Tuula Kieseppä

A Twin Study on Genetic and Environmental Factors in Bipolar I Disorder

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Department of Mental Health and Alcohol Research,
National Public Health Institute, Helsinki, Finland
and
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A TWIN STUDY ON GENETIC AND ENVIRONMENTAL FACTORS IN BIPOLAR I DISORDER

Academic Dissertation

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TIIVISTELMÄ

Tämä tutkimus on osa laajempaa Kansanterveyslaitoksen vakavien mielenterveyden häiriöiden geneettistä epidemiologiaa ja molekyyligenetiikkaa koskevaa hanketta. Väitöskirjatyön aiheena on ympäristö- ja geneettisten riskitekijöiden merkitys kaksisuuntaisessa mielialahäiriössä eli bipolaarihäiriössä, ja se on tehty yhteistyössä suomalaisen kaksoskohorttitutkimuksen kanssa. Bipolaarihäiriö on vakava mielialahäiriö, jolle tunnusomaista on masennus- ja maniavaiheiden jaksottainen esiintyminen. Ns. bipolaarispektriin katsotaan kuuluvaksi vaikeudeltaan eriasteisia häiriön muotoja. Tässä tutkimuksessa keskitytään bipolaarihäiriö tyyppi I:een.

Tutkimusaineisto muodostui kaksosista, joista ainakin toisella voitiin todeta bipolaarihäiriön diagnoosi suomalaisessa sairaaloiden poistoilmoitusrekisterissä ajanjaksolla 1969-1991. Diagnoosit varmennettiin DSM-IV tautiluokituksen kriteereiden mukaisesti sairauskertomuksista. Näin saatiin 74 paria, jotka kutsuttiin tutkimukseen, johon kuului henkilökohtainen haastattelu, neuropsykologinen tutkimus, aivojen magneettikuvaus (MRI) sekä verinäytteen otto molekyyligeneettisiä tutkimuksia varten. Haastattelu muodostui strukturoiduista lomakkeista (SCID I-II, SSAGA, SANS, SAPS), ja elinaikaiset diagnoosit tehtiin noudattaen DSM-IV kriteereitä. Tsygoottisuus määritettiin analysoimalla DNA polyformismeja. Jotta olisimme saaneet tietoa mahdollisista varhaisista ympäristöön liittyvistä riskitekijöistä keräsimme sairauskertomusmerkinnät synnytyssairaaloista ja neuvoloista.

Bipolaarihäiriö tyyppi I:n (BPI) diagnoosin luotettavuus laskettiin samaa sukupuolta olevillle vuosina 1940-1957 syntyneille kaksosille, jotka muodostivat tässä tutkimuksessa epidemiologisesti edustavimman otoksen. Tutkimuksemme mukaan BPI:n diagnostinen luotettavuus suomalaisessa sairaaloiden poistoilmoitusrekisterissä oli korkea, 92%. BPI:n vuosittainen insidenssi 100 000 henkeä kohden oli kaksosaineistossa naisille 6.9 (95% Luottamusväli (LV)=2.6-11.2), miehille 8.3 (95% LV=3.6-13.0) ja kaikille 7.6 (95% LV=4.4-10.8). Samoja rekistereitä käyttäen laskimme BPI:n insidenssin myös koko Suomen väestölle. Aikavälillä 1970-1991 vuosittainen insidenssi syntymäkohorteissa 1954-1959 oli 5.8 (95% LV=5.4-6.3).

Konkordanssit laskettiin vuosina 1940-1957 syntyneille samaa sukupuolta oleville kaksosille. Konkordanssi BPI:lle oli 0.43 monotsygoottisille kaksospareilla ja 0.06 ditsygoottisille kaksospareilla. Rakenneyhtälömalleissa parhaiten sopiva malli selitti sairastumiseen liittyvää vaihtelua sekä geneettisin että yksilöllisin ympäristötekijöin ja antoi periytyvyyden arvioksi 0.93 (95% LV=0.69-1). Raskausaikaan, syntymään tai varhaislapsuuteen liittyvät komplikaatiot eivät näyttäytyneet BPI:n riskitekijöinä tässä tutkimuksessa.

Sekä potilailla että heidän sisaruksillaan havaittiin vasemman aivopuoliskon valkean aineen vähenemää verrattuna verrokkikaksosiin. Vain potilailla havaittiin oikean aivopuoliskon valkean aineen alenemaa. Harmaan aineen alenemaa emme havainneet potilailla tai sisaruksilla verrattuna verrokkeihin. Otsalohkossa harmaan aineen määrä korreloi positiivisesti mielialaa tasaavan lääkkeen, litiumin käyttöön.

Potilaat tai heidän terveet sisaruksensa eivät eronneet kontrolleista WAIS-R sanastotestissä, joka on eräs älyllisen perustason mittareista. BPI potilaat selviytyivät merkittävästi verrokkeja huonommin informaation käsittelyn nopeutta mittaavassa tehtävässä (WAIS-R merkkikoe), ja heidän reaktioaikansa tarkkaavaisuuden ylläpitotehtävässä oli merkittävästi pidempi kuin verrokeilla. BPI kaksoset pärjäsivät kaikissa muistitesteissä verrokkeja huonommin. Heillä ei kuitenkaan esiintynyt merkittävää heikkoutta opiskelun tehokkuudessa tai opitun aineksen säilyttämisessä sanalistatehtävässä. Terveiden sisarusten suoriutuminen ei eronnut merkittävästi verrokeista. Koska naisten osuus sisarusten ryhmässä oli jonkin verran suurempi (68%) verrattuna naisten määrään verrokkiryhmässä (48%), analysoimme kielellisen muistitehtävän tulokset myös erikseen naisille ja miehille. Miesten kohdalla ryhmien välillä ei ollut merkittävää eroa, mutta naisten kohdalla terveiden sisarusten suoriutuminen oli heikentynyt opitun aineksen uudelleen mieleen palauttamisessa verrattuna verrokeihin.

Tämä tutkimus vahvistaa edustavassa väestöpohjaisessa aineistossa geneettisten tekijöiden merkittävän osuuden bipolaarihäiriön etiologiassa. Tutkimus antaa arvokasta tietoa bipolaarihäiriöön liittyvistä piirteistä, jotka voisivat tulevaisuuden tutkimuksessa toimia geneettisesti spesifeinä endofenotyyppeinä. Aivojen magneettikuvauksessa havaitsimme valkean aineen alenemaa myös terveillä kaksossisaruksilla. Siinä ryhmässä, jossa esiintyy valkean aineen alenemista, olisi perusteltua olettaa, että joku bipolaarihäiriöön altistavista geeneistä löytyisi valkean aineen muodostumiseen osallistuvien geenien ryhmästä. Toinen mahdollinen endofenotyyppi löytyi neuropsykologisten tutkimusten muistitehtävistä. Naispuolisilla terveillä bipolaaripotilaiden sisaruksilla esiintyi samankaltaista heikkenemistä opitun aineksen mieleen palauttamisessa kuin potilailla. Tieto bipolaarihäiriöön liittyvistä geneettisistä tekijöistä ja perinnöllisestä alttiudesta auttaa myös kliinikoita, potilaita ja heidän sukulaisiaan paremmin ymmärtämään sairauden esiintymistä ja luonnetta, ja sen tulisi olla osa hoitoprosessiin liittyvää informaatiota.

Asiasanat: kaksostutkimus, kaksisuuntainen mielialahäiriö, perinnölliset taudit

ABBREVIATIONS

A	Additive genetic effect
APA	American Psychiatric Association
BP	Bipolar Disorder
BPNOS	Bipolar Disorder Not Otheewise Specified
BPI	Bipolar I Disorder
BPII	Bipolar II Disorder
BDNF	Brain Derived Neurotrophic Factor
C	Shared environmental effect
CI	Confidence Interval
CPT	Continuous Performance Test
CSF	Cerebrospinal Fluid
CVLT	California Verbal Learning Test
DAOA	D-amino-acid oxidase activator
DARPP-32	Dopamine- and cAMP-regulated phosphoprotein of 32 kDA
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-II	Diagnostic and Statistical Manual of Mental Disorders, 2nd edition
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DZ	Dizygotic
E	Individual specific environmental effect
ECT	Electroconvulsive therapy
EEA	Equal-environment assumption
fMRI	Functional Magnetic Resonance Imaging
ICD	International Classification of Diseases
ICD-6	International Classification of Diseases, 6th edition
ICD-8	International Classification of Diseases, 8th edition
ICD-9	International Classification of Diseases, 9th edition
ICD-10	International Classification of Diseases, 10th edition
LV	Luottamusväli
MRI	Magnetic Resonance Imaging
MZ	Monozygotic
NOS	Not otherwise specified
NRIA	New Region of Interest Analysis

OS	Opposite sex
PENK	Preproenkephalin
RDC	Research Diagnostic Criteria
ROI	Region of Interest
SA-B	Schizoaffective Psychosis, Bipolar type
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SCID	Structured Clinical Interview
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SCID-II	Structured Clinical Interview for DSM-IV Axis II Disorders
SSAGA	Semi-structured Assessment of Genetics of Alcoholism
TAC1	Tachykinin, substance P
WAIS-R	Wechsler Adult Intelligence Scale, Revised
WHO	World Health Organization
WMH	White matter hyperintensities
WMS-R	Wechsler Memory Scale-Revised

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1. ABSTRACT

This study forms part of a larger project, the Genetic Epidemiology and Molecular Genetics of Severe Mental Disorders in Finland, conducted by the National Public Health Institute. This thesis concerns an investigation of environmental and genetic risk factors in bipolar disorder that was carried out in collaboration with the Finnish Twin Cohort Study. Bipolar disorder is a severe mood disorder with periods of depression and mania. Bipolar spectrum includes both mild and severe form of disorder. This study focuses on bipolar I disorder.

The study population comprises twin-pairs in which one or both twins had received a diagnosis of bipolar disorder according to the Finnish Hospital Discharge Register between 1969 and 1991. Diagnoses were confirmed according to DSM-IV criteria from hospital records. The 74 pairs who were subsequently invited to participate in the study were subjected to a personal interview, neuropsychological examination, magnetic resonance imaging (MRI), and a blood sample collection for molecular genetic analysis. The interview consisted of structured instruments (SCID I-II, SSAGA, SANS, SAPS), and life-time diagnoses were made according to DSM-IV diagnostic criteria. Zygosity was determined by examination of DNA polymorphisms. Information about possible early environmental risk factors was collected from records of study subjects from maternity and child welfare clinics, and obstetric hospitals.

The accuracy of bipolar I diagnosis (BPI) was calculated for the same-sex twins born 1940-1957 that epidemiologically form the most representative sample in this study. We found that the accuracy of BPI was high (92%) in the Finnish hospital discharge register. In the twin cohort the annual incidence of BPI per 100,000 population was for women 6.9 (95% CI=2.6-11.2), for men 8.3 (95% CI=3.6-13.0), and overall 7.6 (95% CI=4.4-10.8). Using the same registers we also estimated the incidence of BPI disorder in the whole Finnish population. During the follow-up period 1970-1991, the annual incidence in the 1954-1959 birth cohort was 5.8 (95% CI=5.4-6.3).

The concordance rates were calculated for the same-sex twin pairs born 1940-1957. The rate for BPI was 0.43 for monozygotic twin pairs and 0.06 for dizygotic twin pairs. The best-fitting model including genetic and specific environmental variance gave a heritability estimate of 0.93 (95% CI=0.69-1). Obstetric and early childhood complications were not found to be risk factors for BPI in this study.

Decreased left hemispheric white matter volume was seen both in patients and co-twins compared with control twin subjects. Decreased right hemispheric white matter was seen only in patients. We found no decrease in grey matter volume in either patients or co-twins compared with control twin subjects. Frontal grey matter volume was found to be positively correlated with the use of mood stabilizing medication, lithium.

Neither BPI twins nor non-bipolar co-twins differed significantly from controls in the Wechsler Adult Intelligence Scale (WAIS-R) Vocabulary test measuring general intellectual functioning. However, BPI twins were significantly slower than controls in tasks measuring information processing speed (WAIS-R Digit Symbol), and reaction time (CPT). BPI twins performed worse than controls on all memory tests. However, they were not significantly impaired in learning efficiency and retention, as measured by the California Verbal Learning Test (CVLT). Non-bipolar co-twins did not differ significantly from controls. Because the proportion of women was somewhat greater (68%) among the non-bipolar co-twins compared with controls (48%), we reanalyzed the CVLT test results separately for women and men. Among males, the three study groups did not differ significantly from each other, but the non-bipolar female co-twins showed impairment in learning a word list.

These findings confirm the importance of genetic factors in the etiology of BPI in a representative nationwide population. The study gives valuable information for the future research on where to focus when searching for genetically more specific endophenotypes. Magnetic resonance imaging showed a decrease in white matter volumes in healthy co-twins. It is plausible that among these persons at least some of the genes predisposing to BPI and involved in white matter construction would be detected. Another possible endophenotype was found in the performance of neuropsychological memory tasks. Female BPI twins and their healthy co-twins were similarly impaired in learning a word list. The converging knowledge about the genetic factors in BPI also helps clinicians, patients, and their relatives to better understand the occurrence and type of this severe mental disorder, and this information should be included in patient education.

Keywords: twin studies; bipolar disorder; genetic diseases, inborn

2. LIST OF ORIGINAL PUBLICATIONS

I Kieseppä T, Partonen T, Kaprio J, Lönnqvist J. (2000) Accuracy of register- and record-based bipolar I disorder diagnoses in Finland - a study of twins.
Acta Neuropsychiatrica 12:106-109.

II Kieseppä T, Partonen T, Kaprio J, Lönnqvist J. (2004) High Concordance of Bipolar I Disorder in a Nationwide Sample of Twins. Am J Psychiatry 161(10):1814-21.

III Kieseppä T, van Erp TGM, Haukka J, Partonen T, Cannon TD, Poutanen VP, Kaprio J, Lönnqvist J. (2003). Reduced left hemispheric white matter volume in twins with bipolar I disorder. Biol Psychiatry 1;54(9):896-905.

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

3. INTRODUCTION

Bipolar I disorder (BPI) is a severe mental disorder whose main feature is the occurrence of periods of depressive and manic behaviour, latter characterized by either euforic or irritated mood. Manic episodes cause serious harm to a patient in his or her social and occupational life, and often lead to hospital treatment because of conflicts with other people, attention problems, hypervigilance, inability to sleep, and self-harming behaviour. Many patients quite often have psychotic symptoms, mainly grandiotic or paranoid. Besides manic periods, patients typically have depressive episodes, which can vary from mild mood decrease to severe major depressive episodes with psychotic symptoms. Patients can also have mixed episodes, which means that both manic and depressive symptoms occur during the same day. The course of illness is individually highly variable but depressive episodes are as a rule more frequent than manic periods, and usually more important contributors to disability. Bipolar II disorder (BPII) is diagnosed when a patient has besides depressive episodes hypomanic but not manic episodes.

One episode lasts at least a week, but can take a long course of several months. BPI typically recurs on an episodic basis or follows an intermittent, subthreshold course over years, if not a life-time. Chronicity occurs in 15-20% of cases. (Akiskal 2005) Bipolar disorder may start with depression, and it can take several depressive episodes before the first mania occurs. Among women bipolar disorder may begin with postpartum psychosis (McElroy 2004). In these cases it is often difficult to reach a correct diagnosis, and a family history might be helpful since BPI tends to aggregate in families (Andreasen et al. 1987).

The primary treatment in BPI is mood stabilizing using pharmacotherapy. Although the pharmaceutical industry has made efforts to develop new medicines for the treatment of BPI, lithium remains the first-line agent. Lithium, valproate and olanzapine have unequivocal evidence for efficacy in acute mania, lithium in acute depressive episodes and in prophylaxis of mania and depression, and lamotrigine in prophylaxis of depression (Bauer and Mitchner 2004). When combined with pharmacotherapy, psychotherapeutical approaches seem to benefit bipolar patients. Psychosocial treatments with psychoeducation for patients and their relatives are usable, and some evidence exists for individual cognitive behavioural therapy, which seems to have inluence on symptoms, social functioning and risk of relapse (Jones 2004).

