A genetic spectrum approach to affective and schizophrenic disorders.

A twin- and family study.

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A dissertation for the degree of Philosophiae Doctor in Medicinae

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CONTENTS

Foreword

As a graduating student in psychology at the University of Oslo, I started working as a research fellow on this twin- and family study project, on which the present thesis is based, in 1987. The initiators of the project were Professor Einar Kringlen, Institute of Psychiatry, and Professor Svenn Torgersen, Institute of Psychology, University of Oslo. The original research group consisted of psychiatrists, psychologists, residents in psychiatry, and graduate students in psychology or medicine. Planning and data-collection was my main occupation the first years. The data were collected by personal interviews with the subjects, most often in their homes, in all part of Norway, and even abroad. Each interview lasted on average between three and four hours. Combined with the time spent on travelling, spending the nights at campgrounds and boarding houses; it should be obvious that this was a time-consuming activity. An interesting, but fortunately seldom occurrence, was one interview that lasted twelve hours.

As the time went on and more interviewers were engaged in the interviewing, my work was more and more concentrated on co-ordinating the work, organizing the collected data, making it suitable for data analyses, and finally performing the statistical analyses and further offering guidance to my colleges in performing such analyses. For my part, the first period on the project ended up with a post graduate thesis; “Personlighetsavvik innenfor det schizofrene spektrum. En komparativ undersøkelse av tvillingsøsken og andre 1. grads-slektninger av schizofrene og ikke-schizofrene pasienter” (”Personality disorders/traits within the schizophrenic spectrum. A comparative study of co-twins and other 1. degree relatives of patients with schizophrenia and patients without schizophrenia”), written together with my colleague Oddvar Ask. After graduation, I continued to work as a full time research fellow on the project, and after I attended the medical study at the University of Tromsø in 1991, as an

hourly-paid research fellow. In addition I was later employed as a lecturer (amanuensis II) in a half time job at the Institute of Psychology, University of Tromsø, conducting another large study there. The work for the project during this time mainly consisted of co-ordinating the work, preparing data for analyses and performing the statistical analyses. Since the beginning of the 1990-ies many articles – of which I am a co-author on six - based on the data from this project, have been published in international journals. The project has so far resulted in two PhD degrees and several post graduation theses.

After I got my medical degree in 1997, I started working as a physician and later as resident in psychiatry. A founding from The Psychiatric Research Centre of North Norway in 2004 and later from The Northern Norway Regional Health Authority, made again a more intensive involvement in scientific work - and the current thesis - possible.

Acknowledgements

I have always had an impression of being met with goodwill from my superiors and colleagues at all the different places and in all situations I have work during my time on the project. Naming some persons specifically is not intended to leave out those many not named that have offered invaluable help along the road. That goes not at least for all my co-workers and co-authors in different phases of the project. A special thank though to my main supervisor Professor Svenn Torgersen, whom I have worked with, in all now, over twenty years. The time speaks for itself. In the first period on the project I also worked close with Professor Einar Kringlen. I want to thank him for initiating the project together with Svenn Torgersen, good surveillance and discussions under a wide horizon. Professor Reidun Olstad, as my second supervisor during the work with this actual thesis, has offered an all-embracing help and inspiration. Head of department, chief psychiatrist Reiulf Ø. Ruud, as my local chief at Nordland Hospital Trust, Vesterålen, has through his invitation and flexibility been crucial in providing the working situation that has made this thesis possible.

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Summary

Background: The current definitions of - and demarcations between - different sub-groups of mental disorders are not obvious. They are "man-made" and to some extent arbitrary and based on conventions. The criteria-based diagnostic systems, like DSM-III-R and ICD-10, have made reliability (or agreement between clinicians/researchers) feasible. The central problem is, however, the validity. For instance; do our clinical diagnoses reflect some underlying substrates, or in genetic terms, do our phenotypes reflect underlying genotypes?

For both the two main groups of psychiatric disorders – affective disorders and schizophrenia - the existence of a *spectrum* of aetiologically/genetically related conditions has been indicated. A spectrum consisting of so called 'bipolar spectrum disorders', usually including bipolar I- and II disorders, but also cyclothymic disorder, and other hypomanic states has been indicated. Likewise, results substantiating a more continuous interpretation of unipolar depressive symptoms, including sub-threshold symptoms beyond major depression have been reported. Furthermore, earlier studies have indicated the existence of an aetiological connection between schizophrenia and schizotypal personality disorder (SPD) or schizotypal symptoms. The DSM-IV manual, also states that schizotypal personality disorder, as defined in the manual, tends to aggregate in families and is more frequent among the first-degree biological relatives of individuals with schizophrenia than in the general population. However, the question as to whether only some features defined by the criteria of schizotypal personality disorder truly relates to schizophrenia, remains disputed.

In the present work we have redefined some of the diagnostic categories by, on the one hand, combining two or more subgroups, and on the other, trying to look for central single symptoms or signs, that carry most *aetiological* relevance. An eventual finding that indicates

that a certain disorder phenotype is to a high degree inherited is an important aspect contributing to its validity. Thus, twin studies, as the one reported here, may contribute to the demarcation of phenotypes in future gene-finding efforts and provide the context within which the results of gene-finding studies can be interpreted. Further, a valid definition of the phenotypes may be of great relevance for public health.

The main aims of the present study were firstly to investigate aetiological factors related to bipolar spectrum disorders and unipolar depressive disorders, and secondly, to describe personality features that may be aetiologically related to schizophrenia.

Methods: The sample consisted of a total number of 303 same sexed twin pairs and their first-degree relatives (parents and siblings), and was ascertained by matching the Norwegian Twin Register for twins born between 1936 and 1960 with the National Register for Mental Disorders, and directly from in- and out-patient clinic archives of the University Department of Psychiatry, Vinderen and Modum Bad Hospital, Vikersund.

A questionnaire that had previously predicted zygosity correctly in 95 % of the cases compared with 10 genetic blood and serum markers, was applied for zygosity determination.

The twins and their first-degree relatives were interviewed in person about their lifetime history of mental disorders and personality traits. They were also asked about aspects concerning the twins' birth, early behaviour and experiences. In addition they were asked to complete three (the twins four) questionnaires of which two were related to personality features. The diagnostic classification system employed was the DSM-III-R. The diagnoses were based on the personal interviews with the Structured Clinical Interview for DSM-III

Axis I (SCID-I) rev., and the Structural Interview for DSM-III-R Personality Disorders (SCID II). Concordance rates in paper I and II were calculated by the Crosstabs procedure in SPSS (SPSS Inc., 2003) with Pearson Chi-square-test or Fisher's exact test. Correlations in liability and estimation of the heritability (h^2) with biometrical model fitting were performed with the software package Mx. One-way analysis of variance was used to compare the mean scores on different schizotypal and borderline features among the different groups of relatives in paper III.

Results: Concordance rates were higher among MZ- than DZ- pairs for all the single diagnoses and combinations of diagnoses within the bipolar spectrum. Cross-concordance between different diagnoses was observed. The heritability of Bipolar I was .73, of Bipolar I+II .77 and of Bipolar I+II+Cyclothymia .71. No effects of shared environment (C) was evidenced, and a model including dominant genetic effects (D) did not show a better fit than a model only including additive genetic effects (A) and unique/non-shared environmental effects (E). Thus, on grounds of parsimony an AE-model seemed most reasonable.

Concordance rates were higher among MZ- than DZ- pairs for all the single diagnoses and combinations of diagnoses in the unipolar depressive spectrum. Cross-concordance between different diagnoses was observed. The heritability of Major depression (MD) was .42, of MD+Atypical depression .51, of MD+Atypical depression+Dysthymia .45 and of MD+Atypical depression+Dysthymia+Depressive adjustment disorder .46.
No significant effects of shared environment (C) was evidenced, and a model including dominant genetic effects (D) did not show a better fit than a model only including additive genetic effects (A) and unique/non-shared environmental effects (E). Thus, on grounds of parsimony an AE-model seemed most reasonable.

Individuals with schizotypal personality disorder from families with a member with schizophrenia scored higher than the controls on all schizotypal measure and on some borderline aspects. However, only on inadequate rapport and odd communication did they score higher than individuals with schizotypal personality disorder without schizophrenia among their close biological relatives. Monozygotic non-schizophrenic co-twins of schizophrenic index-twins scored high on inadequate rapport, odd communication, social isolation and delusion/hallucinations. Monozygotic non-schizophrenic co-twins of individuals with schizotypal personality disorder outside the schizophrenic genetic spectrum scored high on illusions, depersonalization, derealization and magical thinking.

Conclusions: The 'bipolar spectrum' category consisting of bipolar I disorder, bipolar II disorder and cyclothymia constitute an entity with high heritability and no shared family environmental effects. An ADE-model did not show a better fit than an AE-model. Thus, on grounds of parsimony, an AE-model seems most reasonable.

The strictly unipolar depressive spectrum studied here is moderately heritable, with no significant effects of shared environment. The tendency is towards higher heritability for the combined categories, especially major depression and/or atypical depression, compared to major depression alone. An ADE model did not show a better fit than an AE model, so on grounds of parsimony, an AE model seems most reasonable for all the combinations of unipolar depressive disorder studied.

Inadequate rapport, odd communication, social isolation and delusion/hallucinations appeared to be the genetic core of schizotypy as it is related to schizophrenia. For non-schizophrenia related schizotypal personality disorder, illusion, depersonalization/derealization and magical

thinking appeared to constitute the genetic core. Generally, in other words; negative schizotypal features appear to be inside the schizophrenic spectrum, while positive borderline-like features are outside having another genetic endowment.

Implications: The results presented in this thesis challenge the aetiological validity of the DSM-IV-TR's splitting of bipolar disorders into three separate diagnostic entities; bipolar I, bipolar II, and cyclothymic disorder. From a quantitative genetic point of view, the disorders appear to be diverse expressions of the same genotype.

Generally however, from a clinician's viewpoint, the differences in severity of symptoms and functional levels of the patients afflicted with these different disorders may still be an argument for categorizing these phenotypic expressions the way that they currently are.

To a lesser degree, still from an aetiological point of view, the results also challenge the validity of the current categorization of unipolar depressive disorders in the DSM system as it arbitrarily separates phenotypes which seem to be expressions of the same unipolar depressive genotype. Perhaps a simplification of the requirements for number of symptoms and duration is warranted, as long as strong emphasis is laid on the core symptoms of depressed mood and lack of positive affects.

Further, the results indicate that only some of the current criteria for schizotypal personality disorder (SPD) should be retained if SPD is supposed to describe a schizophrenia related personality disorder.

