared with the genetic vulnerability for other psychiatric disorders including bipolar disorder, depression, schizoaffective disorder and ADHD [34–38]. This implies an increased vulnerability for a wide range of psychiatric disorders in families of schizophrenia patients.

Given the increased vulnerability for different psychiatric disorders in families with schizophrenia, it can be hypothesized that the familiarity of schizophrenia is also characterized by the clustering of (subclinical) psychotic and other psychiatric symptoms. Investigating the overlap between schizophrenia and other psychiatric disorders at a clinical and subclinical level can give us more insight into the aetiology of the disorders. Moreover, the co-occurrence of psychotic as well as other psychiatric subclinical symptoms in some high risk subjects might represent a subgroup with an increased risk for schizophrenia spectrum disorders.

The GROUP project

The Genetic Risk and Outcome of Psychosis (GROUP) project has been designed to study genetic and non-genetic vulnerability and resilience factors (genetic, somatic, psychological and social) for variation in the expression of non-affective psychotic disorders as well as in the course of these disorders. The project is a naturalistic, longitudinal cohort study in families with a baseline assessment and follow-up at three and six years after baseline. The consortium of this GROUP project consists of four academic psychiatric centers (in Amsterdam, Groningen, Maastricht and Utrecht) and their affiliated mental health care institutions. Together, these mental health care institutions cover about 75% of the population in the Netherlands. At baseline, the total GROUP sample consisted of 1120 patients with non-affective psychotic disorder, 1057 of their siblings, 919 of their parents and 590 healthy controls. The assessments include a psychiatric interview, collection of family history information, questionnaires, a neuropsychological assessment and blood and urine samples [39].[1]

Measurements

In this paragraph, the most frequently used measurements in thesis will be enlightened.

Family history

Family history is assessed with the Family Interview for Genetic Studies (FIGS) [40]. For the FIGS interview the first informant of choice in patient families was the mother. When the mother was not willing or able to provide family history information, the father or sibling of the patient was interviewed. In control families, family history information was usually provided by the participating control. First, a pedigree including all first- and second degree relatives of the patient or healthy control was drawn (see **Figure 1.3**). Second, general screening questions were addressed to check for psychosis, depression, mania, personality disorder and alcohol or drug abuse among the relatives in the pedigree. Confirmative answers to these screening questions were followed up by registration of the age of onset, treatment, duration, severity and number of episodes of the specific disorder. Finally, for those relatives with psychosis, psychotic and affective symptoms were interrogated.

[1] www.group-project.nl

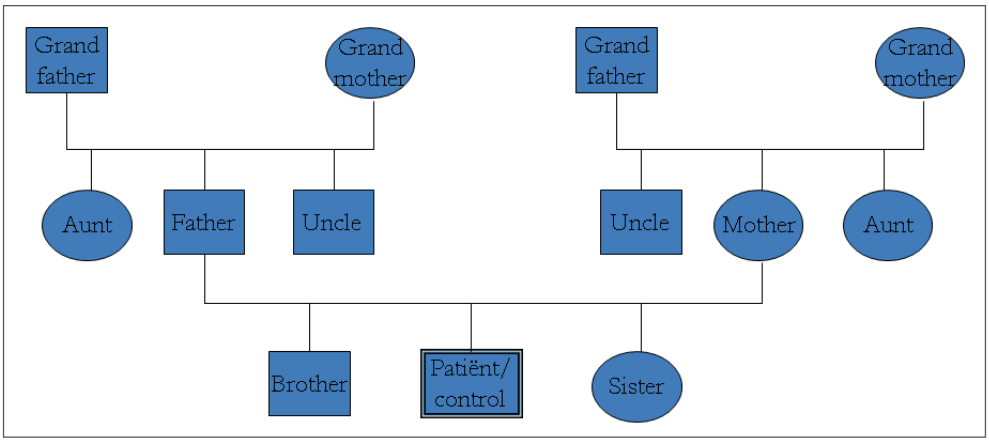

Figure 1.3 | Example of the pedigree used in the FIGS interview

Psychotic symptoms

Self-reported (subclinical) psychotic experiences in the affective and non-affective domains were assessed with the Community Assessment of Psychic Experiences (CAPE) [41]. The CAPE consists of 42 items; 20 items comprise the positive dimension, 14 the negative dimension and 8 the depressive dimension. The frequency as well as the distress of each item is measured. The frequency score is rated on a 4-point scale (1=never, 2=sometimes, 3=often, 4=nearly always). The degree of distress associated with the experience is also rated on a 4-point scale (1=not distressed, 2=a bit distressed, 3=quite distressed, 4=very distressed).

Schizotypy may also reflect subclinical psychotic symptoms. The Structured Interview for Schizotypy-Revised (SIS-R) [42] was used to assess interview-based positive and negative schizotypy. The SIS-R consists of different questions to judge whether 15 schizotypal symptoms and 4 signs are absent or present in a mild, moderate or severe degree. The positive schizotypy scale is made up by the following items: referential thinking ("being watched" and "remarks"), suspiciousness, magical ideation, illusions, psychotic phenomena, and derealisation/depersonalization. The negative schizotypy scale comprises the items: social isolation, introversion, sensitivity, restricted affect, disturbances in associative and goal-directed thinking, poverty of speech, and eccentric behaviour.

Attention deficit hyperactivity disorder symptoms

ADHD symptoms were assessed with the ADHD Rating Scale [43]. The ADHD Rating Scale contains 23 items reflecting DSM-IV criteria for ADHD. All items were rated on a 4-point scale (0=rarely or never, 1=sometimes, 2=often, 3=very often). A score of 2 or higher indicates the presence of that symptom. There are 10 items that reflect half of a symptom

resulting in 9 symptoms for inattention and 9 for hyperactivity/impulsivity. The range of the inattention as well as hyperactivity/impulsivity subscale is 0-9. A score of 6 or higher on the inattention scale corresponds with a childhood diagnosis of ADHD predominantly inattentive type according to DSM-IV. A score of 6 or higher on the hyperactivity/impulsivity scale corresponds with a childhood diagnosis of ADHD predominantly hyperactive/impulsive type. A score of 6 or higher on both dimensions corresponds with a childhood diagnosis of ADHD combined type.

Outline of this thesis

In this thesis we aimed to explore the familiarity of schizophrenia by investigating the impact of family history on phenomenology in patients with schizophrenia and their unaffected siblings. First of all, we address some methodological issues concerning the collection of family history information and the calculation of familial loading. **Chapter 2** investigates the role of a subject's position in a pedigree on the validity of family history data collection. Moreover, we evaluated whether characteristics of the informant such as gender and personal history of psychiatric disorder influenced the assessment of family history. **Chapter 3** describes an improved algorithm to calculate familial loading for schizophrenia in such a way that the algorithm developed by Verdoux and colleagues i) allows for a non-linear increase in risk of illness; ii) takes sex differences into account; and iii) can be applied to data of first- and second degree relatives.

As discussed, a variety of other psychiatric disorders are often present in relatives of patients with schizophrenia. This is why in **chapter 4** the definition of family history of psychosis is expanded with mania, depression and alcohol or drug abuse. We then investigated the association between family history for psychiatric disorder and IQ in patients with schizophrenia, their siblings who are unaffected for psychosis and healthy controls.

The familiarity of schizophrenia is also characterized by the familial clustering of subclinical psychotic and other psychiatric symptoms. **Chapter 5** explores familial clustering of the positive, negative, and depressive symptom dimensions in three groups: (i) patients with psychotic disorder and their healthy siblings, (ii) healthy sib-pairs of affected families, and (iii) healthy control sib-pairs. In **chapter 6** the association between attention deficit, hyperactivity/impulsivity and psychotic symptoms is investigated in patients with schizophrenia, their siblings who are unaffected for psychosis and healthy controls. Finally, **chapter 7** presents summaries and main findings of the abovementioned studies and ends with a general conclusion of this thesis.

Chapter 2

The influence of informant characteristics on the reliability of family history interviews

Kim H.W. Verweij, Eske M. Derks, Eva J.E. Hendriks, Wiepke Cahn

Twin research and human genetics, 2011; 14: 217-220.

Abstract

Family history interviews are widely used in psychiatric research as well as in genetic and twin studies and provide a way to collect family history information quickly and economically. To obtain a valid assessment of family history, it is important to investigate which family member will be able to provide accurate information. Previous research shows that the validity of family history reporting can be influenced by characteristics of the informant such as age, gender and personal history of psychiatric disorder. The aim of this study was to investigate the role of a subject's position in a pedigree on the validity of data collection. Family history data on diabetes and psychiatric disorders were collected in three generations of 33 families by interviewing both an index subject (3rd generation) and his or her mother (2nd generation). Mothers were shown to report higher rates of diabetes and psychiatric disorder in the family compared to the index subjects. There was no significant difference in the disease rate reported by male and female index subjects. Mothers who experienced a depressive episode indicated significantly more family members as having a psychiatric disorder than mothers who never experienced such an episode. This could either be explained by the presence of informant bias but may also result from the fact that depression is a heritable disorder and is therefore actually more prevalent in these families. Our findings suggest that family interview data should be collected by interviewing subjects who have a central position in the pedigree and can therefore provide information on his/her own generation, the previous and the next. In addition, psychiatric status of the informant should be carefully addressed.

Introduction

The assessment of family history is widely used in psychiatric research as well as in primary care practice [44]. Since the acknowledgement that the risk to develop a psychiatric disorder is influenced by genetic factors, many family studies have been conducted. Accurate information about the presence or absence of psychiatric disorders in family members is needed to study these genetic factors. For such a purpose, it is important to assess all members of a pedigree for as many generations as possible.

Family history interviews provide a way to collect family history information quickly and economically. The main advantage is that only one informant provides information on his or her relatives. In this way, information on all the members of a pedigree can be collected. This is important because Heun and colleagues [45] showed that family members willing to participate in research can differ from those who are unwilling. A disadvantage may be reduced validity of data collection, and it is therefore crucial to interview a subject who is capable of providing valid information. This is of particular importance when some of the potential informants may suffer from a psychiatric (e.g. psychotic) disorder.

Past research shows that the validity of family history reporting can be influenced by characteristics of the informant such as age, gender, personal history of psychiatric disorder and familial relationship [44,46–51]. In addition, the validity of data collection may depend on the specific disease or disorder of interest. Milne and colleagues [51] showed that the assessment of family history information on smoking and asthma was more reliable than the assessment of the family history information on psychiatric disorders. Hardt and Franke [52] further showed that family history interview data on severe mental disorders are more reliable than family history data on less severe disorders.

One way to study the validity of family history data collection is to compare disease rates as reported by different informants. For example, a subject might not be informed on the disease status of a grandparent while he or she is probably more likely to be informed on the disease status of his or her parent. In addition, gender and personal psychiatric history may influence the validity of the collected information. The aim of this study is to compare family history interview data on diabetes and psychiatric disorders assessed in subjects of different generations in a pedigree. Thirty-three families with no family history of psychosis participating in the Genetic Risk and Outcome of Psychosis (GROUP) study were included [39]. Data were collected in index subjects, being a member of the third generation and in their mothers, being a member of the second generation. We will test whether the reported rates of diabetes and psychiatric disorder are different between these two types of informants. In addition, we will assess whether gender and psychiatric status influence the assessment of family history.

Methods

The families participating in this study are a subset of the control group from the Genetic Risk and Outcome of Psychosis (GROUP) study [53]. Controls were selected through a system of random mailings to addresses in the catchments areas of the schizophrenia cases. Inclusion criteria for the index subjects were: 1) age between 18 and 50 years, 2) no psychotic disorder and 3) no first or second degree relatives with psychosis. After complete description of the study, all participants provided written informed consent. The Family Interview for Genetic Studies (FIGS) was administered [40] to assess diabetes and psychiatric disorders including depression, mania, personality disorders and alcohol or drug abuse. Both the index subject and his or her mother were interviewed. This resulted in 33 completed interviews by the index subject and 33 completed interviews by his or her mother. The index subjects had a mean age of 32.5 years and 52% was male. Mothers had a mean age of 61.7 years. The 33 families comprised 507 relatives from three generations in whom information on diabetes and psychiatric disorders was obtained. Index subjects were members of the third generation and their mothers of the second generation.

We assumed that a disorder was present if at least one of the informants responded positively. To compare the disease rates of diabetes and psychiatric disorder reported by the index subjects with the disease rates reported by the mother, the McNemar's Test for comparing dependent samples was used as the mothers and the index subjects reported on the same family members. In contrast, the effect of gender and psychiatric status on the assessment of family history was tested with a chi-squared test for independent samples. Data were analyzed using R version 2.12.0 for Windows software.

Results

All results are summarized in **Table 2.1**. In total 22 of the 451 relatives were reported to have diabetes according to at least one of the informants. Of these 22 relatives, the mother identified 19 of the 22 (86%) family members with diabetes and the subject identified 9 of the 22 (41%) family members with diabetes. The mother indicated significantly more family members with diabetes than the index subject ($\chi^2(1)=5.06$, $p=.02$). In total, mothers indicated 3.5% of the family members as having diabetes compared to 1.8% indicated by the index subject. For psychiatric disorders including depression, mania, personality disorders and alcohol or drug abuse, mothers and index subjects reported on 480 family members. The mother recognised 38 (88%) of the 43 cases and the index subjects 18 (42%) of the 43 cases. In total mothers indicated 7.0% of the family members as having a psychiatric disorder compared to 3.5% indicated by the index subjects. This implies that mothers report

significantly higher rates on psychiatric disorders compared to index subjects ($\chi^2(1)=12.03$, $p<.0005$).

Seventeen of the index subjects are male and sixteen are female. The male index subjects reported on 270 family members, while females reported on 240 family members. Male index subjects rated 1.9% of their relatives as having diabetes and 3.7% as having a psychiatric disorder. Female index subjects reported that 1.7% of their relatives had diabetes and 3.3% had a psychiatric disorder. There was no significant difference in the disease rates reported by male and female index subjects for diabetes ($\chi^2(1)=.03$, $p=0.86$) or psychiatric disorders ($\chi^2(1)=.01$, $p=0.91$).

Of the 33 mothers, 7 experienced a depressive episode and 26 did not. The mothers who experienced a depressive episode reported on 129 family members while mothers who did not have a depressive episode reported on 411 family members. Mothers who experienced a depressive episode indicated significantly more family members as having a psychiatric disorder (12.4%) than mothers who never experienced such an episode (5.8%) ($\chi^2(1)=5.25$, $p=.02$). No difference was found for diabetes ($\chi^2(1)=.25$, $p=.62$). Note that the rate of depression in the index subjects was low (N=3) and we could therefore not perform this analysis in index subjects.

Since depression is influenced by genetic factors, it is possible that the prevalence of depression is indeed higher in the families of the mothers with a depressive episode. We therefore compared the prevalences as reported by index subjects with a mother who experienced a depressive episode and index subjects with a mother who did not experienced such an episode. The prevalence of having a psychiatric disorder was 6.3% in index subjects of whom the mother had a depressive episode compared to a prevalence of 2.6% in index subjects with mothers who never had a depressive episode ($\chi^2(1)=2.80$, $p=.09$).

Table 2.1 | The reported rates of diabetes and psychiatric disorder assessed in different types of informants

		Diabetes N affected/total N (%)	Psychiatric disorder N affected/total N (%)
Index subjects		9/451 (2.0%)	18/480 (3.8%)
Mothers		19/451 (4.2%)	38/480 (7.9%)
	Statistics	$\chi^2(1)=5.06$, $p=.02$	$\chi^2(1)=12.03$, $p<.0005$
Male index subjects		5/270 (1.9%)	10/270 (3.7%)
Female index subjects		4/240 (1.7%)	8/240 (3.3%)
	Statistics	$\chi^2(1)=.03$, $p=0.86$	$\chi^2(1)=.01$, $p=0.91$
Mothers with depression		7/129 (5.4%)	16/129 (12.4%)
Mothers without depression		16/411 (3.9%)	24/411 (5.8%)
	Statistics	$\chi^2(1)=.25$, $p=.62$	$\chi^2(1)=5.25$, $p=.02$
Subjects with depressed mother		1/127 (0.8%)	8/127 (6.3%)
Subjects without depressed mother		8/383 (2.1%)	10/383 (2.6%)
	Statistics	$\chi^2(1)=.33$, $p=.56$	$\chi^2(1)=2.80$, $p=.09$

Discussion

We have studied family history interview data on diabetes and psychiatric disorders assessed both in an index subject and in his or her mother and showed that mothers report significantly higher disease rates. As disease status was not confirmed by clinical diagnosis we do not have a gold standard for comparison. However, the percentages as reported by the mother closely resembled the prevalence of diabetes (3.9%[2]) for the global Dutch population in 2008 provided by the Dutch state institution for health and environment. Although the family history interview was administered to assess depression, mania, personality disorders and alcohol or drug abuse, the majority of the family members indicated as having a psychiatric disorder were suffering from depression. The reported prevalence of depression by the mothers resembles the lifetime risk of 10% mentioned by Andrews et al [54]. These findings indicate that the mothers in this study were likely to be more valid informants.

Index subjects had slightly more difficulty with identifying family members with diabetes than family members with psychiatric disorders. This is in contrast with the finding of Milne et al [51] who report that information collected on a physical disorder like asthma is more valid than information about psychiatric diseases. This can possibly be explained by the fact that the occurrence of a somatic disease such as diabetes is more common in elderly (i.e. first generation) family members and therefore unknown by the young index subjects (i.e. third generation). So the finding by Bensen et al [44,44] that older subjects are less accurate informants than younger ones may be explained by generation rather than age.

Previous research shows that gender, personal history of psychiatric disorder and age of the informant influences the validity of data collection [44,46–51]. In contrast to the findings of Milne et al [51], gender did not appear to influence the reliability of the collection of family history data in our study. In agreement with earlier findings, we showed that mothers who had a depressive episode reported significantly higher rates of depression in their family members than mothers who never had a depressive episode. This finding could be due to informant bias but may also result from the fact that depression is a heritable disorder. The latter hypothesis was supported by the finding that index subjects with a mother who experienced a depressive episode also reported higher rates of a psychiatric disorder compared to index subjects who did not have a mother who experienced a depressive episode. In the index subjects themselves it was not possible to compare subjects with or without psychiatric disorder as only 3 of the 33 subjects ever experienced a depressive episode.

