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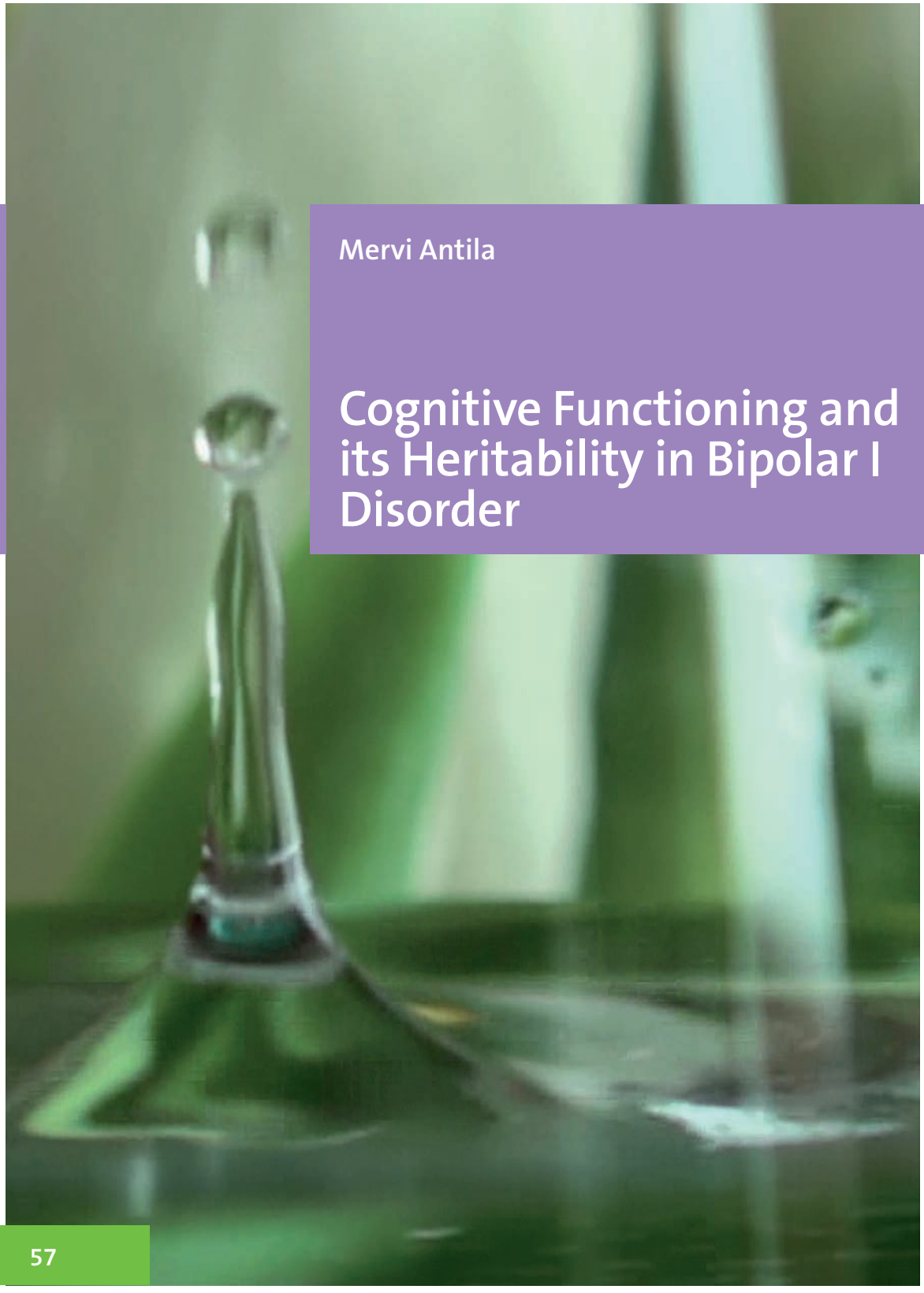

RESEARCH

Mervi Antila

Cognitive Functioning and its Heritability in Bipolar I Disorder

RESEARCH 57

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ACADEMIC DISSERTATION

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Supervisors:

Docent Annamari Tuulio-Henriksson
Social Insurance Institution
Research Department,
National Institute for Health and Welfare
Department of Mental Health and Substance Abuse Services, and
University of Helsinki
Institute of Behavioural Sciences
Helsinki, Finland

and

Docent Timo Partonen
National Institute for Health and Welfare
Department of Mental Health and Substance Abuse Services
Helsinki, Finland