List of papers

Paper I

Edvardsen J, Torgersen S, Røysamb E, Lygren S, Skre I, Onstad S, Øien PA.

Heritability of bipolar spectrum disorders. Unity or heterogeneity?

Journal of Affective Disorders 2008 Mar;106(3):229-40.

Paper II

Edvardsen J, Torgersen S, Røysamb E, Lygren S, Skre I, Onstad S, Øien PA.

Unipolar depressive disorders have a common genotype.

Journal of Affective Disorders, advanced online publication 21. Jan. 2009;

doi; 10.1016/j.jad.2008.12.004

Paper III

Torgersen S, Edvardsen J, Øien PA, Onstad S, Skre I, Lygren S, Kringlen E.

Schizotypal personality disorder inside and outside the schizophrenic spectrum.

Schizophrenia Research 2002 Mar 1;54(1-2):33-8.

I. INTRODUCTION

1.1. Mental disorders; definitions and occurrences.

The current definitions of - and demarcations between - different sub-groups of mental disorders are not obvious. They are "man-made" and to some extent arbitrary and based on conventions. And, as indicated in the articles in this thesis, they are disputed. Further, this is also reflected in the instructions in contemporary nomenclatures e.g. as stated in DSM-IV:…"there is no assumption that each category of mental disorders is a completely discrete entity with absolute boundaries dividing it from other mental disorders or from no mental disorder" (American Psychiatric Association, 2000). The criteria-based diagnostic systems, like DSM-III-R (American Psychiatric Association, 1987) and ICD-10 (World Health Organization, 1993), have made reliability (or agreement between clinicians/researchers) more feasible (Skre et al., 1991; Torgersen et al., 2000). The central problem is, however, the validity. For instance; do our clinical diagnoses reflect some underlying substrates, or in genetic terms, do our phenotypes reflect underlying genotypes? (Kringlen, 1993). On the other hand, a definition of a disorder/illness may of course be "validated" up to other standards, depending on the purpose of the diagnosis; to institute a treatment, to estimate social expenditures, give a health insurance benefit or to study occurrence or prognoses (Sandanger et al., 2002). Anyway, the current definitions of - and demarcations between - different sub-groups of mental disorders are not intuitively correct. In the current work we have redefined some of the diagnostic categories by, on the one hand, combining two or more subgroups, and on the other, trying to look for central single symptoms or signs, that carry most *aetiological* relevance.

Mental disorders are common and constitute one of the leading contributors to the global burden of disease. In Norwegian populations, a life-time prevalence for mental disorders defined according to DSM-III-R, Axis I, between 30 % (rural population) (Kringlen et al., 2006) to more than 50 % (urban population) has been reported. (Kringlen et al., 2001).

Affective disorders

The group of *affective disorders* includes both bipolar (earlier; manic-depressive) disorders and unipolar depressive disorders, and covers a spectrum of conditions from the more severe (e.g. bipolar disorder) to the milder (e.g. dysthymia). They are among the most common mental disorders, and earlier studies have indicated that, at least some of them, tend to run in families (Shih et al., 2004). The WHO World Health Survey (WHS) (Moussavi et al., 2007) that studied the prevalence of depression (depressive episodes according to ICD-10) in 60 different countries, is probably the largest worldwide population-based study that has explored the effect of depression in comparison with other chronic diseases on health state. Moussavi et al. (2007) found a *one year* prevalence for depression alone of 3.2 %. When comparing depression with four common chronic physical diseases; angina, arthritis, asthma and diabetes, they found depression to impair health state to a substantial larger degree than these other diseases. Respondents with depression comorbid with one or more chronic diseases had the worst scores of all the disease states. Depression is, as considered by WHO, the leading cause of disability as measured by YLDs (Years Lived with Disability) and the 4th leading contributor to the global burden of disease (Ustun et al., 2004). The prevalence rates for depression, both one year and life time, vary considerable between different studies. The prevalence rate at 3.2 % from the study by Moussavi et al. (2007) is among the more lower ones. For instance, Alonso et al. (2004) reported somewhat higher one year prevalence for DSM-IV defined major depression (3.9 %) from the European Study of the Epidemiology

of Mental Disorders (ESEMeD). The corresponding *lifetime* prevalence was 12.8 %. For mood disorders considered together the one year prevalence was 4.2 % and the lifetime prevalence 14.0 %. From the National Comorbidity Survey in the United States (NCS), Kessler et al.(1994) reported a one year prevalence of major depression (DSM-III-R) at 10.3 %. The lifetime prevalence was 17.1 %. The corresponding rates for dysthmia were 2.5 % and 6.4 %, respectively. For mania (bipolar I) the figures were 1.3 % and 1.6 %. The one year prevalence for all affective disorders (mood disorders) taken together was 11.3 % and the lifetime prevalence 19.3%.

The results from the study by Kessler et al. are quite comparable to what Kringlen et al. (2001) found in a Norwegian urban population, where the one year- and lifetime prevalences for major depression, dysthymia and bipolar disorder were estimated to 7.3 % and 17.8 %, 3.8 % and 10.0 %, and 0.9 % and 1.6 %, respectively. In an article in the Journal of Norwegian Epidemiology (Torgersen et al., 2002), the authors, reporting from the same sample, commented that the lifetime prevalence for 'all affective disorders taken together' was found to be 22.8 %. The sum of the lifetime prevalence rates of the single disorders exceeds the figures of the category 'all affective disorders taken together' because no hierarchy was applied between MD and dysthymia, i.e. the respondents were diagnosed with both if they ever had fulfilled the criteria. From a rural Norwegian sample, Kringlen et al. (2006) found a one year prevalence for major depression, dysthymia and bipolar disorder at 3.7 %, 1,6 % and 0.1 %, respectively. The corresponding lifetime prevalences were 8.3 %, 6.3 % and 0.2 %. For the bipolar spectrum disorders taken together, Regeer et al. (2004) in a Dutch sample, found a life-time prevalence as high as 5.2 %, and Merikangas et al. (2007), in a large nationally representative North-American sample found a lifetime prevalence for bipolar spectrum disorder (defined as bipolar I-, bipolar II- or subthreshold bipolar disorder) at 4.4

%. Specifically, the prevalence for bipolar I- was 1.0 %, for bipolar II- 1.1 % and for subthreshold bipolar disorder 2.4 %. Grant et al. (2005), also reporting from a large North American sample, found an even higher lifetime prevalence for bipolar I disorder, considered alone (3.3 %).

Schizophrenia and schizophrenia-related disorders

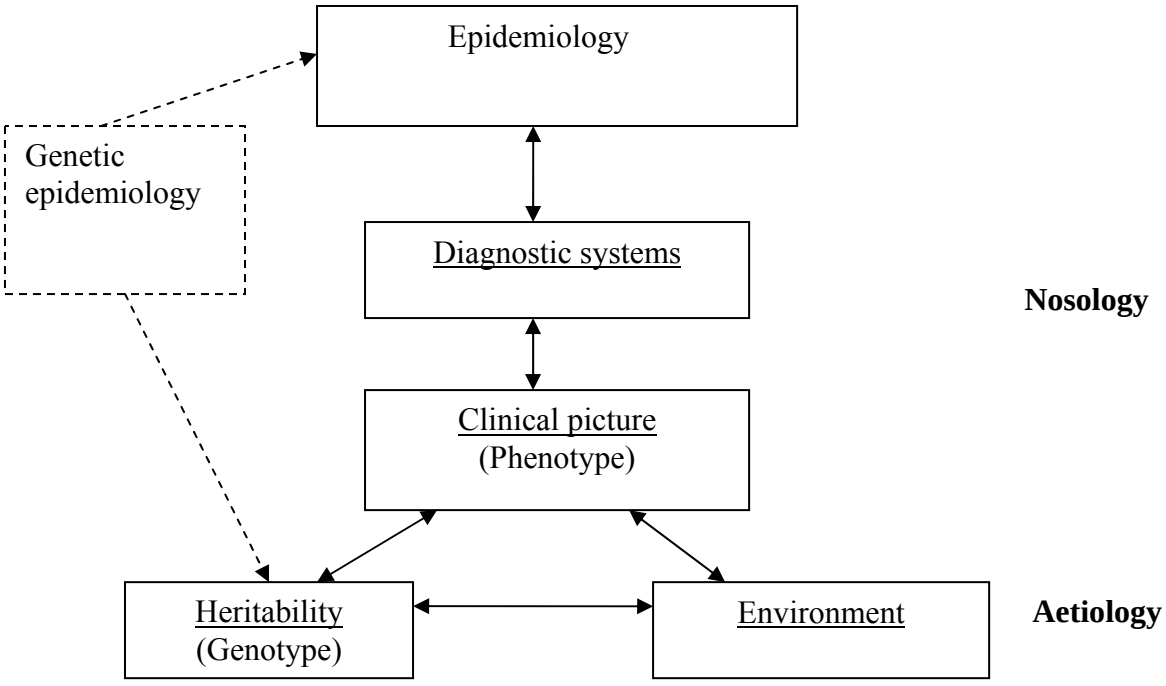
Schizophrenia is often a chronic and debilitating disorder. Epidemiological evidence supports the conclusion that schizophrenia occurs universally and has similar manifestations and age and gender patterns in different populations (Jablensky, 2000). Family studies have consistently shown schizophrenia to clusters in families, and nearly all relevant twin studies have shown concordance rates higher among identical twins than among fraternal (Shih et al., 2004). The general life-time prevalence is estimated at 0.5 – 1.0 % (American Psychiatric Association, 1994; Shih et al., 2004). In the World Health Report, 2001, schizophrenia is listed as the 7th leading cause of YLDs at global level, and the 8th leading cause of disability-adjusted life years (DAYLYs) in 15 – 44-years olds (World Health Organization, 2001). Kringlen et al. (2001; 2006) estimated a life-time prevalence at 0.4 % for "non-affective psychoses", i.e. schizophrenia and paranoid conditions, in two different Norwegian populations. But, as the authors comment, the estimate is probably to low, as individuals who were hospitalized or too ill to participate in the studies, were excluded.

For both these main groups of psychiatric disorders – affective disorders and schizophrenia - the existence of a *spectrum* of aetiologically/genetically related conditions has been indicated (see later).

The main objectives in this thesis is, firstly to examine as to whether such spectrums of genetically related condition exist for the two groups of affective disorders; bipolar and unipolar depressive disorders, secondly to examine and describe personality features ("schizotypal features") possibly genetically related to schizophrenia.

The methodological approach applied in this thesis is within the field of psychiatric epidemiology; more precisely stated - *genetic epidemiology*. Family- and twin study designs are well suited for the study of causes and are commonly applied within in this tradition. The relationship between aetiology, nosology, epidemiology and genetic epidemiology is schematically illustrated in Fig. 1.