[2] http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/endocriene-voedings-en-stofwisselingsziekten-en-immuniteitsstoornissen/diabetes-mellitus/verschillen-internationaal/

In addition to the absence of a gold standard for clinical diagnosis, a second limitation of this study is the fact that the family history interviews were conducted in a cohort of subjects selected for the absence of psychosis in the family. As the presence of mania, personality disorders and alcohol or drug abuse was low, we mainly focused on depression. Future studies should reveal if the results can be generalized to families with psychosis.

In conclusion, studying the collection of family history in a pedigree consisting of three generations, members of the second generation were shown to provide more valid information on family history data compared to the third generation. It could therefore be hypothesized that it is not age, but generation which influences the validity of family history data collection. Our findings suggest that interviewing mothers on her own generation, the previous generation and the next generation, is to be preferred over interviewing the younger index subjects. In addition, psychiatric status of the informant should be carefully addressed, although we have not conclusively shown a reporter bias in informants suffering from a psychiatric disorder.

Chapter 3

The calculation of familial loading in schizophrenia

Eske M. Derks, Kim H.W. Verweij, René S. Kahn, Wiepke Cahn

Schizophrenia Research, 2011; 111 (1-3): 98-99.

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Letter to the Editors

The calculation of familial loading in schizophrenia

Dear Editors,

Patients with a familial form of schizophrenia have a poor outcome [18,21], and a lower age of onset [21] compared to sporadic cases. The distinction between familial and sporadic cases is particularly important in the context of gene-finding studies as the statistical power in these studies could be increased by focusing on patients with a high familial loading. The distinction between familial and sporadic cases can be made by a simple classification of patients based on the presence or absence of affected relatives. However, this fails to take into account the number of relatives and the age of the relatives. Verdoux and colleagues [18] developed an algorithm to calculate the familial loading while taking the number and age of the relatives into account.

Although the algorithm developed by Verdoux and colleagues substantially improves the calculation of familial loading, there are still a number of limitations. Firstly, in this algorithm, the probability that a relative is affected increases linearly from age 15 to 50 years. However, the risk to develop schizophrenia is particularly high between the ages 20 and 30 years [21]. Secondly, the relation between age and risk of illness is not mediated by sex even though it has been shown that males have an earlier age of onset [4] and a higher risk of illness [5] compared to females. Finally, the algorithm of Verdoux and colleagues [18] can only be applied to data of first-degree relatives. In this letter, we describe an algorithm that i) allows for a nonlinear increase in risk of illness; ii) takes sex differences into account; and iii) can be applied to data of first- and second degree relatives. The R code that was used in this paper is available on request from the corresponding author.

The calculation of the likelihood for whether a patient is a familial or a sporadic case consists of three steps. Firstly, functions which describe the relation between the relative's risk of illness as a function of the relative's age, degree of relatedness and sex need to be developed. We assume that the life-time risk of illness is .10 in male first-degree relatives of familial probands and .005 in male first-degree relatives of sporadic probands. In second degree male relatives, the lifetime risks are assumed to be .05 and .0075, for familial and sporadic probands, respectively. The life-time risks in females are assumed to be 1.5 times smaller compared to the life-time risks in males. The exact functions as used in this paper, and the graphical representations of these functions, are available on request from the corresponding author.

A second step is to use Bayes' theorem to calculate the likelihood for whether the proband is familial or sporadic based on the risk of illness in each relative. In **Table 3.1**, we show the likelihood ratios for affected and unaffected relatives as a function of degree of relatedness and sex. As age is part of the likelihood ratio function, we included the likelihood ratios for relatives of 25 and 40 years for illustrative purposes. The third and final step in the calculation of the overall likelihood ratio for the proband is to multiply the likelihood ratios of all individual relatives.

Likelihood ratios larger than one should be interpreted as evidence for the patient being a familial case while likelihood ratios smaller than one should be interpreted as evidence for the patient being a sporadic case. For example, if the proband has an affected female relative of age 25 years, it is 20 times more likely that this proband is a familial case instead of a sporadic case. If the proband has an unaffected male relative of 40 years of age it is 1/.91=1.10 more likely that the proband is a sporadic case instead of a familial case. Familial loading is measured on a probability scale, and does not need to be dichotomized, as would be the case if a simple distinction is made between probands with or without affected relatives. However, if one wishes to dichotomize scores, for example in clinical decision making, the likelihood ratios can be dichotomized by assigning patients with a likelihood ratio larger than one to a familial group and patients with a likelihood ratio smaller than one to a sporadic group.

One limitation of this method is that it is based on the assumption that two different forms of schizophrenia exist: a familial form and a sporadic form. It is possible that these two forms of schizophrenia actually form the two extremes of a continuum, ranging from a highly familial form (e.g., being caused by common genes which run in families) to a highly sporadic form (e.g., being caused by rare genetic mutations).

Table 3.1 | Likelihood ratio's for whether the proband has the familial vs. sporadic form of schizophrenia as a function of the relative's status (i.e., affected vs. unaffected), age, and sex

Relative		Sex	Likelihood ratio as a function of age	Age=25	Age=40
Affected	First degree	Male	.05*(1+((y1-25)/((50 + (y1-25)^2)^.5)))/ .05*.05*(1+((y1-25)/((50 + (y1-25)^2)^.5)))	20	20
		Female	.04*(1+((y1-30)/((50 + (y1-30)^2)^.5)))+.01*(.8+((y1-55)/((60+(y1-55)^2)^.5)))/ .05*(.04*(1+((y1-30)/((50 + (y1-30)^2)^.5)))+.01*(.8+((y1-55)/((60+(y1-55)^2)^.5))))	20	20
	Second degree	Male	.5*.05*(1+((y1-25)/((50 + (y1-25)^2)^.5)))/ .075*.05*(1+((y1-25)/((50 + (y1-25)^2)^.5))	6.667	6.667
		Female	.5*(.04*(1+((y1-30)/((50 + (y1-30)^2)^.5)))+.01*(.8+((y1-55)/((60+(y1-55)^2)^.5))))/ .075*(.04*(1+((y1-30)/((50 + (y1-30)^2)^.5)))+.01*(.8+((y1-55)/((60+(y1-55)^2)^.5))))	6.667	6.667
Unaffected	First degree	Male	(1-(.05*(1+((y1-25)/((50 + (y1-25)^2)^.5))))) / (1-(.05*.05*(1+((y1-25)/((50 + (y1-25)^2)^.5)))))	.952	.909
		Female	(1-(.04*(1+((y1-30)/((50 + (y1-30)^2)^.5)))+.01*(.8+((y1-55)/((60+(y1-55)^2)^.5))))) / (1-(.05*(.04*(1+((y1-30)/((50 + (y1-30)^2)^.5)))+.01*(.8+((y1-55)/((60+(y1-55)^2)^.5))))))	.990	.954
	Second degree	Male	(1-(.5*.05*(1+((y1-25)/((50 + (y1-25)^2)^.5))))) / (1-(.075*.05*(1+((y1-25)/((50 + (y1-25)^2)^.5)))))	.996	.959
		Female	(1-(.5*(.04*(1+((y1-30)/((50 + (y1-30)^2)^.5)))+.01*(.8+((y1-55)/((60+(y1-55)^2)^.5)))))) / (1-(.075*(.04*(1+((y1-30)/((50 + (y1-30)^2)^.5)))+.01*(.8+((y1-55)/((60+(y1-55)^2)^.5))))))	.994	.980

Chapter 4

The association between intelligence scores and family history of psychiatric disorder in schizophrenia patients, their siblings and healthy controls

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PLoS One, 2013; 8(10): e77215

Abstract

Background

The degree of intellectual impairment in schizophrenia patients and their relatives has been suggested to be associated with the degree of familial loading for schizophrenia. Since other psychiatric disorders are also more present in relatives of schizophrenia patients, the definition of family history should be broadened. The association between family history for psychiatric disorder and intelligence scores was investigated in patients with non-affective psychosis, their unaffected siblings and controls.

Methods

A sample of 712 schizophrenia proband families (696 patients and 766 siblings) and 427 healthy control families (517 subjects) participated in this study. Family history of psychiatric disorder was determined while excluding the data of the participating schizophrenia patient. A dichotomous division was made between families with no first- or second degree relative with psychiatric disorder and families with one or more affected relatives. Total intelligence scores were estimated by admission of the short form of the Wechsler Adult Intelligence Scale III.

Results

A significant interaction was found between family history of psychiatric disorder and clinical status ($F(2,1086.87)= 4.17$; $p=.016$). Patients with a positive family history of psychiatric disorder obtained higher intelligence scores compared to patients with no family history (mean IQ scores are 95.52 and 92.72) with an opposite effect in controls (mean IQ scores are 108.71 and 111.19). No significant difference was found between siblings of schizophrenia patients with or without a positive family history (mean IQ scores are 102.98 and 103.24).

Conclusion

In patients with schizophrenia, a negative family history of psychiatric disorder was associated with relatively low IQ suggesting that the aetiology in these patients may involve environmental or genetic factors which are unique to the patient and are not observed in other relatives. Possible factors include severe environmental stressors containing premature birth or brain injury and genetic factors (e.g de novo Copy Number Variants).

Introduction

Schizophrenia is characterized by general intellectual deficits. A consistent finding is an impaired IQ score in patients compared to controls [55–57]. These lower IQ scores can be present prior to the manifestation of the illness [58] and persist in most patients despite improvement of symptoms. Poor cognitive performance has also been found in siblings as compared to healthy control subjects [59,60] and in offspring of patients with schizophrenia [61–63]. These findings suggest that intellectual impairment in schizophrenia has a familial component and can be seen as a genetically mediated risk indicator for schizophrenia [64]. Moreover, lower IQ scores in patients are also seen in other psychiatric disorders such as affective, personality and anxiety disorders [65].

It has been hypothesized that the degree of intellectual impairment is associated with the degree of genetic loading [66]. Since there is no golden standard measure for genetic loading, family history data for psychosis or schizophrenia are frequently used. A group of special interest are those families densely affected by psychosis. Maziade and colleagues demonstrated that patients and unaffected relatives from such families have lower global IQ scores compared to healthy controls [67]. Remarkably, these findings are not exclusive for patients and relatives from densely affected families. Schizophrenia patients with only one affected relative also have impaired IQ scores compared to healthy controls [68] as well as unaffected subjects with one first- or second-degree relative with schizophrenia [69–71]. Only a few studies (n=56-154 subjects) have compared IQ scores between schizophrenia patients with and without relatives affected by psychosis [22,72,73]. Interestingly, most of these studies did not detect a difference between full scale IQ scores for patients with or without affected relatives in the family [72,73]. This is consistent with the conclusion that there are few robust neurocognitive differences between schizophrenia patients with and without relatives affected by psychosis [74,75]. However, Norman and colleagues found higher IQ scores in patients without affected relatives [22].

Although previous studies have assessed family history based on the number of individuals with psychosis, recent findings indicate that the risk of clinically diagnosed schizophrenia is associated with a family history of a much wider range of psychiatric disorders [76]. Moreover, a variety of other psychiatric disorders are often present in relatives of patients with schizophrenia [30]. High rates of axis I disorders such as attention deficit hyperactivity disorder, mood disorder and anxiety disorder have been shown in offspring and siblings from patients with schizophrenia [31–33]. Also, major depressive disorder and substance abuse are frequently reported in first degree relatives of first episode psychotic patients [30] and finally, relatives have an increased prevalence of schizotypal, paranoid, schizoid and avoidant personality disorder [77]. This implies an increased vulnerability for a wide variety of psychiatric disorders in families of schizophrenia patients. The increased vulnerability

for various psychiatric disorders is further supported by recent findings indicating that the genetic risk factors for schizophrenia are partly shared with the genetic vulnerability for other psychiatric disorders including bipolar disorder [35], depression [36], schizoaffective and manic disorder [34]. Therefore, it could be hypothesized that the definition of familial loading based on the presence or absence of psychosis in families of patients with schizophrenia should be broadened by focusing on psychiatric disorder in general irrespective of a specific diagnosis.

Since impaired IQ scores are found in different psychiatric disorders and various psychiatric disorders are often present in relatives of patients with schizophrenia, the aim of this study is to investigate the association between family history for psychiatric disorder and IQ in schizophrenia patients, their non-psychotic siblings and healthy controls. Family history of psychiatric disorder was determined based on the presence or absence of psychiatric disorder in the first- and second-degree relatives of 717 schizophrenia patient families and 427 healthy control families.

Methods

Subjects

The data pertain to baseline measures of an ongoing longitudinal multicenter study Genetic Risk and Outcome in Psychosis (GROUP) [39]. The sample was recruited in the Netherlands and Belgium. Patients with non-affective psychosis were identified through clinicians working in regional mental health services whose caseloads were screened for inclusion criteria. Subsequently, a group of patients presenting consecutively at these services as either outpatients or inpatients were recruited for the study. Family members were recruited through participating patients. Healthy controls were selected through a system of random mailings to addresses in the catchment areas of the patients. Inclusion criteria were (1) age range of 16 to 50 years; (2) good command of the Dutch language; and (3) being able and willing to give informed consent. Patients had to meet the DSM-IV criteria for non-affective psychotic disorder, as assed by clinical interview with the Comprehensive Assessment of Symptoms and History (CASH) [78]. The unaffected sibling and healthy control status was defined by the absence of any lifetime psychotic disorder by CASH interview. An additional inclusion criterion for the control group was no first or second degree relatives with psychotic disorder.

At baseline, the total GROUP sample consisted of 1120 patients with non-affective psychotic disorder, 1057 of their siblings and 590 unrelated controls. For the present study we excluded data from participants with incomplete information on family history of psychiatric disorder. This resulted in the exclusion of 239 patients, 153 siblings and 62 controls. In

addition, IQ scores were missing or incomplete for 46 patients, 15 siblings and 6 controls and these subjects, therefore, were also excluded from this study. Patients (n=139) and their siblings (n=123) with missing DSM IV diagnosis or a diagnosis of delusional disorder or psychotic disorder in the context of substance abuse or somatic disorder were excluded because the relationship with impaired cognitive functioning and increased vulnerability for psychiatric disorder is unclear. Finally, there were 5 healthy controls with a first- or second-degree relative with psychosis: they were excluded as they did not meet inclusion criteria. In total 696 patients, 766 siblings from 712 families and 517 healthy controls from 427 families participated in the study. The patients had a mean age of 27.0 years (SD=7.1) and 78% was male. Siblings had a mean age of 27.5 years (SD=8.1) and 46% was male. Controls had a mean age of 30.4 years (SD=10.6) and 46% was male. The majority of the patients (81%) were diagnosed with schizophrenia, while the remaining patients were diagnosed with schizophreniform disorder (6%), brief psychotic disorder (2%) or psychotic disorder not otherwise specified (11%). The majority of the siblings (86.8%) and controls (90.7%) had no lifetime psychiatric diagnosis. The remaining siblings were diagnosed with depression (11.5%), bipolar disorder (0.7%), autism (0.4%), adjustment disorder (0.3%), anorexia nervosa (0.3%) and personality disorder (0.1%). The remaining controls were diagnosed with depression (8.7%), bipolar disorder (0.2%), adjustment disorder (0.2%) and obsessive compulsive disorder (0.2%).

Ethics statement

The study was approved by the standing ethics committee "Medisch Ethische Toetsingscommissie (METC) Utrecht". All of the subjects gave written informed consent in accordance with the committee's guidelines. When participants aged 16 or 17 were included, written informed consent was also given by a parent or caretaker. Patients with non-affective psychosis were identified through clinicians working in regional mental health services. These clinicians assessed if patients were mentally competent and asked if they were interested in the study. When they were interested, the study was verbally explained to them by a research employee and the informed consent was given to the patient to read at home. Only when the patient was willing to participate in the study, the family members were approached. Participation in this study was not interfering with treatment. All potential participants who declined to participate or otherwise did not participate were eligible for treatment (if applicable) and were not disadvantaged in any other way by not participating in the study.

Family history of psychiatric disorder

The Family Interview for Genetic Studies (FIGS) was administered [40] to assess the presence of psychiatric disorders including psychosis, depression, mania and alcohol or drug abuse. In

patient families, the first informant of choice for the FIGS interview was the mother. When the mother was not willing or able to provide family history information, the father or sibling of the patient was interviewed. In control families, family history information was usually provided by the participating control. As this may cause systematic differences between patient and control families, a subset (N=33) of the mothers from the healthy controls was approached and interviewed using the FIGS. Family history of psychiatric disorder was determined while excluding the data of the participating schizophrenia patient. In patients, relatives as well as in controls a dichotomous division was made between individuals with no first or second degree relative with psychiatric disorder (excluding the proband schizophrenia patient) and individuals with one or more affected relatives. A within and not a between group comparison was made. That is, in patients a comparison is made between patients with and without affected relatives. In siblings, siblings with a single affected relative were compared to siblings with multiple affected relatives. The same comparison was made for controls. No comparisons were made between patients on the one hand and siblings or controls on the other hand. Since controls were selected for absence of psychosis in first and second degree relatives, the positive family history group in controls comprises family members affected with depression, mania and alcohol or drug abuse.

IQ

Total IQ was estimated by admission of the short form of the Wechsler Adult Intelligence Scale III (WAIS III) [79]. All participants completed the subscales Arithmetic, Digit Symbol-Coding, Block Design and Information [80]. Following the example of Blyler (2000), IQ was calculated by the weighted average of the scaled scores multiplied by 11/4 as the WAIS comprises 11 subscales to calculate total IQ scores while only 4 of them are completed by the participant.