In the general psychiatric literature the lifetime prevalence of BPI has been reported to to be up to 2.4 percent, and the 1-year prevalence between 0.9 to 1.3 percent, and the lifetime prevalence of BPII between 0.3 to 4.8 percent (Rihmer and Angst 2005). These figures correspond to prevalence estimates of schizophrenia and panic disorder (Vos and Mathers 2000). However, a recent systematic review reported the rates for both bipolar

disorder and major depressive disorder in high quality studies to be generally lower (Waraich et al. 2004). Prevalence rates of BPI have not been studied in Finland, but the annual incidence of the first bipolar episode was 12 per 100 000 among hospitalized Finnish population (Räsänen et al. 1998).

Modern studies of pathophysiology have revealed several biological connotations related to bipolar disorder. One of the most evident facts is that BPI involves a genetically transmitted vulnerability (Kennedy et al. 2003). Molecular genetics and genetic epidemiology are inspiring research areas in bipolar disorder, and a promising candidate gene for BPI, brain-derived neurotrophic factor (BDNF) was chosen as one of the discoveries of the year 2003 by Science magazine (Staffs 2003). Possible gene-derived alterations in brain function and structure can be studied by modern brain imaging methods (i.e. magnetic resonance imaging, positron emission tomography, magnetic resonance spectroscopy, and diffusion tensor imaging) (McDonald et al. 2004a), and by neuropsychological examinations (Glahn et al. 2004). However, defects are not necessarily caused by genes but environmental factors. Little evidence exists of environmental risk factors predisposing to bipolar disorder (Browne et al. 2000; Mortensen et al. 2003). Early maternal loss (Mortensen et al. 2003) and childhood physical or sexual abuse (Leverich et al. 2002) have been reported.

The project of "The Genetic Epidemiology and Molecular Genetics of Severe Mental Disorders in Finland", run by the Department of Mental Health and Alcohol Research and the Department of Human Molecular Genetics at the National Public Health Institute, aims to characterize the genetic epidemiology of severe mental disorders in Finland, and to investigate genetic and environmental risk factors. The present thesis focuses on diagnostic accuracy, on quantification of genetic component of BPI, and on neuropsychological performance and brain magnetic resonance imaging as endophenotypes for BPI. The study was performed with a population-based sample of bipolar twins in co-operation with the Finnish Twin Cohort Study.

4. REVIEW OF THE LITERATURE

4.1 Definition of bipolar disorder

Bipolar I disorder is a serious psychiatric disorder with a life-time prevalence of 0.1-2.6 percent (Rihmer and Angst 2005). It is characterized by alternating manic, hypomanic, mixed or depressive episodes, with periods of normal mood between. Typically it is recurrent. The outcome is poor (i.e. chronic) in 15-20 percent (Akiskal 2005). The age of onset is most commonly around 20 years of age (Rihmer and Angst 2005). Between extremes of bipolar I disorder and major depressive disorder, there exists an intermediary form characterized by major depressive episodes and hypomania, bipolar II disorder (Akiskal 2005).

Bipolar disorder causes great disability. A two year follow-up of 166 first-episode bipolar disorder patients showed that although 98% of subjects achieved syndromal recovery (DSM-IV criteria for disorder no longer met), only 43% achieved functional recovery (Tohen et al. 2003), which was defined as both occupational level and residential status returning to the highest levels experienced in the preintake year. A prospective study of the long-term natural history of BPI patients showed that patients were symptomically ill 47.3% of weeks throughout a mean of 12.8 years of follow-up (Judd et al. 2002). Depressive symptoms (31.9% of weeks) predominated over manic/hypomanic symptoms (8.9%) or cycling/mixed symptoms (5.9%). Studies indicate considerable increase in mortality, averaging approximately 2.3 times the expected rates (Goodwin and Jamison 1990). The main reason for this is the elevated risk of suicide in bipolar disorder (Goodwin and Jamison 1990). According to a recent survey by World Health Organization (WHO), bipolar disorder accounts for a marked share of the global burden of mental disorders in society (premature deaths, sick leaves, and poor health-related quality of life), and is comparable to schizophrenia in this regard (Vos and Mathers 2000).

Bipolar disorder, or manic-depressive illness as it was previously named, is among the most consistently identifiable of all mental disorders (Goodwin and Jamison 1990). It was probably first described by Aretaeus Cappadocia in 30 AD: "And they with whose madness joy is associated, laugh, play, dance night and day, and sometimes go openly to the market crowned, as if victors in some contest of skill; this form is inoffensive to those around. Others have madness attended with anger." (Adams 1978) (p.302) He also states that there is another kind of madness: "But the modes are infinite in those who are ingenious and docile, -untaught astronomy, spontaneous philosophy, poetry truly from the muses; for

docility has its good advantages even in disease." (Adams 1978) (p.302), which seems to refer to the schizophrenic type disorder. When describing melancholy Aretaeus writes: "and it appears to me that melancholy is the commencement and a part of mania" (Adams 1978) (p.299). He also states: "mania intermits, and with care ceases altogether" (Adams 1978) (p.299).

However, it was finally Kraepelin (1919), who formulated the concept of manic-depressive insanity. He argued that both dementia precox and manic-depressive illness were caused by organic brain lesions, but differed from each other in the course of illness. Manic-depressive patients had more ability for self-observation, and the illness had a periodic course with intervals of complete restoration of psychic and social functioning. (Kraepelin 1919) The Kraepelin concept of manic-depressive illness included pure depression and melancholia. The subdivision of patients with both mania and depression from those with only depression into bipolar and monopolar (later called unipolar) subgroups, was proposed by Leonhard (1957).

4.1.1 Diagnosis of bipolar disorder - the development of diagnostic systems: ICD and DSM

The World Health Organization (WHO) was the first to try to establish a universal diagnostic system for psychiatric disorders in 1948, when the International Classification of Diseases (ICD-6) was published. The ICD was derived from systematic research and it was designed as a system that could be applied throughout the world. It was to promote international comparability of health care statistics. Successive versions, now undergoing its tenth revision (ICD-10) (WHO 1993), represent the official diagnostic systems used by clinicians throughout the world. The major exception is the United States, where clinicians use the American Psychiatric Association’s Diagnostic and Statistical Manual (DSM). The first version was published in 1952, and the revised version (DSM-II) paralleled already with the eight revision of the ICD in 1968. (Goodwin and Jamison 1990) However, these first diagnostic systems were still insufficient especially from the research point of view. Specific descriptive criteria were needed. Spitzer and his colleagues developed the Research Diagnostic Criteria (RDC) (Spitzer et al. 1977), which provided a diagnostic instrument with a high level of reliability and stability. It formed the basis for DSM-III. (Goodwin and Jamison 1990) Although bipolar disorder or manic-depressive illness has been relatively consistent and stable diagnostic category, there has been some important changes in its description during the development of diagnostic classifications, and they will be described below.

4.1.2 International Classification of Diseases, 8th, 9th, and 10th Revisions

The World Health Organization launched the eight revision of the International Classification of Diseases (ICD-8) (WHO 1967), which already differentiated bipolar and unipolar depression, but had no specific criteria for making a diagnosis (Table 1). ICD-8 was the official diagnostic classification used in Finland between 1969 and 1986.

Table 1. ICD-8: 296 Affective psychosis

296.0 Involutional melancholia	
Agitated depression Agitated melancholia Climacteric insanity	Climacteric melancholia Involutional depression Menopausal melancholia
296.1 Manic-depressive psychosis, manic type	
Hypomania NOS Hypomanic psychosis Mania NOS Manic psychosis	Manic-depressive reaction: hypomanic manic
296.2 Manic-depressive psychosis, depressed type	
Endogenous depression Psychotic depression	Melancholia (senile) Manic-depressive reaction, depressive
296.3 Manic-depressive psychosis, circular type	
Alternating insanity Circular insanity	Cyclothymia Manic-depressive reaction, circular
296.8 Other Manic stupor	Unproductive mania
296.9 Unspecified Affective psychosis NOS	Manic-depressive reaction NOS

(WHO 1967)

In the ninth edition of the International Classification of Diseases (WHO 1977), the classification of manic-depressive psychosis had changed (Table 2). Involutional melancholia (296.0) was placed under manic-depressive psychosis, depressive type (296.1). Manic-depressive psychosis, manic type (296.1) was otherwise unchanged, but included in the new version (296.0) a state called manic disorder. Manic-depressive psychosis, depressive type (296.2) remained nearly same, but this category included in addition involutional melancholia, monopolar depression, and psychotic depression (296.1). Senile

melancholia was not mentioned any more. Manic-depressive psychosis, circular type (296.3) was divided in four different categories: currently manic (296.2), currently depressed (296.3), currently mixed (296.4), current condition not specified (296.5). Cyclothymia or manic-depressive reaction, circular were not anymore mentioned under any of circular types. Other (296.8) and unspecified categories (296.9) were merged to be manic-depressive psychosis, other and unspecified (296.6). (Table 1 and 2) This version was never used for psychiatric diseases as such in Finland.

Table 2. Comparison of ICD-9, DSM-III-R and Finnish classification of Affective psychoses (296)

ICD-9	DSM-III-R	Finnish classification
296.0 Manic-depressive psychosis, manic type Hypomania NOS Hypomanic psychosis Mania (monopolar) NOS Manic disorder Manic psychosis Manic-depressive psychosis or reaction: hypomanic, manic	296.4x Bipolar disorder, manic 301.13 Cyclothymia	2962- Psychosis bipolaris manica
296.1 Manic-depressive psychosis, depressive type Depressive psychosis Endogenous depression Involutional melancholia Manic-depressive reaction, depressed Monopolar depression Psychotic depression	296.2x Major Depression, single episode 296.3x Major Depression, Recurrent 300.40 Dysthymia	2961- Depressio mentis gravis
296.2 Manic-depressive psychosis, circular type but currently manic Bipolar disorder, now manic	296.4x Bipolar Disorder, manic	2962- Psychosis bipolaris manica
296.3 Manic-depressive psychosis, circular type but currently depressed Bipolar disorder, now depressed	296.5x Bipolar Disorder, depressed	2963- Psychosis bipolaris depressiva
296.4 Manic-depressive psychosis, circular type, mixed	296.6x Bipolar Disorder, mixed	2964- Psychosis bipolaris circularis
296.5 Manic-depressive psychosis, circular type, current condition not specified		
296.6 Manic-depressive psychosis, other and unspecified Manic-depressive psychosis: NOS, mixed type Manic-depressive: reaction NOS, syndrome NOS	296.70 Bipolar Disorder Not Otherwise Specified	2967A Psychosis bipolaris NOS
296.8 Other		2968 Depressio mentis NOS
296.9 Unspecified Affective psychosis NOS Melancholia NOS	311.0 Depressive Disorder Not Otherwise Specified	2968 Depressio mentis NOS

(WHO 1977, APA 1987, Lääkintöhallitus 1986)

The tenth edition of the International Classification of Diseases (ICD-10) (WHO 1993), which is used currently in Finland, was published in 1993. It provides a different kind of coding system, and it is the first ICD edition to define operationalized criteria for research purposes. It differentiates mania (F30) and bipolar disorder (F31) (Table 3).

Table 3. ICD-10 Criteria for mania and bipolar disorder

F30	Manic episode All the subdivisions of this category should be used only for a single episode. Hypomanic or manic episodes in individuals who have had one or more previous affective episodes (depressive, hypomanic, manic, or mixed) should be coded as bipolar affective disorder (F31). Includes: bipolar disorder, single manic episode
F30.0	Hypomania A disorder characterized by a persistent mild elevation of mood, increased energy and activity, and usually marked feelings of well-being and both physical and mental efficiency. Increased sociability, talkativeness, overfamiliarity, increased sexual energy, and a decreased need for sleep are often present but not to the extent that they lead to severe disruption of work or result in social rejection. Irritability, conceit, and boorish behavior may take the place of the more usual euphoric sociability. The disturbances of mood and behavior are not accompanied by hallucinations or delusions.
F30.1	Mania without psychotic symptoms Mood is elevated out of keeping with the patient's circumstances and may vary from carefree joviality to almost uncontrollable excitement. Elation is accompanied by increased energy, resulting in overactivity, pressure of speech, and a decreased need for sleep. Attention cannot be sustained, and there is often marked distractibility. Selfesteem is often inflated with grandiose ideas and overconfidence. Loss of normal social inhibitions may result in behavior that is reckless, foolhardy, or inappropriate to the circumstances, and out of character.
F30.2	Mania with psychotic symptoms In addition to the clinical picture described in F30.1, delusions (usually grandiose) or hallucinations (usually of voices speaking directly to the patient) are present, or the excitement, excessive motor activity, and flight of ideas are so extreme that the subject is incomprehensible or inaccessible to ordinary communication. Mania with: - mood-congruent psychotic symptoms - mood-incongruent psychotic symptoms Manic stupor
F30.8	Other manic episodes
F30.9	Manic episode, unspecified Mania NOS
F31	Bipolar affective disorder A disorder characterized by two or more episodes in which the patient's mood and activit levels are significantly disturbed, this disturbance consisting on some occasions of an elevation of mood and increased energy and activity (hypomania or mania) and on others o a lowering of mood and decreased energy and activity (depression). Repeated episodes of hypomania or mania only are classified as bipolar. Includes: manic-depressive: - illness - psychosis - reaction Excludes: bipolar disorder, single manic episode (F30), cyclothymia (F34.0)
F31.0	Bipolar affective disorder, current episode hypomanic The patient is currently hypomanic, and has had at least one other affective episode (hypomanic, manic, depressive, or mixed) in the past.
F31.1	Bipolar affective disorder, current episode manic without psychotic symptoms The patient is currently manic, without psychotic symptoms (as in F30.1), and has had at least one other affective episode (hypomanic, manic, depressive, or mixed) in the past.

F31.2	Bipolar affective disorder, current episode manic with psychotic symptoms The patient is currently manic, with psychotic symptoms (as in F30.2), and has had at least one other affective episode (hypomanic, manic, depressive, or mixed) in the past.
F31.3	Bipolar affective disorder, current episode mild or moderate depression The patient is currently depressed, as in a depressive episode of either mild or moderate severity (F32.0 or F32.1), and has had at least one authenticated hypomanic, manic, or mixed affective episode in the past.
F31.4	Bipolar affective disorder, current episode severe depression without psychotic symptoms The patient is currently depressed, as in severe depressive episode without psychotic symptoms (F32.2), and has had at least one authenticated hypomanic, manic, or mixed affective episode in the past.
F31.5	Bipolar affective disorder, current episode severe depression with psychotic symptoms The patient is currently depressed, as in severe depressive episode with psychotic symptoms (F32.3), and has had at least one authenticated hypomanic, manic, or mixed affective episode in the past.
F31.6	Bipolar affective disorder, current episode mixed The patient has had at least one authenticated hypomanic, manic, depressive, or mixed affective episode in the past, and currently exhibits either a mixture or a rapid alteration of manic and depressive symptoms. Excludes: single mixed affective episode (F38.0)
F31.7	Bipolar affective disorder, currently in remission The patient has had at least one authenticated hypomanic, manic, or mixed affective episode in the past, and at least one other affective episode (hypomanic, manic, depressive, or mixed) in addition, but is not currently suffering from any significant mood disturbance, and has not done so for several months. Periods of remission during prophylactic treatment should be coded here.
F31.8	Other bipolar affective disorders Bipolar II disorder Recurrent manic episodes NOS
F31.9	Bipolar affective disorder, unspecified

(WHO 1993)

4.1.3 Diagnostic and Statistical Manual for Mental Disorders, Third Edition, Revised

DSM-III was launched in 1980, and its revised version (DSM-III-R) (American Psychiatric Association 1987) in 1987. They differed from previous internationally used diagnostic classifications in that operational diagnostic criteria were provided for each disorder (Table 4), as was later the case in ICD-10. For this reason DSM-III and its revised versions have been frequently used in psychiatric research. The essential feature of bipolar disorder was one or more manic episodes, usually accompanied by one or more major depressive episodes.