Fig 1. The relationship between aetiology, nosology, epidemiology and genetic epidemiology of mental disorders



The current common diagnostic systems in psychiatry contain mainly descriptive diagnoses. The manuals say little about aetiology. The point of departure taken in the current work is the study of causes, i.e. to try to disclose and describe phenotypes that may be useful to consider in further aetiological research as well as clinical praxis and epidemiological studies, as they seemingly may have some aetiological factors in common. Showing that one approach/definition towards diagnosing "the same" disorder produces a higher heritability than another approach, may testify to a higher aetiological validity of the first definition compared with the second. Apart from the obvious importance in its own, clarifying the aetiological factors behind common, main psychiatric disorder might also have consequences for future nosological systems.

The study descried in paper number one and two in this thesis applied a twin-design. A combined twin-and family design was applied in the study described in paper three. Some general remarks and methodological considerations concerning nosology, genetic epidemiology and the twin-study-method in special are thus appropriate and are presented in the subsequent sections.

1.2. Psychiatric diagnoses and diagnostic systems (Nosology)

As mentioned previously, the criteria-based diagnostic systems, like DSM-III-R (American Psychiatric Association, 1987) and ICD-10 (World Health Organization, 1993), have made reliability (or agreement between clinicians/researchers) feasible (Skre et al., 1991; Torgersen et al., 2000). The central problem is, however, the validity. Many authors have pointed out or argued that, at least from a genetic point of view, the current boundaries, as defined by DSM-III-(R) and ICD-10, for different main groups of psychiatric disorders, may be to narrow

(Karkowski and Kendler, 1997; Kelsoe, 2003; Kendell and Jablensky, 2003; Kendler et al., 1995d; Kendler et al., 1995c; Kendler and Gardner, Jr., 1998a; Kringlen, 1993; Rutter, 2003).

As for affective disorders, a spectrum consisting of so called 'bipolar spectrum disorders', usually including bipolar I- and II disorder, but also cyclothymic disorder, and other hypomanic states, has been indicated (Akiskal, 2002; Akiskal et al., 2006; Angst, 1998; Angst and Gamma, 2002; Perugi and Akiskal, 2002). Likewise, results substantiating a more continuous interpretation of unipolar depressive symptoms, including sub-threshold symptoms beyond major depression have been reported (Angst et al., 2000; Angst and Merikangas, 1997; Judd et al., 1998; Kendler and Gardner, Jr., 1998a; McGuffin et al., 1991; Oquendo et al., 2004; Rapaport et al., 2002). And lastly, indications of an aetiological connection between bipolar affective disorders one the one hand and unipolar major depression one the other, have been brought forward (Karkowski and Kendler, 1997; McGuffin et al., 2003; Shih et al., 2004).

Concerning the other main diagnostic group, besides affective disorders, in the Neo-Kraepelinian nomenclature; the schizophrenias, the existence of a spectrum of aetiologically/genetically related conditions has also been indicated since long time ago, especially after the publication of the landmark Danish Adoption Study (Kety et al., 1968; Kety et al., 1978; Spitzer et al., 1979) up to present time (Kendler et al., 1995c; Siever et al., 1993; Tienari et al., 2003). (See later for more).

1.3. Psychiatric epidemiology with special emphasis on genetic epidemiology

There are two main categories of epidemiology studies, *descriptive* and *analytic*. Descriptive studies are concerned with the existing distribution of variables; they do not test hypotheses or

make inferences concerning causality. Analytic studies are designed to examine associations, particularly hypothesized causal relationships, and focus on identifying or measuring the effects of specific risk factors. *Genetic epidemiology* can be either descriptive, or analytic, as the methods applied in this thesis.

The steps of an analytic genetic epidemiological research can be described as the following:

1. Establishing that there is a genetic component to the disorder.

2. Establishing the relative size of that genetic effect in relation to other sources of variation in disease risk i.e. environmental effects such as intrauterine environment, physical and chemical effects as well as psychological and social aspects.

3. Identifying the gene(s) responsible for the genetic component.

Genetic epidemiology is commonly divided into quantitative genetic epidemiology (point 1 and 2 above), gene finding research and molecular genetics. *Quantitative genetic epidemiology* includes family-, twin- and adoption studies. The aim of quantitative genetic epidemiology is to study how much of the variation in a characteristic is due to *genetic variation*, and how much is due to variation in *environment*. The genetic variation can be additive or non-additive (implying the configuration of genes). The environment can be the effect of growing up in a particular shared environment (e.g. family) that makes individuals more similar to each other (shared/common environment) or the effect of factors only influencing one family member (non-shared/unique environment).

The twin study method and the combined twin-family study method, as applied in this thesis, are designs often utilized in such aetiological studies (i.e. the study of causes) or more specific; in quantitative genetic epidemiological studies.

1.3.1. The twin study method

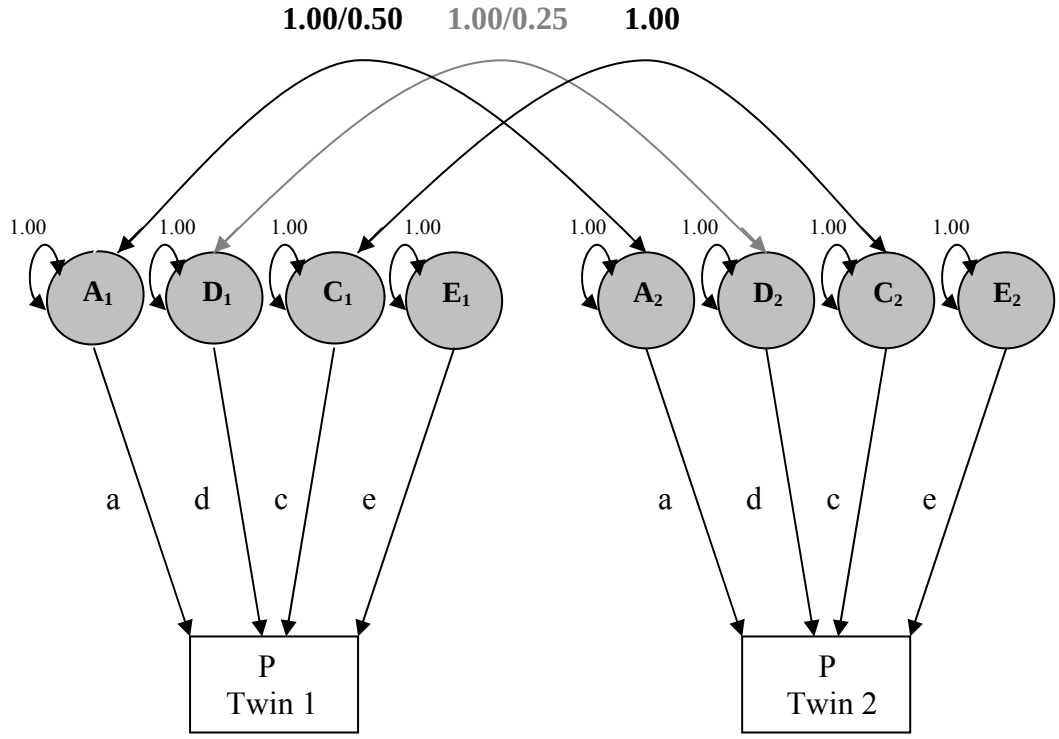
General considerations

Identical or monozygotic twins (MZ) are basically considered as genetically identical as they arrive from the same zygote. Fraternal or dizygotic twins (DZ) share on average 50 % of their genes, just like ordinary siblings. The environment that are shared by twins reared together (shared environment/common environment, C) is per definition the same both for DZ- and MZ twin pairs. The common genes and common environment are the factors that cause twins in a pair, or for that matter others family members, to resemble each other. The unique genes and the non-shared environment/unique environment (E) makes individuals differ from each other. Accordingly, if a trait or a disorder is influenced genetically, we would expect monozygotic twins to be more similar than dizygotic twins as they share the same "amount" of common environment as DZ-twins and in addition all their genes, while the DZ-twins on average only share 50 % of their genes.

Recent advances in statistical modelling like Structural Equation Modelling (SEM) have given rise to considerable advances in genetic epidemical research, twin-studies included. SEM is a technique used to estimate models of linear relationship among variables, both measured- (e.g. phenotypes) and latent variables. Applied on a classical twin study design, a structural equation model will be a hypothesized pattern of directional and bidirectional (e.g. correlations) relations among a set of phenotypes and latent parameters; additive genetic effects (A), dominant genetic effects (D), common environmental effects (C) and unique environmental effects (E), as graphically illustrated by the path diagram in Figure 2. In structural equation modelling the effects (a,c,d, and e) caused by A, C, D, and E are modelled as regression coefficients in a linear regression of measured variables on unobserved, latent sources of variance ($P = aA + dD + cC + eE$). Estimates of these effects are derived by

parameterizing the model according to the differential degree to which pair of MZ- and DZ twin pairs are correlated for genetic effects. In the figure, squares represent observed variables (phenotypes) and circles latent (unmeasured) variables. Double-headed arrows represent covariance between variables due to a common cause and/or reciprocal causations. Single headed arrows represent paths; a causal relationship between the variable at the tail on the variable at the head of the arrow. The variance of each single latent variable is standardized to one, indicated in the figure by small double headed loops connected to the variables. The numbers typed in bold face on the top of the figure express the co-variance between twin 1 and twin 2 both for MZ's and DZ's, separated by a slash. Since the twins in an MZ-pair share all their additive genes and the DZ's, in average, half of them, the co-variance for A_1 og A_2 are fixed to 1.0 for MZ's and 0.5 for DZ's. The variables D_1 and D_2 correlate 1.0 for MZ's and 0.25 for DZ's. The C variables are perfectly correlated (1.0) for both MZ- and DZ pairs. The E variables are by definition unique to the individual person and consequently do not contribute to the covariance between the twins in a pair.

Figure 2. Path diagram showing different sources of phenotypic variation and co-variation between twins in a pair.



Abbreviations: A = Additive genetic effect; D = Non-additive (dominant) genetic effect; C = Common (shared) environmental effect; E = Unique (non-shared) environmental effect.