Analysis

Data were analyzed using SPSS version 20.0 for Windows. To investigate differences in demographic variables, ANOVA was used for continuous variables and χ^2 test was used for categorical variables. The main outcome measure in this study is the IQ score of patients, siblings, and controls with and without a family history of psychiatric disorder. Linear Mixed model analysis was used to investigate differences in IQ scores including clinical status, family history for psychiatric disorder (present/absent), and the interaction effect between clinical status and family history as independent variables while controlling for dependency of the data due to familial relatedness. As a covariance type, compound symmetry was used. Gender and psychiatric diagnosis of the subject were included as covariates in this analysis. A type-I error rate of 0.05 was used.

Results

Sample

Patients and siblings with a family history of psychiatric disorder were significantly younger compared to patients (F(1,695)=7.72; p=.01) and siblings (F(1,765)=4.40, p=.04) with no family history. However, the differences are small. The mean age in patients with and without a family history is 26.5 years [25.9-27.1] and 28.2 years [27.1-29.2], respectively, while the respective mean ages of siblings are 27.1 years [26.4-27.8] and 28.4 years [27.4-29.4]. In controls, age was not significantly different for participants with and without a family history of psychiatric disorder. We investigated whether age of onset differences explained the significant difference in age between patients with and without affected relatives. Age of onset was not significantly different between patients with and without relatives affected by psychiatric disorder and we therefore did not include age of onset as a covariate in statistical analyses. In siblings with a family history of psychiatric disorder the highest degree of education was lower and the prevalence of a lifetime diagnosis for a psychiatric disorder was significantly higher compared to siblings with a negative family history of psychiatric disorder. No such differences were found between patients or controls with and without a family history of psychiatric disorder. Gender, parental education and gross income a month were not significantly different between family history groups. The proportion of patient families assigned to the group with a family history of psychiatric disorder (70%) was higher than the proportion of control families (43%) which is expected as schizophrenia is associated with an increased prevalence of psychopathology in the relatives of patients. Sample characteristics of the patient and control families and the participating patients, siblings and controls in the positive and negative family history groups are summarized in **Tables 4.1 and 4.2.**

Table 4.1 | Descriptives of the negative (FH-) and positive (FH+) family history groups

	FH- patient families	FH+ patient families	FH- control families	FH+ control families
Number of families	214	498	244	183
Mean amount of family members	17.84 (SD=7.44)	18.31 (SD=7.10)	18.46 (SD=8.76)	18.26 (SD=7.32)
Relatives with psychosis	n.a.	N=219 (2.40%)	n.a.	n.a.
Relatives with depression	n.a.	N=789 (8.65%)	n.a.	N=258 (7.72%)
Relatives with mania	n.a.	N=68 (0.75%)	n.a.	N=14 (0.42%)
Relatives with substance abuse	n.a.	N=208 (2.28%)	n.a.	N=64 (1.92%)

Table 4.2 | Descriptives of the participants in the negative (FH-) and positive (FH+) family history group

				Statistics		
		FH -	FH +	*F (df=1)*	*X^2(df=1)*	*p*
Patients	**N**	207	489			
	Age	28.17 (SD=7.78)	26.54 (SD=6.77)	7.72		.01
	Gender, male	78.3%	77.9%		.01	.92
	Education, highest degree[a]	4.20 (SD=2.09)	3.94 (SD=2.03)		2.47	.12
	Parental education[a]	4.64 (SD=2.18)	4.52 (SD=2.20)		.34	.56
	Gross income a month[b]	1.14 (SD=.79)	1.08 (SD=.78)		0.58	.45
	Mean IQ score	92 (SD=15.7)	95 (SD=16.1)	4.47		.04
	Diagnosis, % schizophrenia	N=172 (83.1%)	N=394 (80.6%)		.61	.44
	Age of onset first psychosis	22.9 (SD=7.1)	21.9 (SD=6.4)	3.22		.07
Siblings	**N**	241	525			
	Age	28.40 (SD=7.82)	27.09 (SD=8.07)	4.40		.04
	Gender, male	49.0%	45.1%		.97	.33
	Education, highest degree[a]	5.31(SD=2.02)	4.98 (SD=2.13)		3.81	.05
	Parental education[a]	4.64 (SD=2.19)	4.58 (SD=2.25)		.10	.75
	Gross income a month[b]	1.93 (SD=.87)	1.80 (SD=1.01)		1.97	.16
	Mean IQ score	103 (SD=16.1)	102 (SD=15.4)	.00		.95
	Lifetime diagnosis, % yes	N=19 (7.9%)	N=82 (15.6%)		8.6	.00
	No diagnosis	N=222 (92.1%)	N=443 (84.4%)			
	Bipolar	n.a.	N=5 (1.0%)			
	Depression	N=18 (7.5%)	N=70 (13.3%)			
	Other[c]	N=1 (0.4%)	N=7 (1.3%)			
Controls	**N**	304	213			
	Age	30.38 (SD=11.10)	30.45 (SD=9.85)	.01		.94
	Gender, male	45.1%	46.0%		.05	.83
	Education, highest degree[a]	5.30 (SD=1.75)	5.59 (SD=1.75)		3.44	.06
	Parental education[a]	4.20 (SD=2.17)	4.42 (SD=2.22)		1.25	.26
	Gross income a month[b]	1.85 (SD=.86)	1.68 (SD=1.04)		2.82	.09
	Mean IQ score	111 (SD=14.8)	108 (SD=15.1)	3.47		.06
	Lifetime diagnoses, % yes	N=30 (9.7%)	N=18 (8.5%)		.30	.59
	No diagnosis	N=274 (90.1%)	N=195 (91.5%)			
	Bipolar	n.a.	N=1 (0.5%)			
	Depression	N=30 (9.9%)	N=15 (7.0%)			
	Other[c]	n.a.	N=2 (0.9%)			

Mean values are given for age, education, income, IQ and age of onset [95% confidence interval]
[a] Education (Verhage): range 0 (no education), 3-5 (school diploma) to 8 (university degree).
[b] Gross income a month: 1= minimal or below, 2= above minimal, below modal, 3= above modal
[c] Other diagnosis: depression, bipolar disorder, autism, adjustment disorder, anorexia nervosa, personality disorder and obsessive compulsive disorder

IQ

Schizophrenia patients obtained lower IQ scores (mean=94.69 [93.53-95.85]) compared to controls (mean=110.17 [108.82-111.51]) with intermediate scores in the siblings of schizophrenia patients (mean=103.06 [101.95-104.16], F(2,1978)=149.2; p<.001). IQ distribution of patients, siblings and controls is shown in **Figures 4.1, 4.2 and 4.3**. Comparison of IQ scores in individuals with and without a family history of psychiatric disorder revealed a significant interaction between family history and clinical status (F(2,1086.87)= 4.17; p=.016). In patients, the presence of psychiatric disorder in the pedigree was associated with higher IQ scores, while in controls the presence of psychiatric disorder was associated with lower IQ scores (see **Figure 4.4**). No significant difference was found between siblings of schizophrenia patients with or without a positive family history.

The analysis was repeated in the subset of control families where the mothers provided family history information. The results revealed similar IQ differences in controls with and without family history for psychiatric disorder with highest IQ scores in controls without a family history for psychiatric disorder.

Post hoc analyses were conducted to investigate if the significant differences in total IQ scores can be explained by specific subscales. These analyses demonstrate that the mean differences between familial loading groups had the same direction for all subscales and are therefore the result of differences in cognitive performance in all domains (data not shown).

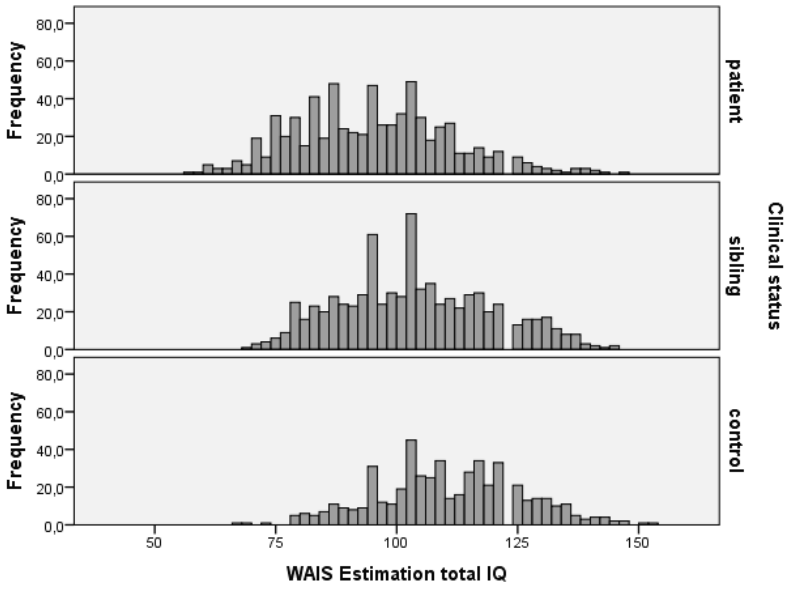

Figure 4.1 | IQ distribution for patients, siblings and controls
Mean IQ patients=94.69 [93.49-95.88], mean IQ siblings=103.06 [101.95-104.17], mean IQ controls=110.17 [108.88-111.46]

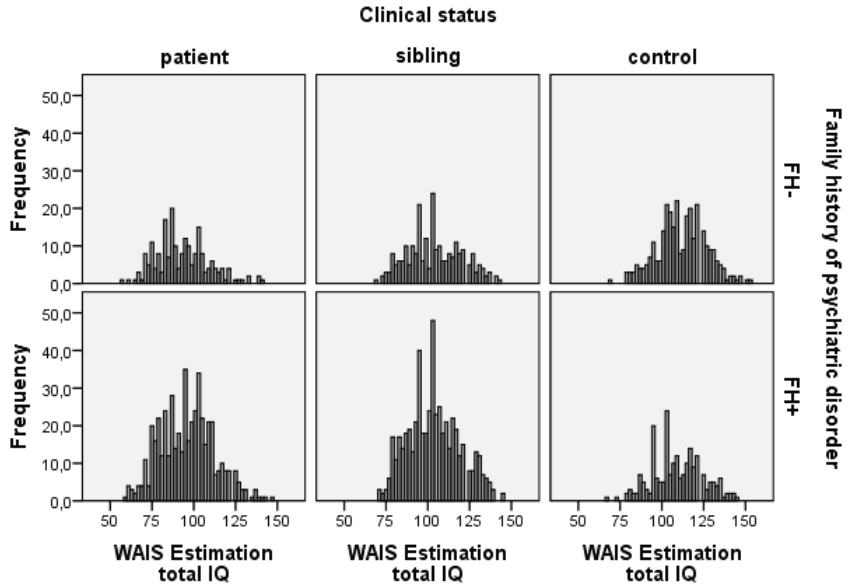

Figure 4.2 | IQ distribution for patients, siblings and controls with and without affected relatives

FH+ patients mean IQ=95.52 [94.08-96.95], FH- patients mean IQ=92.72 [90.57-94.88]
FH+ siblings mean IQ=102.98 [101.65-104.30], FH- siblings mean IQ=103.24 [101.19-105.29]
FH+ controls mean IQ=110.17 [108.71-110.76], FH- controls mean IQ=111.19 [109.52-112.85]

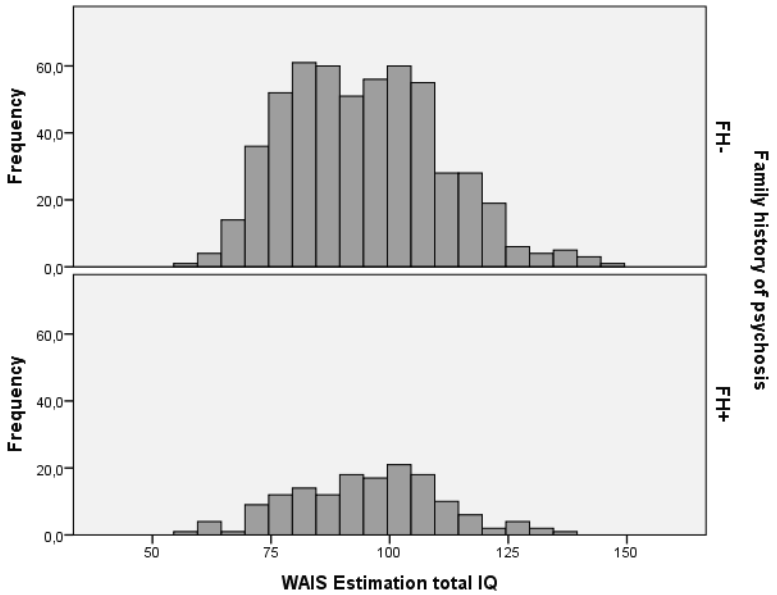

Figure 4.3 | IQ distribution for patients with and without relatives with psychosis

FH- patients (n=544) mean IQ=94.53 [93.17-95.89], FH+ patients (n=152) mean IQ=95.23 [92.71-97.75]

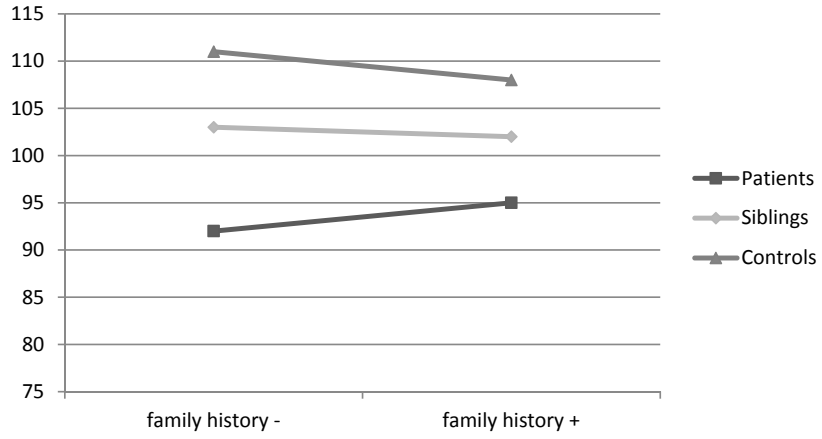

Figure 4.4 | Interaction between family history and subject status
Schizophrenia patients obtained lower IQ scores (mean=94.69 [93.49-95.88]) compared to controls (mean=110.17 [108.88-111.46]) with intermediate scores in the siblings of schizophrenia patients (mean=103.06 [101.95-104.17]). A significant interaction was found between family history of psychiatric disorder and clinical status ($F(2,1086.87)=4.17$; $p=.016$). Patients with a positive family history of psychiatric disorder obtained higher intelligence scores compared to patients with no family history (mean IQ scores are 95.52 [94.08-96.95] and 92.72 [90.57-94.88], respectively) with an opposite effect in controls (mean IQ scores are 108.71 [106.67-110.76] and 111.19 [109.52-112.85], respectively). No significant difference was found between siblings of schizophrenia patients with or without a positive family history (mean IQ scores are 102.98 [101.65-104.30] and 103.24 [101.19-105.29], respectively)

Discussion

The relationship between family history of psychiatric disorder and IQ was analyzed in 712 schizophrenia proband families (696 patients and 766 siblings) and 427 healthy control families (517 subjects). Patients obtained lower IQ scores compared to controls with intermediate scores in the siblings. A significant interaction was found between family history of psychiatric disorder and clinical status in the sense that patients with a positive family history of psychiatric disorder obtained higher IQ scores, while controls with a positive family history of psychiatric disorder obtained lower IQ scores. No significant association between family history and IQ was found in the siblings of patients with psychosis.

Patients with one or more affected relatives obtained higher IQ scores compared to patients who are the only affected subject in the family. This finding is inconsistent with previous studies that found no difference in full scale IQ between patients with or without affected relatives [72,73] or found higher IQ scores in patients without affected relatives in the family [22]. These inconsistencies could be explained by differences in recruitment strategies, sample size, definition of full scale IQ and study design. The most important difference

between this study and previous studies is that this study focuses on family history for all psychiatric disorders and not only on psychosis. Limiting the definition of family history to psychosis could have underestimated the psychopathology risk in families. Since impaired cognitive functioning is found in other psychiatric disorders besides psychosis, some of the individuals with impaired cognitive functioning due to their family history for psychiatry in general but not for psychosis would previously have been assigned to an incorrect group. This is strengthened by a sensitivity analysis in which family history was restricted to psychosis only. This analysis demonstrated no significant differences between IQ scores for patients and siblings with and without family history of psychosis, consistent with previous research [66,72,73]. Unfortunately, controls could not be included in this analysis since controls were selected only if no psychosis was present in their first and second degree relatives.

The lower IQ scores in patients with a negative family history of psychiatric disorder may suggest that the aetiology in these patients involves environmental or genetic factors which are unique to this patient and which are not present in the other individuals in the same pedigree. Possible factors include severe environmental stressors including brain injury or premature birth which have been shown to be associated with the risk of schizophrenia [81,82] as well as impaired intellectual functioning [83,84]. Alternatively, genetic factors such as de novo Copy Number Variants (CNVs) may be involved as CNV burden has been found to be increased in schizophrenia patients [10] and is also associated with impaired intellectual functioning. We may hypothesize that patients with no family history of psychiatric disorder more often carry a de novo CNVs compared to patients with a family history of psychiatric disorder. This is supported by the findings of Xu and colleagues who report significantly increased rates of de novo CNVs in schizophrenia patients who are the only affected subject in the family compared to schizophrenia patients with multiple affected relatives [85]. Since increased CNV rates have also been found to be associated with intellectual disability [86], it could be hypothesized that the lower IQ scores in patients without affected relatives reflect an increased vulnerability to CNVs in this group. The notion that individual risk factors together cause the onset of psychosis is supported by recent articles stating that schizophrenia can be seen as a neurodevelopmental disorder in which brain development is disturbed by (epi)genetic and environmental factors eventually leading to psychosis [74,87]. This neurodevelopmental approach is applicable for a variety of psychiatric disorders. The group of patients without relatives affected by any psychiatric disorder included in this study forms an interesting sample to learn about differences between psychosis and other related psychiatric disorders. Studying a sample like this is useful in unraveling the clinical, etiological and pathological overlap from schizophrenia with other psychiatric disorders [88].