Reviewers:

Professor Irving I. Gottesman, PhD, Hon.FRCPsych
University of Minnesota
Department of Psychology
Minneapolis, Minnesota, United States

and

Docent Sari Lindeman
University of Oulu
Department of Psychiatry
Oulu, Finland

Opponent:

Docent Tuula Ilonen
University of Turku
Department of Psychiatry
Turku, Finland

To Pekka

Abstract

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Bipolar disorder is a severe psychiatric disorder characterized by episodic mood alterations that can be manic, depressive or mixed. Bipolar disorder seems to be highly genetic, but the etiology of this complex disorder has remained elusive. In recent years several studies have investigated cognitive functioning in patients with bipolar disorder, and have found impairments particularly in executive functioning, verbal learning and memory, as well as in other functions. These impairments tend to be present also among some of the euthymic patients, thus suggesting that they may be state independent trait markers. They may also be present in some of the relatives of these patients, who may be vulnerable to the disorder but do not have the confounding effects of medication and other illness- related factors on their cognitive functioning. Using neuropsychological variables as endophenotypes, i.e. intermediate phenotypes between genes and the phenotypes, has been suggested to aid search for the etiological background of the disorder, but evidence is sparse on whether these variables fulfill the criteria for endophenotypes.

The present thesis is part of the Genetic Epidemiology and Molecular Genetics of Severe Mental Disorders in Finland project. The specific aim of the thesis was to investigate whether neuropsychological test variables would indicate genetic liability to the disorder and could therefore be regarded as endophenotypes in families with this disorder. Thus, cognitive functions and their heritability were studied in bipolar I disorder patients and in their unaffected first-degree relatives from a population-based sample of families, comparing them to a population-based control group. In order to add homogeneity to the subgroups of bipolar I disorder patients and their relatives, cognitive functions and their heritability were further studied in patients and their unaffected relatives in a group of families affected by bipolar I disorder only (bipolar families) and another group of families affected by both bipolar I disorder and schizophrenia or schizoaffective disorders (mixed families). Finally, the effect of processing speed on other cognitive functions was investigated in the families with bipolar disorder.

The study showed that some cognitive functions, especially executive functioning and psychomotor processing speed, fulfilled the endophenotype criteria. Impairments in these functions were found in bipolar I disorder patients and also in their unaffected relatives, and were also highly heritable in these families. In addition,

the results of the study showed that these impairments may represent vulnerability markers or endophenotypes of bipolar I disorder irrespective of other severe psychopathology in the family. Study also showed that generalized impairment in verbal memory may associate more with bipolar disorder than to vulnerability to other psychotic disorders, and be more related to fully developed disease as the impairments in verbal learning and memory were found only in patients, and were not found to be highly heritable. Finally, the most potential endophenotype, i.e. psychomotor processing speed, seemed to contribute to a range of other cognitive dysfunctions seen in bipolar disorder patients. Psychomotor processing speed, in particular, has also been shown to be a valid endophenotype in subsequent association analyses in psychiatric genetics in Finland and internationally.

Information concerning cognitive impairments and their association with the psychosocial consequences of bipolar disorder is important in planning treatment. It is also important to understand and acknowledge that patients may have cognitive impairments that affect their everyday life. Psychosocial interventions and neuropsychological rehabilitation may supplement other conventional treatments for bipolar patients.

Keywords: attention, bipolar I disorder, cognitive functions, endophenotype, executive functioning, family study, memory, neuropsychology, population-based sample, processing speed

Tiivistelmä

Mervi Antila. Cognitive functioning and its heritability in bipolar I disorder [Kognitiiviset muutokset ja niiden periytyvyys bipolaari I tyypin häiriössä]. Terveyden ja hyvinvoinnin laitos (THL). Tutkimus 57. 143 sivua. Helsinki 2011.
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Kaksisuuntainen mielialahäiriö eli bipolaarihäiriö on vakava psykiatrinen sairaus, johon liittyy masennus- ja maniajaksojen tai sekamuotoisten mielialajaksojen toistuva vaihtelu. Viime vuosina tehdyissä tutkimuksissa bipolaaripotilailla on havaittu kognitiivisia eli tiedonkäsittelyyn liittyviä vaikeuksia myös sairauden oireettomassa vaiheessa. Kognitiiviset muutokset näyttäisivät olevan, ainakin osalla potilaista, pysyviä sairauden piirretekijöitä, jotka eivät liity vain esimerkiksi mielialatekijöihin. Nykytiedon perusteella on epäselvää, ovatko potilailla havaitut kognitiiviset muutokset olemassa jo ennen sairauden puhkeamista vai ovatko ne vasta sairauden aiheuttamia muutoksia. Vaikka bipolaarihäiriön tiedetään olevan periytyvä sairaus, on tämän monitekijäisen sairauden etiologian selvittäminen edelleen kesken.