One basic assumption in so-called biometrical twin models is that the susceptibility for a disorder is distributed continuously following a normal distribution in the population (Reicborn-Kjennerud, 2002). Psychiatric disorders are usually categorically defined and are assumed to manifest themselves in subjects where the susceptibility surpasses a certain threshold. Tetrachoric correlations, which are a form of simulated Pearson-correlations based on dichotomized variables, are thus used in these analyses. Given a certain (underlying) bivariate normal distribution, the correlation will be independent of the actual threshold chosen for diagnosing the disorder, and unlike concordance figures, tetrachoric correlations,

and heritability estimates that rests on such correlations, can be interpreted independent of the prevalence for the actual disorder (Tambs, 2002). The observed data can either be presented to the software program e.g. Mx (Neale et al., 1999) as variance-covariance matrices (summary statistics) or as raw data. In the papers in this thesis the analyses were performed with raw data in Mx, based on the full sample of psychiatric patients, i.e. including both unaffected pairs and affected (discordant and concordant) pairs. The raw data analysis involves testing the specified models for each pair of twins.

The twin study method, as such, rests on some fundamental assumptions. The first and, perhaps the most central, is *'the equal environment assumption'* (EEA) which assumes that MZ- and DZ twins are to the same extent exposed to shared environmental influences that are of aetiological relevance for the disorder studied. If this assumption is violated because MZ twins experience more similar environments than DZ twins, for instance because they are treated more similar as they look more alike, dress more alike etc, this violation would inflate the genetic influence. Some authors have seriously questioned the validity of result derived from twin studies because they consider the equal environment assumption violated in such designs (Joseph, 2002). However, attempts to test 'the equal environments assumption' have in general proven it reasonable for most traits (Kendler et al., 1993b; Kendler et al., 1993a; Kendler et al., 1994; Kendler and Gardner, Jr., 1998b; McGuffin et al., 1996; Plomin et al., 2001). Kendler and Gardner Jr. (1998b) suggest the following "prudent" conclusions from their study: "substantial biases in twin studies of psychiatric and substance dependence disorders resulting from differential environmental experiences of MZ and DZ twins in childhood and adolescence are unlikely."

Another aspect, familiar to clinicians, is that the quality of facets of a "quantitatively" shared environment, e.g. family environment, may not be de facto shared between the twins, and consequently, some experiences also from a so called shared environment may contribute to the effect of E (not C). Put in other words; some of what traditionally is defined as the shared environment (objectively) may probably have a non-shared effect (effectively).

Assortative mating, usually indicated by a positive correlation between the phenotypes of mates, constitutes another possible threat to the assumptions underlying classical twin-studies. Assortative mating tends to increase correlations between relatives, making e.g. DZ twins more similar to MZ twins, and thus inflate the shared environment estimates and deflate the genetic component estimates. Moderate assortative mating for psychiatric disorder probably exists. Maes et al. (1998) found that significant but moderate primary assortment for psychiatric disorder existed, but concluded that the bias caused by ignoring this small amount in twins studies is negligible. Anyway, to the extent that assortment exists for the disorder considered in this thesis, it will here, as in other twin studies, tend to deflate the heritability estimates.

Prenatally, MZ twins may experience greater environmental differences than DZ twins, especially for the majority of MZ twins that share the same chorion. Since such single-chorion twins compete for the same placental blood supply, one twin may receive significantly more nourishment than the other. The consequences of this on the later development of the twins can include considerable phenotypic differences even before postnatal influences of the family are considered. For instance, MZ twins show greater birth weight differences than DZ twins (Plomin et al., 2001). To the extent that MZ twins

prenatally experience greater environmental differences than DZ twins, the twin study method will underestimate heritability (and overestimate the effect of specific postnatal environment).

Another important issue is that MZ twins, both as children and grown ups, may have more similar experiences than DZ twins because they are more genetically similar, i.e. some experiences may be genetically driven. This is though not a violation of the equal environment assumption as the differences are not caused environmentally. For instance Kendler and Karkowski-Shuman (1997) found that genetic liability to major depression was associated with a significant increased risk of experiencing several stressful life events. This is an example of what have been described as genetic control over exposure to environment (Kendler and Baker, 2007; Kendler and Eaves, 1986), an example of what traditionally is called *gene – environment correlations* (G - E), but that perhaps more correctly should have been denoted *gene – experience* correlations, because environment pr definition is an independent latent factor that cannot be correlated with genes. Anyway, what the expression implies is that genetic propensities are correlated with individual differences in experiences. This may cause that what appears to be an environmental risk might actually reflect genetic factors.

Along with the above mentioned gene – environment correlations, *gene x environment interaction* is also worth considering when interpreting results from twin studies or in general, genetic epidemiological studies. Gene x environment interaction referrers to the way genes and environment affect phenotype depending on genetic sensitivity to different environments. A probably well known example of genetic sensitivity to a particular environmental factor is that of phenylketonuria/Følling's disease (PKU). Children born with two recessive alleles for PKU will develop mental retardation if their food is not controlled for phenylalanine. A diet

low in phenylalanine has a major effect on these children; it prevents mental retardation. For other children a diet without phenylalanine has neither positive nor negative effects. Kendler et al. (1995a) found that genetic factors influenced the risk of onset of depression partly by altering the individuals' sensitivity to the effect of stressful life events. In a study by Caspi et al. (2003) a common functional polymorphism in the serotonin transporter gene (5-HTTLPR) was found to moderate the influence of stressful life events on depression. The study was replicated by Kendler et al. (2005) and this finding was broadly confirmed.

As mentioned above, identical or monozygotic twins (MZ) have traditionally been assumed to be genetically identical, but this assumption probably has to be modified in the light of new knowledge. Both *genetic and epigenetic differences* may exist between these twins (Kato et al., 2005). A very recent study (Bruder et al., 2008) found that even though the genome is virtually identical in identical twins, there are in fact tiny difference and these differences are relatively common. The researchers studied 19 pairs of identical twins (nine pairs discordant for a neurodegenerative phenotype and ten phenotypically unselected normal concordant pairs) and found that they had indeed the same DNA, but nevertheless evidenced differences in the number of copies of individual DNA segments, so called Copy-Number-Variation (CVN). A segment might be missing or more copies might exist in one twin. Such differences may prove to be one of several possible explanations for the relatively often observed discordance in phenotype between some identical twins.

Another crucial point concerning the twin study method is whether or not the samples in such studies are *representative* of the population in general. Twins tend to have shorter gestation times, lower birth weight and the intrauterine environment can be adverse as twins share one womb. In addition, twins on average learn to walk and talk later compared with singletons.

Most studies that have found differences between singletons and twins have examined young twins. However, the differences observed between singletons and twins in early life seem to a large extent to be "washed out" during childhood (Evans and Martin, 2000), and in a study by Nilsen et al.(1984), comparing older twins and singletons, no differences in physical characteristics or cognitive abilities were found. Likewise, adult twins seem to exhibit similar statistics as singleton for most traits and diseases (Kendler et al., 1995b).

Interpreting heritability

In quantitative genetic methodology, as applied in this thesis, *heritability* (h^2) denotes the proportion of the phenotypic variance that is attributable to genetic variance. In the case of monozygotic and dizygotic twins, h^2 is estimated by doubling the differences in intraclass correlations observed between the MZ- and DZ pairs. The formula most commonly used is thus: $h^2 = 2(r_{MZ} - r_{DZ})$. What the formula accomplishes is to estimate how much of an increase in similarity between individuals is achieved given that the genetic component is twice as great for MZ twins as for DZ twins. It is essential to observe that heritability refers to the genetic contribution to individual differences (variance) in a population and not to the phenotype of a single individual. Further, heritability is specific to the population on which it is calculated. It only describes the extent to which genes contribute to the observed differences between individuals growing up in the same environments (i.e. from the same population) and provides no information concerning differences, related to the same trait, between groups in different populations (Bronfenbrenner and Ceci, 1994). Values of h^2 for the same trait/disorder may vary from one population to another, and from one cohort to an other, which of course underscore the usefulness of studying the same trait in different populations and at different times. Still further, as expressed by Plomin et al. (2001), causes of individual differences within groups have no implications for the average differences between groups.

Even with a high heritability within the groups, the average difference *between* groups could still be due exclusively to environmental causes.

Another, perhaps at first glance, contra-intuitive point, is that h^2 increases the more egalitarian the population or society in which it is measured is. The reason for this is logical and is perhaps best illustrated with an extreme supposition. Suppose that the environments were made exactly the same for everyone in a population; then all individual differences would be due exclusively to genetic differences because no other differences existed. For instance, Sundet et al. (1988), using IQ scores as outcome data, found some support for the results from a previous study of educational attainment (Heath et al., 1985) that had shown an increase in h^2 for twins born in Norway after 1940. They interpreted this finding to be due to the fact that Norwegian post-war governments had made education more equally accessible for all youngsters seeking education, for instance by offering loans.

Shared environment

The term *shared environment* or common environment (c^2) as used in quantitative genetic methodology, refers to the kind of environment that make individuals similar to each other, e.g. parental styles, common experience with peers, education and occupation.
Shared environment is per definition supposed to affect MZ- and DZ twins equally and in both instances contribute to make them similar. c^2 in a twin design can be expressed by the following formula: $c^2 = r_{MZ} - 2(r_{MZ} - r_{DZ})$, as any DZ-correlation more than half of the MZ-correlation is due to shared environment. Any DZ-correlation lower than half the MZ-correlation will be indicative of a dominance effect (D) or epistasis.

Non-shared environment

The *non-shared environment* or unique environment component (e^2) of variance refers to variance not explained by heredity or by shared family environment and also includes random error of measurement. Non-shared environment exhibits an idiosyncratic effect on the individual and contribute to make members of the same family dissimilar. In a twin design, e^2 contribute in direction of making both MZ and DZ-twins more dissimilar. MZ-twins reared together provide a direct test of the effect of non-shared environment. Because they are genetically identical, with the above mentioned possible reservations, and are reared together (i.e. have the same shared environment) differences within pairs can only be due to non-shared environment. Consequently, e^2 can be expressed by the following formula: $e^2 = 1 - r_{MZ}$. Unfortunately, less than ideal reliability is included in the non-shared environmental effect. Since the sum of the effects (of genes, shared and non- shared environment) is 100 %, bloated non-shared environment effect wrongly reduces the effects of genes (heritability) as well as shared environment.

1.4. Heritability of mental disorders – earlier studies

Psychopathology has long time been the most active area of research in behavioural genetics. Though simple patterns of inheritance have generally not been found, results from family-, twin- and adoption studies have in general been indicative of a genetic influence in the aetiology, especially behind the more severe disorders like bipolar affective disorder and schizophrenia, but also for the "less severe" disorders like major depression and anxiety disorders. For comprehensive reviews see; Plomin et al. (2001), Shih et al. (2004) and Kringlen (1999).