There was no association between family history of psychiatric disorder and IQ in siblings. This finding is consistent with a previous study that demonstrated no differences in IQ scores between first degree relatives with one or more relatives with schizophrenia [66]. IQ scores

in siblings appear to be influenced by the genetic vulnerability for the disorder since siblings - as a group - consistently obtain lower IQ scores as compared to healthy controls. Since the association between IQ scores and family history of psychiatric disorder in siblings is not extensively investigated, more research is needed to further address this question.

Several limitations of this study should be considered. First, the operationalization of family history of psychiatric disorder is limited to psychosis, depression, mania and substance abuse. Although these are common disorders, family history scores could have been different when anxiety and developmental disorders such as autism would have been taken into account. Second, it was not documented which family member provided family history information. In patients, this would usually be the mother of the patient. Informant differences could potentially influence the reliability of the collected information since previous research indicates that a person with a central position in the pedigree should be the informant of choice [89]. However, the impact on the findings of this study is expected to be small because we would not expect this informant bias to be different in families with and without a family history of psychiatric disorder. This was also supported by the similar results that were found in the subset of control families where the mothers provided family history information. Third, family history information was based on an informant and not on clinical interviews. This might have caused some bias which is strengthened by the fact that 8% of the siblings and 10% of the controls in the group without family history had a psychiatric diagnosis as assessed by the CASH interview. It should be noticed that it is possible to meet DSM IV criteria for a psychiatric diagnosis according to the CASH interview without the experience of being mentally ill. This is confirmed by the fact that the majority of the siblings (90%) and half of the controls (52%) with a psychiatric diagnosis didn't receive treatment. Finally, the assessment of IQ was based on the short form of the WAIS. Although this short form seems to be a valid instrument and short forms has been used in previous studies, the estimation of IQ based on the full WAIS might have been slightly different since admission of this short form somewhat overestimates IQ scores [79].

This study provides evidence for increased cognitive impairment in schizophrenia patients without a family history of psychiatric disorder compared to patients with a positive family history. Impaired IQ scores are found in different psychiatric disorders and a variety of psychiatric disorders are often present in relatives of patients with schizophrenia. Following the example of Mortensen et al [76], the definition of family history was broadened by focusing on psychiatric disorder in general irrespective of a specific diagnosis. In controls the presence of psychiatric disorder was associated with lower IQ scores, while in patients the presence of psychiatric disorder in the pedigree was associated with higher IQ scores. We hypothesize that the lower IQ in patients with no family history of psychiatric disorder are explained by environmental or genetic factors which are unique in a pedigree. Possible factors include severe environmental stressors including premature birth or brain injury

and genetic factors (e.g. Copy Number Variants). These factors may increase the risk for schizophrenia but are also associated with intellectual disability. Further research is needed to test this hypothesis.

Chapter 5

Effect of illness expression and liability on familial associations of clinical and subclinical psychosis phenotypes

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Acta Psychiatrica Scandinavica, March 2013 (Epub ahead of print)

Abstract

Objective

Given the familial influences on schizophrenia, it may be hypothesized that specific symptom domains also cluster within families, and that this applies to both clinical and subclinical levels of expression. This hypothesis was put to the test in a group of patients with a DSM-IV diagnosis of psychotic disorder together with their unaffected siblings, and a group of healthy sib-pairs.

Method

Subclinical positive, negative and depressive symptoms in relatives and healthy controls were assessed with the Community Assessment of Psychic Experiences. Positive and negative schizotypy in relatives and controls was measured with the Structured Interview for Schizotypy-Revised. Multilevel linear regression analyses were conducted to investigate clustering of symptom dimensions within patient-relative sib-pairs (N=811 pairs), healthy sib-pairs of affected families (N=136 pairs), and healthy control sib-pairs (N=58 pairs).

Results

Familial clustering of symptoms was found in all three groups. Effect sizes were largest in healthy control sib-pairs, smallest in patient-relative sib-pairs, and intermediate in healthy sib-pairs of affected families.

Conclusion

Studies of sibling associations in genetic studies of psychometric expression of psychosis liability need to take into account the fact that the higher levels of background genetic risk and presence of diagnosed illness are inversely associated with sibling associations.

Introduction

The diagnosis of schizophrenia clusters within families [90], and first-degree relatives of patients show an increased prevalence of schizotypal personality disorder [91,92]. Familial clustering at the level of diagnostic constructs [93] has been followed-up by finer grained analyses examining familial continuity between *subclinical* dimensions of schizotypy and *clinical* dimensions of psychotic disorder [94,95]. These studies, analyzing associations between symptom dimensions or clinical diagnosis in patients, and corresponding schizotypal traits in first-degree relatives, generally have yielded small to moderate familial associations [94,96,97].

However, this type of patient-relative association may be difficult to interpret, as it may be attenuated by disease-specific environmental (e.g., medication use in patients) or genetic (e.g., risk genes that are present in the patient, but not in the unaffected relative) factors [98]. It is therefore important to additionally investigate and compare cross-sibling (subclinical) psychopathological associations in (i) healthy unaffected sib-pairs who have a further sibling with a diagnosis of psychotic disorder and (ii) sib-pairs from families without an affected first-degree relative. Although several psychopathological dimensions have been investigated across schizotypy and psychotic disorder phenotypes [99–103], the positive and negative symptom dimensions are the domains that are most consistently replicated across latent variable approaches.

We are aware of only a single study investigating cross-sibling associations of symptom dimensions in patients and their healthy relatives and comparing these familial associations to those found in healthy control sib-pairs. The authors report that familial associations for negative symptoms were greater in healthy control sib-pairs than in pairs consisting of a schizophrenia patient and his unaffected sibling [104]. These findings suggest that negative symptoms may represent only a weak indicator of genetic risk for the disorder and/or that cross-sibling associations may be confounded by disease-specific environmental factors like antipsychotic medication use in the patients.

In the current study, an attempt was made to control for possible disease-related confounding and the focus was on the arguably more homogenous symptom dimensions rather than the heterogeneous schizophrenia disease construct. To this end, three different groups were investigated with both self-report and interview-based questionnaires, collected as part of a large multisite study on Genetic Risk and Outcome in Psychosis (GROUP).

Aims of the study

To investigate familial clustering of the positive, negative, and depressive symptom dimensions in three groups: (i) patients with psychotic disorder and their healthy siblings, (ii) healthy sib-pairs of affected families, and (iii) healthy control sib-pairs. It was hypothesized that familial clustering would be strongest in healthy control sib-pairs and healthy sib-pairs of affected families, since these groups suffer the least illness-related confounding.

Material and Methods

Sample

Data were derived from the baseline measures of an ongoing longitudinal study (GROUP) in Europe. Patients were recruited from clinics/clinician referrals in selected representative geographical areas in the Netherlands and in Belgium. Persons identified as potentially eligible were given detailed explanation of the study procedures and were asked informed consent for detailed assessment and for contacting their first-degree family members (brothers, sisters, parents). Healthy controls were selected through a system of random mailings to addresses in the catchment areas of the patients [39].

The full GROUP sample (data release 2.0) consisted of 1100 patients, 1057 healthy siblings of these patients, 919 parents of these patients, 19 parents of patients who were also diagnosed with psychotic disorder, 562 healthy controls, and 27 parents of these healthy controls. The current analyses included the (i) patients with psychotic disorder and their healthy siblings (hereafter: patient sib-pairs), (ii) healthy sib-pairs of affected families (hereafter healthy sib-pairs OAF; 2 healthy brother(s) and/ or sister(s) of the patients included in the study), and (iii) healthy control sib-pairs.

Patients were included in the GROUP sample if they had a diagnosis of psychotic disorder in the schizophrenia spectrum (DSM-IV-TR code 295.x) or other psychotic disorder (DSM-IV-TR code 297/ 298). Another inclusion criterion, for patients, siblings, and controls was good command of the Dutch language. Diagnosis in the three groups was based on DSM-IV-TR [105] criteria assessed with the Comprehensive Assessment of Symptoms and History interview [78] or Schedules for Clinical Assessment for Neuropsychiatry version 2.1 [106].

Ethical issues

The standing Ethical Review Board approved the study protocol. After full verbal and written information about the study, written informed consent was obtained from all participants before the start of the first assessment. Confidentiality of data was maintained by using a

unique research ID for each respondent, which enables identification of individuals without the use of names or other identifiers.

Assessment of (sub)-clinical psychotic experiences in the whole sample

Self-reported (subclinical) psychotic experiences in the affective and non-affective domains were assessed with the previously validated Community Assessment of Psychic Experiences (CAPE) [107,108] (http://www.cape42.homestead.com/). The CAPE is based on the Peters *et al* Delusions Inventory [109], modified to also include hallucinatory experiences. For the current analyses, mean scores on frequency of positive, negative, and depressive symptoms were used (allowing a maximum of 30% missing values per subscale).

Interview-based scores on positive and negative subclinical psychotic symptoms were measured in the non-patients with the Structured Interview for Schizotypy-Revised (SIS-R) [110]. A mean score on the following items was entered in the analyses as "positive schizotypy" (30% maximum partially missing data allowed): referential thinking ("being watched" and "remarks"), suspiciousness, magical ideation, illusions, psychotic phenomena, and derealisation/depersonalization. A "negative schizotypy" variable was calculated by taking the mean score on the items social isolation, introversion, sensitivity, restricted affect, disturbances in associative and goal-directed thinking, poverty of speech, and eccentric behaviour (with a maximum of 30% missing data, conform previous analyses in this sample:[53]).

Analyses

Multilevel linear regression analyses using the XTREG command in STATA 11.2 (taking clustering at the family level into account) were conducted to test the difference in mean scores on the CAPE and SIS-R subscales in the three groups of patient-relative sib-pairs, healthy sib-pairs OAF, and healthy control sib-pairs.

Familial clustering of the CAPE in patient-relative sib-pairs

Multilevel linear regression analyses were conducted to test the association between CAPE positive, negative, and depressive subscale scores in the patients (hereafter CAPEpos_pat, CAPEneg_pat, and CAPEdep_pat, respectively), and CAPE subscale scores in the healthy siblings of these patients (variable names: CAPEpos_sib, CAPEneg_sib, CAPEdep_sib). Within-symptom dimension associations were tested in three different models: CAPEpos_sib= B0 + B1 CAPEpos_pat + Error; CAPEneg_sib= B0 + B1 CAPEneg_pat + Error; CAPEdep_sib= B0 + B1 CAPEdep_pat + Error. In addition, cross-symptom dimension associations were tested, such as CAPEpos_sib = B0 + B1 CAPEneg_pat + Error and CAPEpos_sib= B0 + B1 CAPEdep_pat + Error. All analyses in patient-relative sib-pairs were *a priori* controlled for sex, age, education level, ethnicity, illness duration in the patient, and clustering at the family

level. Only families who contributed at least 1 patient and 1 sibling were used for these analyses. To avoid duplication of redundant data, a single patient was chosen at random from families with multiple patients.

Familial clustering of the CAPE and SIS-R in healthy sib-pairs OAF and healthy control sib-pairs

Linear regression analyses were conducted in healthy sib-pairs OAF and healthy control sib-pairs to test the between-sibling associations on the different subscales of the CAPE and SIS-R (regression model: CAPE/SIS-Rsubscale_proband = B0 + B1 CAPE/SIS-R subscale_co-sibling + Error). Only families that contributed at least 2 unaffected siblings of patients with a non-affective psychotic disorder were used. To avoid duplication of redundant data, a single sibling pair was chosen at random from families with more than 2 siblings. Assignment of siblings as proband and co-sibling was also at random. Data for these analyses were in the wide-format with one observation per family (i.e., CAPE/ SIS-R scores in the proband and co-sibling presented on the same row in the dataset), and were therefore analyzed with the REGRESS command without controlling for clustering at the family level. Again, both within- and cross-symptom dimension associations were tested, *a priori* controlled for sex, age, education level, and ethnicity in the co-sibling. The same approach was used for healthy control sib-pairs.

Within-subject associations on subscales of the CAPE and SIS-R in siblings and controls

In addition to familial associations, within-subject associations were tested in healthy siblings of affected families and in healthy control sib-pairs across different symptom dimensions in separate multilevel linear regression models taking the family-level of clustering into account (e.g., CAPE/SIS-Rpos_sib1= B0 + B1 CAPE/SIS-Rneg_sib1 + Error).

Results

Descriptives

The total GROUP sample (release 2.0) comprised 491 healthy control families who contributed a total of 562 healthy control participants, and 1066 affected families who contributed 1100 patients with a non-affective psychotic disorder, and 1057 healthy siblings of these patients. Affected families contributed a single patient (209 families, 209 subjects), a single sibling (6 families, 6 subjects), a patient and a sibling (643 families, 1286 subjects), 2 patients (23 families, 46 subjects), 1 patient and 2 siblings (132 families, 396 subjects), 2 patients and 1 sibling (6 families, 18 subjects), 3 patients (2 families, 6 subjects), 1 patient and 3 siblings (30 families, 120 subjects), 2 patients and 2 siblings (5 families, 20 subjects), 3 patients and

1 sibling (1 family, 4 subjects), 1 patient and 4 siblings (8 families, 40 subjects), and 1 patient and 5 siblings (1 family, 6 subjects). Control families contributed a single healthy control participant (425 families, 425 subjects), a control sib-pair (61 families, 122 subjects), and a control sib-trio (5 families, 15 subjects).

Subsamples for familial analyses

For the patient-sib-pair analyses the following families and participants were excluded: (i) families contributing a single patient (209 families, 209 subjects); (ii) families contributing 2 patients but no siblings (23 families, 46 subjects), (iii) contributing 3 patients but no siblings (2 families, 6 subjects), and (iv) families contributing a single sibling (6 families, 6 subjects). Furthermore, for those families contributing more than one patient, one patient was randomly selected for the analyses (13 patients were randomly excluded). All participants who had missing data on either one of the dependent, independent or confounding variables were also excluded for these analyses, leaving a total of 811 pairs, contributing 641 patients, and 811 healthy siblings of these patients.

For the analyses of healthy sib-pairs OAF, only those families contributing at least 2 healthy siblings OAF where included, and again participants with missing data on the relevant variables were excluded, leaving data of 272 healthy sibs OAF for the analyses (136 pairs). For the analyses of healthy control sib-pairs, after similar selection as in the healthy sib-pairs OAF, data of 116 healthy control sibs (58 healthy control sib-pairs) remained.

Descriptive statistics for the different analyses are depicted in **Table 5.1**, and the mean scores on dependent and independent variables in **Table 5.2**. Patients and relatives differed significantly on all three dimensions of the CAPE. In the comparison between relatives and controls, a significant difference was apparent for the negative schizotypy subscale of the SIS-R (**Table 5.2**).

Familial clustering of the CAPE in patient-relative sib-pairs

The multilevel linear regression analyses testing the CAPE within-symptom dimension association across patients and their healthy siblings revealed small but significant associations (**Table 5.3**, marked in grey). Similarly, small but significant familial associations were found in the CAPE cross-symptom dimension analyses (**Table 5.3**).

Table 5.1 | Demographic and clinical characteristics.

	Patients (N=641)	Siblings (N=811)*	Siblings (N=272)**	Controls (N=116)
Age (years)	M=27.5 (SD=7.5), range 15-57	M=28.1 (SD=8.5), range 14-60	M=28.3 (SD=8.3), range 15-60	M=27.6 (SD=9.6), range 16-56
Gender	Male: 490 Female: 151	Male: 372 Female: 439	Male: 117 Female: 155	Male: 44 Female: 72
Ethnicity				
Caucasian	523	685	244	106
Other	116	125	28	10
Missing	2	1	-	-
Education level (highest degree)				
No education	4	1	1	-
Primary school	75	55	12	1
Secondary school	207	166	42	23
Highschool	168	158	55	35
Vocational education	162	329	121	51
University	25	98	40	6
Unknown	-	4	1	-
Average IQ	M=96.4 (SD=15.1), range 70-146	M=103.4 (SD=15.4), range 70-144	M=105.7 (SD=15.3), range 70-140	M=110.7 (SD=13.3), range 84-144
Cannabis-abuse/ dependence	N=273 (42.6%)	N=111 (13.7%)	N=36 (13.2%)	11 (9.5%)
DSM-IV diagnosis				
Schizophrenia	443	-	-	-
Other psychotic disorder	195	-	-	-
Bipolar disorder	3	5	1	-
Depression	-	86	32	9
Schizotypal personality disorder	-	1	1	
Other non-psychotic disorder	-	13	3	1
Postponed diagnosis	-	2	1	-
No diagnosis	-	704	234	106
Number of psychotic episodes	M=1.8 (SD=1.2), range 1-8			
Illness duration in years	M=4.6 (SD=4.1), range .02-41.1			

*Siblings for the patient-sib analyses
**Siblings for the sib-sib analyses (only those families where a minimum of 2 healthy sibs participated were included for these analyses)

Table 5.2 | Comparison of means for the three groups on CAPE and SIS-R subscales in patients (N=641), healthy siblings of affected families (N=811) and controls (N=116).

	Mean (SD)	Patients vs. Controls	Relatives vs. Controls	Patients vs. Relatives
CAPE positive symptoms		*P-value*[#]	*P-value*[#]	*P-value*[#]
Patients	.70(.51)	0.000	0.760	0.000
Relatives	.20(.20)			
Controls	.19(.18)			
CAPE negative symptoms				
Patients	1.06(.55)	0.000	0.158	0.000
Relatives	.55(.38)			
Controls	.48(.33)			
CAPE depressive symptoms				
Patients	1.04(.59)	0.000	0.056	0.000
Relatives	.63(.40)			
Controls	.55(.34)			
SIS-R positive schizotypy				
Relatives	.39(.41)	-	0.127	-
Controls	.46(.44)			
SIS-R negative schizotypy				
Relatives	.28(.26)	-	0.019	-
Controls	.34(.26)			

[#]P-values corresponding to the multilevel linear regression analyses testing the difference in mean scores on the different subscales of the CAPE and SIS-R between the three groups, while controlling for age, gender, education, ethnicity, and clustering at the family level.