Table 4. DSM-III-R criteria for manic episode

Note:	A "Manic Syndrome" is defined as including criteria A, B, and C below. A "Hypomanic Syndrome" is defined as including criteria A and B, but not C, i.e., no marked impairment.
A.	A distinct period of abnormally and persistently elevated, expansive, or irritable mood.
B.	During the period of mood disturbance, at least three of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree: (1) inflated self-esteem or grandiosity (2) decreased need for sleep, e.g., feels rested after only three hours of sleep (3) more talkative than usual or pressure to keep talking (4) flight of ideas or subjective experience that thoughts are racing (5) distractibility, i.e., attention too easily drawn to unimportant or irrelevant external stimuli (6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (7) excessive involvement in pleasurable activities which have a high potential for painful consequences, e.g., the person engages in unstrained buying sprees, sexual indiscretions, or foolish business investments
C.	Mood disturbance sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others.
D.	At no time during the disturbance have there been delusions or hallucinations for as long as two weeks in the absence of prominent mood symptoms (i.e., before the mood symptoms developed or after they have remitted).
E.	Not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder NOS.
F.	It cannot be established that an organic factor initiated and maintained the disturbance. Note: Somatic antidepressant treatment (e.g., drugs, ECT) that apparently precipitates a mood disturbance should not be considered an etiologic organic factor.

(APA 1987)

In 1983, in anticipation of the widespread adoption of the DSM-III criteria, work started on a specific instrument for making diagnoses. A semistructured interview was developed to increase diagnostic reliability through standardization of the assessment process and to increase diagnostic validity by facilitating the application of the diagnostic criteria, and by systemically probing for symptoms that might be overlooked. The Structured Clinical Interview (SCID) for DSM-III-R was published in 1990 (American Psychiatric Association 1987; First et al. 1997).

In 1987, the general medical diagnostic classification system in Finland was updated to ICD-9, but the diagnostic criteria for mental disorders (Lääkintöhallitus 1986) were adopted with slight modifications from DSM-III-R (Table 2). In this system, the first four numbers in the diagnostic codes correspond to the ICD-9 codes, but the fifth digit was unique to the Finnish coding system and allowed subclassification similar to that used in DSM-III-R. (Kuoppasalmi et al. 1989) The fifth digit refers to the severity of a current episode. This system was used in Finland until 1996, whereupon ICD-10 diagnostic codes and criteria were introduced. The comparison of ICD-9, DSM-III-R and Finnish classification of affective psychoses is presented in Table 2.

4.1.4 Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, and Text Revision

The fourth edition of DSM was published in 1994 (American Psychiatric Association 1994). There were only slight differences in diagnostic criteria for manic episode (Table 5). The minimum duration of one week (or any duration if hospitalization is necessary) of the episode was added in the criteria. Exclusion criteria for other psychotic disorders were erased. Psychotic symptoms were stated in diagnostic criteria for bipolar I disorder. The notion of organic factor as a cause was defined such as the symptoms should not be due to the direct physiological effects of a substance use or a general medical condition.

Table 5. DSM-IV criteria for manic episode

A.	A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).
B.	During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree: (1) inflated self-esteem or grandiosity (2) decreased need for sleep (e.g., feels rested after only three hours of sleep) (3) more talkative than usual or pressure to keep talking (4) flight of ideas or subjective experience that thoughts are racing (5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli) (6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (7) excessive involvement in pleasurable activities which have a high potential for painful consequences (e.g., engaging in unstrained buying sprees, sexual indiscretions, or foolish business investments)
C.	The symptoms do not meet criteria for a mixed episode.
D.	The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
E.	The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).
Note:	Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder.

(APA 1994)

DSM-IV defines bipolar I disorder, in which the essential feature is a clinical course that is characterized by the occurrence of one or more manic episodes (Table 5), or mixed episodes. Often individuals have also had one or more major depressive episodes (Table 6). Mixed episode is characterized by a period of time (lasting at least 1 week) in which the criteria are met both for a manic episode and for a major depressive episode nearly every day. Episodes induced by substance use or general medical condition do not count toward a diagnosis of bipolar I disorder. In addition, the episodes should not be better accounted for by schizoaffective disorder, schizophrenia, delusional disorder, or psychotic disorder not otherwise specified.

Table 6. DSM-IV criteria for depressive episode

A.	Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly do to a general medical condition, or mood-incongruent delusions or hallucinations. (1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood. (2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others). (3) Significant weight loss when not dieting or weight gain (e.g., change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains. (4) Insomnia or hypersomnia nearly every day (5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down) (6) Fatigue or loss of energy nearly every day (7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly ever day (not merely self-reproach or guilt about being sick) (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others) (9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without specific plan, or a suicide attempt or a specific plan for committing suicide
B.	The symptoms do not meet criteria for a mixed episode.
C.	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D.	The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).
E.	The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

(APA 1994)

The work for the revision of the SCID began in 1993, and the final version for DSM-IV was produced in 1996. The SCID-I for DSM-IV criteria (First et al. 1997) is divided into six modules: A. Mood episodes, B. Psychotic Symptoms, C. Psychotic Disorders, D. Mood Disorders, E. Substance Use Disorders, and F. Anxiety and Other Disorders. It can be administered to either psychiatric or general medical patients, and when needed it may be used as a diagnostic checklist, with information obtained from other sources than a face-to-face interview. (First et al. 1997)

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (American Psychiatric Association 2000) was published by the American Psychiatric Association to set forth diagnostic criteria, descriptions and other information to guide the classification and diagnosis of mental disorders in 2000 replacing DSM-IV. The criteria for bipolar disorder were not changed.

4.1.5 Summary

In ICD-8, which was used in Finland 1969-1986, the categories Manic-depressive psychosis, manic type (296.1) and Manic-depressive psychosis, circular type (296.3) correspond to the criteria of bipolar disorder in current diagnostic systems (ICD-10 and DSM-IV). In this study these codes were chosen to identify possible cases. During the period we used to search cases, the diagnostic system in Finland changed. In the new Finnish coding system (Lääkintöhallitus 1986), the categories Psychosis bipolaris manica (2962), Psychosis bipolaris depressiva (2963), and Psychosis bipolaris circularis (2964) correspond to the current criteria, and were chosen to detect possible cases for the study. However, internationally these codes refer to the DSM-III-R codes 296.4, 296.5, and 296.6, respectively. Final bipolar diagnoses were confirmed according to the DSM-IV criteria, which parallel well with currently used ICD-10 system. The latter only differentiates single manic episode from bipolar affective disorder.

4.2 Accuracy of bipolar diagnosis in registers

Only few studies focus on the accuracy of bipolar diagnosis in registers. Danish study of Kessing (1998) compared manic-depressive diagnosis (ICD-8, 296) at the first discharge to the lifetime affective disorder diagnosis (ICD-10). They found that among the random subsample of 100 manic-depressive patients, 95 received a lifetime ICD-10 diagnosis of affective disorder. However, they did not differentiate those patients who received at the first discharge code 296.1 or 296.3 implying manic episodes. The Finnish study of the accuracy of the Finnish Hospital Discharge Register showed that in the group of mental disorders the accuracy was 98%, but bipolar disorder was not evaluated separately (Keskimäki and Aro 1991).

A study of a voluntary bipolar disorder case register compared self-reported bipolar diagnosis to the face-to face Structured Clinical Interview for DSM-IV (Spitzer et al. 1997) bipolar diagnosis (Unutzer et al. 2000). 96% of the subjects who had been diagnosed with bipolar disorder by a professional, received bipolar diagnosis according to the DSM-IV. The concordance specifically for bipolar I disorder was not evaluated. A review of a random sample of medical records indicated that the diagnosis of bipolar disorder was confirmed with a false positive rate of less than 10% in the inpatient diagnostic data in the area of western Washington. The definition of bipolar disorder was not given.

4.3 Prevalence and Incidence of bipolar disorder

The lifetime prevalence of bipolar disorder has varied from 0.1 to 4.8 percent in the general population (Rihmer and Angst 2005). The higher values have included bipolar II disorder. A recent Australian study reported 12-month prevalence of 0-5% for bipolar disorder (I and II) (Mitchell et al. 2004). The annual incidence of bipolar disorder has varied from 3 to 10 persons per 100 000 (Rihmer and Angst 2005). In Finland, there have been few studies on the epidemiology of bipolar disorder; the incidence of a first hospital admission of mania in the northern region was reportedly as low as 1.7 persons per 100 000 per year (Veijola et al. 1996). The study population was composed of 6007 men and 5757 women born in northern Finland in 1966, and psychiatric morbidity was followed using the Finnish Hospital Discharge Register from 1967 to 1993. However, a more recent study reported the incidence of first hospital admissions for bipolar disorder during 1994 to be 12 persons per 100 000 (Räsänen et al. 1998). Data for the study was collected from the Finnish Hospital Discharge Register, searching for persons with any DSM-III-R diagnoses coded 296.40-296.70 between 1987 and 1994. The hospital admission was assumed to be initial if there were no further entries in the registry during 1987-1993.

4.4 Pathogenesis of bipolar disorder

The pathogenesis of bipolar disorder is still poorly known. Biological and especially genetic factors based on family and twin studies seem to be important for the vulnerability. Environmental factors might act more as modifying agents either increasing the risk or supporting against disorder. However, it may still be possible that a person without any biological risk factors develops bipolar disorder. Family-, twin- and adoption studies can be used for the estimation of the overall genetic contribution in the disorder. With these methods we can evaluate the quantitative amount of genetic and environmental proportion explaining the risk for bipolar disorder. Specific gene loci increasing risk can be searched using molecular genetic methods, and candidate gene studies test if theoretically plausible genes associate with the disorder.

4.4.1 Family studies

Family studies (Angst et al. 1980; Gershon et al. 1982; Mendlewicz and Rainer 1974; Rice et al. 1987; Weissman et al. 1984; Winokur et al. 1995) have shown that bipolar disorder aggregates in families. The lifetime prevalence of bipolar disorder in the first degree relatives of bipolar patients ranges from 1.5 to 17.9 percent (McGuffin and Katz 1989). The weighted average for these figures is 7.8 percent, which is much higher than lifetime prevalence (0.1-2.4%) in normal population (Rihmer and Angst 2005). A meta-analysis of 18 family studies (Smoller and Finn 2003) arrived at a weighted estimate of morbid risk of relatives of bipolar I and II probands to have bipolar I and II disorder of 8.7 percent. The risk for unipolar depression was 14.1 percent.

4.4.2 Twin studies

The question if there are genetic factors predisposing to bipolar disorder can be answered using a twin method. Twin studies are based on an assumption that both mono-and dizygotic twins share the same environment (Kendler et al. 1993a) but only monozygotic have 100 percent of their genes in common. Differences between monozygotic twins have to be attributed to the environment, while differences between dizygotic twins may be due to both genetic and environmental factors. In the classical twin method one compares statistically monozygotic and dizygotic pairs in respect of their concordance for the traits or illness in question. A pair is called concordant if both have the same illness, for instance, bipolar I disorder; discordant, if one is ill and the other one is not ill, i.e., if one has bipolar I disorder and the co-twin has not (Allen et al. 1967).

Significantly higher concordance rates in the group of monozygotic twin pairs compared to dizygotic twin pairs have been regarded as evidence in support of a genetic background of the illness concerned. This simple pairwise concordance rate has been since replaced with the probandwise concordance rate, which method is taken from the general field of population genetics (Allen et al. 1967). It gives the numbers of persons having affected partners, i.e., the concordance rate here is same as the probability of the co-twin being affected.

Concordance rates are used for binary traits like psychiatric diagnoses. Twin data can also be utilized for continuous variables, like weight, blood pressure, personality, abilities, and mental health. Almost everything that can be measured in humans shows variation around the mean value of population (Neale and Maes 2000). Although there are large individual differences for almost every trait, the trait values of family members are often quite similar. If we study, for example weight, we see that the correlation will become greater, when the relatives are more alike genetically (Neale and Maes 2000). The much greater resemblance of MZ twins in weight compared to DZ twins establishes a strong evidence for the contribution of genetic factors to differences in weight. The proportion of variation associated with genetic effects is termed the broad heritability. The bulk of genetic variation is usually explained by additive genetic effects, but two general types of non-additivity may be important: dominance and epistasis. (Neale and Maes 2000) Mendel's classical experiments showed that the progeny of a cross between two pure breeding lines often resembled one parent more than the other. This interaction between alleles at the same locus is called dominance. Epistasis describes the interaction between alleles at different loci, and it occurs whenever the effects of one gene on individual differences depend on which genotype is expressed at another locus.

Twin method has some strong assumptions. As previously was mentioned it assumes that MZ and DZ twins are equally correlated for their exposure to relevant environmental influences. If this equal-environment assumption (EEA) is not correct, then the greater similarity of MZ pairs over DZ pairs could in part be explained by environmental and not solely by genetic factors. Several methods have been designed to test the validity of the EEA in twin studies (Kendler et al. 1993a). Some argue that trait similarities of twins are caused by a similar behavior of the social environment as a reflection of the physical similarity of twins. It has been tested if the physical similarity of twins would correlate with the trait similarity (e.g. intelligence), and none of the studies so far supports this (Matheny et al. 1976; Plomin et al. 1976). The second method studied parental behavior to MZ and DZ twin children, and it turned out that parental treatment was a response to a child's behavior not to a similarity of physical appearance or known zygosity (Lytton 1977). Another argument is that certain features of the childhood and adult environments are more similar for MZ than DZ twins, and they might influence twin similarity. However, several studies have found no support for this hypothesis (Kendler et al. 1986; Loehlin and Nichols 1976). The fourth method involves a comparison of trait similarity as a function of confirmed zygosity and parental perceived zygosity, assuming that perceived zygosity should influence twin similarity. A study on major depression,

generalized anxiety disorder, phobia, bulimia, and alcoholism found no evidence for a significant influence of perceived zygosity on twin resemblance for any of the five disorders (Kendler et al. 1993a).

Epidemiological genetic models usually assume random mating, but in nature people tend to select partners who at least in some respect (education, personality, social position) are similar, which is called assortative mating. Assortative mating may be substantial for mood disorders (Maes et al. 1998). Positive phenotypic assortative mating increases the genetic and environmental correlations between relatives, and thus it tends to increase similarity of DZ twins relative to MZ twins. (Neale and Maes 2000) It might lead to an underestimation of heritability if ignored in twin analyse.

Only the most recent twin studies examine bipolar disorder as a distinct disorder which has been defined comparable with modern diagnostic criteria. Probandwise concordance rates for bipolar disorder in these studies are shown in Table 7.

Table 7. Twin studies of bipolar disorder

Study	Population	N pairs	Diagnostic Criteria	Methods[a]	Probandwise concordance MZ	DZ	Heritability estimate
Allen et al. 1974	USA Male veteran	22	own	rec	0.33	0	0.86 (95% CI=0.41-1)
Bertelsen et al. 1977	Danish twin register	43	Kraepelin	int, que, rec	0.80	0.13	0.99 (95% CI=0.99-1)
Torgersen 1986	Norway	10	DSM-III	int, rec	0.75	0	-
Kendler et al. 1993	Swedish twin register	35	DSM-III-R	que	0.38	0.04	0.79 (95% CI not available)
Cardno et al. 1999	Maudsley twin register	49	RDC	int, rec	0.36	0.07	0.84 (95% CI=0.75-0.93)

[a] int indicates an interview, que, a questionnaire, and rec, hospital records

Genetic effect seems to be strong but its strength varies between studies. In the study of Allen et al. (Allen et al. 1974) the twin population comprises only male veterans, which could explain the low concordance rate. The panel was composed of 15 909 pairs of twins born between 1917 and 1927, among whom both twins served in the U.S. Armed Forces. The computerized Veterans Affairs records were screened for a diagnosis of psychosis or affective reaction following entry on active duty until 1972. Medical records were reviewed in detail. The study used the unipolar/bipolar classification indicating whether

depression occurred without mania (unipolar) or in cycles with mania (bipolar). The criteria for bipolar illness (mania along with depression) were: euphoria or frantic mood, elation, grandiosity, impatience, extravagance, excessive talkativeness, flight of ideas, short attention span, increased psychomotor activity, decreased need for sleep, and relating to others in an infectious way. The strength of the study is that it was the first to differentiate unipolar and bipolar disorder. However, it seems that the study did not include cases with pure mania, which are currently considered as belonging to bipolar disorder. The criteria of mania resemble greatly modern diagnostic criteria, but it is not stated how they should have been fulfilled. The diagnoses based only on medical records, the twins were not met personally. That might also explain low concordance. Although the screening method was extensive, the population itself was not representative, but comprised selected males, who have attended U.S. military service.