1.4.1. Affective disorders

Genetic influences in the aetiology of bipolar mood disorders, especially bipolar I disorder, have been suggested in several twin- and adoption studies (e.g. Bertelsen et al., 1977; Cardno et al., 1999; Kendler et al., 1995d; Kieseppä et al., 2004; McGuffin et al., 2003; Mendlewicz and Rainer, 1977; Torgersen, 1986). Linkage- and association studies have given some indications, but have to date not yielded consistently reproducible findings. The lack of reproducible findings has raised the question about the validity of the description of the main phenotypes, and many authors have argued for a widening of the boundaries of the bipolar spectrum to include hypomania, cyclothymia, and bipolar disorder not otherwise specified (included bipolar II). Besides, the boundaries between major depression and other, less severe, unipolar affective disorders and subsyndromal depressive states are diffuse, and the clinical manifestations of major depression are variable, including several proposed sub-types. Cross-concordance, especially between MZ-twins, for different subgroups of depression is common (e.g. Kendler and Gardner, Jr., 1998a; McGuffin et al., 1991; Torgersen, 1986).

A consistent finding dating back many years, is that affective disorders tend to aggregate in families, **(**cf. e.g. McGuffin, 2008; Shih et al., 2004). A moderately high heritability of major depression (MD), ranging from about 33 % to about 54 %, in general, between 33 % and 45 % (Shih et al., 2004), has been indicated in several studies (Bierut et al., 1999; Fu et al., 2002; Karkowski and Kendler, 1997; Kendler et al., 1995d; Kendler et al., 2001; Kendler et al., 2006; Lyons et al., 1998; McGuffin et al., 1996; Sullivan et al., 2000; Torgersen, 1986). The corresponding estimates for bipolar disorders, either bipolar I, or bipolar I and II considered together, have generally tended to be higher, ranging from about 79 % to 93 % (Cardno et al., 1999; Kendler et al., 1995d; Kieseppä et al., 2004; McGuffin et al., 2003; Shih et al., 2004). A spectrum consisting of so called 'bipolar spectrum disorders', usually including bipolar I-

and II disorders, but also cyclothymic disorder, and other hypomanic states have been indicated e.g. (Akiskal, 2002; Akiskal et al., 2006; Angst, 1998; Angst and Gamma, 2002; Perugi and Akiskal, 2002). Likewise, results substantiating a more continuous interpretation of unipolar depressive symptoms, including sub-threshold symptoms beyond major depression have been reported. (Angst et al., 2000; Angst and Merikangas, 1997; Judd et al., 1998; Kendler and Gardner, Jr., 1998a; McGuffin et al., 1991; Oquendo et al., 2004; Rapaport et al., 2002).

Summing up; although some earlier studies have indicated the existence of a spectrum of bipolar disorders, and others given reasons for a more continuous interpretation of unipolar depressive symptoms, the heritability of these spectra compared with the main single diagnoses encompassed by the same spectra is largely unknown. As for *bipolar disorders;* even though it is widely believed that there is a large body of twin studies, there really is not. Besides, in some of the older studies the diagnostic criteria are diffuse and not easy to match with modern diagnostic criteria. Further, earlier twin-studies on bipolar disorders have usually only included bipolar I disorder or the combination of bipolar I and II disorder, not cyclothymia. Still further, comparable earlier studies (Cardno et al., 1999; McGuffin et al., 2003), that explicitly have reported heritability estimates for bipolar disorders, defined as bipolar I- or bipolar II disorder taken together, are, to our knowledge, based solely on samples from British populations, and consequently, none on a Scandinavian sample. Lastly, an examination of the heritability of the single disorder in the bipolar spectrum, and different combinations of these, may give indications as to whether these disorders may represent a common genotype or not, and in that way contribute to the definition of valid phenotypes.

Concerning *unipolar depressive disorders* the indications of the existence of a continuum of symptom or a spectrum of disorders come mainly from clinical epidemiological or follow–up studies. To our knowledge, no twin-studies have attempted to estimate the heritability for the whole range of unipolar disorders, identically defined in probands and co-twins, considered together. The study by Torgersen (1986) is, again to our knowledge, the closest approximation to this, but in Torgersen's study the definition of caseness in these comparisons was not identical in probands and co-twins.

1.4.2. Schizophrenia spectrum

Heritability estimates for schizophrenia are usually reported at 82-85 % (Shih et al., 2004). Also, concerning this other main diagnostic group, besides the affective disorders, in the Neo-Kraepelinian nomenclature, a spectrum concept has been proposed, not only including other symptom diagnoses, like non-affective psychosis, but first of all sc*hizotypal personality disorder*.

The concept of schizotypal personality disorder (SPD) and its aetiological relation to schizophrenia have been heavily discussed since its introduction to the official classification of mental disorder in DSM-III. Many authors have argued that only some personality features included in the definition of schizotypal personality disorder truly relate to schizophrenia.

Spitzer et al. (1979) tried to differentiate between patients who were similar to non-psychotic relatives of patients with schizophrenia and those who were outside the schizophrenia spectrum. Their factor analytic differentiation resulted in two factors that were not completely independent, but made the basis for the two DSM-III diagnoses; schizotypal (SPD) and borderline personality disorder (the former supposed to be related to schizophrenia). Later, a

possible aetiological connection especially between schizophrenia and schizotypal personality disorder (or schizotypal symptoms) has been indicated in many studies e.g. (Baron et al., 1983; Baron et al., 1985b; Baron et al., 1985a; Gunderson et al., 1983; Kendler et al., 1981; Kendler and Gruenberg, 1984; Lowing et al., 1983; Mednick et al., 1987; Torgersen et al., 1993a). But also a broader spectrum including both schizotypal/paranoid personality disorder and non-schizophrenic psychosis has been indicated (Kendler et al., 1995c). Concerning schizotypal personality disorder, some authors have maintained that the definition of DSM-III schizotypal personality disorder did not really correspond to the true nature of a schizophrenia related personality disorder (Gunderson et al., 1983), and that only some of the symptoms criteria included in the DSM-III definition were useful in this regard. Only the so-called "negative criteria" of schizotypal personality disorder, namely the odd, eccentric, aloof, affective-restricted features, were in accordance with the earlier description of the relatives of schizophrenic probands (Kendler, 1985). Torgersen (1984) and (1985) stated that only the negative traits were genetically transmitted. On the other hand, Frances (1985) defended the criteria, stating that the combination of negative and positive symptoms often was observed among clinical cases, if not among relatives of schizophrenic probands. In a study of 176 non-schizophrenic first-degree relatives (both co-twins and other first-degree relatives) and 101 co-twins and first-degree relatives of probands with major depression, Torgersen et al. (1993a) found that DSM-III-R schizotypal personality disorder was partly defined by a set of criteria that described a "true" schizophrenia-related personality disorder, and partly features that were not specific for relatives of schizophrenic probands. They stated that the negative criteria of the DSM-III-R schizotypal personality disorder definition, namely odd speech, constricted affect, odd behaviour and excessive social anxiety, seemed to constitute the "true" schizophrenia-related schizotypal disorder. Odd speech and excessive social anxiety were found to be especially important criteria. Excessive social anxiety seemed to the best marker

of a possible genetic link between the disorders, as it was significantly more frequent among monozygotic co-twins of schizophrenic probands than among other non-co-twin first-degree relatives. The so-called "positive" schizotypal criteria – ideas of reference, suspiciousness, recurrent illusions and odd beliefs as well as social isolation - were partly, although not significantly, more common among relatives of probands with major depression. Thus, the results indicate that the criteria for DSM-III-R schizotypal personality disorder describe two different types of SPD, with only some features that are more specific for relatives of schizophrenic probands.

In conclusion, earlier studies, as referred above, have indicated the existence of an aetiological connection between schizophrenia and schizotypal personality disorder. The DSM-IV manual (American Psychiatric Association, 1994), also states that schizotypal personality disorder, as defined in the manual, tends to aggregate familially and is more frequent among the first-degree biological relatives of individuals with schizophrenia than in the general population. However, the question as to whether only some features defined by the criteria of schizotypal personality disorder truly relates to schizophrenia remains disputed, as indicated above. Perhaps the most potent method to examine this is, as done in paper three here, to study which features that characterize schizotypal personality disorder among co-twins and other first degree relatives of individuals with schizophrenia, compared to schizotypal disorder among individuals who are not co-twins or first degree relatives of individuals with schizophrenia. Succeeding in separating personality features that are inside the spectrum of schizophrenia and thus may be aetiological connected to schizophrenia, from those that are not, can perhaps tell us something about core psychopathology of schizophrenia. To make a perhaps little halting, but yet illustrating analogue with internal medicine, from Kendler (1985); as hypertensive relatives of individuals with hemorrhagic

stroke can tell us something about the pathophysiology underlying stroke, the characteristic symptoms of the schizotypal/aberrant relatives of schizophrenic probands may tell us something important about the fundamental psychopathology underlying schizophrenia.

II. OBJECTIVES

The main aims of the study were firstly to investigate aetiological factors related to bipolar spectrum disorders and unipolar depressive disorders, and secondly, to describe personality features that may be aetiologically related to schizophrenia.

The specific objectives for the separate papers were the following;

- To estimate the contribution of genetic, shared/common- and non-shared/unique environmental factors in the aetiology of the three different 'bipolar spectrum disorders'; bipolar I disorder, bipolar II disorder and cyclothymia and the different combinations of these, and to investigate whether these three disorders in the 'bipolar spectrum' may be viewed as various expression of an underlying genetic commonality. *(Paper I)*

- To estimate the contribution of genetic, shared/common- and non-shared/unique environmental factors in the aetiology of major depression, and major depression (MD) combined with other unipolar depressive disorder (atypical depression, dysthymia, and depressive adjustment disorder), and to investigate whether MD and these other unipolar depressive disorders may be viewed as various expression of an underlying genetic commonality. *(Paper II)*

- To investigate the difference between schizotypal personality disorder (SPD) within and outside the genetic spectrum of schizophrenia by comparing the occurrence of a broad realm of schizotypal-borderline features among individuals with SPD related to (co-twin or 1. degree relative) and not related to a person with schizophrenia. *(Paper III)*

III. MATERIALS AND METHODS

The study descried in paper number one and two applied a twin-design. A combined twin-and family design was applied in the study described in paper three.

3.1. Sample

The sample consisted of a total number of 303 same sexed twin pairs and their first-degree relatives (parents and siblings), and was ascertained by matching the Norwegian Twin Register for twins born between 1936 and 1960 with the National Register for Mental Disorders, and directly from in- and out-patient clinic archives of the University Department of Psychiatry, Vinderen and Modum Bad Hospital, Vikersund. The Central Bureau of Statistics has been in charge of the registration of multiple births in Norway from 1946. The register of twins born before 1946 was compiled by Kringlen (1978). The National Register of Mental Disorder, established in 1936, is now closed, but was in operation during the first part of the sampling procedure.