Table 5.3 | Patient-sib analyses.

After controlling for confounders in the patients: gender, ethnicity, education, illness-duration, and age	**CAPE patients N= 811 pairs, N=811 healthy siblings OAF, N=641 patients**		
	Positive symptoms **ß**	Negative symptoms **ß**	Depressive symptoms **ß**
CAPE siblings			
Positive symptoms	0.12**	0.13***	0.14***
Negative symptoms	0.12**	0.16***	0.16***
Depressive symptoms	0.10**	0.12**	0.10**

ß: standardized regression coefficient representing the magnitude of the association between the different subscale-scores of the CAPE
*P<.05, **P<.01, ***P<.001

Familial clustering of the CAPE and SIS-R in healthy sib-pairs OAF and healthy control sib-pairs

In healthy sib-pairs OAF, significant within-symptom associations were apparent for the positive, and negative dimension of the CAPE and for the positive schizotypy subscale of the SIS-R (**Table 5.4**, upper section, marked in grey). Cross-symptom associations were significant only for CAPE positive symptoms in sib 1 and CAPE negative symptoms in sib 2; and for CAPE negative symptoms in sib 1 and CAPE depressive symptoms in sib 2 (**Table 5.4**, upper section). Effect sizes were in the low range for these analyses.

In healthy control sib-pairs, all within-symptom-dimension associations for CAPE and SIS-R were significant (**Table 5.4**, lower section, marked in grey). Significant cross-symptom associations were found for CAPE and SIS-R, with the exception of the association between the positive symptom dimension of the CAPE in sib 1 and the negative symptom dimension of the CAPE in sib 2 (**Table 5.4**, lower section). Effect sizes for these analyses were in the moderate range.

Within-subject associations on subscales of the CAPE and SIS-R in siblings and controls

All within-subject associations were significant, with effect sizes in the moderate range (also shown in **Table 5.4** in bold under 'ß(w)').

A series of multilevel linear regression analyses aimed at testing whether the familial associations were significantly smaller in the patient-relative sib-pairs compared to the healthy control sib-pairs showed significantly larger within-symptom-dimension familial associations in the healthy control sib-pair group relative to the patient-relative sib-pair group (left side of **Table 5.5**). The linear regression analyses testing whether the familial associations were significantly smaller in healthy sib-pairs OAF compared to healthy control sib-pairs showed no significant differences (right side of **Table 5.5**).

Table 5.4 | Sib-sib analyses in healthy sib-pairs of affected families (upper section), and in healthy control sib-pairs (lower section).

Sib-sib analyses in HEALTHY SIBLINGS of affected families			
After controlling for confounders gender, ethnicity, education, and age in sib2	**CAPE sib1** **N=271 sibs for within-analyses#** **N= 136 sib-pairs for between-analyses**		
	Positive symptoms **ß(w)**, ß (b)	Negative symptoms **ß (w)**, ß (b)	Depressive symptoms **ß (w)**, ß (b)
CAPE sib2			
Positive symptoms	**1**, 0.27**		
Negative symptoms	**0.43*****, 0.19*	**1**, 0.18*	
Depressive symptoms	**0.55*****, 0.12	**0.76*****, 0.21*	**1**, 0.12
	SIS-R sib1		
	Positive schizotypy **ß(w)**, ß (b)	Negative schizotypy **ß (w)**, ß (b)	
SIS-R sib2			
Positive schizotypy	**1**, 0.33***		
Negative schizotypy	**0.46*****, 0.07	**1**, 0.13	

Sib-sib analyses in HEALTHY CONTROLS			
After controlling for confounders gender, ethnicity, education, and age in sib2	**CAPE sib1** **N=115 controls for within-analyses#** **N= 58 healthy control sib-pairs for between-analyses**		
	Positive symptoms **ß(w)**, ß (b)	Negative symptoms **ß (w)**, ß (b)	Depressive symptoms **ß (w)**, ß (b)
CAPE sib2			
Positive symptoms	**1**, 0.52***		
Negative symptoms	**0.27****, 0.16	**1**, 0.41**	
Depressive symptoms	**0.35*****, 0.31*	**0.65*****, 0.35**	**1**, 0.34*
	SIS-R sib1		
	Positive schizotypy **ß(w)**, ß (b)	Negative schizotypy **ß (w)**, ß (b)	
SIS-R sib2			
Positive schizotypy	**1**, 0.55***		
Negative schizotypy	**0.52*****, 0.52***	**1**, 0.44**	

ß(w): standardized regression coefficient representing the magnitude of the within-person association on the different subscales of the CAPE/ SIS-R
ß(b): standardized regression coefficient representing the magnitude of the between-person association on the different subscales of the CAPE/ SIS-R
 # The number of subjects for within- and between-analyses are not equal due to missing values on confounders in 1 subject.
*P=<.05, **P<.01, ***P<.001

Table 5.5 | Regression analyses testing whether the familial associations were significantly smaller in patient-relative sib-pairs and healthy sib-pairs OAF compared to healthy control sib-pairs.

SIB 1	SIB 2	Patient-relative sib pairs vs. Healthy control sib-pairs		Healthy sib-pairs OAF vs. Healthy control sib-pairs	
CAPE		ß[#]	95%CI	ß[##]	95%CI
Capepos	Capepos	-0.41	-0.67 - -0.15**	-0.25	-0.54 - 0.03^
Capepos	Capeneg	0.01	-0.26 - 0.27	0.06	-0.25 - 0.37
Capepos	Capedep	-0.21	-0.47 - 0.06	-0.18	-0.49 - 0.13
Capeneg	Capeneg	-0.26	-0.53 - -.0003*	-0.24	-0.54 - 0.07
Capeneg	Capedep	-.21	-0.48 - 0.05	-0.13	-0.43 - 0.18
Capedep	Capedep	-0.18	-0.45 - 0.08	-0.17	-0.48 - 0.14
SIS-R					
SIS-Rpos	SIS-Rpos			-0.24	-0.53 - 0.05
SIS-Rpos	SIS-Rneg			-0.20	-0.51 - 0.10
SIS-Rneg	SIS-Rneg			-0.30	-0.61 - 0.01^^

Capepos: positive symptom score on the CAPE, Capeneg: negative symptom score on the CAPE, Capedep: depressive symptom score on the CAPE, SIS-Rpos: positive schizotypy measured with the SIS-R, SIS-Rneg: negative schizotypy, ß: standardized regression coefficient representing the between group difference in the familial association between the different subscale scores of the CAPE/ SIS-R, 95%CI: 95% Confidence Interval, ^P= 0.09, ^^P= 0.06 *P= 0.05, **P<.01 [#]Multilevel analyses controlled for clustering at the family level, and for gender, education, ethnicity, and age in sib 1. [##]Analyses controlled for gender, education, ethnicity, and age in sib1.

Discussion

Main findings

In this study, familial clustering of positive, negative, and depressive symptom dimensions was examined in patient-relative sib-pairs, in healthy sib-pairs OAF, and in healthy control sib-pairs. Given the inclusion of these three different groups, an attempt was made to elucidate possible disease-related factors. Interestingly, associations grew weaker with more evidence of vulnerability for psychotic disorder as the strongest associations were found in healthy control sib-pairs, the weakest in patient-relative sib-pairs, and intermediate strength associations in sib-pairs of affected families.

Evidence for shared aetiology?

Overall, the associations between symptom dimensions were small in patient-relative sib-pairs. This is in line with evidence from previous research where small associations were revealed [96,104,111]. In addition, no specific pattern of clustering was found for positive, negative, and depressive symptoms in patient-relative sib-pairs. This finding is inconsistent

with one previous study where positive and negative symptoms in the patients predicted corresponding schizotypal symptoms in non-psychotic relatives [94]. However, even Fanous and colleagues [94] found a number of cross-symptom dimension associations in addition to the within-symptom dimension associations. These findings suggest that familial factors contribute to the vulnerability to develop psychotic symptoms in general, rather than directly influencing which specific symptoms arise. Moreover, small familial associations in patient-relative sib-pairs and healthy sib-pairs OAF compared to moderate familial associations in healthy control sib-pairs demonstrate the influence of disease and disease vulnerability. The low familial associations in the sib-pairs OAF were not merely the result of overall low scores in this group, since their scores on all three CAPE dimensions did not significantly differ from the CAPE scores of healthy control sib-pairs.

Familial clustering and influence of disease-specific factors

Disease-related genetic or environmental influences may explain why symptom scores are less strongly associated in patient-relative sib-pairs. Results correspond with a previous study, in which the heritability was calculated for working memory, executive functioning, and episodic memory; higher estimates were found in control sibling pairs compared to patient-sibling pairs [98]. Similarly, significant positive associations for negative symptoms were found in control sibling pairs but not in patient-sibling pairs [104]. These results suggest that heritability and familial clustering is decreased in the presence of the disease and liability to disease. This could be explained in several ways. Psychotic symptoms in the patients may arise under the influence of unique environmental factors (for a review see:[6]) such as childhood trauma [112–114], and cannabis use [115,116]. In addition, epigenetic changes as a result of such environmental risk factors, and disease-specific *de novo* mutations may contribute to the development of symptoms in patients [117–119]. Alternatively, it could be hypothesized that protective factors prevent the unaffected sibling from developing schizophrenia. That is, the healthy sibling may have protective variants of schizophrenia-related genes or may have been exposed to environmental factors that protect against expression of illness given the presence of vulnerability. This is illustrated by findings from an explorative study by Glatt and colleagues who found changes in some genes in peripheral blood in non-psychotic siblings but not in their affected siblings nor in healthy comparison subjects [120].

Thus, disease-related factors in the patient and protective factors in the unaffected sibling may contribute to small familial associations in the patient-relative sib-pairs. At the same time, the absence of these disease-related factors in healthy controls may explain why familial associations were greater for these pairs. Consequently, it could be hypothesized that familial associations are also greater in patient-patient sib-pairs since they share disease-specific influences such as medication use. Hence, a previous study has shown within-symptom

associations in patient-patient sib-pairs [121]. Unfortunately, in the GROUP sample, only 37 patient-patient sib-pairs were included. Due to missing data on the CAPE in some, and missing values on some of the illness-related confounders, only 22 pairs remained for the cross-sibling analyses. Explorative *post-hoc* analysis of this small sample did not suggest large associations (none of them were significant, with a mean effect size of -0.08 for positive symptoms, 0.01 for negative symptoms, and -0.23 for depressive symptoms).

Strengths and weaknesses

One of the strengths of this study is the inclusion of healthy control sib-pairs. These controls are not influenced by genetic or environmental disease-related factors. Due to the inclusion of these controls, it was possible to measure familial clustering in a healthy population and a comparison could be made with healthy siblings from schizophrenia patients.

Another strength of the current study is the inclusion of healthy sib-pairs OAF, which, to the best of our knowledge, is the first to include such sib-pairs. Investigating these unaffected pairs with genetic vulnerability for the illness allows for the exploration of symptom associations without treatment-specific influences such as medication use. Nevertheless, these unaffected sib-pairs formed part of a family where at least one person developed schizophrenia and therefore disease-related factors are still of influence, which likely contributes to the relatively small sib-sib familial associations.

A possible limitation may be that of the healthy siblings in affected families who took part in the study, those with the lowest level of expression of schizotypy participated, whereas those with higher levels did not, or vice versa. The former selection could have contributed to the small number of associations observed between patients and siblings.

Another possible limitation may be that some siblings of schizophrenia patients could have used a defensive method of answering. Although difficult to measure objectively, it has been hypothesized that questionnaires with overt psychotic-like contents are more vulnerable to a defensive response style in the relatives of schizophrenia patients [122]. Both CAPE positive and negative symptom scores, and SIS-R positive schizotypy scores did not differ between healthy siblings of patients compared to controls. Since these symptoms were expected to be higher in siblings of schizophrenia patients due to familial vulnerability for psychotic symptoms, this suggests that defensive answering in some siblings could have lowered associations in healthy sib-pairs OAF.

Furthermore, given the symptomatic and genetic overlap between schizophrenia and bipolar disorder, including siblings OAF with a diagnosis of bipolar disorder (N=5 in the patient-relative sib-pair analyses, and N=1 in the healthy sib-pairs OAF analyses) may have influenced the results on familial associations. However, repeating the analyses after excluding these participants did not change the results.

Finally, the sample was not balanced in terms of statistical power for the different comparisons, as the number of patient-relative sib-pairs was much higher than in the other two groups. Therefore, interpretation of results was driven by size of the associations, and not only on statistical significance.

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R39

Chapter 6

Unravelling the association between ADHD and psychosis using principal component analysis of (sub)clinical symptoms in patients with schizophrenia, their siblings and controls

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In preparation

Abstract

Background

It is currently unknown whether the reported overlap between schizophrenia and attention deficit hyperactivity disorder (ADHD) is limited to a few specific symptoms or is explained by a specific subset of symptoms. The aim of this study is to investigate the association between ADHD and psychosis at a more detailed level comparing subclinical ADHD and psychotic symptom dimensions in patients with non-affective psychosis, their siblings unaffected for psychosis and healthy controls.

Methods

50 patients with non-affective psychosis, 81 of their unaffected siblings and 63 controls participated in this study. ADHD symptoms were assessed with the ADHD Rating Scale (ARS) and a Poisson regression analysis was used to investigate differences in ADHD scores between patients, siblings and controls. Psychotic experiences in the affective and non-affective domains were measured with the Community Assessment of Psychic Experiences (CAPE). A principal Component analysis was conducted to investigate the pattern of clustering between ADHD and subclinical psychosis in patients, siblings and controls at an item-level.

Results

Patients and siblings reported more ADHD symptoms compared to controls. The Principal Component Analysis defined three factors representing ADHD, positive and negative/depressive symptomatology. Investigating the association between these three factors showed a significant correlation between the ADHD factor and the negative/depressive factor in patients and siblings but not in controls. Positive and negative/depressive symptoms correlated in all three groups.

Conclusion

Increased levels of ADHD symptomatology were shown in schizophrenia patients and in their siblings unaffected for psychosis, supporting the aetiological overlap between ADHD and schizophrenia. The overlap between ADHD and schizophrenia is primarily explained by an association between ADHD and negative/depressive symptoms. Our data further suggest that ADHD symptoms could be used as an endophenotype for future high-risk studies in schizophrenia.

Introduction

The overlap between schizophrenia and attention deficit hyperactivity disorder (ADHD) has been established at a familial/genetic, clinical and subclinical level and suggests a common origin. Family studies have shown clustering of schizophrenia and ADHD within families; the prevalence of ADHD is increased in children from patients with schizophrenia [31,33]. A large population based study performed in 61,187 persons with ADHD and their first- and second degree relatives showed that first-degree relatives of these patients are at two-fold increased risk to develop schizophrenia compared to first-degree relatives of controls. In second degree relatives, the risk to develop schizophrenia was also reported to be increased but to a much lesser extent (OR ~1.1) [123] indicating the importance of genetic factors. Indeed, it has been shown that Copy Number Variants (CNV's) in children with ADHD are enriched for loci previously reported in schizophrenia [38]. Moreover, polygenic risk score analysis has shown that alleles, which are overrepresented in patients with schizophrenia, are also more common in children with ADHD compared to children without ADHD. A polygenic score based on all Single Nucleotide Polymorphisms (SNPs) associated at $p<0.5$ in schizophrenia significantly discriminates between ADHD cases and controls, although the explained proportion of variability is low (pseudo-R^2=0.45%)[124]. Summarizing, familial and genetic data are in agreement with a shared genetic susceptibility between adult schizophrenia and childhood ADHD.

At a clinical level, previous work showed evidence for clustering of schizophrenia and ADHD within subjects. Using retrospective psychiatric interviews in 187 patients with schizophrenia, it was shown that adult patients with schizophrenia more frequently fulfil DSM-IV criteria for ADHD inattentive subtype and ADHD hyperactive subtype in childhood compared to controls [125]. The largest study to date includes 61,187 probands with ADHD of whom 0.8% was diagnosed with schizophrenia compared to 0.1% of the controls (OR=6.7) [123]. In addition to this increased comorbidity at a diagnostic level, it is noteworthy that impaired attention is not only a core symptom of ADHD [126] but is also one of the main cognitive deficits in patients with schizophrenia [127,128].

Finally, an overlap in symptomatology has also been reported at a subclinical level in subjects who are at increased risk to develop schizophrenia. A study in 63 healthy first-degree relatives of schizophrenia patients reported an association between disorganized schizotypy and sustained attention. Relatives with high scores at disorganized schizotypy performed worse at a sustained attention task compared to relatives with low scores [129]. Similar findings have been reported in children from patients with schizophrenia. Keshavan and colleagues clinically assessed 75 children from patients with schizophrenia and demonstrated that children with externalising disorders (e.g., ADHD) obtained relatively high scores on schizotypy [130]. Moreover, a small study including 26 children and 3 young

siblings from patients with schizophrenia showed that children with a diagnosis of ADHD obtained higher schizotypy scores compared to children without a diagnosis of ADHD [131]. Summarizing, the co-occurrence of inattention and psychotic symptoms has been reported in schizophrenia patients and their relatives and is in agreement with a shared aetiology of the two disorders.

Previous studies indicate that ADHD and schizophrenia show overlap at a genetic, clinical, and subclinical level. However, very few of these studies have investigated the overlap at a more detailed level comparing subclinical ADHD and psychotic symptom dimensions. It is currently unknown whether the reported comorbidities are limited to a few specific symptoms (e.g., difficulty sustaining attention, easily distracted) or are explained by a specific subset of symptoms (e.g., positive symptoms in schizophrenia which correlate with hyperactive/impulsive symptoms in ADHD). Since the nature of the relationship between ADHD and schizophrenia remains unclear, the present study intends to unravel the association between both disorders. The aims of this study are threefold: (1) to compare the prevalence of subclinical symptoms of inattention as well as hyperactivity/impulsivity between patients with non-affective psychosis, their full siblings who are unaffected for psychosis and unrelated healthy controls; (2) to determine the latent constructs of ADHD and psychosis by performing a principal component analysis of ADHD and psychotic symptoms; and (3) to investigate the correlations between these constructs in patients, siblings and controls.