The other studies have also some methodological limitations. Bertelsen and others made a good use of excellent Danish registers (Bertelsen et al. 1977). The Danish Psychiatric Twin Register is based on the Danish Twin Register and the Danish Central Psychiatric Register. The Danish Twin Register consists of same-sex twins born in Denmark between 1870 and 1920. In 1967, of 11 288 pairs 6 723 were traced to their present residence or to their death, and a questionnaire with inquiries about hospital admissions and various diseases and disorders was sent to them. The Danish Central Psychiatric Register collects information about all the admissions to Danish mental hospitals and psychiatric departments, and through the 1940s and 1950s it became fairly complete. The Danish Psychiatric Twin Register was composed linking the information from the two registers. The final bipolar disorder study composition was ready in 1975, when 126 probands of 110 twin pairs were ascertained to have mood disturbances according to all available case material by Bertelsen. Of 220 twin partners 138 were alive, and 133 were interviewed. If neither of the partners in a pair was alive, the nearest living relative was traced and visited for an interview. However, no structured interview schedule was used, and the diagnoses were made according to Kraepelin’s concept, which is less definitive than current diagnostic systems. Bipolar disorders were defined as disorders with at least one episode of elated mood including hypomania, but concordance rates were calculated separately for the cases of mania not only hypomania. In addition to diagnostic vagueness another weakness of the study is in zygosity determination. Of 110 pairs only in 53 pairs the zygosity determination was based upon 16 to 25 independent systems of erythrocyte types, tissue types, serum protein variants and isoenzymes. One might also speculate what kind of distortion make that of original population only 59.6% was traced in a first place. However, the authors argue that it’s unlikely that they have missed any serious affective cases. The strength is that their follow-up time was long, which might explain high concordance rates.

The Norwegian study was originally intended to include only neurotic and borderline psychotic probands (Torgersen 1986), and twins with psychotic disorders according to the psychiatric records were omitted. The ten index twins, who turned out to have bipolar disorder according to interview and DSM-III-criteria, cannot thus be seen as representative sample. Interesting is that still the concordance rate resembles that of Danish study (Bertelsen et al. 1977).

In the Swedish study (Kendler et al. 1993b), the study population was composed in two different ways. Index cases were first ascertained from the Swedish Psychiatric Twin Registry, which is formed by matching the Swedish Twin Registry covering the birth years from 1886 to 1967 to the Swedish "discharge" Psychiatric Registry for the years 1968 to 1983. Using ICD-8 diagnostic codes the authors detected 2017 bipolar or unipolar cases, whom were sent a mailed questionnaire that contained expanded version of the sections of the Structured Clinical Interview for the DSM-III-R for mania and major depression adapted to a self-report format. Another sample of twins were collected from the Swedish Twin Registry using one-for-one matching to index twins according to age, gender, and county of residence or birth. The questionnaire was also sent to them. Final diagnoses based on self-assessment via a mailed questionnaire, to which the overall response rate was as low as 42.4%. Both the diagnostic accuracy and the representativeness of the study are weaknesses, but still concordance rates accord well with the other twin study of 1990s (Cardno et al. 1999).

Cardno et al. (1999) concentrated on the full range of non-organic psychoses, and they did not actually diagnose BPI but lifetime occurrence of affective psychosis, manic type, according to the Research Diagnostic Criteria (RDC) (Spitzer et al. 1977). In another study of the same sample they use DSM-IV (American Psychiatric Association 1994) criteria, but combine BPI and BPII disorder patients. In that study they report concordance of 0.40 for MZ twins, and 0.05 for DZ twins (McGuffin et al. 2003). The sample itself what they have used is not a nationwide, but local and clinical. The Maudsley Twin Register consists of patients of multiple birth who had attended any facility of the Maudsley Bethlem Royal Hospitals between 1948 and 1993 for clinical reasons unrelated to being a twin, and who had suffered psychotic symptoms, or an episode of RDC mania or hypomania at some time in their lives (Cardno et al. 1999). The main problem in the study is that while the authors are specially interested on psychosis as such they describe inadequately bipolar subsample, and do not give any concordance rates for BPI. The strength of the study is in its elegant statistical methods, and heritability estimates based on modern genetic model fitting techniques.

Concordance rates offer the possibility to estimate heritability value of a disorder. Heritability means the proportion of variation of a feature in the population that is accounted for additive genetic factors (Falconer 1965; Owen and McGuffin 1997). The additive genetic variance is attributable to the average effects of genes considered singly, as transmitted in the gametes. The non-additive genetic variance is attributable

to the additional effects of these genes, like dominance and epistasis. The dominance variance represents the nonlinear interaction effects between alleles at the same locus, and the epistatic variance represents the nonlinear interaction effects between alleles at different loci (Khoury et al. 1993). We calculated heritability estimates for studies of Allen et al. (1974) and Bertelsen et al. (1977) (Table 7), and they were 0.68, and 0.99, respectively. Because in the study of Torgersen (1986) the numbers were very small, we did not make model fitting. The number of discordant MZ pairs was one, concordant MZ pairs three, discordant DZ pairs six, and concordant DZ pairs zero. In the Swedish study the heritability estimate for BPI was 0.79 (Kendler et al. 1995), and in the British study 0.84 for mania (Cardno et al. 1999). McGuffin et al. (2003) calculated in the Maudsley Twin Series a heritability estimate for bipolar affective disorder including both BPI and BPII, and they got estimate of 0.85.

4.4.3 Adoption studies

An adoption study of 29 adoptees suffering from bipolar disorder reported more mood disorders among biological parents (in 31%) compared with adoptive parents (in 12%) (Mendlewicz and Rainer 1977). Another study failed to show significant difference in hard affective-spectrum disorders between first-degree relatives of bipolar and control adoptees (Wender et al. 1986). The number of bipolar probands was ten. The occurrence of hard affective-spectrum disorders in their relatives (N=71) was 3 (4.2%), when the occurrence in relatives (N=346) of healthy control adoptees was 8 (2.3%). Bipolar disorder was not studied separately. The small number of cases and the bias related to the adoption itself limit the generalization of the results of adoption studies.

4.4.4 Molecular genetic studies

Significant genetic contribution to the susceptibility of bipolar disorder has been established through numerous family, adoption, and twin studies. Intensive efforts to identify or localize susceptibility genes for bipolar disorder have not thus far yielded any consensus of any particular predisposing locus to bipolar disorder. To date, bipolar disorder is thought be a complex and multigenic disorder determined by several genes and their interaction, in addition to environmental factors. This phenomena gives rise to large heterogeneity reaching the extent that the susceptibility genes might be different in different families even within the same population (Baron 2002; McGuffin and Katz 1989). Current regions of interest based on linkage studies include the following eight chromosomal regions: 6q16-q22, 9p22-p21, 10q21-22, 12q23-24, 13q32-34, 14q24-q32, 18, and 22q11-q22 (Craddock et al. 2005).

In an extended Finnish pedigree a putative susceptibility locus was identified on chromosome Xq24-q27.1 already in 1995 (Pekkarinen et al. 1995), which was later confirmed using a denser marker map covering the critical linkage region (Ekholm et al. 2002). A recent genome scan study of 40 Finnish families provided evidence for linkage, in addition to 12q23 and Xq25, to two additional loci on 4q32 and 16p12 (Ekholm et al. 2003).

In order to get a more unified picture of the numerous linkage regions reported, a meta-analysis of all genome-wide scans in bipolar disorder was conducted. This analysis included 18 genome scans world-wide, among those was also the previously mentioned Finnish genome-wide scan. The most promising linkage results ($p<0.01$) that emerged out of this study were observed on chromosome 9p22.3-21.3 and 10q11.21-22.1 for a diagnostic model including BPI and SA-B, and on 14q24.1-32.12 for a broader diagnostic model additionally including BPII (Segurado et al. 2003). Surprisingly only nominally significant p values were observed on chromosomes 14q and 18p-q that were the strongest candidate regions prior to the analysis. Also another meta-analysis of 11 studies was conducted. However, this study provided confounding results, showing the strongest evidence for linkage to chromosomes 13q and 22q (Badner and Gershon 2002).

Identifying particular genes being specific for bipolar disorder has proven difficult. The strongest evidence is found for D-amino-acid oxidase activator (DAOA) and brain derived neurotrophic factor (BDNF) genes on 13q33.2 and 11p14.1 respectively (Craddock et al. 2005). Serotonin transporter gene has constantly been one of the most prominent candidate genes, and indeed a recent meta-analysis showed significant association to bipolar disorder (Lasky-Su et al. 2005). A recent study suggest that neuregulin 1 plays a role in influencing susceptibility to both bipolar disorder and schizophrenia (Green et al. 2005). A convergent functional genomics approach has integrated gene expression data from relevant animal models with human linkage data, and produced following topping list of candidate genes: dopamine- and cAMP-regulated phosphoprotein of 32 kDA (DARPP-32), preproenkephalin (PENK), and tachykinin, substance P (TAC1) (Ogden et al. 2004).

4.4.5 Brain imaging studies

The improvement of magnetic resonance imaging (MRI) techniques offers intriguing possibilities to study the relationship between psychiatric disorders and neuropathology. Recent reviews (Bearden et al. 2001; Beyer and Krishnan 2002; Haldane and Frangou 2004; Strakowski et al. 2005) of structural brain changes in bipolar I disorder report a large variety of findings, but their consistency seems to be vague, and the etiology remains unresolved. However, all four reviews point out the abnormalities found in the frontal lobe and the plausible implication that frontal lobe, limbic, and basal ganglia circuits play a role in the pathology of BPI. Negative mood was found to be associated with increases in limbic-paralimbic blood flow (subgenual cingulate, anterior insula) and decreases in neocortical regions (right dorsolateral prefrontal, inferior parietal) (Mayberg et al. 1999). With recovery of depression the reverse pattern, limbic metabolic decreases and neocortical increases were seen. A volumetric MRI study of BPI patients reports a trend of smaller frontal area (Coffman et al. 1990), but two other studies found no significant frontal differences compared to controls (Strakowski et al. 1993; Zipursky et al. 1997). A segmentation study, which separates gray and white matter, reported smaller gray matter volumes in the left superior and middle and right prefrontal subregions (López-Larson et al. 2002). Interestingly, two studies reported smaller left subgenual

cingulate areas in a familial type of BPI (Drevets et al. 1998; Hirayasu et al. 1999), but one study did not (Brambilla et al. 2002). Decreased prefrontal volume in BPI patients, which was associated with impaired performance in the Continuous Performance Test, was found by Sax et al. (1999). The presence of abnormalities in prefrontal cortex is consistent with reports of prefrontal histological abnormalities in bipolar patients (Ongur et al. 1998; Rajkowska 2002).

The theory that neuroanatomic circuitry is implicated in the pathology of bipolar disorder would imply the involvement of the temporal lobe, particularly the hippocampus and amygdala, which project into prefrontal-striatal-thalamic networks that modulate human emotional, cognitive and social behaviour. Volumetric studies report both increased and decreased size of temporal lobes in BPI patients, as well as no change (Beyer and Krishnan 2002). Findings are slightly more consistent when evaluating the amygdala and hippocampus. Three studies have found increased amygdala volumes (Altshuler et al. 2000; Brambilla et al. 2003; Strakowski et al. 1999), but one study found decreased volumes (Pearlson et al. 1997). The hippocampus was reported to be of equal size to controls (Strakowski et al. 2005). A number of investigators have examined striatum in bipolar patients and have reported increased striatal size compared with healthy subjects although this has not been a universal finding (Strakowski et al. 2005). Two studies have observed increased thalamic volumes in BPI patients, but four studies did not (Strakowski et al. 2005). Few segmentation studies of a whole temporal lobe exist. Zipursky et al. (1997) studied white and grey matter volumes separately for frontal-temporal region, but found no differences compared with controls. Harvey et al. (Harvey et al. 1994) found decreased grey matter volumes in temporal lobes, and no difference in white matter volumes.

Three segmentation studies reported decreased overall brain grey matter volumes (Davis et al. 2004; Lim et al. 1999; López-Larson et al. 2002), while others found no difference compared with controls (Brambilla et al. 2001; Sassi et al. 2002; Schlaepfer et al. 1994; Strakowski et al. 1993; Zipursky et al. 1997). No decrease in overall white matter volumes was found in five studies (Brambilla et al. 2001; Lim et al. 1999; López-Larson et al. 2002; Sassi et al. 2002; Zipursky et al. 1997), but Strakowski et al. (1993) observed a decreasing trend in white matter volumes in first-episode mania patients, and a significant decrease in cerebral white matter volume was detected in male familial BPI patients (Davis et al. 2004). The association of BPI with increased occurrence of white matter hyperintensities has been shown in several (Bearden et al. 2001; Benabarre et al. 2002; Strakowski et al. 2005), but not all (Davis et al. 2004) studies. A recent study using a diffusion tensor imaging method observed abnormal frontal white matter tracts in bipolar patients (Adler et al. 2004).

The only meta-analysis so far of regional morphometric MRI studies demonstrated that bipolar disorder was associated with right lateral ventricular enlargements, but surprisingly, no significant differences in the other structures examined (McDonald et al. 2004b). However, considerably heterogeneity existed in the results of the studies, and the authors conclude that it remains unclear whether volumetric deviations exist in regions

such as the amygdala, thalamus, and prefrontal cortex in BPI. The finding of right lateral ventricular enlargement echoes with evidence that bipolar disorder is likely to be associated with right-side cerebral pathology (McDonald et al. 2004b). Studies also suggest that ventriculomegaly occurs in BPI as a consequence of repeated affective episodes (Strakowski et al. 2005). Brain imaging studies of BPI have shown abnormalities in several and often different brain areas. Imaging techniques develop fast and older studies might not have been able to detect small differences between groups because of broad image slices and low resolutions. In addition the study samples are not comparable between studies but vary in sex distribution, educational level of patients, disorder severity, and occurrence of comorbidity, like substance use disorder. The effects of medication or mood state have rarely been studied. Sample sizes have been relatively small, which makes it difficult to find differences between study groups.

Although MRI studies of BPI report somewhat mixed results, the emerging pattern seems to be consistent with a neuroanatomical model of mood regulation (Beyer and Krishnan 2002; Blumberg et al. 2004; Strakowski et al. 2005). The causal relationship between these findings and bipolar disorder is still to be resolved. It has been proposed that the findings represent neurodevelopmental abnormalities, originating either from genetic or environmental risk factors. In both cases, we would expect to see alterations already at a very early stage of the disorder. Hirayasu et al. (1999) reported a decrease in subgenual cingulate cortex volumes in first-episode manic patients with a family history of BPI. Strakowski et al. (1993) observed several structural brain abnormalities in first-episode mania. Friedman et al. (1999) found frontal sulcal increase in adolescent BPI patients. Striatal enlargement occurred already first-episode patients and in adolescence (Strakowski et al. 2005). A fMRI study of children and adolescents with bipolar disorder showed abnormalities in the regulation of prefrontal-subcortical circuits during visuospatial working memory task and in an affective task involving positively, neutrally, or negatively valenced pictures (Chang et al. 2004). Several studies have shown white matter hyperintensities already in children and adolescents with BPI (Botteron et al. 1995; Lyoo et al. 2002; Pillai et al. 2002).

A valid method to further examine the role of neurodevelopmental defects in bipolar disorder would be to investigate relatives of BPI patients. This also offers the possibility to dissect genetic factors predisposing to the disorder, a rational notion to emerge from studies showing high heritability for bipolar disorder (Cardno et al. 1999; Kendler et al. 1995). A few MRI studies of relatives of bipolar patients exist to date. A study (Ahearn et al. 1998) examined white matter hyperintensities in a family of 21 members with a high loading of BPI disorder, and found a high prevalence of findings in both affected and unaffected family members. A MRI study of six discordant monozygotic twin pairs with six control twin pairs was performed by Noga et al. (2001). They measured basal ganglia, the amygdala-hippocampus, and cerebral hemispheres, and found larger caudate nuclei and no typical asymmetry of hemispheres among healthy co-twins of bipolar twins compared with controls. Recently, 22 unaffected relatives from bipolar families showed reductions in anterior thalamic and caudate grey matter density (McIntosh et al. 2004). An

elegant MRI study of McDonald et al. (2004a) investigated the relationship between genetic risk and structural variation throughout the entire brain in 37 patients and their 50 unaffected first-degree relatives sampled from multiply affected bipolar families. Genetic risk for BPI was specifically associated with grey matter deficits in the right anterior gyrus and ventral striatum. Genetic risk for psychosis was associated with white matter volume reduction in the left frontal and temporoparietal regions.