Sub-samples of the total sample have been described elsewhere (Onstad et al., 1991; Skre et al., 1993; Skre et al., 2000; Torgersen et al., 1993b; Torgersen et al., 2000) and a thorough

description of the whole sample of twins is given in paper one and two in this thesis. The criterion for inclusion was that at least one of the twins in a pair had been treated for a non-organic mental disorder in an in- or out-patient clinic. When both twins were registered as cases, the pair was entered twice (19 cases) following the probandwise method. Only same sexed twins were included. Pairs, in which it was known at the time of sampling that one of the twins was dead, were excluded. In eight of the sampled twin pairs one of the twins turned out to be deceased before the interview. These twins had been interviewed in an earlier survey by the senior investigators in the research group, and the information from these interviews, in combination with hospital journals and/or interviews with other sources, allowed for determining reliable DSM-III-R Axis I diagnoses. Pairs in which one of the twins was too ill to participate or it was not possible to locate/trace the twin, were excluded. An exception was made for two twins, (one was mute and the other could not be traced) as information from an interview by a senior author from an earlier survey and reliable information from other informants were available. Seventeen percent of the twin pairs that first were contacted were lost as one or both twins in the pair refused to participate. The twins were first contacted by mail with a short presentation of the study. They were later contacted by telephone. The first-degree relatives were contacted by telephone after an overview provided by the probands and with their consensus. All twins and relatives that were included participated voluntarily and after informed consent was obtained.

3.2. Zygosity

A questionnaire that had previously predicted zygosity correctly in 95 % of the cases compared with 10 genetic blood and serum markers (Torgersen, 1979), was applied for zygosity determination. All subjects, both the twins and their first-degree relatives, completed this inventory independently, thus further enhancing the reliability of the method. The result

of this method was uncertain in only two pairs, in which blood analyses were performed to ensure the correct assignment of zygosity.

The total sample of same-sexed monozygotic and dizygotic twin pairs (where 19 pairs are counted twice following the probandwise method) and their first-degree relatives now consist of 303 probands, 303 co-twins and 389 first-degree relatives. One hundred and thirty five (44.6 %) of the twin pairs were monozygotic (MZ) and 168 (55.4 %) were dizygotic (DZ). The proportion of the sample included in the different analyses in this study varied, of course, depending on the actual diagnoses that were considered, and is accounted for in the different papers.

3.3. Diagnostic procedures

The twins and their first-degree relatives were interviewed in person about their lifetime history of mental disorders and personality traits. They were also asked about aspects concerning the twins' birth, early behaviour and experiences. In addition they were asked to complete three (the twins four) questionnaires of which two were related to personality features. For practical reasons, most often the same interviewer interviewed both twins in a pair. The relatives were, however, most often interviewed by another interviewer. The interviewers were initially blind to the zygosity of the twins. The interviews occasionally took place in hospitals, but most often in the homes of the subjects throughout Norway and even abroad. Each interview lasted on average between three and four hours. The interviewers were residents in psychiatry, psychologists, and graduate students in psychology or medicine, who were trained by the senior investigators in the diagnostic criteria of the DSM-III-R and accomplishing the SCID-interviews (Structured Clinical Interview for DSM-III Axis I and Axis II) (Spitzer and Williams, 1984; Spitzer and Williams, 1985). Regular meetings in the

research group and supervision were carried out to enhance the reliability and validity. In cases of doubt, the case was discussed with the senior investigators before a diagnosis was assigned.

In the diagnostic approach, a life-time perspective was applied so that the respondents were diagnosed according to DSM-III-R criteria if the disorder in question had *ever* been present, independent of whether it was actually present at the time of the interview. Except for schizophrenia, there was no hierarchy among the diagnoses and the respondents were given more than one diagnosis if they fulfilled the criteria.

The diagnostic classification system employed was the DSM-III-R. The diagnoses were based on the personal interviews with the Structured Clinical Interview for DSM-III Axis I (SCID-I) rev. version 5/1/84 (Spitzer and Williams, 1984) and the Structural Interview for DSM-III-R Personality Disorders, (SCID II) (Spitzer and Williams, 1985). The diagnostic criteria in these versions were based upon the proposal for revision of the DSM-III (American Psychiatric Association, 1980) and were closer to DSM-III-R (American Psychiatric Association, 1987) than DSM-III, and as DSM-III-R was published during the first period of data collection, all subjects were diagnosed according to the final revision. The SCID-I was translated into Norwegian by Alnæs (1989), and the SCID-II by one of the senior investigators in the present study (S.0.).

In addition, Baron's (1980) Schedule for Interviewing Borderlines (SIB) including Schedule for Schizotypal Personalities (SSP) and Schedule for Borderline Personalities (SBP) was applied to assess schizotypal and borderline features.

In cases where the subjects earlier had been hospitalised in a psychiatric hospital or clinic, permission to access the discharge papers (epicrises) was acquired, and information from these supplemented the information acquired through the interviews.

3.4. Reliability testing of diagnoses

For reliability testing, a random sample of fifty-four SCID-interviews was audio taped and rated independently by 3 raters. The overall kappa obtained for mood disorder was 0.93, confirming that the SCID-interviews yield highly reliable diagnoses (Skre et al., 1991). Specifically, the kappa was 0.93 for major depressive disorder, 0.79 for bipolar disorder (only two cases), 0.88 for dysthymia, 0.80 for cyclothymia and 0.74 for adjustment disorder. The highest interrater agreement was observed for schizophrenia (0.94). The over all kappa for anxiety disorder was 0.82. The kappas for the Axis II disorders were, as expected, generally somewhat lower, though for the personality disorder relevant for this thesis (paper III), schizotypal personality disorder, it was 0.79 (Torgersen et al., 1993a).

3.5. Statistical analyses

The specific statistical analyses are accounted for in the different papers, respectively. Concordance rates in paper I and II were calculated by the Crosstabs procedure in SPSS (SPSS Inc., 2003) with Pearson Chi-square-test or Fisher's exact test. One-way analysis of variance was used to compare the mean scores on different schizotypal and borderline features among the different groups of relatives in paper III. The more advanced analyses used in the biometrical model fitting (Structural Equation Modelling; SEM) in paper one and two, were performed with the software package Mx (Neale et al., 1999). These analyses deserve some more detailed comments here. As mentioned in the introduction, SEM is a statistical technique used to estimate models of linear relationship among variables, which

may include both *measured variables* (e.g. phenotypes as MD or not MD) and *latent variables* (hypothetical constructs, like twin parameters). Applied on twin design, a structural model will be a hypothesized pattern of directional and bidirectional (e.g. correlations) linear relationship among a set of phenotypes and the latent parameters; additive genetic effects (A), dominant genetic effect (D), shared/common environmental effects (C) and non-shared/individual specific/unique environmental effects (E). The aim is to partition the phenotypes' deviation from the population mean into the variance components A, D, C and E. Model fitting implies the process of deciding on the appropriate constellation of these components, that fits the observed data best. This is done by checking the alternative models with the data. LISREL (Jöreskog and Sörbom, 1999) and Mx (Neale et al., 1999), the one used in this thesis, are examples of SEM based software program for such analyses. The analyses in the papers in this thesis were performed with *raw data* in Mx, based on the full sample of psychiatric patients, i.e. including both unaffected pair and affected (discordant and concordant) pairs. The raw data analysis involves testing the specified models for each pair of twins. The fit of the models was evaluated with a Chi-Square test, and the model with the best combination of goodness of fit and parsimony was preferred, in accordance with Akaike's (1987) information criterion (AIC). According to this criterion, the model with lowest value (largest negative value) of AIC, given by the formula AIC = χ^2 – 2 *df,* provides the best fit.

IV. SYNOPSIS OF THE PAPERS

4.1. Paper I

Edvardsen J, Torgersen S, Røysamb E, Lygren S, Skre I, Onstad S, Øien PA.
Heritability of bipolar spectrum disorders. Unity or heterogeneity?
J Affect Disord. 2008 Mar;106(3):229-40.

The aims of the paper was to estimate the contribution of genetic, shared/common- and non-shared/unique environmental factors in the aetiology of the three different 'bipolar spectrum disorders'; bipolar I disorder, bipolar II disorder and cyclothymia and the different combinations of these, and to investigate whether these three disorders in the 'bipolar spectrum' may be viewed as various expression of an underlying genetic commonality.

A sample consisting of same-sexed mono (MZ)- and dizygotic (DZ) twin pairs was drawn from in- and outpatient registers (N=303). The twins were interviewed in person with the Structured Diagnostic Instrument for DSM-III, Axis I (SCID-I). DSM-III-R criteria were applied for final diagnostic assessment. Fifty three probands fulfilled the criteria for one or another bipolar spectrum disorder. Reliability testing demonstrated high interrater reliability; for mood disorders the overall kappa was 0.93.

Cross-tabulations were used to compare concordance rates for different definitions of the bipolar spectrum. Correlations in liability and estimates of the heritability (h^2) with biometrical model fitting were performed.

The results showed that rather more than 42 % of the monozygotic co-twins of individuals presenting with a bipolar spectrum disorder, had a bipolar spectrum disorder themselves. This

compared with 11 % of dizygotic co-twins of probands who had a bipolar spectrum disorder, and 3.8 % of monozygotic co-twins of probands who had another psychiatric disorder. This finding indicate that bipolar spectrum disorders defined as either bipolar I disorder, bipolar II disorder, or cyclothymia are connected to a genetic disposition that is quite specific for these disorders and not for psychiatric disorders in general.

Concordance rates were clearly higher for MZ pairs than for DZ pairs for all single diagnoses and their combinations within the bipolar spectrum. Regarding the situations where the definition of bipolar spectrum/caseness was identical in probands and co-twins; twenty five percent of the MZ co-twins of bipolar I disorder probands had the same diagnosis (bipolar I disorder), compared to 0 % among the DZ co-twins. Slightly more than 38 % of the MZ co-twins of probands with either bipolar I or bipolar II disorder had one or the other of these two diagnoses, compared to 8 % among DZ co-twins. Among the MZ co-twins of probands with either bipolar I disorder, bipolar II disorder or cyclothymia, 42.3 % had one or another of these diagnoses, compared to 11.1 % among DZ co-twins. Further, an indication of the unity between bipolar spectrum disorders came from the considerable cross-concordances between different bipolar diagnoses that were observed. For example, a quarter of monozygotic co-twins of bipolar I probands had a bipolar II diagnosis, and consequently half of these monozygotic co-twins had either bipolar I or bipolar II disorder.