Methods

Subjects

Subjects were recruited as part of the Genetic Risk and Outcome of Psychosis (GROUP) study [39]. The GROUP study has been set up to study genetic and non-genetic vulnerability and resilience factors for the variation in the course and the expression of non-affective psychotic disorders. Patients with non-affective psychosis were identified through clinicians working in regional mental health services whose caseloads were screened for inclusion criteria. Subsequently, a group of patients presenting consecutively at these services as either outpatients or inpatients were recruited for the study. Family members were recruited through participating patients. Healthy controls were selected through a system of random mailings to addresses in the catchment areas of the patients. Inclusion criteria were (1) age range of 16 to 50 years; (2) good command of the Dutch language; and (3) being able and willing to give informed consent. Patients had to meet the DSM-IV-TR criteria for non-affective psychotic disorder, as assed by the Comprehensive Assessment of Symptoms and History (CASH) [78]. Additional inclusion criteria for the control group were (1) no lifetime diagnosis of psychotic disorder and (2) no first or second degree relatives with psychotic

disorder. The study was approved by the standing ethics committee, and all of the subjects gave written informed consent in accordance with the committee's guidelines.

The present study is an add-on study in Utrecht and therefore comprises a subset of the total GROUP sample. Initially 63 patients, 90 siblings and 74 controls completed the ADHD rating scale. Participants with incomplete information on diagnosis were excluded. This resulted in the exclusion of 13 patients, 9 siblings and 10 controls. In total 50 patients with non-affective psychosis, 81 of their unaffected siblings and 63 controls could be included in the analysis comparing ADHD sum scores between subjects. Familial relatedness in this subsample is as follows: 19 families include 1 patient and his/her sibling; 4 families include 1 patient and 2 siblings; 2 families include 1 patient and 3 siblings while 1 family includes 1 patient and 4 siblings. In addition, the sample includes 6 control sib-pairs. In total, 2 patients, 4 siblings and 5 healthy controls had three or more missing values in their CAPE scores and therefore were excluded from the analyses investigating the clustering between ADHD and psychotic item scores. To rule out systematic differences between this subsample and the total GROUP sample, comparisons in age, gender, education and diagnosis were made between the subsample and the total sample.

Measures

Self-reported childhood ADHD symptoms were assessed with the previously validated ADHD Rating Scale [43,132]. The ADHD Rating Scale contains 23 items reflecting DSM-IV criteria for ADHD. All items were rated on a 4-point scale (0=rarely or never, 1=sometimes, 2=often, 3=very often). A score of 2 or higher indicates the presence of that symptom. These 23 items assesses the eighteen symptoms of ADHD (eight inattentive symptoms and eight hyperactive/impulsive symptoms); ten items are combined into five symptoms. The range of the inattention as well as hyperactivity/impulsivity subscale is 0-9. A score of 6 or higher on the inattention scale corresponds with a childhood diagnosis of ADHD predominantly inattentive type according to DSM-IV [105]. A score of 6 or higher on the hyperactivity/impulsivity scale corresponds with a childhood diagnosis of ADHD predominantly hyperactive/impulsive type. A score of 6 or higher on both dimensions corresponds with a childhood diagnosis of ADHD combined type. Two different outcome measures were used. First, we calculated sum scores of the total number of items with a score of 2 or higher by subscale (i.e., inattention and hyperactivity/impulsivity) and for the total number of items. Second, item scores were obtained by dichotomizing the ADHD symptoms as present (item score of 2 or higher) and absent (item score of 0 or 1).

Self-reported (subclinical) psychotic experiences in the affective and non-affective domains were assessed with the Community Assessment of Psychic Experiences (CAPE)[133]. Reliability and validity of the CAPE has been demonstrated in previous studies [107,108]. The CAPE consists of 42 items; 20 items comprise the positive dimension, 14 the negative

dimension and 8 the depressive dimension. The frequency as well as the distress of each item is assessed. For the current analyses, item scores on frequency of positive, negative and depressive symptoms were used. The frequency score is rated on a 4-point scale (1=never, 2=sometimes, 3=often, 4=nearly always). Because of low frequencies in some of the item categories, items were recoded in such a way that each answer category includes at least 10 observations (see **Table S6.1**). The frequency of two of the items (Capgras and influenced by devices) remained low and therefore these items were excluded from subsequent analyses.

Analysis

Data were analyzed using SPSS version 20.0 for Windows. To investigate differences in socio-demographic variables between patients, siblings and controls, ANOVA was used to compare measures of continuous variables and χ^2 tests were used to compare categorical variables between groups.

A comparison of CAPE and ADHD scale scores between patients, siblings and controls

An Anova was conducted to investigate differences in positive, negative and depressive symptoms assessed with the CAPE between patients, siblings and controls. Age and gender were included as covariates. Post hoc analyses were used to compare patients with siblings, patients with controls and siblings with controls. Because the summed item scores from the ADHD Rating scale were not normally distributed, a Poisson regression analysis was used to investigate differences in inattention, hyperactivity/impulsivity and total ADHD scores between patients, siblings and controls. Healthy controls were included as the reference group and gender and age were included as covariates in this analysis.

The clustering of ADHD and subclinical psychosis at an item-level: a Principal Component Analysis

To investigate the association between ADHD and subclinical psychotic symptoms and to explore the correlation of (subsets) of item scores, a Principal Component Analysis was conducted including the 18 symptoms of the ADHD Rating Scale and the 40 items of the CAPE. Factors were promax rotated to facilitate interpretation of the factors. A scree plot of the eigenvalues was checked and factor loadings patterns were examined to decide on the number of factors.

Next, mean factor scores were compared between patients, siblings and controls. Because the distribution of factor scores was skewed, scores were compared using a Kruskal-Wallis non-parametric test.

This analysis was followed by calculation of non-parametric Spearman's correlations to investigate the association between the factors obtained by the Principal Component

Analysis in patients, siblings and controls separately. For all analyses, a type-I error rate of .05 was used.

Results

Sample

The socio-demographic and clinical characteristics of the patients, siblings and controls are summarized in **Table 6.1**. The patients had a mean age of 27.6 years (SD=6.1) and 84% was male. Siblings had a mean age of 26.7 years (SD=7.4) and 46.9% was male. Controls had a mean age of 30.6 years (SD=9.9) and 38.1% was male. Controls were significantly older compared to siblings and, as expected, patients were significantly more often male compared to siblings and controls. Therefore, age and gender were included as covariates in the analysis comparing the scores on the CAPE and the ADHD rating scale. The majority of the patients (88.0%) was diagnosed with schizophrenia, while the remaining patients were diagnosed with schizophreniform disorder (6.0%) or psychotic disorder not otherwise specified (6.0%). The majority of the siblings (79.1%) and controls (93.7%) had no lifetime psychiatric diagnosis. The remaining siblings were diagnosed with depression (18.5%), autism (1.2%) and anxiety disorder (1.2%). The remaining controls were diagnosed with depression (6.3%). Twenty-four % of the patients, 7% of the siblings and 3% of the controls fulfil DSM-IV criteria for a diagnosis of ADHD according to the ADHD Rating Scale. This was significantly different between the three groups (χ^2(df=2)=14.34;p=.001). However, post hoc analyses demonstrated no significant difference between siblings and controls (χ^2(df=1)=1.21;p=.27). As expected, statistical differences in IQ were found between the three groups. As this could have influenced the self-reported ADHD symptoms, the Poisson regression analysis comparing ADHD sum scores between patients, siblings and controls was repeated with IQ as a covariate.

To rule out systematic differences between this subset and the total GROUP sample, comparisons in age, gender, education, IQ and diagnosis were made. No significant differences in these variables were found which shows that the sample included in the present study is representative for the total GROUP sample (see **Table 6.2**).

Table 6.1 | Socio-demographic and clinical sample characteristics

	Patients	Siblings	Controls	Statistics		
	n= 50	*n*= 81	*n*= 63	F or χ^2	df	p-value
Age (years)	27.6 (SD=6.1)	26.7 (SD=7.4)	30.6 (SD=9.9)	4.40	193, 2	.014
Gender, male (%)	84.0%	46.9%	38.1%	26.13	2	<.001
WAIS III estimated IQ	91.9 (SD=13.6)	103.8 (SD=14.9)	110.8 (SD=15.8)	22.22	191, 2	<.001
DSM IV diagnosis lifetime, *n* (%)						
Schizophrenia	44 (88.0%)	-	-			
Schizophreniform disorder	3 (6.0%)	-	-			
Psychotic disorder NOS	3 (6.0%)	-	-			
Depression	-	15 (18.5%)	4 (6.3%)			
Autism	-	1 (1.2%)	-			
Anxiety disorder	-	1 (1.2%)	-			
No diagnosis	-	64 (79.1%)	59 (93.7%)			
ADHD diagnosis childhood*, *n* (%)	12 (24.0%)	6 (7.4%)	2 (3.2%)	14.34	2	.001
Combined type	5 (10.0%)	4 (4.9%)	-			
Inattentive type	5 (10.0%)	1 (1.2%)	1 (1.6%)			
Hyperactive-Impulsive type	2 (4.0%)	1 (1.2%)	1 (1.6%)			

*According to the ADHD Rating Scale

Table 6.2 | Comparisons between subsample and total GROUP sample

				Statistics		
		subsample	total sample	χ^2 or F	df	p-value
Patients	N	50	1042			
	Age (years)	27.6 (SD=6.1)	27.2 (SD=7.4)	.12	1091, 1	.73
	Gender, male (%)	84.0%	76.6%	1.48	1	.22
	Educational degree subject	3.8 (SD=2.0)	4.1 (SD=2.1)	.71	1073, 1	.41
	WAIS III estimated IQ	91.9 (SD=13.6)	94.9 (SD=16.1)	1.67	1032, 1	.20
	Diagnosis, % schizophrenia	12.0%	22.7%	1.36	1	.24
Siblings	N	81	936			
	Age (years)	26.7 (SD=7.4)	27.9 (SD=8.4)	1.58	1043, 1	.21
	Gender, male (%)	45.7%	46.9%	.05	1	.83
	Educational degree subject	5.3 (SD=2.1)	5.1 (SD=2.1)	1.01	1028, 1	.31
	WAIS III estimated IQ	103.8 (SD=14.9)	102.6 (SD=15.8)	.48	1016, 1	.49
	Lifetime diagnosis, % yes	21.0%	16.6%	1.05	1	.31
Controls	N	63	499			
	Age (years)	30.6 (SD=9.9)	29.5 (SD=10.3)	.62	561, 1	.43
	Gender, male (%)	38.1%	47.9%	2.16	1	.14
	Educational degree subject	5.5 (SD=1.5)	5.4 (SD=1.8)	.22	559, 1	.64
	WAIS III estimated IQ	110.8 (SD=15.8)	109.2 (SD=15.0)	.64	552, 1	.43
	Lifetime diagnosis, % yes	6.3%	9.6%	.71	1	.40

A comparison of CAPE and ADHD scale scores between patients, siblings and controls

Mean ADHD and CAPE scale scores for the three groups are listed in **Table 6.3**. Moreover, mean ADHD scores are shown in **Figure 6.1**. CAPE positive ($F(2,6.45)=44.82;p<.001$), negative ($F(2,5.42)=35.92;p<.001$) and depressive ($F(2,3.08)=27.63;p<.001$) scores were significantly different between patients, siblings and controls with increased scores in patients and similar scores in siblings and controls (see **Table 6.3**). With respect to ADHD symptoms, patients reported more inattention ($\chi^2(df=1)=21.95$; $p<.001$), hyperactivity/impulsivity ($\chi^2(df=1)=26.39$; $p<.001$) and total ADHD symptoms ($\chi^2(df=1)=48.33$; $p<.001$) compared to controls. Likewise, siblings reported significantly more inattention ($\chi^2(df=1)=5.74$; $p=.017$), hyperactivity/impulsivity ($\chi^2(df=1)=17.89$; $p<.001$) and total ADHD symptoms ($\chi^2(df=1)=21.94$; $p<.001$) compared to controls. Finally, patients and siblings significantly differed regarding inattention ($\chi^2(df=1)=8.51$; p.004) and total ADHD symptoms ($\chi^2(df=1)=9.68$; p.002) but not in hyperactivity/impulsivity ($\chi^2(df=1)=2.13$; p.144). When we included IQ as covariate, this did not change the results, except for a moderately increased p-value for the difference on the inattention scale between patients and controls ($\chi^2(df=1)=6.32;p=.012$) and siblings and controls ($\chi^2(df=1)=4.08;p=.044$).

Table 6.3 | Mean, SD and test statistics for ADHD Rating Scale, CAPE and factor analysis

		Patients (*n*=50)	Siblings (*n*=81)	Controls (*n*=63)	Statistics		
Instrument	Outcome measures	M (SD)	M (SD)	M (SD)	χ^2 or F	df	p-value
CAPE	Positive	.68 (.49)	.20 (.15)	.15 (.12)	44.82	183, 2	<.001
	Negative	1.06 (.56)	.49 (.34)	.42 (.27)	35.92	183, 2	<.001
	Depressive	.92 (.48)	.55 (.31)	.47 (.23)	27.63	184, 2	<.001
ADHD	Attention deficit	2.84 (2.82)	1.51 (2.17)	.95 (1.70)	23.27	2	<.001
Rating	Hyperactivity/impulsivity	2.28 (2.59)	1.54 (2.21)	.71 (1.51)	26.96	2	<.001
Scale	Total ADHD	5.12 (5.12)	3.05 (4.04)	1.67 (2.94)	48.42	2	<.001
Factor	Factor 1: ADHD	.46 (1.22)	.02 (0.96)	-.36 (.65)			<.001
Analysis	Factor 2: Positive symptoms	1,12 (1.38)	-.38 (.29)	-.43 (.24)			<.001
	Factor 3: negative/depressive	.75 (1.22)	-.20 (.85)	-.36 (.63)			<.001

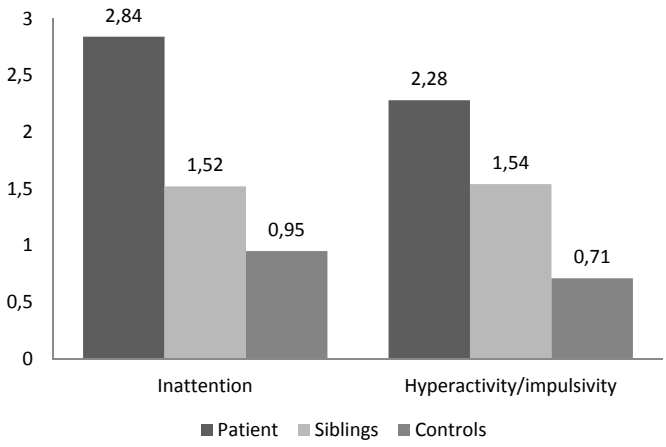

Figure 6.1 | Mean ADHD scores in patients, siblings and controls

The clustering of ADHD and subclinical psychosis at an item-level: a Principal Component Analysis

The scree plot of the eigenvalues suggested four factors. However, the fourth factor was difficult to interpret since the items loading on this factor were quite dissimilar in content. Therefore three factors were extracted which were easily interpretable and had low to moderate (.29-.54) factor correlations in the total sample.

The three factors represent ADHD, positive and negative/depressive symptomatology. **Table 6.4** shows the items per factor and the factor loadings. The first factor includes all ADHD Rating Scale items. The second factor includes those items from the CAPE which measure positive symptoms while the majority of the negative and depressive items from the CAPE load on the third factor. The three factors were represented as "ADHD", "positive", and "negative/depression". There were no cross loadings > 0.4 suggesting that none of the ADHD and psychotic items loaded highlyon two factors.

The mean factor scores for patients, siblings and controls are listed in **Figure 6.2** and **Table 6.3**. As expected, patients obtained significantly higher factor scores on all three factors compared to controls. Siblings scored significantly higher on the ADHD factor compared to controls. No significant differences between siblings and controls were found for the positive and the negative/depressive factor.

Table 6.4 | Three factor solution for CAPE and ADHD Rating Scale (ARS) items.