4.4.6 Neuropsychological performance

Possible genetic factors predisposing to bipolar disorder should affect brain development and its functions. Euthymic bipolar disorder patients do indeed show impairments in brain functions such as verbal learning and memory compared to healthy volunteers (Deckersbach et al. 2004; Glahn et al. 2004; Martinez-Aran et al. 2004; Thompson et al. 2005). Euthymic or remitted bipolar patients have usually performed as well as controls in nonverbal memory tasks (Quraishi and Frangou 2002), but some studies show impairment in spatial recognition memory (Rubinsztein et al. 2000; Thompson et al. 2005). In tests of executive function, the degree of impairment appears to be associated with the presence of residual symptoms (Quraishi and Frangou 2002), but some studies report defects that remain significant after controlling residual mood symptoms (Thompson et al. 2005). The evidence for attention dysfunction in euthymic BPI patients is demonstrated fairly routinely (Clark et al. 2005; Glahn et al. 2004; Martinez-Aran et al. 2004; Tabares-Seisdedos et al. 2003; Thompson et al. 2005). Interestingly, although a preliminary fMRI study of sustained attention failed to differentiate between the performance of ten BPI patients and controls, abnormal activation of limbic, paralimbic, and ventrolateral prefrontal areas was found among the patients (Strakowski et al. 2004).

Although bipolar patients show some memory defects independent of clinical state, it remains unclear whether these impairments reflect biological etiological factors of the illness, or its inheritance, or are instead caused by the expression of the illness, medication, or other iatrogenic inputs. If we could see defects already in the very early stages, it would lend some support to the view that there are biological changes predisposing to the disorder. Furthermore, a degree of neurobiological defects detected also in healthy relatives would be strong evidence for familiality. And if these defects were more apparent among MZ compared to DZ healthy twins of bipolar probands, it would imply that genetic factors related to these functions account partly for the vulnerability to bipolar disorder. To date there have been few studies focusing on cognitive functions in relatives of bipolar patients. An early twin study comparing neuropsychological performance of seven MZ twin pairs to seven healthy twin pairs found that defects in verbal learning may be related to the genetic vulnerability to bipolar illness (Gourovitch et al. 1999). More recently, Kéri and colleagues (Kéri et al. 2001) reported long-term

verbal memory impairments in 20 healthy siblings of BPI probands. In an experiment involving acute tryptophan depletion 20 unaffected relatives of BPI patients showed impairments in speed of information processing, planning, and verbal memory compared to controls (Sobczak et al. 2002). However, these findings are somewhat controversial; others have failed to find deficits in verbal memory (Ferrier et al. 2004; Kremen et al. 1998), or sustained attention (Clark et al. 2005) in healthy relatives of BPI patients.

4.4.7 Environmental risk factors

Specific environmental risk factors would ideally be detected following a cohort of people from birth to death, and studying whether certain environmental factors precipitate occurrence of the illness. However, the studies to date have only analyzed retrospectively for the presence of an excess of specific life-events among those who have subsequently developed bipolar disorder.

It appears that the majority of studies report an association between bipolar disorder and social class, with those of upper social class being at higher risk (Goodwin and Jamison 1990). However, there are several methodological problems in these studies, and the interpretation of data is difficult (for review see Goodwin and Jamison 1990, pp. 169-173). Being single or divorced does not seem to be, as such, a risk factor for bipolar disorder (Goodwin and Jamison 1990), although it is also plausible that stressful marriages might precipitate affective episodes and vice versa. Results of urban-rural comparisons have been inconclusive (for review see Goodwin and Jamison 1990, p. 176) and suggest that differences in prevalence rates of affective disorders between rural and urban areas may have to do with the interplay of living location, migration patterns, socioeconomic status and environment.

Early parental loss is a putative environmental risk factor for psychiatric illness. Although there is some evidence of an excess of early parental loss among depressed and schizophrenic patients, this is unclear in bipolar disorder (Agid et al. 1999; Furukawa et al. 1999; Mortensen et al. 2003). Stressful life-events later in life may predispose to mania or depression in bipolar patients, but their association with the onset of the first episode remains controversial (Ambelas 1987; Ellicott et al. 1990; Sclare and Creed 1990). One study reports a strong relationship between mania and childhood physical abuse (Levitan et al. 1998). Labour and delivery complications are a suggested risk factor for schizophrenia, but this has been far less examined in bipolar disorder patients, and the results have been contradictory (Browne et al. 2000; Kinney et al. 1998).

4.5 Possible endophenotypes in bipolar disorder

Although the genetic contribution to bipolar disorder seems constantly high, the results of searching risk genes have not been convincing. One reason may be the limitations of using categorical diagnostic systems to identify a genetically homogenous bipolar group (Faraone et al. 2004; Leboyer et al. 1998). Maybe it is not bipolar I disorder which is genetically determined but symptoms, for instance, reflecting psychosis, psychomotor acceleration, and irritability (Faraone et al. 2004). These mood and behavioral changes are probable caused by brain structural and functional defects, which themselves are influenced by genetic factors.

Another factor hindering the gene finding is the role of environment as modulating genetic effects. Bipolar and related disorders might be speculated to involve a reaction to external stimuli in the form of modified cell communication, infrastructure changes, tissue remodelling, and a consequent altered behavioral output (Ogden et al. 2004). For example, in genetically vulnerable persons, disturbances in sleep cycles might trigger a biological pathway leading altered genetic expressions and finally to manic behavior (Johansson et al. 2003; Wehr et al. 1987). In a Finnish twin sample bipolar twins showed greater seasonal changes in sleep length and mood compared with their siblings with no mental disorder (Hakkarainen et al. 2003). Other environmental triggers could involve alcohol drinking, distress, or postpartum hormonal changes.

Bipolar disorders among other common mental disorders are considered as complex disorders (Berrettini 1998), which means that genes and environment combine to confer susceptibility to the development of disease. Douglas Falconer’s multifactorial threshold model (1965) for diabetes and other common, non-Mendelizing diseases is adapted also to a polygenic model of bipolar disorder presupposing several common genes with modest effect size in the population (Baron 2002; Kendler and Kidd 1986). The diseases, which have complex genetic background, are not optimally determined on the basis of overt phenotype for genetic dissection. The concept of "endophenotypes" (Gottesman and Gould 2003) might be more appropriate in studying polygenic disorders. It refers to inherited or intrinsic phenotypes discoverable by a specific test, or examination. The term is adapted from a paper by John and Lewis (1966), who had used it to explain concepts in entomology. They wrote that the geographical distribution of grasshoppers was a function of some feature not apparent in their "exophenotypes"; this feature was "the endophenotype, not the obvious and external but the microscopic and internal."

The identification of endophenotypes could help to resolve questions about etiological models. The rationale for the use of endophenotypes held that if an endophenotype associated with a disorder is very specialized and represents relatively straightforward more elementary phenomena (as opposed to behavior), the number of genes required to produce variations in the trait may be fewer than those involved in producing a psychiatric diagnostic entity (Gottesman and Gould 2003). Endophenotypes provide a means for identifying the "downstream" traits of clinical phenotypes, as well as the "upstream" consequences of genes (Gottesman and Gould 2003) The intervening variables could mark the path between the genotype and the behavior of interest, and might Mendelize in a predicted manner. So the underlying genes would be easier to detect using genetic methods. The methods available for endophenotype analysis have advanced considerably psychiatric genetics, and include neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, and neuropsychological. Advanced tools of neuroimaging such as functional magnetic resonance imaging (fMRI), morphometric MRI, diffusion tensor imaging, single photon emission computed tomography (SPECT), and positron emission tomography (PET) promise to expand the possibilities even more (Gottesman and Gould 2003).

However, not every biological sign related to the disorder, is endophenotype. These "subclinical traits," and "vulnerability markers," may reflect associated findings caused by illness process or environment, not genetic vulnerability. The real endophenotype must fulfill certain indicators: 1. it should be associated with illness in the population; 2. it should be heritable; 3. it should be state-independent which means that it manifests in an individual whether or not illness is active; 4. within families, endophenotype and illness should co-segregate; 5. it should be found in non-affected family members at a higher rate than in the general population (Gottesman and Gould 2003).

The search for endophenotypes has been recently of great interest especially in schizophrenia. Working memory defects have been detected in patients with schizophrenia independently of the state of disorder, and in their healthy twin siblings (Cannon et al. 2000). The trait co-segregates with the illness in families, and it shows heritability. Thus it seems to be plausible endophenotype for schizophrenia. A study of Finnish twins by Gasperoni and colleagues (Gasperoni et al. 2003), which used an endophenotype-based strategy, suggested linkage and association to a region of chromosome 1. They found that visual working memory performance was highly significantly linked to 1q41 (P=0.007), a region previously suggested in traditional linkage studies of schizophrenia.

In bipolar disorder an interesting possibility for an endophenotype arises from structural brain alterations related to the mental disorders (McDonald et al. 2004a). Genetic influence on brain structure is high, and a three-dimensional brain map study of Finnish twins revealed significant genetic influence on Broca’s and Wernicke’s language areas, as well as frontal brain regions (Thompson et al. 2001).

Neuropsychological performance is among the most studied endophenotype categories in schizophrenia. It is reasonable to postulate that mental disorders affecting brain function, like schizophrenia and bipolar disorder, are related to the cognitive alterations measurable by tests of memory-, attention-, or executive function. Although these alterations could be caused by the illness or medications used for it, it is plausible to assume that they might also represent real genetic endophenotypes forming a basis for the actual clinical disorder structures. Healthy relatives of patients offer ideal material for a study attempting to identify such endophenotypes; they have higher genetic loading of possible risk genes compared to the general population, but they do not show established illness.

5. AIMS OF THE STUDY

The general aim of the study was to investigate epidemiological and genetic risk factors of bipolar I disorder in a nationwide, population based twin sample, and find possible endophenotypes for genetic studies. The study consisted of four original publications, the aims of which were:

(I) To investigate the accuracy of bipolar I disorder diagnosis in the hospital discharge register compared with DSM-IV diagnosis based on a structured interview.

(II) To investigate the incidence of bipolar I disorder in the Finnish twin population, to estimate heritability for bipolar I disorder, and to investigate the role of prenatal and early childhood complications as risk factors.

(III) To detect brain structural defects which are related to bipolar disorder or genetic vulnerability to it using magnetic resonance imaging (MRI).

(IV) To detect brain functional defects which are related to bipolar disorder or genetic vulnerability to it using a neuropsychological test battery

6. METHODS

6.1 The Genetic Epidemiology and Molecular Genetics of Severe Mental Disorders in Finland project

This study forms part of the collaborative project "The Genetic Epidemiology and Molecular Genetics of Severe Mental Disorders in Finland" run by the Department of Mental Health and Alcohol Research and the Department of Human Molecular Genetics at the National Public Health Institute (Hovatta et al. 1997). The project was initiated in 1994, and its principal investigators are professors Jouko Lönnqvist and Leena Peltonen. The aims of the project are to characterize the epidemiology of severe mental disorders in Finland, especially genetic epidemiology, to investigate genetic and environmental risk factors, and to identify genes predisposing to severe mental disorders. The project was approved by the Ethics Committee of National Public Health Institute (25 May 1994) and by the Ministry of Social Affairs and Health. The current substudy focuses on bipolar disorder in twins, and it was started in 1997. The sample collection ended in 2000. The study was approved by the Ministry of Social Affairs and Health, and the Ethics Committee of the National Public Health Institute. Written informed consent was obtained from all subjects after they had received a complete description of the study.

6.2 Subjects

Probands for the bipolar twin-study have been identified from the National Hospital Discharge Register with the help of the National Population Register and the Finnish Twin Cohort (for details see Study 1). The procedure is covered in the Figure 1.

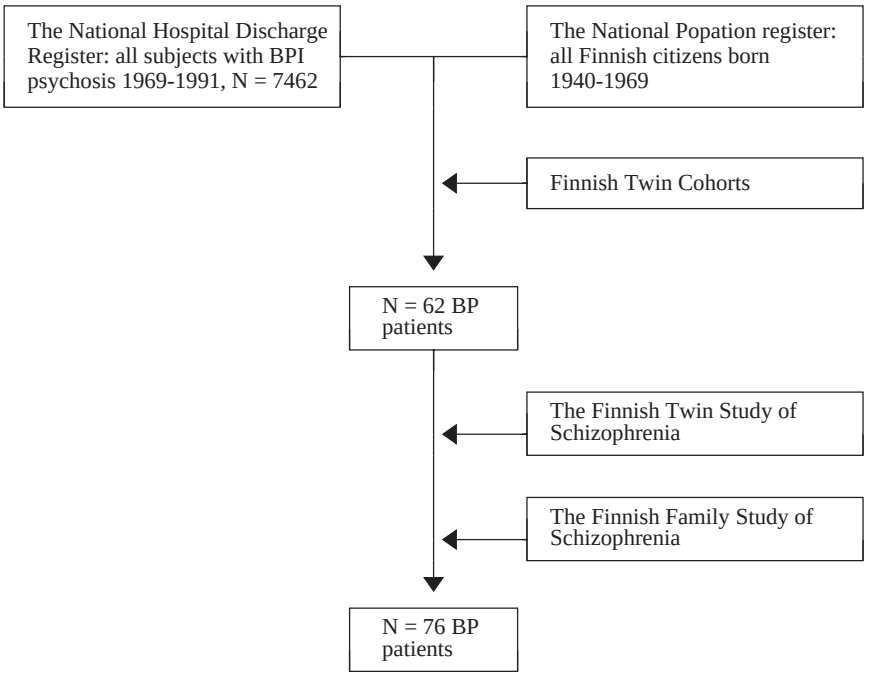

Figure 1. The compilation of the study sample

6.3 Diagnostic ascertainment

6.3.1 Hospital record-based diagnostic ascertainment before the interview

After identifying the bipolar probands from the registers, we requested all available medical records. A psychiatrist and a trainee in psychiatry assessed the diagnosis on the basis of the medical records, blind to each other and according to DSM-IV-criteria (American Psychiatric Association 1994) (see Study I). Only patients with bipolar disorder or the manic type of schizoaffective disorder were regarded as eligible probands.

6.3.2 The study procedure

All probands, except one who had a secret address and no known current treatment, were mailed an invitation to participate in the study via the treating clinician. The co-twin was also asked to participate. If the proband was deceased, the invitation was anyway sent to the co-twin. The interviews and neuropsychological tests were performed whenever possible at National Public Health Institute in Helsinki. The schedule for the day was following:

9.00 am	Coffee or tea; Study introduction; Informed consent
9.30 am	Either the SCID-interview with other questionnaires or neuropsychological testing + blood sample collection
around 12.00	Lunch
1.00 pm	Either the SCID-interview or neuropsychological testing
around 16.30	Brain MRI at Teslamed in Helsinki

The selection of starting either with a SCID-interview or a neuropsychological testing was random. The twins were provided to attend the study together in a same day, or separately depending on, which one suited better for them. If they arrived from a long distance, they were provided an accommodation at the Patient Hotel of Meilahti Hospital. The twins were always ask to attend the study in Helsinki, but if that was not possible the study was performed at a hospital or psychiatric clinic nearby where a twin lived. In one case the interview was performed at twins home. The MRI apparatus and programs were similar enough to that in Helsinki at Seinäjoki Central Hospital and at Oulu University Hospital to be used in the study. Three pairs were imaged with these machines. When the study was done outside Helsinki, the twins gave blood samples at a local health centre, from where they were mailed to Helsinki in an appropriate way.

6.3.3 SCID based diagnostic ascertainment

The second step was to confirm the diagnosis of the probands and assess possible mental disorders of co-twins using the SCID I and II interviews (Spitzer et al. 1997). Interviews were performed by the author (see Study I). Interviews were carried out between October 1997 and November 2000, and the minimum follow-up time after the register diagnosis was 6 years. The life-time and current DSM-IV axel I and II diagnoses were assessed. The demographic variables included age, sex, marital status, and education. The current medication was asked as doses per day. For antipsychotics the haloperidol equivalents were calculated using standard methods (Sadock and Sadock 2000). The length of use of medication in years was evaluated using information derived both from interviews and medical records. Alcohol use was asked as doses (one beer, wine or spirit, i.e. 14g alcohol) per month. In addition alcohol drinking was evaluated using Semi-structured Assessment of Genetics of Alcoholism (SSAGA), which questionnaire was also used for collection of family history (Bucholz et al. 1994).