In all instances, except for the situation when bipolar II disorder was considered alone, the MZ- correlations, expressed as liabilities, for the single diagnoses and for all the different identical constellations of diagnoses among probands and co-twins presented above, were more than twice as high as the corresponding DZ-correlations. This indicated that there was no common environmental effect (C) present for the actual disorders or combinations of disorders. Thus an ADE-model was preferred before an ACE-model as the full model in the

model fitting. From the differences between the MZ- and DZ correlations, one could expect the influence of some non-additive genetic effects, but the full ADE-model did not improve fit over a nested model that included only A- and E effects. Thus, on grounds of parsimony, an AE-model seemed most reasonable. The heritability (h^2) of bipolar I disorder was .73, of bipolar I+II disorder .77 and of bipolar I+II disorder + cyclothymia .71 As for bipolar II disorder considered alone, where the MZ-correlation was .56 and the DZ-correlation .37, a model fitting starting with an ACE-model also was applied. Still an AE model turned out best with no significant effect of common environment (C).

The main results from this study were the relatively high heritability estimate for the combination of bipolar I and bipolar II disorder, and also for the combination of bipolar I, bipolar II disorder and cyclothymia. The results indicate that the 'bipolar spectrum' consisting of bipolar I disorder, bipolar II disorder and cyclothymia constitute an entity with high heritability and no shared family environment effects. In clinical practice and genetic research, it seems prudent to not overlook the mild variants of the spectrum as they are quite possibly an expression of the same liability expressed by the severe variants.

4.2. Paper II

Edvardsen J, Torgersen S, Røysamb E, Lygren S, Skre I, Onstad S, Øien PA.
Unipolar depressive disorders have a common genotype.
Journal of Affective Disorders, advanced online publication 21. Jan. 2009;
doi; 10.1016/j.jad.2008.12.004

The purpose of the present study was to estimate the contribution of genetic-, common/shared– and unique environmental factors in the aetiology of pure unipolar major

depression (MD), and MD combined with the other unipolar depressive disorders; atypical depression/depression NOS, dysthymia and depressive adjustment. Further, to investigate to which extent these disorders can be viewed as various expression of an underlying genetic commonality.

A sample consisting of same-sexed mono-and dizygotic twin was drawn from in- and outpatient hospital registers (N=303). DSM-III-R criteria were assessed by personal interviews. One hundred and forty-three of the probands fulfilled the criteria for one or another unipolar depressive disorder. Reliability testing demonstrated high interrater reliability; for mood disorders the overall kappa was 0.93.

Cross-tabulations were used to compare concordance rates for major depression and major depression combined with other unipolar depressive disorders. Correlations in liability and estimates of the heritability (h^2) with biometrical model fitting were performed.

Concordance rates were higher among MZ-than DZ pairs for both major depression (MD) considered alone, and for all the different combinations of MD and other unipolar depressive disorders. Besides, cross-concordance between MD and other unipolar disorders was observed, especially among MZ pairs. MZ-concordance for MD considered alone was 32.7 %, compared to a DZ-concordance at 22.1 %, giving a MZ/DZ-concordance ratio at 1.48. When the definition of caseness was extended to include, besides MD, also atypical depression, the MZ concordance rose to 44.2 % and the DZ concordance to 25.7 %, giving a MZ/DZ-concordance ratio at 1.72. When also dysthymia was included the MZ concordance was 48.3% and the DZ concordance 28.2 %. When, finally, also depressive adjustment

disorder was included in the definition of caseness the MZ concordance was 52.5 % and the DZ concordance 30.5 %.

The largest difference in concordance rate between MZ- and DZ pairs emerged when the frequency of MD, atypical depression, dysthymia or depressive adjustment disorder among the co-twins of MD- or atypical depression probands was compared. Almost 54 % of the MZ co-twins of these probands had either MD, atypical depression, dysthymia or depressive adjustment disorder compared to 28.6 % of the DZ co-twins, giving a MZ/DZ ratio at 1.88.

In all instances, except for the situation when MD was considered alone, the MZ-correlations were more then twice as high as the corresponding DZ correlations. This indicated that there was no common environmental effect (C) present for any of the different definitions of the unipolar depressive spectrum, with the possible exception for MD considered alone. Based on this observation, an ADE-model, instead of an ACE-model, was chosen as the main full model for the further model fitting. For MD considered alone, where the MZ-correlation was .39 and the DZ-correlation .27, a possible C-effect was indicated. However, when tested, only a small *non-significant* effect (0.15) was observed. From the other differences between MZ- and DZ correlations, one could expect the influence from some non-additive genetic effects, but an ADE model did not show a better fit than an AE model, so on grounds of parsimony, an AE model was the most reasonable. The heritability (h^2) of MD was .42, of MD+atypical depression .51, of MD+atypical depression+dysthymia .45 and of MD+atypical depression +dysthymia+depressive adjustment disorder .46.

The main findings from the present study were that the strictly unipolar depressive spectrum studied here is moderately heritable, with no significant effects of shared environment, and

that the tendency is towards higher heritability for the combined categories, especially MD and/or atypical depression, compared to MD alone. The unipolar depressive disorders appear to have the same genetic aetiology, being severity variations of the same underlying liability.

4.3. Paper III

Torgersen S, Edvardsen J, Øien PA, Onstad S, Skre I, Lygren S, Kringlen E.
Schizotypal personality disorder inside and outside the schizophrenic spectrum.
Schizophr Res. 2002 Mar 1;54(1-2):33-8.

The aim of the present study was to investigate the difference between schizotypal personality disorder (SPD) within and outside the genetic spectrum of schizophrenia by comparing the occurrence of a broad realm of schizotypal-borderline features among individuals with SPD related to (co-twin or 1. degree relative) and not related to a person with schizophrenia. Individuals with other mental disorders or no mental disorder served as controls.

The sample, consisting of same-sexed mono-and dizygotic twins and their 1.degree relatives, was ascertained through probands from in and out patient registers. DSM-III-R criteria for Axis I and Axis II disorders were assessed by personal interviews. In addition Baron's (1980) Schedule for Interviewing Borderlines (SIB) including Schedule for Schizotypal Personalities (SSP) and Schedule for Borderline Personalities (SBP) was applied to assess schizotypal and borderline features. Reliability testing demonstrated high interrater reliability for Axis I disorders and moderate to high interrater reliability for most Axis II disorders. Specifically, the kappa was 0.94 for schizophrenia and 0.79 for schizotypal personality disorder. One-way-analysis of variance was used to calculate differences between the groups with respect to different schizotypal and borderline features.

The results showed that individuals with schizotypal personality disorder from families with a member with schizophrenia scored higher than the controls on all schizotypal measure and on some borderline aspects. However, only on inadequate rapport and odd communication did they score higher than individuals with schizotypal personality disorder without schizophrenia among their close biological relatives.

Individuals with schizotypal personality disorder outside the schizophrenic spectrum scored higher than individuals with schizotypal personality disorder inside the schizophrenic spectrum on ideas of reference, suspiciousness, paranoia, social anxiety, self-damaging acts, chronic anger, free-floating anxiety and sensitivity to rejection.
When comparing the SIB standard scores among non-schizophrenic MZ co-twins, DZ co-twins and other first degree relatives of respectively schizophrenic index twins, schizotypal index twins and other index twins (controls), the following observations were made:
Monozygotic non-schizophrenic co-twins of schizophrenic index-twins scored high on inadequate rapport, odd communication, social isolation and delusion/hallucinations.
Monozygotic non-schizophrenic co-twins of individuals with schizotypal personality disorder outside the schizophrenic genetic spectrum score high on illusions, depersonalization, derealization and magical thinking.

Based on this study, inadequate rapport, odd communication, social isolation and delusion/hallucinations appeared to be the genetic core of schizotypy as it is related to schizophrenia. For non-schizophrenia related schizotypal personality disorder, illusion, depersonalization/derealization and magical thinking appeared to constitute the genetic core. Generally, in other words; negative schizotypal features appear to be inside the schizophrenic

spectrum, while positive borderline-like features are outside having another genetic endowment.

V. DISCUSSION

The more specific implications and limitations concerning the results are discussed in the different papers. In this section the focus for the discussion will be on a more general and fundamental level.

The different constellation of disorders and symptoms studied in the present studies are not randomly chosen. As for affective disorders, although different in some ways, they have a central phenomenological core in common; mood disturbances, most often depressed mood, sometimes a fluctuation between depressed and elevated mood, and less frequently, only elevated mood. In other words, mood disturbances, one way or the other (or both ways), constitute an important common basis for the face-validity of these diagnoses. The search for common aetiological factors, behind phenomena that seemingly have something in common, follows naturally. Furthermore, concerning paper III; if it is assumed that certain personality features are aetiologically connected to a certain Axis I disorder, the way to test this assumption is to study the relatives, especially the monozygotic twins, of probands with that actual Axis I disorder.

The sample in the present study; same-sexed mono-and dizygotic twins and other first degree relatives drawn from in- and outpatient registries, and the methods; diagnostic assessment in accordance with contemporary diagnostic criteria through personal interviews, constitute a

solid design for studying different etiological connection between different diagnostic categories and symptoms.

As the study presented was based on the employment of the twin-study method (and the combined twin-family-study method), all the methodological considerations connected to the method, presented in the introduction, are of relevance.

As indicated in the introduction, generalization from twin samples may have caveats. Among other things, twins might not be representative of the general population because of a higher risk of intrauterine complications (Bryan, 1986). Furthermore, the calculation of concordance rates and correlations does not take into account possible differences in the within pair environment between MZ- and DZ pairs. (Cf. the EEA). Kendler and Gardner Jr. (1998b) found that compared with DZ twins, MZ twins reported comparable resemblance in their childhood treatment, but socialized together more frequently and reported that parents, teachers and friends more commonly emphasized their similarity. However, none of these three factors significantly predicted twin resemblance for *major depression*, generalized anxiety disorder, panic disorder, phobias, nicotine dependence or alcohol dependence. One the other hand, co-socialization significantly predicted twin resemblance for smoking initiation and perhaps bulimia. Another approach to examine the validity of the equal environment assumption (EEA) is to study the effect of perceived vs. true zygosity on phenotypic similarity in twins. Kendler et al. (1993a) applied this test of the EEA to five common psychiatric disorders; major depression, generalized anxiety disorder, phobia, bulimia and alcoholism. They found no evidence for a significant influence of perceived zygosity on twin resemblance for any of the five disorders. Further, Kendler et al. (1994) found that parents that perceived their twins as identical twins were more likely to report that

they, in rearing the twins, emphasized their similarities more than their differences. However, the parents approach to raising the twins had no significant influence on twin resemblance for the four examined psychiatric disorders; major depression, generalized anxiety disorder, phobia and alcoholism. The results indicate that the differential treatment of MZ and DZ twins by their parents is unlikely to represent a significant bias in twin studies of these major psychiatric disorders. Though, despite the substantial evidence supporting the "equal environment assumption" for most psychiatric symptoms and disorders, it cannot be precluded that social experiences, that may be relevant for some phenotypes, and are shared more by MZ- than DZ twins, might bias upwards estimates of heritability. Another momentum is that MZ twins, both as children and grown ups, may have more similar experiences than DZ twins because they are more genetically similar i.e. some experiences may be genetically driven. If this is the case, the equal environment assumption is not violated.