Factor 1 ADHD		Factor 2 Positive symptoms		Factor 3 Negative, depressive symptoms	
(ARS) Lack of attention	**.772**	(CAPE) Double meaning	**.486**	(CAPE) Feeling sad	**.714**
(ARS) Agitation	**.651**	(CAPE) TV messages have meaning	**.704**	(CAPE) Lack of enthusiasm	**.696**
(ARS) Trouble listening	**.686**	(CAPE) False appearance	**.454**	(CAPE) Not talkative with others	**.598**
(ARS) Difficulty organizing	**.613**	(CAPE) Persecution	**.594**	(CAPE) Lack of emotions	**.406**
(ARS) Overactive	**.550**	(CAPE) Conspiracy	**.715**	(CAPE) Feeling pessimistic	**.698**
(ARS) Avoid concentration	**.564**	(CAPE) Important person	**.638**	(CAPE) No future	**.592**
(ARS) Talkative	**.582**	(CAPE) Special person	**.721**	(CAPE) Suicidal	**.512**
(ARS) Lose things	**.613**	(CAPE) Telepathy	**.703**	(CAPE) No interest in others	**.711**
(ARS) Talk before thinking	**.572**	(CAPE) Voodoo	**.401**	(CAPE) Lack of motivation	**.718**
(ARS) Easily distracted	**.669**	(CAPE) Thought withdrawal	**.600**	(CAPE) Crying	**.480**
(ARS) Difficulty awaiting turn	**.659**	(CAPE) Empty mind	.295	(CAPE) Lack of energy	**.805**
(ARS) Forgetful	**.428**	(CAPE) Thought insertion	**.761**	(CAPE) Odd look	.303
(ARS) Interrupt others	**.713**	(CAPE) Thought broadcasting	**.722**	(CAPE) Lack of activity	**.716**
(ARS) Don't pay attention	**.643**	(CAPE) Thought echo	**.451**	(CAPE) Blunted affect	**.618**
(ARS) Don't finish things	**.701**	(CAPE) External control	**.862**	(CAPE) Lack of spontaneity	**.628**
(ARS) Can't sit still	**.701**	(CAPE) Hallucinations	**.837**	(CAPE) Blunted emotions	**.552**
(ARS) Easily bored	**.681**	(CAPE) Voices conversing	**.687**	(CAPE) Lack of personal hygiene	.378
(ARS) Likes crowed, noisy places	**.621**	(CAPE) Visual hallucinations	**.580**	(CAPE) Unable to terminate	.325
				(CAPE) Lack of hobbies	**.664**
				(CAPE) Guilty	**.477**
				(CAPE) Failure	.397
				(CAPE) Feeling tense	**.574**

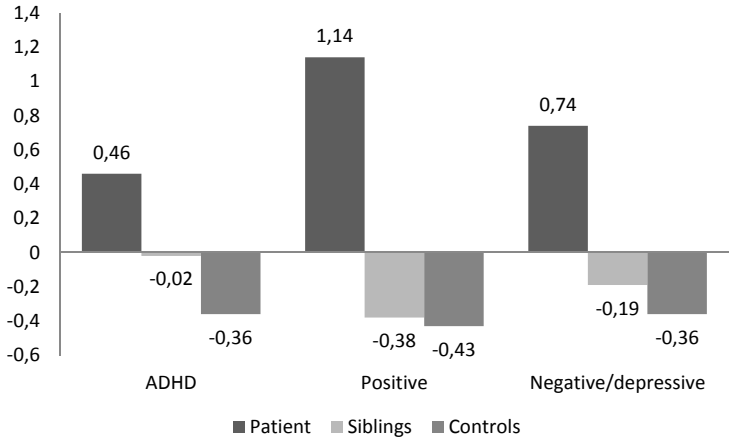

Figure 6.2 | Mean factor scores in patients, siblings and controls

Correlation between (sub)clinical symptoms in patients, siblings and controls

Table 6.5 summarizes the correlations between the three factors in patients, siblings and controls. A significant, positive, correlation between the ADHD factor and the negative/depressive factor was found in patients and siblings but not in controls. The correlation between the positive and the negative/depressive factors was significant in all three groups.

Table 6.5 | Correlations between the ADHD, positive and negative-depressive factors for patients, siblings and controls.

		ADHD	Positive
Patients	Positive	.266	
	Negative/depressive	.502**	.390**
Siblings	Positive	.152	
	Negative/depressive	.379**	.387**
Controls	Positive	.078	
	Negative/depressive	.049	.507**

** Correlation is significant at the .01 level (2-tailed)

Discussion

In this study the clustering of ADHD and psychotic symptom dimensions in patients with non-affective psychosis, their siblings unaffected for psychosis and controls was investigated. By including ADHD and psychotic symptoms at an item level, an attempt was made to unravel the nature of the association between the two disorders.

A comparison of ADHD and psychotic scores between patients, siblings and controls

As expected, patients reported significantly higher levels of positive, negative and depressive symptoms compared to siblings and controls. These differences were observed in CAPE scale scores and also became evident when comparing factor scores between groups. There were no differences in positive, negative and depressive scores between siblings and controls. This is in line with previous studies using GROUP data [134,135]. Generally, studies comparing subclinical psychotic symptoms between first-degree relatives and healthy controls yielded mixed results. One study demonstrated a significant difference in positive but not negative subclinical psychotic symptoms [136] while another studies showed the opposite [137] and a third study demonstrated differences in some subclinical psychotic symptoms (social anhedonia and perceptual aberration) but not in others (physical anhedonia and magical ideation) [138]. These inconsistencies could be explained by differences in the assessment of subclinical psychotic symptoms, sample size and definition of first-degree relatives as previous studies have included siblings, parents and offspring of schizophrenia patients. Overall, the evidence in favor of higher levels of psychotic symptoms in relatives of schizophrenia patients compared to controls is not convincing, suggesting that ADHD symptomatology may be a better indicator of familial risk for schizophrenia than psychotic symptoms.

At a clinical level, 24% of the patients, 7% of the siblings and 3% of the controls fulfil DSM-IV criteria for a diagnosis of ADHD according to the ADHD Rating scale. The occurrence of ADHD is thus much more common among patients compared to siblings and controls. The prevalence of childhood ADHD in our sample of schizophrenia patients is relatively low as Rubino [125] and colleagues demonstrated that 42% of the patients with schizophrenia and 10% of the general population fulfil DSM-IV criteria for ADHD. Moreover, a recent population-based meta-analysis estimates the prevalence of self-reported ADHD among adolescents at 8.5% [139]. This estimate is also higher compared to the prevalence that we found in our sample of siblings of schizophrenia patients and controls. The relatively low prevalence of ADHD in siblings and controls in our study might be due to collecting a combination of retrospective and self-reported data.

At a subclinical level, patients and unaffected siblings reported higher levels of childhood inattention as well as hyperactivity/impulsivity compared to controls. This is in line with previous research demonstrating increased rates of childhood ADHD problems in offspring and siblings from patients with schizophrenia [33,140]. The fact that unaffected siblings of patients with schizophrenia display elevated levels of ADHD symptoms compared to controls demonstrates the vulnerability in these subjects for ADHD symptomatology.

The clustering of ADHD and subclinical psychosis

The results of the principal component analysis did not support the existence of separate negative and depressive factors within the CAPE as reported in a population study [108] nor the existence of separate inattentive and hyperactive/impulsive domains within ADHD as

reported in a meta-analysis [126]; the items of the ADHD questionnaire were represented by a single factor. This may be explained by the relatively small sample size of this study or by the specific characteristics of the study sample (e.g., subjects were not recruited based on the presence of ADHD).

It was yet unknown whether the comorbidity and the overlap at a subclinical level between ADHD and schizophrenia is caused by specific symptoms or by a specific subset of symptoms. Using principal component analysis, we demonstrated that ADHD items clustered into a single factor while positive and negative/depressive also clustered into separate factors. The lack of high cross loadings indicates that the association between ADHD and psychosis is not explained by a few specific symptoms which overlap in content.

Correlations between (sub)clinical symptoms in patients, siblings and controls

Positive and negative/depressive factor scores significantly correlated in all subjects confirming the fact that positive and negative symptoms are different components of the same disorder. In patients and siblings, but not controls, ADHD scores correlated significantly with negative/depressive factor scores. The co-occurrence of ADHD and the negative/depressive symptom domain in patients with schizophrenia as well as their unaffected relatives supports the previously suggested aetiological overlap between ADHD and schizophrenia [141] and suggests that this overlap is primarily explained by an overlap with negative symptomatology. Interestingly, negative symptoms seem to have a stronger genetic component than positive symptoms [142] and are more strongly associated with impaired intellectual functioning [143]; a core component of schizophrenia [144]. Together these data suggest that there may be an underlying mechanism which causes negative symptoms, ADHD symptomatology, and impaired IQ scores.

ADHD as an endophenotype?

It has been hypothesized that deficits in sustained attention may function as an endophenotype of schizophrenia [145,146]. An endophenotype is a trait with a highly genetic component but not directly tied to the illness itself and may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive or neuropsychological in nature [147]. Moreover, one of the criteria for an endophenotype is that a trait that is found in patients is also found in unaffected relatives at a higher rate compared to the general population [148]. It appears that not only deficits in sustained attention, but also hyperactive/impulsive symptoms may function as an endophenotype. Indeed, we showed that patients obtained the highest ADHD scores, unaffected siblings of patients with schizophrenia intermediate scores and control subjects the lowest scores. Moreover, siblings of patients with schizophrenia could be differentiated from control subjects only through ADHD symptoms and not by their psychotic symptoms.

Limitations

Several limitations of this study should be considered. First, childhood inattention and hyperactivity/impulsivity symptoms were retrospectively assessed. Differences in ADHD and psychotic symptoms between siblings and controls could have been due to reporter bias with siblings reporting higher symptom levels compared to controls. Since relatives of schizophrenia patients actually tend to use a defensive response style [137], it seems unlikely that this would be the case. Furthermore, scores on positive and negative symptoms are similar in siblings and controls, which would be incongruent if reporter bias would be the primary explanation for higher scores on ADHD symptoms. Second, we did not control for 52% of the patients and 19% of the controls being related, because a multi-level principal component analysis cannot be performed in the statistical package that we used. However, a previous study using the GROUP data [135] showed low symptom correlations between patients and siblings (range .10-.16) and moderate symptom correlations between control sib pairs (range .16-.52). Given the low symptom correlations between patients and siblings and the small number of related control pairs in our sample, we would expect very minor deviation of true standard errors. Finally, the results of the principal component analysis did not support the existence of inattentive and hyperactive/impulsive domains within ADHD as reported in a meta-analysis [126]; the items of the ADHD questionnaire were represented by a single factor. This might be due to the fact that the variation of ADHD symptoms in this sample is low compared to the variation in a sample that includes patients with ADHD.

In conclusion, this study provides evidence for increased levels of ADHD symptomatology in schizophrenia patients and in their siblings unaffected for psychosis. In line with previous studies [38,141], these findings are in agreement with an aetiological overlap between ADHD and schizophrenia. Furthermore, ADHD symptom dimensions could be used as an endophenotype for future high-risk studies in schizophrenia.

Table S6.1 (supplementary). | Item frequencies CAPE before and after recoding.

	Original frequencies				Frequencies after recoding		
	Never	Sometimes	Often	Always	Never	Sometimes	Often
Double meaning	104	71	11	2	104	71	13
TV messages have meaning	156	28	2	1	156	31	
False appearance	128	47	13		128	47	13
Persecution	159	23	5		159	28	
Conspiracy	162	17	8	1	162	26	
Important person	157	27	4		157	31	
Special person	137	46	4		137	50	
Telepathy	136	37	13	2	136	37	15
Influenced by devices*	180	7		1	180	8	
Voodoo	149	27	8	4	149	27	12
Thought withdrawal	176	9	1		176	10	
Empty mind	146	40	2		146	42	
Thought insertion	168	16	4		168	20	
Thought broadcasting	166	15	4	3	166	22	
Thought echo	167	17	4		167	21	
External control	165	17	4	1	165	22	
Hallucinations	165	13	8	2	165	13	10
Voices conversing	176	7	3	1	176	11	
Visual hallucinations	170	13	4		170	17	
Feeling sad	28	143	15	2	28	143	17
Lack of enthusiasm	108	65	13	2	108	65	15
Not talkative with others	92	74	18	4	92	74	22
Lack of emotions	121	50	13	3	121	50	16
Feeling pessimistic	120	60	8		120	68	
No future	156	25	5	1	156	31	
Suicidal	144	40	2		144	42	
No interest in others	75	96	15	2	75	96	17
Lack of motivation	58	108	19	3	58	108	22
Crying	138	47	3		138	50	
Lack of energy	56	102	21	8	56	102	29
Odd look	136	43	9		136	52	
Lack of activity	116	53	15	3	116	53	18
Blunted affect	136	34	15	2	136	35	17
Lack of spontaneity	98	68	17	2	97	68	19
Blunted emotions	124	47	12	3	124	47	15
Lack of personal hygiene	155	28	4		155	32	
Unable to terminate	105	63	14	5	105	63	19
Lack of hobbies	126	52	7	2	126	61	
Guilty	81	90	15	1	81	90	16
Failure	137	41	7	2	137	50	
Feeling tense	43	110	28	6	43	110	34
Capgras*	181	3	2		181	5	

* Items excluded from Principal Component Analysis because of low frequencies

Chapter 7

Main findings and conclusion

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In this thesis we explored the familiarity of schizophrenia by investigating the impact of family history on phenomenology in patients with schizophrenia and their unaffected siblings. The strongest risk factor to develop schizophrenia is the familial risk, thus having a family member with schizophrenia, as the risk also increases with the degree of relatedness to the patient. There are two important methods to study familiarity. First, the comparison between families with sporadic cases and multi-affected families (familial loading, chapter 2-4). Second, investigating the clustering of (sub)clinical symptoms in schizophrenia families (familial clustering, chapter 5&6). Both methods are addressed in this thesis.

Familial loading

To obtain information about affected relatives in families, a family history interview provides a way to collect family history information quickly and economically. To obtain a valid assessment of family history, it is important to investigate which family member will be able to provide accurate information. Previous research shows that the validity of family history reporting can be influenced by characteristics of the informant such as age, gender and personal history of psychiatric disorder [47,51]. Moreover, it can be hypothesized that the role of a subject's position in a pedigree influences the validity of data collection. Therefore, **chapter 2** compares family history interview data on diabetes and psychiatric disorders assessed in subjects of different generations in a pedigree. Family history data were collected in three generations of 33 families by interviewing both an index subject (3rd generation) and his or her mother (2nd generation). Mothers were shown to report higher rates of diabetes and psychiatric disorder in the family compared to the index subjects. Furthermore, mothers who experienced a depressive episode indicated significantly more family members as having a psychiatric disorder than mothers who never experienced such an episode. Our findings suggest that family interview data should be collected by interviewing subjects who have a central position in the pedigree and can therefore provide information on his/her own generation, the previous and the next. In addition, psychiatric status of the informant should be carefully addressed.

Family history data are frequently used to estimate the degree of genetic risk for complex disorders such as schizophrenia. To reliably compare family history of schizophrenia between large and small families with different aged relatives, the familial loading for schizophrenia can be calculated. Verdoux and colleagues [18] developed an algorithm that comprises age and family size into the calculation of familial loading. Although the algorithm developed by Verdoux et al. substantially improves the calculation of familial loading, there are still a number of limitations. First, the probability that a relative is affected increases linearly from age 15 to 50 years while the risk to develop schizophrenia is particularly high between the ages 20 and 30 years [21]. Second, the relation between age and risk of illness is not

mediated by sex even though it has been shown that males have an earlier age of onset [4] and a higher risk of illness [5] compared to females. Finally, the algorithm of Verdoux et al. can only be applied to data of first-degree relatives. **Chapter 3** describes an improvement of the algorithm so that it i) allows for a non-linear increase in risk of illness; ii) takes sex differences into account; and iii) can be applied to data of first- and second degree relatives. Although previous studies have assessed family history and familial loading based on the number of individuals with psychosis, recent findings of twin and genetic studies indicate that the risk of clinically diagnosed schizophrenia is associated with a family history of a much wider range of psychiatric disorders [76]. Moreover, a variety of other psychiatric disorders are often present in relatives of patients with schizophrenia. Therefore, one could hypothesize that the definition of familial loading in schizophrenia, now based on the presence or absence of psychosis in family members, should be broadened to all psychiatric disorders. **Chapter 4** explores the association between family history of psychiatric disorder and IQ in patients with schizophrenia, their siblings and controls. Family history of psychiatric disorder was determined, excluding the data of the participating schizophrenia patient. A dichotomous division was made between families with no first- or second degree relative with psychiatric disorder and families with one or more affected relatives. A significant interaction was found between family history of psychiatric disorder and clinical status (patient, sibling, control). Patients with a positive family history of psychiatric disorder obtained higher intelligence scores (IQ) compared to patients with no family history of psychiatric disorder with an opposite effect in controls. A sensitivity analysis in which family history was restricted to psychosis demonstrated no significant differences between IQ scores for patients with and without family history of psychosis. This strengthens the hypothesis that the psychopathology risk in families is underestimated by limiting the definition of family history to psychosis only.

Familial clustering of symptoms

Given the familial influences on schizophrenia, one could hypothesize that specific symptom domains also cluster within families, and that this applies to both clinical and subclinical levels of expression [94,97,98]. To test this hypothesis, **chapter 5** investigates the clustering of (sub)clinical positive, negative and depressive symptom dimensions within patient-relative sib-pairs, healthy sib-pairs of affected families and healthy control sib-pairs. Interestingly, associations grew weaker with more evidence of vulnerability for psychotic disorder as the strongest associations were found in healthy control sib-pairs, the weakest in patient-relative sib-pairs, and intermediate strength associations in healthy sib-pairs of affected families. These results suggest that heritability and familial clustering is decreased in the presence of the disease and liability to disease. Moreover, small familial associations in patient-relative sib-pairs suggest that familial factors contribute to the vulnerability to develop psychotic symptoms in general, rather than directly influencing which specific symptoms arise.

High rates of axis I disorders such as attention deficit hyperactivity disorder, mood disorder, anxiety disorder and substance abuse have been shown in first-degree relatives from patients with schizophrenia [30–33]. Since these disorders also cluster in families with schizophrenia, there might be familial clustering of symptoms of other psychiatric disorders besides the clustering of psychotic symptoms. For example a clustering between psychotic and attention deficit hyperactivity disorder (ADHD) symptoms. Previous research suggest commonalities between schizophrenia and (ADHD) at a familial/genetic and clinical level. However, it is currently unknown whether this can be explained by a few common symptoms or by a clustering of schizophrenia and ADHD symptoms. **Chapter 6** investigates the pattern of clustering between ADHD and (sub)clinical psychosis assessed with the Community Assessment of Psychic Experiences (CAPE) in patients with non-affective psychosis, their siblings unaffected for psychosis and controls. A Principal Component Analysis defined three factors representing ADHD, positive and negative/depressive symptomatology. This implies that the overlap between ADHD and schizophrenia can not be explained by clustering of specific symptoms between the two disorders. The association between ADHD and negative/depressive symptoms in patients and siblings but not in controls supports the familial influences on both disorders. Moreover, the co-occurrence of psychotic and ADHD symptoms in siblings from patients with schizophrenia might reflect the vulnerability for all psychiatric disorder in this population.