Current and life-time negative and positive symptoms were rated using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1983) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984).

6.3.4 The Finnish Twin Cohort questionnaires

We were able to use some additional information from the Finnish Twin Cohort questionnaires (Kaprio and Koskenvuo 2002). The older part of the Finnish Twin Cohort comprises all same-sex Finnish twin pairs born before 1958, with both co-twins alive in 1975. The Finnish Twin Cohort Study has surveyed the entire older cohort three times. The overall response rate was 89% in the 1975 survey, 84% in 1981 and 77% in 1990. The lifetime occurrence of any specified mental disorders was asked on each occasion. From these questionnaires we also used information related to education, and twin specific topics, like similarity in the childhood, and the frequency of contact in the adulthood.

6.4 Obstetric and early childhood complications

To get information about possible environmental risk factors we collected records of study subjects from maternity and child welfare clinics, and from obstetric hospitals. A research assistant blind to the diagnosis, or any other information, used a standard form to code data on maternal health, fetal monitoring, prenatal and perinatal complications, and neonatal and early childhood conditions.

6.5 Neuropsychological examination

The test-battery has been previously used in the Finnish schizophrenia twin-study (Cannon et al. 2000). Neuropsychological examination was performed by a trained psychologist Annamari Tuulio-Henriksson, and under her supervision by two students of psychology: Tiia Pirkola, and Susanna Juselius. The test procedures are described in detail in Study IV.

6.6 Magnetic resonance imaging

The magnetic resonance images were acquired using a 1.0-T scanner (Siemens Medical Systems, Iselin, NJ, USA) in a private medical centre (Teslamed, Helsinki, Finland). The protocol and the analysis method are described in detail in Study III.

6.7 Molecular genetic analysis

Zygosity determination based on genetic marker analysis in 27 pairs in which both twins were alive, and in three cases of five pairs in which either or both twins were deceased. For the method see Study II. Ten pairs were of opposite sex. For the remaining pairs zygosity was assessed with questionnaires on resemblance and confusability in childhood (Sarna et al. 1978), and childhood photographs whenever available (see Study II).

6.8 Data analysis

6.8.1. Selection of subjects in Studies I-IV

An overview of subjects in different substudies is given in Table 8. In Study I we divided the sample to the subgroups depending on the representativeness. The results of accuracy of bipolar I diagnosis were first calculated for the same-sex twins born 1940-1957 that form epidemiologically the most representative sample (N=42) . In the second stage we included in addition the OS pairs born 1940-1957 (N=3) and the pairs born in 1958-1960 (N=4). Finally, we calculated same estimators for the sample of young twins (N=15).

After identifying the most representative sample of bipolar probands (N=42) from the Hospital Discharge Register and the Twin Cohort study (Kaprio and Koskenvuo 2002), we assessed the primary diagnosis using the method described above. Only patients with BPI (N=38) or the bipolar type of schizoaffective disorder (N=1) were regarded as eligible probands. The participation rate was 68% (N=27). This sample was used to calculate probandwise concordances and heritability estimates, and to evaluate the role of obstetric and early childhood complications (Study II).

For the data analysis of neuropsychological tests and magnetic resonance imaging we included all participants who fulfilled the appropriate criteria. Only twins with BPI and their co-twins were included in the MRI-study (Study III). Other psychotic disorders, neurological disorders affecting the brain, or brain injuries were criteria for exclusion. 16 bipolar probands with co-twins, 5 bipolar probands without a co-twin, and 6 co-twins without a proband were included. A control group of 34 twin subjects without any psychotic disorder was recruited from the same Finnish twin cohorts, and matched to the age, sex and zygosity distribution of the patient sample.

The neuropsychological sample (Study IV) contains 26 BPI twins (6 MZ, 20 DZ twins) without evidence of other psychotic disorders, neurological disorders, brain injury, or current alcohol dependence. At the time of study, BPI twins were in full symptom remission according to the DSM-IV criteria. Co-twins were excluded if they met the criteria for bipolar disorder type II (BPII), bipolar disorder not otherwise specified (BPNOS), cyclothymia, or recurrent major depression, or met any of the exclusions outlined for BPI twins. Finally, 13 discordant pairs (2 MZ, 11 DZ), seven BPI twins without a non-bipolar co-twin, and six non-bipolar co-twins without a BPI twin were included. In addition, three pairs were concordant for BPI (2 MZ, 1 DZ), and both twins in these pairs were included in the patient group, which thus totalled 26 patients. A control group of 114 twins (46 twin pairs + 22 twin subjects) without a history of any psychotic disorder was recruited from the same Finnish twin cohorts. Diagnoses of schizophrenia or any psychosis, BPI, recurrent major depressive disorder, BPII, cyclothymia, BP NOS, neurological disorders affecting the brain, brain injury, or current alcohol dependence were criteria for exclusion from these analyses. The exclusion criteria were same as for bipolar and non-bipolar co-twins.

Table 8. An overview of subjects in different substudies

Twin pairs detected from registers: N = 74					
Sample	Same-sex pairs born 1940-1958			Whole sample	
Study number	Study I		Study II	Study III	Study IV
Study name	Accuracy: medical records	Accuracy: SCID interview	Concordance	MRI	Neuro-psychological functioning
N (subjects)	42	29	52	39	45
N (BP patients)	42	29	27	24	26
N (co-twins)	0	0	25	15	19
Female/Male	17/25	13/16	20/34	20/19	28/17
MZ whole pairs	1	1	7	3	4
DZ whole pairs	0	0	19	13	12

In each study basic demographic and clinical characteristics of BP participants were compared with non-participants of the sample. Here we used the information from the National Hospital Discharge Register (the age at onset, the number of inpatients admissions, the number of days spent in psychiatric hospitals, the history of alcohol disorder diagnosis in registers), the National Population Register (age, sex, marital status, census data), and the Finnish Twin Cohort Questionnaires (education). These analyses revealed no significant differences between BP participants and non-participants.

Demographic characteristics of the four study groups were derived basically from the SCID-interview: sex, age, marital status, education, life-time alcohol dependence, life-time anxiety disorder, occurrence of current symptoms, possible use of lithium in mg/day, possible use of any psychotropic medication, the length of use of medication in years, the duration of illness in years, and life-time occurrence of psychotic symptoms. In addition we used the National Hospital Discharge Register for information of age at onset, number of inpatients admissions, number of days spent in psychiatric hospitals, and the history of alcohol disorder diagnosis in registers. Characteristics of the study groups are given in the Table 9.

Table 9. Characteristics of the bipolar patients in the four study groups.

Twins detected from registers: N = 76				
Study number	Study I	Study II	Study III	Study IV
Study name	Diagnostic Accuracy	Concordance	MRI	Neuro-psychological functioning
N (BP patients)	38	27	24	26
Female/Male	17/21	17/10	11/13	15/11
Age	48	48	44	44
Married	21 (54%)	15 (56%)	14 (58%)	15 (59%)
Education[a]	3.6	3.5	3.9	4.1
Age at onset	28	28	26	26
Number of inpatient admissions	6	6	4	4
Number of days spent in psychiatric hospitals	313	303	208	224
History of alcohol disorder diagnosis in registers	8 (20%)	5 (18%)	3 (12%)	2 (9%)
Life-time alcohol dependence	12 (30%)	6 (22%)	7 (29%)	6 (23%)
Life-time anxiety disorder	9 (23%)	8 (30%)	7 (29%)	7 (27%)
Current symptoms	-[b]	-[b]	2 (8.0)	0
Lithium mg/day[c]	-[b]	-[b]	927	927
Any psychotropic medication	27 (69%)	17 (63%)	16 (67%)	17 (65%)
Length of use of medication in yrs	19	13	16	16
Duration of illness in yrs	24	23	22	24
Life-time occurrence of psychotic symptoms	30 (77%)	21 (77%)	21 (87%)	20 (76%)

[a] Education was classified according to the SCID classification.
[b] There was not enough information of each person.
[c] This was calculated only for those who used lithium.

6.8.2. Statistical methods in Studies I-IV

Diagnostic accuracy
The diagnostic agreement between the two raters was calculated using the Cohen's kappa (Study I). Two-sided t-tests for independent samples and the Fisher's exact test were calculated to explore background differences between the interviewed subjects and those assessed with data on medical records only (Study I).

Incidence
To verify the representativeness of the sample we calculated the first admission annual incidence rate for BPI derived from this sample. We chose the follow-up period to start from 1976 (as the first Twin Cohort Survey was undertaken in 1975) and end in 1991. The morbid risk estimate for BPI was calculated by dividing the ascertained BPI cases by the number of individuals in the beginning of the follow-up.

Representativeness
To determine, if those who participated in the study differed from those who refused, we compared clinical and demographic data between these two groups using Fisher's exact test (for sex, occurrence of alcohol abuse or dependence, treatment setting, and death), χ^2 test (for marital status), Student's t-test (for age at onset) and Mann-Whitney rank sum test (for education, number of psychiatric hospitalisations, number of days spent in psychiatric hospitals). All tests were two-tailed. The baseline information was acquired from the Finnish Twin Cohort Surveys and the Hospital Discharge Register, and analysed as it pertained to the sample in 1991. The follow-up information was asked from the treating persons and twins during contact procedure, or acquired from the National Population Register.

Concordance rates and heritability estimate
The probandwise concordance rate (Study II) is defined as the proportion of proband twins that have an affected co-twin. It can be thought to display the risk for a twin to be affected if his co-twin has the disorder. This kind of one variable data (yes, no) can be summarized as a contingency table:

Number of pairs	Twin 1 affected	Twin 1 non-affected
Twin 2 affected	a	b
Twin 2 non-affected	c	d

Probandwise (casewise) concordance is calculated using formula 2a/(2a + b + c). Probandwise concordance gives estimates of the morbid risk of disease for MZ and DZ co-twins of affected persons (Allen et al. 1967). Correlations in liability (Study II) were calculated for BPI according to the method described by Falconer (1965) using information from contingency table. The Mx program (Neale 1997) was used for biometrical model fitting to provide estimates of the genetic and environmental components of variance in the underlying liability to disease (Study II). Model-fitting procedures and assessment of model fit employed standard methods, and it can be illustrated by a path diagram (Neale 1997) (Figure 1). Rectangles are used to enclose observed (manifest or measured) variables, like disease status. These are dependent variables, which are assumed to be explained by independent, latent variables, surrounded by circles or ellipses. Single-headed arrows represent this causal relationship. Double-headed arrows represent a covariance between two variables. Here the structural equation model is configured with three latent variables. *A* refers to an additive genetic effect, and its correlation coefficient is 1.0 in MZ pairs and 0.5 in DZ pairs. *C* indicates shared environmental effects, and its correlation coefficient is 1.0 in both types of twin-pair, if they have lived in the same family. *E* indicates individual specific environmental effects (uncorrelated between twins) (Posthuma et al. 2003).

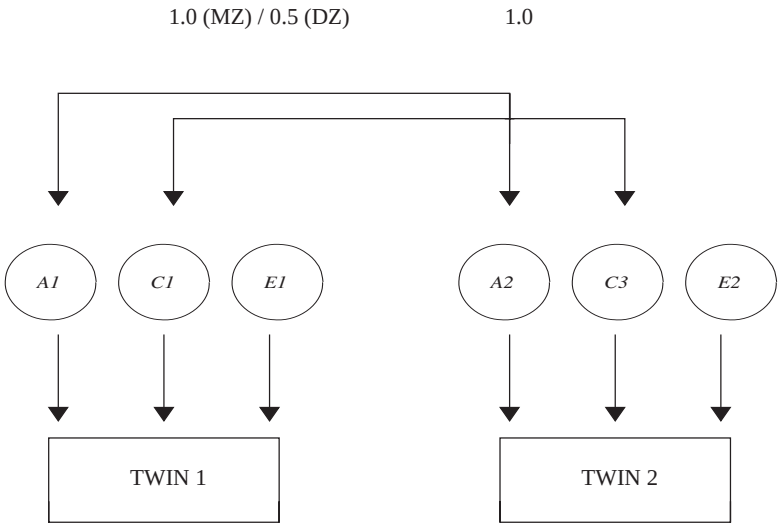

Figure 2. Path diagram of ACE model and measured environment.
Lower rectangles indicate observed variables in twin 1 and 2. Ellipses surround latent variables: *A* indicates genetic variance, *C* common environmental variance, and *E* specific environmental variance. Single-headed arrows (lower) represent causal relationship, and double-headed arrows (upper) covariance.

The probandwise concordance rates, were calculated for MZ and DZ pairs for narrow and broad levels of concordance (Study II). The narrowest diagnostic category included only BPI, the intermediate category BPI and schizoaffective disorder, bipolar type (SA-B), and the broad category in addition bipolar II disorder, bipolar disorder not otherwise specified, cyclothymia, and recurrent major depressive disorder. The occurrence of schizophrenia was also evaluated.

The twin method is predicated on the equal-environment assumption that monozygotic and dizygotic twins share the same environment relevant to the disorder under study (Kendler et al. 1993a). We were able to assess the environmental similarity and psychiatric resemblance using the length of cohabitation and frequency of contact as environmental variables (see Study II). Possible effects of other confounding variables to the concordance (Kendler et al. 1993b) were examined (see Study II).

Contingency tables with actual numbers of concordant and discordant twin-pairs were used for model-fitting. Significance levels for differences in pairwise concordance rates between MZ and DZ twins were calculated using Monte Carlo simulation method (Mustonen 1992) (N=10 000 000 simulations) and the Fisher's exact test. We used a one-tailed test, because the prior studies indicate that MZ concordance rate will be higher than DZ concordance rate. The probandwise concordance method and model fitting assumes that each twin has same probability to be ascertained in the study. The twins were screened using Hospital Discharge Register, and Twin Cohort Questionnaires, in which the probability to be detected as a proband were similar to both twins in a pair. However, the possibility that final diagnostic ascertainment has violated the assumption will be considered in discussion.

Obstetric and early childhood complications
The difference between concordant and discordant pairs related to physical and mental problems of a mother during pregnancy or delivery was calculated using Fisher's exact test (Study II). The difference between BPI patients and co-twins in the occurrence of postnatal complications, and mean heights and weights at birth were analyzed using adjusted Wald test for clustered continuous data, and the calculations were computed using Stata programme (STATA 2001), as well as in the occurrence of childhood infections, or reported physical or behavioural complications (Study II).

Magnetic resonance imaging
For MRI analysis (Study III) the data were divided in three status groups: (1) BPI patients (N=24), (2) co-twins without any psychotic or affective disorder (N=15), and (3) control twin subjects without any psychotic or affective disorder (N=27). The data were analyzed using a random-effects model for non-independent data, treating each twin pair as a cluster in modelling (Laird and Ware 1982) (see Study III).

Neuropsychological analysis
Neuropsychological data were analyzed using three risk groups: (1) BPI patients (N=26), (2) non-bipolar co-twins (N=19), and (3) control twins (N=114). Group differences in the neuropsychological test scores were analyzed using generalized estimation equation model for non-independent data (Liang and Zeger 1986) (see Study IV).

7. RESULTS

7.1. The accuracy of register- and record-based bipolar I disorder diagnosis

The results of accuracy of bipolar I diagnosis were first calculated for the same-sex twins born 1940-1957 that form epidemiologically the most representative sample (Study I: Table 2). The accuracy of bipolar I diagnosis (either bipolar I disorder or manic type of schizoaffective disorder) was 92% in the hospital discharge register.

In the sample also including the OS pairs born in 1940-1957 (N=3) and the pairs born in 1958-1960 (N=4), the estimation for the accuracy of register diagnosis was 93%. In the sample of younger twins (N=15), the overall rate of false positive cases in the hospital discharge register was 13%.

7.2. The incidence and genetic epidemiology of bipolar I disorder, and the role of environmental factors

7.2.1 Incidence

The annual incidence of BPI per 100,000 population was for women 6.9 (95% CI=2.6-11.2), men 8.3 (95% CI=3.6-13.0), and overall 7.6 (95% CI=4.4-10.8) (Study II). Using same registers we also estimated the incidence of BPI disorder in the whole Finnish population. During follow-up period 1970-1991, the annual incidence in the birth cohort 1954-1959 was 5.8 (95% CI=5.4-6.3).