One of the simplest and most powerful methods utilized to disentangle the influence of environmental and genetic factors on human characteristics is the study of mononzygotic- and dizygotic twins who were separated early in life and reared apart (MZA and DZA). Results from the Minnesota Study of Twins Reared Apart (MINSTRA) indicate that on multiple measures of cognitive abilities (IQ), personality (among others, MMPI-scales), temperament and social attitudes, monozygotic twins reared apart are about as similar as monozygotic twins reared together. The effect of being reared in the same home is negligible (Bouchard, Jr. et al., 1990; DiLalla et al., 1996; Tellegen et al., 1988). Results from the Swedish Adoption/Twin Study of Aging (SATSA) points in the same direction both concerning general cognitive ability, personality, stature, physical health and regular tobacco consumption (Kendler et al., 2000; Pedersen et al., 1992b; Pedersen et al., 1992a). Based on

their results from the study of resemblance in regular tobacco consumption in twins reared apart and together, Kendler et al. (2000) makes the following comment, relevant to the discussion concerning EEA: "Our ability, in this combined twin-adoption design, to replicate closely the results from studies of twins reared together suggest that the traditional twin design, when applied to psychiatric and substance use-related phenotypes, is likely to provide relatively accurate answers and not to be substantial biased."

The importance of gene-environment interaction (G x E) and epigenetic mechanisms in the aetiology of human behavioural traits, mental disorders included, is increasingly acknowledged (Caspi et al., 2003; Eley et al., 2004; Frodl et al., 2008; Kendler et al., 1995a; Kendler et al., 2005; Plomin et al., 2001; Uher, 2008; Uher and McGuffin, 2008; Zubenko and Hughes, III, 2008). Kendler et al. (1995a) found that genetic factors influenced the risk of onset of depression partly by altering the individuals' sensitivity to the effect of stressful life events. In the study by Caspi et al. (2003) a common functional polymorphism in the serotonin transporter gene (5-HTTLPR) was found to moderate the influence of stressful life events on depression. The study was replicated by Kendler et al. (2005) and this finding was broadly confirmed. Twin studies, designed as the current, are not able to differentiate between the effects of the *interaction* between genes and shared environment on the one hand, and purely additive genetic effects on the other, and consequently, in such studies, the effects of an eventual interaction between genes and shared environment are allocated to the additive effects of genes (Sham, 2006). However, as no main effect of shared environment was evidenced in the present studies, a substantial interaction effect of G x E seems unlikely in this sample.

The probands in the present study were sampled from the National Register for Mental Disorder and hospital registers. This may represent a limitation as these probands may have had more severe and "heritable" versions of the disorders compared to probands sampled from the general population. This is somewhat mitigated in that the hospital registers also included outpatients, and further that the inclusion of the "milder" diagnoses in the definition of caseness both in paper I and II did not appreciably change the heritability estimates. Further, Kendler et al (1993b) reported a twin study that studied a broader category of "affective illness" in which they compared twins in samples identified by psychiatric hospitalization vs. samples from the general population. They concluded that heritable factors appeared to be equally important in affective illness in both samples.

Correct assessment of zygosity is crucial in twin research, particularly in small samples. Blood typing may offer the more reliable assessment of zygosity than the use of a questionnaire. Ethical, practical and economic reasons favoured the use of a questionnaire in this study. Questionnaires are widely employed for zygosity determination in twin research, and the one applied in the present study has proven to give high accuracy in comparison with blood analysis of ten genetic markers (Torgersen, 1979). Anyway, incorrect assessment of zygosity will tend to *deflate* the heritability estimates as it will mask eventual differences in concordance rates/correlation between MZ- and DZ twins and represent a sort of measurement error.

Depending on how cases have been ascertained in twin studies, pairs may be counted probandwise or pairwise in the statistical analyses. In the present study the subjects were independently ascertained and consequently a twin pair was counted twice if both twins were identified in the registers (probandwise method). Interestingly, in paper I, where the

concordance rates were calculated by both methods, the tendency was towards higher MZ/DZ concordance ratios for the main comparisons when calculated pairwise.

The model fitting in article I and II were performed with raw data in Mx, based on the full sample of psychiatric patients, i.e. including both unaffected pairs and affected (discordant and concordant) pairs. The raw data analysis has the advantage of testing the specified models for each pair of twins. The chose was made not to include specific population based morbidity rates, as this precludes the employment of the raw-data method. In addition, morbidity-rates are infested with considerable uncertainty and imply the often problematic estimation of standard error. As specific morbidity rates were not included, our findings might represent slight under-estimates of population values, but we believe the results are generalizable to the population of psychiatric patients. Moreover, the estimates and confidence intervals found, accord highly with previous studies, thus implying a mutual validation of the results.

A serious objection to the present study may be that most often the same research worker interviewed both twins in each pair. The risk for possible biases that could have been introduced by this was however reduced, by the employment of structured interview guides (SCID-I, SCID-II and SIB), definite criteria for each disorder, the oversight provided by the senior investigators and by the use of consensus diagnoses in cases of doubt. Further, the generally high interrater reliability, especially for Axis I diagnoses, also served to reduce diagnostic uncertainty. Besides, though the highly valuated technique of letting different interviewers interview the twin partners (usually used in population studies), may reduce bias connecting to falsely rating monozygotic twins as too similar, another interviewer bias may be introduced. The two interviewers may be different as to how good they are in making the twins talk about their problems and they may have different thresholds for rating verbal

answers as a symptom. Hence the concordance of the twins is falsely reduced. Generally, since random error of measurement is included in the e^2 component, any measurement errors will reduce heritability and the effect of shared environment, independent of design and technique. It applies, of course, also to the methods applied in the present study.

Among the strengths of the present study was the thorough diagnostic process of the structured personal interviews, often supplemented by information from earlier interviews, hospital-records and information from informants yielding a high interrater reliability. The efforts expended in contacting and getting an interview with the sampled probands and their co-twins ensured that relatively few sampled twin-pairs were lost, and a sample including twins situated in all parts of Norway and even outside Norwegian borders. Another strength is that those who refused to participate were relatively few (17%).

The heritability estimates for the main of the constellations of disorders studied in the present study were from moderately to above moderately high and in accordance with results from comparable studies. There was no evidence of dominant genetic effects, and no significant effect of shared/common environment was detected. However, it is important to bear in mind that lack of evidence does not prove absence, and that larger samples probably would be required to detect small effects. Although, concerning possible shared environmental effects, the size of the difference between MZ and DZ correlations and the relatively low correlation in DZ twins is such that any shared environmental factors would necessarily be of limited magnitude. Lastly, it should be noted that especially for the unipolar disorders (paper II), non-shared environmental events (E) accounted for a substantial portion of the variance in liability. But, note also that the effect of this factor includes the random error of measurement which tends to inflate the effect.

VI. CONCLUSIONS

6.1. Conclusions

Bearing in mind possible limitations as discussed above, the following main conclusions seem reasonable:

The 'bipolar spectrum' category consisting of bipolar I disorder, bipolar II disorder and cyclothymia constitute an entity with high heritability and no shared family environmental effects. An ADE-model did not show a better fit than an AE-model. Thus, on grounds of parsimony, an AE-model seems most reasonable.

The strictly unipolar depressive spectrum studied here is moderately heritable, with no significant effects of shared environment. The tendency is towards higher heritability for the combined categories, especially major depression and/or atypical depression, compared to major depression alone. An ADE model did not show a better fit than an AE model, so on grounds of parsimony, an AE model seems most reasonable for all the combinations of unipolar depressive disorder studied.

Inadequate rapport, odd communication, social isolation and delusion/hallucinations appeared to be the genetic core of schizotypy as it is related to schizophrenia. For non-schizophrenia related schizotypal personality disorder, illusion, depersonalization/derealization and magical thinking appeared to constitute the genetic core. Generally, in other words; negative schizotypal features appear to be inside the schizophrenic spectrum, while positive borderline-like features are outside having another genetic endowment.

6.2. Implications

The results presented in this thesis challenge the aetiological validity of the DSM-IV-TR's (American Psychiatric Association, 2000) splitting of bipolar disorders into three separate diagnostic entities; bipolar I, bipolar II, and cyclothymic disorder. From a quantitative genetic point of view, the disorders appear to be diverse expressions of the same genotype.

Generally however, from a clinician's viewpoint, the differences in severity of symptoms and functional levels of the patients afflicted with these different disorders may still be an argument for categorizing these phenotypic expressions the way that they currently are.

To a lesser degree, still from an aetiological point of view, the results also challenge the validity of the current categorization of unipolar depressive disorders in the DSM system as it arbitrarily separates phenotypes which seem to be expressions of the same unipolar depressive genotype. Perhaps a simplification of the requirements for number of symptoms and duration is warranted, as long as strong emphasis is laid on the core symptoms of depressed mood and lack of positive affects.

Further, the results indicate that only some of the current criteria for schizotypal personality disorder (SPD) should be retained if SPD is supposed to describe a schizophrenia related personality disorder.

6.3. Suggestions for further research

The results from the current work questions the validity of some of the current diagnostic categories in the DSM system. A replication in another population, preferentially with a lager sample, would however be advantageous. Concerning the indication of a common genetic liability between some diagnoses/phenotypes, observed in the current study, a *multivariate modelling*, would be valuable as it allows for *quantifying the extent* to which the observed genetic variance is shared between the relevant phenotypes and to what extent it is specific for a single phenotype. A larger sample size would be advantageous for such analyses. At the same time as findings as those presented in the current thesis can guide further gene-finding efforts and provide the contexts within which the results of gene-finding studies can be interpreted, molecular genetic research can hopefully provide further advances in this field and the final answers to the questions here raised. Finally, unique environmental events (E) accounted for a substantial portion of the variance in liability, especially concerning the

unipolar depressive disorders. An important and exiting endeavour for future research would be the dissection of this effect.

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