Methodological issues

A number of methodological issues or limitations should be taken into account by the studies presented here in this thesis. First, family history interviews (**chapter 2 and 4**) and family history information was based on an informant and not on clinical interviews so disease status was not confirmed by a clinical diagnosis for all members in the pedigree. Furthermore, no gold standard for comparison exists. Second, the operationalization of family history of psychiatric disorder (**chapter 4**) was limited to psychosis, depression, mania and substance abuse. Since there is an overlap between psychosis, ADHD (**chapter 6**) and other developmental disorders, familial loading for psychiatric disorders in the GROUP study is underestimated. Third, family studies may bring on some statistical challenges. In a few analyses it was impossible to control for familiarity (**chapter 6**). Moreover, the GROUP sample was not matched for the different subject groups, as the number of patient-relative sib-pairs of families with schizophrenia was much greater than the relative-relative sib-pairs and the healthy control sib-pairs (**chapter 5**).

Conclusion

Taken together, the results of this thesis raise some important issues for unraveling the familiarity of schizophrenia. First, family studies encounter various methodological problems, which should also be addressed when examining schizophrenia. Second, the

familiarity of schizophrenia includes more than psychotic disorders alone. For future studies in schizophrenia it is necessary to broaden the definition of family history to all psychiatric disorders, as narrowing the definition of family history to psychosis underestimates the psychopathology in families of schizophrenia patients. Moreover, as the familiarity of schizophrenia also includes subclinical symptoms across psychiatric disorders, one should consider assessing these in patients' relatives. Understanding the clinical (endo)phenotypes might further enhance the prediction of the transition to psychosis in (high risk) populations.

Chapter 8

Nederlandse samenvatting

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Hoewel de exacte etiologie van schizofrenie nog onbekend is, zijn er verschillende genetische en omgevingsfactoren van invloed op de ontwikkeling en het beloop van de ziekte. De grootste tot op heden bekende risicofactor voor het ontwikkelen van schizofrenie is familiaire belasting, het hebben van een familielid met schizofrenie. Het vaker vóórkomen van de diagnose schizofrenie of (subklinische) psychotische symptomen binnen bepaalde families wijst op de familiariteit van schizofrenie. In dit proefschrift worden verschillende exploratieve studies beschreven die als doel hebben de familiariteit van schizofrenie verder te ontrafelen. De **hoofdstukken 2, 3** en **4** hebben hierbij betrekking op familiaire belasting en de **hoofdstukken 5** en **6** gaan in op familiaire clustering van symptomen.

Voor de studies in dit proefschrift is grotendeels gebruik gemaakt van onderzoeksdata die verzameld zijn in het Genetic Risk and Outcome of Psychosis (GROUP) onderzoek[3]. Dit is een longitudinale studie met als doel kwetsbaarheid- en beschermende factoren voor zowel het ontwikkelen van als de variatie in het beloop van een psychotische stoornis te onderzoeken. Aan het onderzoek hebben patiënten met een niet affectieve psychose deelgenomen, hun broers en zussen en gezonde controle personen.

Familiaire belasting

Om de familiaire belasting te bepalen moet per patiënt de familiegeschiedenis in kaart gebracht worden. De meest efficiënte manier om dit te doen, is door één persoon per familie te interviewen. In **hoofdstuk 2** is onderzocht welk familielid de meest betrouwbare en complete familiegeschiedenis kan verschaffen. We hebben hiervoor een vergelijking gemaakt tussen informatie gegeven door moeders (2de generatie) en hun zoon of dochter (3de generatie) over de familiegeschiedenis voor zowel diabetes als psychiatrische klachten. In totaal zijn voor 33 families zowel de zoon of dochter als hun moeder geïnterviewd met behulp van de Nederlandse versie van de FIGS (family interview for genetic studies). In vergelijking met hun zoon of dochter rapporteerden moeders meer diabetes en psychiatrische klachten bij familieleden. Daarnaast rapporteerden moeders die zelf ooit een depressieve episode hadden meegemaakt meer depressieve klachten bij familieleden dan moeders die nooit een depressieve episode hadden meegemaakt. Wij concludeerden dat informatie over familiegeschiedenis het beste kan worden ingewonnen bij personen met een centrale positie in de stamboom die daardoor informatie kunnen verschaffen over hun eigen generatie, de vorige en de volgende. Daarnaast moet er bij het verzamelen van informatie over familiegeschiedenis rekening worden gehouden met het feit of de informant zelf psychiatrische klachten heeft of niet.

[3] www.group-project.nl

Informatie over familiegeschiedenis wordt regelmatig gebruikt om de mate van familiaire belasting in te schatten bij complexe aandoeningen zoals schizofrenie. Om familiaire belasting betrouwbaar te kunnen vergelijken, hebben Verdoux en collega's een algoritme ontwikkeld dat rekening houdt met de grootte van een familie en de leeftijd van de familieleden. Hoewel dit algoritme de berekening van familiaire belasting substantieel verbetert ten opzichte van een dichotome verdeling (wel of geen familieleden met psychotische klachten), blijven er nog steeds een aantal beperkingen bestaan. **Hoofdstuk 3** beschrijft een drietal aanpassingen op het bestaande algoritme. Dit vernieuwde algoritme berekent een niet-lineaire risicoscore, houdt rekening met sekseverschillen en is ook toepasbaar op tweedegraads familieleden. We verwachten dat de aanpassingen ervoor zorgen dat het algoritme een betere schatting geeft van de risicoleeftijd voor het ontwikkelen van schizofrenie voor mannen en vrouwen en dat het breder toepasbaar is aangezien ook tweedegraads familieleden kunnen worden opgenomen.

Het is aangetoond dat het risico om schizofrenie te ontwikkelen geassocieerd is met de aanwezigheid van andere psychiatrische aandoeningen in de familie. Het is hierdoor aannemelijk dat de berekening van familiaire belasting alleen gebaseerd op het aantal familieleden met psychotische klachten te beperkt gedefinieerd is en zou moeten worden uitgebreid naar psychiatrische klachten in het algemeen. Daarnaast zijn verschillende psychiatrische aandoeningen geassocieerd met een verlaagd IQ. In **hoofdstuk 4** onderzoeken wij het verband tussen familiaire belasting voor psychiatrische stoornissen in het algemeen en IQ. Hiervoor zijn de psychiatrische klachten binnen een familie in kaart gebracht. De volgende psychiatrische ziektebeelden zijn hierin meegenomen: psychose, depressie, manie en alcohol- en drugsmisbruik. In patiënten, broers en zussen zonder psychotische klachten en gezonde controles is een dichotome verdeling gemaakt tussen individuen met een positieve familiaire belasting en een negatieve familiaire belasting; patiënten met en zonder een familiaire belasting voor psychiatrische stoornissen zijn met elkaar vergeleken evenals controles met en zonder een familiaire belasting. Bij broers en zussen is een vergelijking gemaakt tussen broers/zussen met één familielid met psychiatrische klachten (namelijk de deelnemende patiënt) en broers/zussen met meerdere familieleden met psychiatrische klachten.
Onze resultaten laten een interactie effect zien tussen familiaire belasting voor psychiatrische stoornissen en "klinische status" (patiënt, broer/zus, controle). Patiënten mét familiaire belasting halen hogere IQ scores dan patiënten zonder familieleden met psychiatrische klachten. In controles wordt echter het tegenovergestelde gevonden: controles zonder familiare belasting halen hogere IQ scores. Wanneer alleen wordt gekeken naar familiaire belasting voor psychotische klachten worden geen verschillen gevonden tussen patiënten met en zonder familieleden met psychose. Dit resultaat bevestigt de hypothese dat er een

onderschatting van de familiaire belasting plaatsvindt wanneer er alleen gekeken wordt naar familieleden met psychotische klachten.

Familiaire clustering van symptomen

Het frequenter vóórkomen van psychotische symptomen binnen bepaalde families (clustering) kan zowel op klinisch niveau plaats vinden (meerdere personen met de diagnose schizofrenie binnen één familie) als op subklinisch niveau (meerdere personen met subklinische psychotische symptomen binnen één familie). In **hoofdstuk 5** is de associatie tussen positieve, negatieve en depressieve symptomen onderzocht in drie verschillende groepen: (1) patiënten met schizofrenie en hun gezonde broer en/of zus, (2) een tweetal broers en/of zussen zonder psychotische klachten van patiënten met schizofrenie en (3) een tweetal broers en/of zussen uit controle families. Door het patroon van clustering te vergelijken tussen deze drie groepen kan rekening worden gehouden met ziektegerelateerde factoren zoals medicatiegebruik of bepaalde genetische verschillen. Onze resultaten laten zien dat er geen specifiek patroon van clustering van symptomen is. Familiaire factoren zijn dus vooral van invloed op de kwetsbaarheid voor het ontwikkelen van (sub)klinische symptomen, in plaats van dat ze voorspellen welke symptomen iemand zal ontwikkelen. Ten tweede vonden we dat de associatie het sterkst was voor tweetallen uit gezonde controle families en het minst sterk voor patiënten en hun broer of zus. Dit suggereert dat de familiare clustering van symptomen afneemt wanneer ziektefactoren of kwetsbaarheid voor het ontwikkelen van schizofrenie een rol spelen. Door ziektefactoren, risicofactoren en/of beschermende factoren lijken patiënten en hun gezonde broers/zussen minder op elkaar waardoor de familiaire clustering lager is dan in broers en zussen uit de controle families waarin deze factoren geen rol spelen.

Naast psychotische symptomen komen ook symptomen van andere psychiatrische aandoeningen zoals ADHD vaker voor binnen families waarin iemand schizofrenie heeft. Hoewel de samenhang tussen ADHD en schizofrenie op verschillende gebieden (familiair/genetisch, klinisch en subklinisch) is aangetoond, is het tot op heden onduidelijk hoe het verband op het niveau van symptoomdimensies eruit ziet. In **hoofdstuk 6** wordt de samenhang tussen subklinische ADHD en psychotische symptomen onderzocht in drie verschillende groepen: (1) patiënten met schizofrenie, (2) hun broers en zussen die geen psychotische klachten hebben en (3) gezonde controles. Dit onderzoek geeft een drietal resultaten. Allereerst vonden wij dat ADHD, positieve en negatieve/depressieve symptomen van elkaar verschillen en dat de ladingen onderling laag zijn. Dit betekent dat de overlap tussen ADHD en schizofrenie niet verklaard kan worden door overeenkomstige (subsets van) symptomen. Daarnaast vonden wij dat er bij broers/zussen en patiënten een associatie is tussen ADHD en negatieve/depressieve symptomen terwijl deze niet gevonden wordt bij

de controles. Dit ondersteunt de hypothese dat ADHD en schizofrenie een gezamenlijke etiologie hebben. Tot slot toonden wij aan dat alleen ADHD symptomen verschillen tussen broers/zussen van patiënten met schizofrenie en gezonde controles en niet de psychotische symptomen. Dit zou kunnen betekenen dat ADHD symptomen van toegevoegde waarde kunnen zijn in onderzoek naar personen met een verhoogd risico om schizofrenie te ontwikkelen.

Samenvattend kan worden gesteld dat de verschillende studies die worden beschreven in dit proefschrift ons verder helpen bij het ontrafelen van de familiariteit van schizofrenie. Allereerst zijn er een aantal methodologische problemen beschreven waar familiestudies naar schizofrenie rekening mee moeten houden. Daarnaast omvat de familiariteit van schizofrenie meer dan alleen psychotische symptomen waardoor er niet alleen naar deze symptomen moet worden gekeken bij familieleden van patiënten met schizofrenie maar naar psychiatrische symptomen in het algemeen. Het onderzoeken van psychiatrische symptomen in personen met een verhoogd risico om schizofrenie te ontwikkelen kan de kennis van de klinische (endo)fenotypes vergroten en daarmee wellicht de transitie naar psychose.

References

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Dankwoord

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De afgelopen jaren heb ik met veel plezier met verschillende mensen samen gewerkt om dit proefschrift op te bouwen. Ik heb veel hulp, steun en inspiratie gehad van vele mensen op allerlei gebieden. Dank daarvoor! Graag maak ik van deze gelegenheid gebruik om een aantal mensen extra te bedanken.

Allereerst wil ik alle proefpersonen die hebben deelgenomen aan het GROUP onderzoek bedanken voor hun tijd en inzet. Zonder jullie medewerking zou dit onderzoek niet mogelijk zijn geweest.

Mijn (co)promotoren, prof. dr. René Kahn, prof. dr. Eske Derks en dr. Wiepke Cahn wil ik danken voor de prettige begeleiding de afgelopen jaren.
Geachte prof. Kahn, beste René, hartelijk dank voor het richting geven aan en mogelijk maken van mijn promotie. Je kritische blik en directe feedback hebben een significante verbetering gebracht aan zowel de artikelen als het leertraject.
Beste Eske, zonder jou had deze promotie nog lang niet afgerond kunnen worden. Niet alleen reageer jij standaard binnen een paar uur op mijn mails, ook zorg jij ervoor dat er afspraken komen over wanneer analyses of volgende versies af zijn. Dank voor al je uitleg, geduld en betrokkenheid. Ik vind het een eer om als eerste promovendus bij jou als professor te mogen promoveren.
Beste Wiepke, dank voor je enthousiasme, creativiteit, optimisme en gastvrijheid. Jouw vertrouwen in mij als clinicus en onderzoeker maakte het mogelijk om een promotie traject te combineren met de GZ-opleiding. Dank daarvoor! Ik vond het uitdagend maar vooral heerlijk om wetenschappelijk onderzoek en de klinische praktijk met elkaar te kunnen afwisselen. De borrels en etentjes bij jou thuis hebben de afgelopen jaren voor een familiaire sfeer gezorgd.

De leden van de beoordelingscommissie, prof. dr. S. Durston, prof. dr. H.E. Hulshoff Pol, prof. dr. M. Dekovic, prof. dr. T.J.C. Polderman en prof. dr. L. de Haan wil ik danken voor hun bereidheid om dit manuscript kritisch te lezen en te beoordelen.

Tineke Lataster wil ik bedanken voor de samenwerking bij het schrijven van hoofdstuk 5 uit dit proefschrift. Tineke, het was een heel karwei maar het was voor mij erg prettig om te kunnen leren van jouw ruime wetenschappelijke ervaring.

Beste Ewan Clark, bedankt voor de revisie van het Engels en je altijd snelle reactie. Your comments improved the readability.

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D

Mijn (oud)collega's van de psychiatrie, Afke, Marit, Rachel, Paula, Jessica, Elemi, Wanda en Thomas, wil ik bedanken voor de leuke tijd die we samen hebben gehad bij congressen, vrijdagmiddagborrels en werkoverleggen. Monica, Sander en Marloes, het is bizar hoeveel je van elkaar weet als je jaren een kamer deelt. Soms zag ik jullie meer dan mijn eigen familie. Dank voor alle nuttige en nutteloze discussies en gesprekken. Marijn, Willemijn, Marloes, Joyce en Jacobine, fijn dat onze samenwerking heeft geleid tot een vriendschap buiten het werk.

Collega's van de neurologie, lieve Martine, Esther, Carla, Irene, Marieke en Haike, dank voor jullie steun en interesse zowel op professioneel als persoonlijk gebied. De etentjes bij Martine, kerstontbijtjes en verjaardagstaarten maken ons ook een soort familie waarin ik me volledig thuis voel.

Mijn paranimfen Heleen en Mariska. Lieve Heleen, jij hebt mij vanaf mijn allereerste werkdag in het UMC "onder je hoede genomen" en me veel over wetenschappelijk onderzoek geleerd. We hebben jaren samen gewerkt (zowel wetenschappelijk als klinisch) en veel van en met elkaar mee gemaakt. Je bent in de loop der jaren naast een collega ook een goede vriendin geworden. Ik vind het heel fijn dat je mijn paranimf wilt zijn.
Lieve Mariska, jij bent als een soort personal coach betrokken geweest bij mijn carrière de afgelopen jaren. Via jou ben ik ooit begonnen in het GROUP onderzoek. Je bent een van mijn beste vriendinnen en doordat we de liefde voor het combineren van wetenschappelijk en klinisch werk delen, begrijp je precies wat de plus en minpunten kunnen zijn. Het is ontzettend fijn om frustraties en overwinningen met jou te kunnen delen. Het is voor mij meer dan logisch dat jij mijn paranimf bent, het voelt heel prettig dat jij met de verdediging achter me staat!

En dan zijn er buiten het UMC nog een aantal mensen die heel dichtbij mij staan en daardoor het hele promotie traject op de voet hebben gevolgd. Lieve unigirlz, wat had ik het moeilijk toen ik dit jaar niet met jullie mee kon op ons jaarlijkse weekendje weg. Het is niet voor niets geweest, het proefschrift is af! Jullie vriendschap is mij heel dierbaar. Dank voor alle leuke, mooie, gezellige, steunende en waardevolle momenten. Dat er nog vele mogen volgen!
Lieve Suus, helaas kun je niet bij de verdediging zijn omdat jullie aan jullie eigen avontuur begonnen zijn. Ik weet dat je in gedachten met me mee leeft, we kennen elkaar al zo lang. Ik kijk er nu al naar uit dat jullie over iets minder dan 4 jaar weer in de buurt wonen.

Lieve familie en schoonfamilie, dank voor al jullie support de afgelopen jaren, niet alleen moreel maar ook praktisch. Doordat jullie op de jongens konden passen of voor ons kookten, was er net weer even wat extra tijd om aan dit proefschrift te werken. Zonder jullie steun, hulp en begrip had ik dit nooit kunnen bereiken. Ik prijs me gelukkig met de band die wij onderling hebben. Het laat zich moeilijk in woorden vangen maar is duidelijk voelbaar!

Lieve pap en mam, van jullie heb ik geleerd dat je met hard werken veel kunt bereiken. Dank voor jullie geloof in mij en de stabiele basis die jullie me hebben gegeven.

En dan als laatste, allerliefste Jeroen, Sven en Ties, er is voor mij geen groter geluk dan mijn leven met jullie te kunnen delen. Jeroen, dank voor het lezen van, meedenken over en van feedback voorzien van de teksten in dit proefschrift. Respect dat het jou in zulke stressvolle tijden altijd weer lukt om mij te laten lachen. Jullie zijn de overtreffende trap van family matters!!

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