7.2.2 Concordance rates

The concordance for BPI was 0.43 for MZ twins, and 0.06 for DZ twins (Study II: Table 2). When we included schizoaffective manic type patients as cases, the rates were 0.50 and 0.05, respectively. The concordance for broad level of affective spectrum was 0.75 for MZ twins, and 0.10 for DZ twins. No schizophrenia occurred in this sample.

7.2.3 Heritability

On the grounds of parsimony, the model of genetic and specific environmental variance (*AE*) was the best-fitting model, with a heritability estimate of 0.93 (95% CI=0.69-1). However, it should be noted that in the full model (*ACE*) confidence limits for both genetic (0.67 (95% CI=0-0.99) and environmental factors included zero (Study II: Table 4).

7.2.4 Obstetric and early childhood complications as environmental risk factors

There were no significant difference between reported postnatal complications between BPI patients and co-twins ($F_{1,28}$=0.04, P=0.85). BPI patients and healthy co-twins did not differ from each other according to the occurrence of childhood infections ($F_{1,23}$=0.44, P=0.51), or reported physical or behavioural complications ($F_{1,22}$=1.56, p=0.24). (see Study II)

7.3 Magnetic resonance imaging

7.3.1 Whole brain

Whole brain total volume did not differ between study groups ($F_{2,81}$=0.93, P=0.40). Decreased left hemispheric white matter volume was seen both in patients and co-twins compared with control twin subjects. (Study III: Table 3) Decreased right hemispheric white matter was seen only in patients. We found no decrease in hemispheric grey matter volume in either patients or co-twins compared with control twin subjects.

7.3.2 Frontal lobe

Significantly decreased white matter was detected in the frontal region of BPI patients but not in co-twins compared with control twin subjects. (Study III: Table 3) The disparity was apparent both in left and right frontal regions. We found no decrease in frontal grey matter volume in either patients or co-twins compared with control twin subjects. There was no difference between discordant BP twins and co-twins (N=9) in either white or gray matter volumes (Ps>0.54). BPI patients showed increases in frontal sulcal volumes. In addition to the intracranial volume (effect size 0.04; S.D. 0.01; P<.0001) and age (effect size 0.3; S.D. 0.1; P=0.03), a lifetime occurrence of substance use disorder (effect size 6.6; S.D. 2.1; P=.0009) was positively correlated with frontal sulcal volumes. A paired analysis of discordant pairs showed a trend to a significance in difference (P=0.09) between BP twins and co-twins in frontal sulcal volumes.

7.3.3 Temporal lobe

We found no decrease in temporal white or grey matter volumes in either patients or co-twins compared with control twin subjects. (Study III: Table 3) There was also no difference between discordant BP twins and co-twins (N=9) in either volumes (Ps>0.50). BPI patients showed increases in temporal sulcal volumes. However, a paired analysis of discordant pairs did not show significant difference (Ps>0.39) between BP twins and co-twins.

7.3.4 Ventricular volumes

No ventricular enlargement was seen in BPI patients or co-twins compared with control twin subjects (Study III: Table 3). No difference (Ps>0.31) between twins was seen in a subgroup of discordant BP pairs (N=9).

7.3.5 Medication

To check for a possible effect of lithium use on white matter volume among patients we dropped the risk status from the above-described model, and inserted lithium use (mg/day) as an independent variable. Lithium use had no effect on white matter volumes. By the same method we analyzed the effects of neuroleptics, with their use calculated as haloperidol equivalents per day. We found that use of neuroleptics was negatively correlated with temporal white matter volume (effect size -0.5; S.D. 0.2; $P < 0.001$).

Frontal grey matter volume was found to be positively correlated with the use of lithium. The effect size for doses of 1000 mg per day was 8 (S.D. 4; P=0.03). Lithium use had no effect on temporal grey matter volume. No correlation with any other regional grey matter volumes was detected. A paired analysis of discordant pairs (N=5) revealed a nearly significant difference (P=0.06) in right frontal gray matter volume between those BPI twins who used lithium and co-twins.

Lithium use had no effect on cerebrospinal fluid volumes. The use of neuroleptics correlated with larger left (effect size 0.3; S.D. 0.1; P=0.01) and right (effect size 0.3; S.D. 0.1; P=0.009) ventricular volumes, but not with sulcal sizes.

7.4. Neuropsychological functioning

7.4.1 General intellectual functioning and information processing speed

Neither BPI twins nor non-bipolar co-twins differed significantly from controls in the WAIS-R Vocabulary test (Study IV: Table 3). However, BPI twins performed significantly worse than controls in the Digit Symbol Test (Study IV: Table 3), and the CPT reaction time was significantly longer in BPI twins compared with controls.

7.4.2 Memory functions and verbal learning

BPI twins performed worse than controls in non-verbal and verbal memory tasks, and in long delay free recall after verbal learning. (Study IV: Table 3). They did not show significant impairment in learning efficiency and in retention. Non-bipolar co-twins did not differ significantly from controls (Study IV: Table 3). Among females both the BPI twins and non-bipolar co-twins showed impairment in total recall (Study IV).

7.4.3 Information processing speed as a confounding variable

The performance in a Digit Symbol Test had a highly significant effect ($p < 0.0001$) on working memory tasks, on visual reproductions, on story recall, on total recall in CVLT, and in memory efficiency (Study IV: Table 3).

While BPI twins performed significantly worse than controls in reaction time derived from CPT, another measure of information processing speed (Study IV: Table 3), we examined whether reaction time is a better predictor than the Digit Symbol Test for the level of performance. It showed similar effect on memory tasks as the Digit Symbol Test.

7.4.4 Medication

We modelled memory functioning entering the lithium dosage as a covariate with age and sex, but it did not have significant effect on any of memory tests used in this study. Its estimated coefficient was in all cases negative, but had no statistical significance. Neuroleptics had a nearly significant negative effect on delayed visual recognition ($P=0.04$), and a significant effect on the CVLT total recall ($P<0.0001$). (Study IV)

BPI twins performed significantly worse than controls on the Digit Symbol Test (Study IV: Table 3). We checked if medication would explain this, but this was not the case (Study IV).

7.4.5 Psychotic symptoms and the duration of illness

Using a score derived from the SAPS and the SANS, we analyzed whether psychotic symptoms had any predictive value for memory functions or verbal learning impairment, but they did not. (Study IV) We examined whether the duration of illness had any predictive value for memory and verbal learning functions. After adjusting for sex and age, it did not have significant effect on any of the test variables in BP twins.

7.5 Summary

An overview of main results in different substudies is given in the Table 10.

Table 10. An overview of main results in different substudies

Study I	Study II	Study III	Study IV
Accuracy	BPI Concordance and heritability	Magnetic resonance imaging	Neuropsychological functioning
Accuracy of BPI diagnosis in a hospital discharge register: 92%	MZ / DZ probandwise concordance rates: 42.9 / 5.6	BPI patients: hemispheric and frontal white matter decrease	BPI patients: information processing speed and delayed memory functioning impaired
	Heritability: 0.93 (95% CI=0.69-1)	Healthy co-twins: left hemispheric white matter decrease	Female co-twins: impairment in long-term memory functioning

8. DISCUSSION

The study comprised a nationwide population of twins, who had either been treated because of BPI or had self-reported having BPI, along with their co-twins. The twins were born between 1940 and 1969, and were ascertained from the central hospital discharge register or twin cohort questionnaires. We used face-to-face SCID interviews for diagnostic evaluation. Our main findings were that the heritability of BPI is high, and that there were two possible genetic trait markers for vulnerability to disorder: left hemispheric white matter decrease, and impairment in long-term verbal memory. Obstetric or early childhood medical complications did not appear to predispose to BPI. Our analysis also revealed that the diagnosis of BPI in the Finnish Hospital Discharge Register was highly accurate. In the following, methodological issues and the findings in each of the publications are discussed in detail.

8.1 Methods and methodological limitations

This study used three nationwide, population-based data sources both to identify the subjects and to collect additional information to supplement the interviews: the Finnish Hospital Discharge Register, the Finnish Twin Cohort Study, and the National Population Register. The overall accuracy of psychiatric diagnoses in the Finnish Hospital Discharge Register was studied in 1986 and found to be excellent. When entries in the register were compared with the data on hospital case notes, the primary diagnosis in the register and hospital case notes was identical in 98% for all mental disorders (Keskimäki and Aro 1991). The questionnaires of the Finnish Twin Cohort Study twin cohort provided additional data on mental health disorders and any medications (Kaprio 1994). The National Population Register provided data on marital status, census data, and first-degree relatives for each subject.

These three data sources enabled us to detect all the twins who had ever been treated in hospital because of BPI. An initial concern in the study was that a proportion of BPI patients is never hospitalized, so in addition we used information from the Finnish Twin Cohort questionnaires, which asked if a twin had ever had any major medical, including psychiatric, problems, and if so, specifically what. Although the response rates were high we cannot be sure that people correctly reported their psychiatric problems. It might thus be that our study sample was somewhat biased towards a more severe form of BPI, the

severest form of which includes psychotic symptoms. However, when we checked the occurrence of psychotic symptoms in the sample using SCID information, we found that 23% had never had psychotic symptoms. Nonetheless, we were able to detect them using register and questionnaire information. In an ongoing family study of BPI, we have interviewed, using SCID, 42 families with a BPI proband. Preliminary results show that it seems to be very rare to be diagnosed with BPI without having been hospitalised.

A strength of the study was that the final diagnoses were confirmed using SCID. A limitation was that study subjects were not assessed with mania or depression rating scales. Thus we were not able to study the possible correlations of mood symptoms with brain structural or functional findings. However, the life-time and current SCID based DSM-IV diagnoses were made on the very same day that the subjects performed neuropsychological tests, and we excluded all those who were not in full remission.

An assumption underlying the model fitting is the multifactorial threshold model, which presupposes many common genes with modest effect size in the population (Kendler and Kidd 1986). Most of the evidence to date supports this assumption (Craddock and Jones 1999). Twins classified as concordant for nonaffection were not interviewed. The number of discordant pairs may thus have been underestimated. Thus, our estimate of familiality may be somewhat biased upwards. However, there is no reason to believe that the underestimation would differ by zygosity, and the incidence of disease corresponded with expectations.

Although the study is a population study, the evident limitation is the relatively small number of subjects. That limited the power to reject inappropriate genetic models for heritability estimate. The failure to find statistically significant difference in concordance for BPI disorder between MZ and DZ twins is probably due to lack of power. In the analysis of MRI and neuropsychological data the sample was of limited size for comparing MZ and DZ discordant pairs, which would have been ideal for analyzing genetic vulnerability. Intrapair differences between discordant MZ pairs would have given information about non-genetic factors either related to the vulnerability or disorder itself, and the possibility to compare MZ, DZ and control co-twins would have given information about genetic vulnerability. Our results may reflect genetic vulnerability, but other factors causing familiality, could be a reason, too. However, as compared to the ordinary sibling study, our study has a certain advantage. The common family environment is entirely shared by the twins as they are born in the same family in the same time point.

Finally, the sample itself was representative: not restricted to academic health centres but covering various treatment settings in the whole country. The annual incidence in the sample was in accordance with previous studies (Daly et al. 1995; Leff et al. 1976). We were able to check the annual incidence in the 1954-1959 Finnish birth cohort during the follow-up period 1970-1991, and found it to be well in accord with the incidence in our twin population. And although the sample comprised only twins, this does not invalidate

its representativeness, because there is no reason to believe that bipolar disorder or the diagnostic procedure among adult twins would be different compared to other subjects (Kendler et al. 1996).

8.2 The accuracy of register- and record-based bipolar I disorder diagnosis

Our study shows that the accuracy of the hospital discharge register diagnosis of bipolar I disorder equalled that of schizophrenia (Mäkikyrö et al. 1998). The special strength of the study is that diagnostic ascertainment was made after following the patients from the first admission for at least six years. During their treatment history the patients had often had another psychosis diagnosis (e.g. psychosis NOS). However, our study shows that if a person ever had bipolar I diagnosis in the hospital discharge register, it was both highly reliable and stable.

The subjects were detected using both ICD-8 and DSM-III-R coding system. Unfortunately our study population was not large enough to compare these two diagnostic system.

8.3 Contribution of genetic factors: concordance rates and heritability

This first twin study of bipolar disorder involving a representative nationwide twin sample, in which BPI was diagnosed using structured face-to-face interviews and long-term follow-up data, confirms previous findings that the heritability for BPI is high. However, the concordance rate in MZ twins was still far from 100 percent. The traditional explanation for only one MZ twin having a clinical disorder is based on so-called non-shared environmental effects, like obstetric complications (Kinney et al. 1998), infections (Torrey et al. 2000), or early losses (Agid et al. 1999). Complications during pregnancy, birth or post-natally, early childhood infections or preschool physical or behavioural complications did not explain vulnerability to BPI in our study.

Some researchers have challenged the whole idea of full genetic identity in MZ twins (Hall 1996). MZ discordance might be due to endogenous accidents of development and differentiation, like somatic mutation, somatic recombination, differences in tissue-specific methylation patterns and the timing of such events (Martin et al. 1997). However, molecular studies of MZ twins are rare, and findings of genomic differences are even less common. Recently, the putative role of epigenetic dysregulation of gene activity in psychiatric disorders has been suggested (Petronis et al. 2003). Unlike DNA sequences, which usually remain stable throughout the lifetime of an organism, epigenetic mechanisms, like DNA methylation and chromatin structure, are quite dynamic processes. Epigenetic

regulation of gene activity is subjected to developmental stage, and tissue-specific, age-dependent, and environmentally induced changes as well as to stochastic events. A substantial degree of epigenetic dissimilarity and therefore differential gene expression can be accumulated over years in the cells of the same tissue (e.g., brain) of two genetically identical organisms. In a study of a discordant and a concordant schizophrenic MZ pair, it was detected that affected twin of the discordant pair was epigenetically closer to the affected concordant twins than to his unaffected co-twin (Petronis et al. 2003). No such studies exist among bipolar twins.

Although the correlations in liability to BPI were much greater for MZ than DZ twins, indicating the importance of genetic contribution, we were unable to conclusively reject the model with no genetic component. Nevertheless, it fitted clearly worse than the models with both genetic and environmental components. The best-fitting model with additional genetic and specific environemental component (*AE*) explaining variance gave a heritability estimate of 0.93 for BPI. The full model produced a heritability of 0.67. Both Kendler et al (1995) and Cardno et al. (1999) report the *AE* model as best fitting, with heritability estimates of 0.79 and 0.84, respectively. When we calculated heritability estimates for bipolar disorder using Mx structural equation modelling for the studies of Allen (1974), Bertelsen (1977), and Torgersen (1986), the best-fitting model was consistently *AE* model. Heritability estimates varied from 0.86 to 0.99, being relatively close to our and others estimates.

Based on epidemiological and molecular genetic studies bipolar disorder seems not be a single gene illness, but a complex disorder (Baron 2002). It is plausible that at least some of the genes involved affect brain development, structure and function (Boomsma et al. 2002). Subtle alterations, together with other genetic changes and environmental factors, would then lead to a clinical disorder. The genetically determined traits constituting part of an increased risk for a disorder are called endophenotypes. In this study we concentrated on neuropsychological tests measuring brain function, and magnetic resonance imaging measuring brain structures. Our twin sample offered the potential to evaluate possible defects, i.e. endophenotypes, first in bipolar patients and then in genetically high risk but mentally healthy twin siblings.

These persuasive results of a high genetic contribution to the etiology of BPI imply the importance of genetic research. Finding genes which inluence the risk of being affected will make it possible to obtain knowledge of the pathogenic mechanisms that lead to the disorder. This will be of use in the development of more specific pharmaceuticals and other treatments, and for determining more specific timing of a treatment.

8.4 The brain magnetic imaging

The patients with BPI and their co-twins without BPI both showed decreased left hemispheric white matter volumes compared with control twin subjects. This finding could be interpreted as reflecting a familial (possibly genetic) marker for vulnerability to BPI. Unfortunately our sample was not large enough to compare separately discordant MZ and DZ pairs to study more specifically genetic vulnerability. In the regional analysis co-twins did not show white matter decrease either in frontal or temporal lobes. Hemispheric volumes included midbrain structures like thalamus and striatum, which were not analyzed separately. While the basal ganglia and thalamus appear to contribute to neural networks that modulate mood (Strakowski et al. 2005), one could hypothesize that white matter decrease seen both in co-twins and BPI patients might be localized in the area connecting these structures and frontal lobe. Another possibility is that the white matter reduction is localized in the posterior lobe, which was not analyzed separately

To our knowledge this is the fourth study to report significant or nearly significant decrease in brain white matter volumes in BPI. A significant decrease in cerebral white matter volume was detected in male familial BPI patients (Davis et al. 2004). A recent study showed that genetic risk for bipolar disorder was associated with white matter deficits in the anterior corpus callosum and bilateral frontal, left temporoparietal, and right parietal regions (McDonald et al. 2004a). Several earlier studies have found no loss in white matter volumes compared with control twin subjects (Brambilla et al. 2001; Lim et al. 1999; López-Larson et al. 2002; Sassi et al. 2002; Zipursky et al. 1997). The studies have used different methods and smaller samples, which might explain the results. However, white matter atrophy is not specific to BPI, but it is seen in neurological disorders like dementia and multiple sclerosis, as well as in psychiatric disorders like posttraumatic stress disorder (Villarreal et al. 2002) and schizophrenia (Kubicki et al. 2003), but not in early-onset depression. As a matter of fact, the study of McDonald et al. (2004) showed that left frontal and temporoparietal reduction in white matter volume was a generic association for both schizophrenia and BPI. Also, a Finnish study of first-episode schizophrenia and severe depression patients supports the view that white matter reduction correlates with psychotic disorder (Salokangas et al. 2002).

Several reports of excess white matter hyperintensities (WMH) in bipolar disorder imply the relevance of white matter in the pathogenesis of this disorder (Bearden et al. 2001; Benabarre et al. 2002; Strakowski et al. 2005), and our findings provide some support for that view. White matter reduction could be involved in the abnormalities of specific frontosubcortical functional circuits hypothesized to occur in bipolar disorder (McDonald et al. 2004a; Pearlson 1999; Soares and Mann 1997). A diffusion tensor imaging study supports the view that WMH indicate damage to white matter tracts (Taylor et al. 2001), and a recent study observed abnormal frontal white matter tracts in bipolar patients (Adler et al. 2004).

Focal white matter lesions seem to occur more often in mood disorders when compared to schizophrenia, but more studies are warranted to define possible differences between BPI and unipolar disorder patients (Harrison 2002; Lyoo et al. 2002). Although the basic form of pathology in unipolar and bipolar disorder appears to be similar in terms of the glial and morphometric differences in the prefrontal cortex, the findings of subcortical structures seem to differ somewhat between these two disorders. Still, no good evidence yet exists for a neuropathological separation of bipolar from unipolar disorder. We should probably focus on different kind of subdivisions like familial vs. sporadic, or try to find underlying subtype of 'white matter mood disorder' (Harrison 2002). Rather than being linked to any diagnostic category, neuropathology might map onto specific symptoms. The ventral tegmentum, ventral striatum and medial prefrontal cortex may be relevant for anhedonia, amygdala for anxiety, and left anterior cingulate for agitation (Harrison 2002).

In accordance with previous studies (Brambilla et al. 2001; Sassi et al. 2002; Schlaepfer et al. 1994; Strakowski et al. 1993; Zipursky et al. 1997) no significant reduction of grey matter was found in BPI patients or co-twins in this study. Three other investigations (Davis et al. 2004; Lim et al. 1999; López-Larson et al. 2002) detected overall reductions in cortical grey matter, but their study subjects differed from ours in chronicity, severity, and educational level. The grey matter deficits seem indeed be more prominent in schizophrenia (Cannon et al. 1998; Salokangas et al. 2002) compared with BPI.

Our study showed somewhat increased left and right hemispheric grey matter volumes in BPI patients and co-twins. As this phenomenon was most prominent in the patients, we examined whether lithium use was related to it. Some recent findings suggest that lithium might have neuroprotective effects (Moore et al. 2000; Sassi et al. 2002). We did indeed find slight positive correlation between lithium use and frontal grey matter volumes, and a paired analysis of discordant twins showed right frontal gray matter increase among those BPI twins who used lithium when compared with co-twins. The meaning of increased grey matter volume has not been widely discussed in the psychiatric literature, and it should be examined in further studies.

We also considered other possible effects of medication. Most subjects with mood disorders have been treated with antidepressants, lithium, antipsychotics, or minor tranquillizers, and some with electroconvulsive therapy (ECT). These treatments can potentially cause neuropathological effects. A comprehensive review concluded that ECT produces no demonstrable neuropathological effects (Devanand et al. 1994). No neuropathological effects of long-term therapeutic levels of lithium (0.4-1.0mmol/l) have been described (Harrison 2002) A MRI study reported that lithium treatment increases cortical gray matter volume suggesting that lithium is neurotrophic (Sassi et al. 2002). Antidepressants may regenerate monoaminergic axons and promote neurogenesis in animal models, but it is unknown whether these processes occur in patients (Harrison 2002). The neuropathological effects of antipsychotic drugs have been relatively well studied, and comprise alterations in

synaptic and neuronal morphology, particularly in the caudate-putamen (Harrison 2002). Increased glial density has been reported in the prefrontal cortex of monkeys treated chronically with antipsychotics (Selemon et al. 1999). White matter volume reduction was detected in our study, and we checked if it was related to medication. Use of lithium was not correlated with any regional white matter loss, and use of neuroleptics correlated only with the decrease in temporal white matter.

We did not find a significant increase in ventricular volumes in bipolar patients or co-twins. As ventricular increases have been reported quite consistently (McDonald et al. 2004b), this was somewhat surprising. Our population and register based sample with a lifetime diagnosis of BPI represents the whole spectrum of BPI, not only the most severe form, which might explain our finding of no ventricular increase. Strakowski et al. (Strakowski et al. 2002) have reported that although multiple episode BPI patients exhibit greater ventricular volumes compared with first-episode patients and healthy controls, the latter two groups do not differ from each other. While several studies have also reported ventricular increase in schizophrenia patients (Cannon et al. 1998), and in psychotic depression (Salokangas et al. 2002), we suspect that this abnormality is not disease specific, but relates to the occurrence of psychotic symptoms, and reflects factors secondary to severe mental illness or its treatment.

In accordance with our results, two previous studies have reported sulcal enlargement in bipolar patients (Davis et al. 2004; Friedman et al. 1999), and a trend was detected in two others (Harvey et al. 1994; Lim et al. 1999). The co-twins did not show increased sulcal volume. In a paired analysis of discordant twins this volumetric difference had a trend to significance which implies that sulcal increase is related to the disorder state, not to genetic vulnerability. In our study the sulcal increase was positively correlated with the alcohol consumption. To our knowledge this association has not been studied in previous studies.

Our findings imply the importance of white matter changes in a pathogenesis of BPI, but more specific methods are needed to localize and evaluate specific defects related to the disorder. Modern diffusion tensor techniques offer a sophisticated method to analyze white matter tracts, and represent one of the most promising research areas at the moment. So far, the clinical meaning of the decrease in white matter volumes remains obscure and demands further studies focusing on possible clinical or neuropsychological correlates. Another interesting result was the correlation of a lithium use and a grey matter volume, and further brain studies should evaluate the possible neurotrophic effects of medication, especially lithium and antidepressants.

8.5 Neuropsychological functioning

One of the main findings of the study was that the population-based euthymic sample of BPI twins performed worse than controls on all memory tests, and on information processing tasks. This strengthens recent findings that there is chronic impairment in cognitive functioning in BPI (Deckersbach et al. 2004; Glahn et al. 2004; Martinez-Aran et al. 2004; Thompson et al. 2005). Information processing speed tasks were the only ones in which the affected twins differed significantly from the non-bipolar co-twins. This impairment is thus likely to be associated with the pathogenic process of the disorder. Our results are in accordance with two recent studies that found BPI patients (Clark et al. 2005), but not their unaffected first-degree relatives (Clark et al. 2005; Ferrier et al. 2004) to have a deficit in a visual information processing task. It is interesting that an increased activation of limbic, paralimbic, and ventrolateral prefrontal areas in euthymic BPI patients have been detected in a fMRI study while performing the CPT, a method to measure the information processing speed (Strakowski et al. 2004). However, impairment in information processing speed is not specific to BPI, but occurs also in schizophrenia (Cannon et al. 2000; Cavanagh et al. 2002; Tabares-Seisdedos et al. 2003) and major depressive disorder (Quraishi and Frangou 2002). It might be related to severity of the disorder rather than a specific diagnosis.

To our knowledge, this is the first study showing that the information processing speed is significantly related to memory functions and verbal learning in a bipolar patient sample. After adjusting the memory and verbal learning tasks for information processing speed, the difference between study groups disappeared most strikingly in working memory span and immediate memory tasks. However, BPI twins still performed worse than controls in delayed story recall and visual reproduction. In the CVLT long delay free recall, they showed nearly significant impairment. Our results suggest that at least part of the memory deficiencies of the BPI patients may be mediated via impairment in information processing speed. We propose that adjusting memory tasks for information processing speed helps to dissect real disorder specific defects. The affected twins showed impairment in delayed memory recalls, irrespective of the degree of slowed information processing speed.

Contrary to the study of Gourovitch et al.(1999), we did not find significant cognitive impairments in co-twins. Two of the seven siblings in their study had some psychiatric symptoms, while in our sibling sample of 19 twins, only one co-twin had had a major depressive episode several years before but no current symptoms. When we divided the sample according to sex, both female BPI twins and female co-twins showed impairment in the CVLT total recall and long delay free recall compared with controls. The findings are in accordance with a study of delayed verbal recall in siblings (Kéri et al. 2001), and

first-degree relatives of BPI patients (Sobczak et al. 2002) implying that dysfunction in delayed verbal recall may be related to the genetic factors associated with BPI. However, we do not assume that this defect is sex specific. Probably the CVLT test used here is more sensible to detect differences among females compared to males, former being often practised in making shopping lists.

The current use of lithium had no significant effect on any of the memory tasks, and the use of neuroleptics only on the CVLT total recall. Thus, the impairment seem not to be explained by medication. Neither the occurrence of psychotic symptoms nor the duration of illness explained the impairment in memory tasks and verbal learning in this study sample.

Our results support the view that defects in mechanisms underlying verbal memory are related to the increased risk of bipolar disorder. Theoretically it is possible that decrease in left hemispheric white matter, which was detected in our study in both BPI twins and healthy co-twins, would be manifested in these kind of memory impairments (see Figure 3). To test this hypothesis we would need more specific methods, like functional imaging and diffusion tensor analysis of white matter tracts connecting areas related to the memory functioning. Our results also emphasised the important effect of information processing speed on neuropsychological variables. In BPI twins a great deal of the low performance was explained by lowered information processing speed, and we recommend that this should be taken account in future studies. A fairly substantial lowering of neuropsychological performance among BPI patients has great clinical importance. Defects in memory functioning cause distress and strongly affect working ability, and should be noted when evaluating the overall functional capacity of BPI patients. Neuropsychological rehabilitation might be a useful element in the treatment of BPI. The effects of medication on neuropsychological performance should be evaluated in follow-up studies.

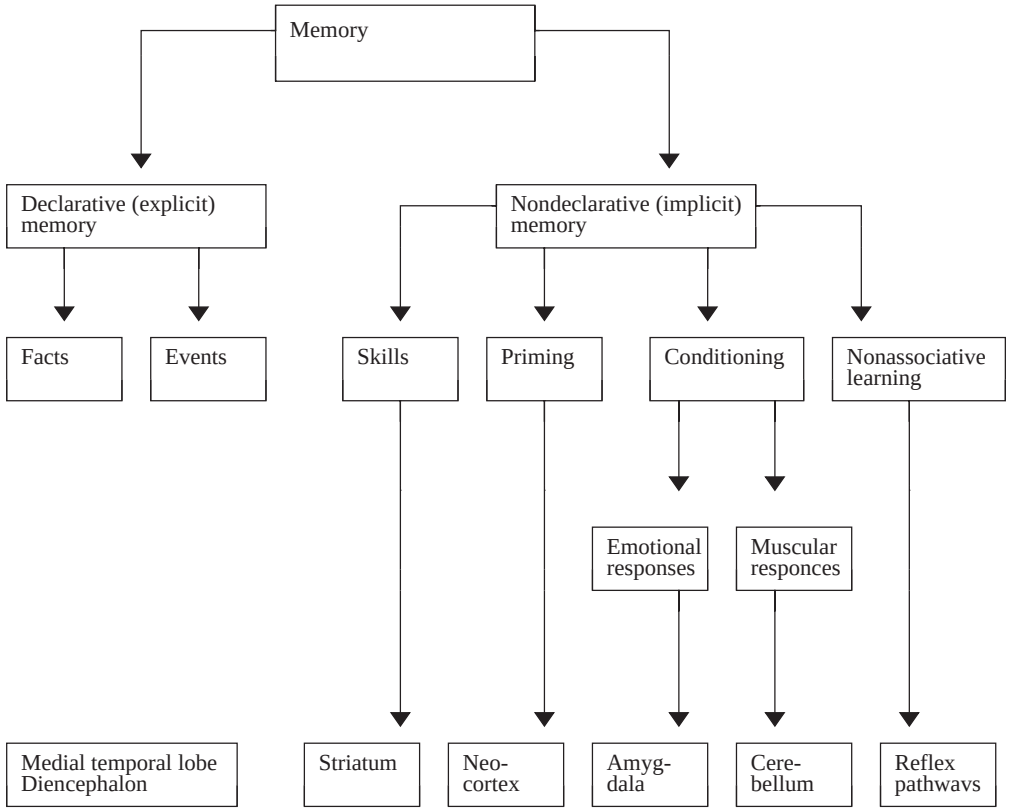

Figure 3. A long-term memory system: verbal memory tasks in the present study represent the box called 'Facts'. (Gazzaniga et al. 1998) (p.273)

9. CONCLUSIONS

9.1 Main results

The accuracy of the BPI diagnosis in Finland's Hospital Discharge Register was as high as 92% and comparable to that for the diagnosis of schizophrenia. This was first time when the accuracy of the BPI diagnosis as defined in DSM-IV has been evaluated in registers.

This first twin study of bipolar disorder involving a representative nationwide twin sample in which BPI was diagnosed using structured face-to-face interviews and long-term follow-up data confirmed that the heritability for BPI is high, being 0.93 (95% CI 0.69-1).

The magnetic resonance imaging study showed that BPI patients had decreased hemispheric and frontal white matter volumes, and that healthy co-twins had left hemispheric white matter decrease compared with controls.

The examination of neuropsychological functioning revealed that euthymic BPI patients had defects in information processing speed and delayed memory functioning. Healthy female co-twins showed impairments in long-term memory functioning.

9.2 Clinical implications

Our findings support strongly the converging knowledge about the importance of genetic factors in BPI. The knowledge helps the clinicians, patients, and their relatives better to understand the occurrence of this severe mental disorder. When evaluating the proper diagnosis, or the risk that major depressive disorder may turn out to be the first episode of bipolar disorder, the family anamnesis gives valuable information about the possible genetic loading for BPI. A positive family history may guide the choose of suitable medication. In addition, the genetic information should be included in patient education, and discussed in situations where patients want to know about the risk of their children getting the illness.

Clinically relevant is the fact that bipolar patients showed significant impairment in nearly all memory tasks and information processing speed, and a decrease in frontal white matter. When evaluating work ability and possible neuropsychological rehabilitation these aspects should be noted and studied in BPI patients. The clinical importance of the mild defects found in healthy co-twins might be minor, or none.

9.3 Implications for future research

The finding of a high accuracy of the BPI diagnosis may have important implications, as participation rates among bipolar patients in psychiatric studies are usually relatively low. If we can assume that the diagnostic information in registers and medical records is reliable, we have no need to interfere in the patient's life, and we can still proceed with epidemiological studies.

Furthermore, we found possible genetic trait markers for the disorder, namely left hemispheric white matter decrease, and in females long-term verbal memory defects. The impairment in information processing speed was related to the disorder already established. These findings imply the importance of genetic factors in the etiology of BPI, and give valuable information for the future research focused on trying to find genetically more specific endophenotypes. Also the possible relationships between neuropsychological defects and brain structural changes should be evaluated. That would help us better to understand human cognition, and its biological correlates.

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