Bipolaaripotilailla tehtyjen neuropsykologisten tutkimustulosten tulkintaa vaikeuttavat monet muut sairauteen liittyvät tekijät, kuten lääkehoito. Potilaiden terveillä perheenjäsenillä ei pitäisi olla tällaisia sairauteen liittyviä tekijöitä, jotka vaikuttaisivat kognitiiviseen suoriutumiseen. Joissakin kognitiivisissa toiminnoissa bipolaaripotilailla ja heidän perheenjäsenillään voidaan havaita samanlaisia vaikeuksia, jotka perheenjäsenillä ovat yleensä lievempiä. Tiettyjä kognitiivisia toimintoja neuropsykologisin menetelmin arvioituna voidaankin pitää mahdollisina sairauden endofenotyyppeinä, sisäisinä ilmiasuina, jotka vaikuttavat tiettyjen perintötekijöiden luenta-asun ja ihmisessä ilmiasuna havaittavien ominaisuuksien välillä (fenotyyppi). Näitä endofenotyyppejä voidaan pitää merkkinä mahdollisesta geneettisestä alttiudesta sairaudelle sen puhkeamisesta riippumatta.

Tämä väitöstutkimus on osa laajempaa bipolaarihäiriön geneettisen etiologian tutkimusta suomalaisessa väestössä. Väitöstutkimuksessa oli tarkoituksena tarkastella bipolaarihäiriön neuropsykologisia endofenotyyppejä perheissä, joissa esiintyy runsaasti tyypin I bipolaarihäiriötä. Tutkimuksen tarkoituksena oli selvittää, voidaanko joitakin potilailla esiintyviä kognitiivisia muutoksia pitää merkkinä geneettisestä sairastumisalttiudesta, ja pitää niitä sairauden puhkeamisesta riippumattomina piirteinä. Tutkimuksessa verrattiin suhteellisen oireettomien bipolaari I tyypin potilaiden, heidän terveiden lähisukulaisten ja väestöpohjaiseen otokseen perustuvan kontrolliryhmän kognitiivista suoriutumista toisiinsa sekä tutkittiin kognitiivisten piirteiden periytyvyyttä bipolaarihäiriöperheissä. Lisäksi tutkimuksessa oli tarkoituksena selventää, voidaanko kognitiivisen suoriutumisen ja sen

periytyvyyden suhteen löytää yhdenmukaisia ryhmiä tarkastelemalla samassa perheessä esiintyvien erilaisten vakavien mielenterveyshäiriöiden yhteyttä kognitiivisiin häiriöihin. Tämä tapahtui vertaamalla perheitä, joissa esiintyy vain yhtä vakavaa mielenterveyshäiriötä (bipolaarihäiriö I tyyppi) perheisiin, joissa esiintyy useampaa vakavaa mielenterveyshäiriötä (bipolaarihäiriö I tyyppi ja skitsofrenia ja/tai skitsoaffektiivinen häiriö). Lopuksi, mahdollisen endofenotyypin, prosessointinopeuden, vaikutusta muihin kognitiivisiin toimintoihin tarkasteltiin bipolaarihäiriöperheissä.

Tutkimuksessa ilmeni, että erityisesti toiminnanohjaus ja prosessointinopeus saattavat olla sairauden puhkeamisesta riippumattomia, bipolaarihäiriölle mahdollisesti altistavia piirteitä eli ns. sairauden endofenotyyppejä. Vaikeuksia näissä toiminnoissa esiintyi sekä oireettomilla potilailla että terveillä sukulaisilla väestöpohjaiseen kontrolliväestöön verrattuna ja ne olivat myös periytyviä ominaisuuksia bipolaarihäiriöperheissä riippumatta perheissä ilmenevistä muista vakavista mielenterveyshäiriöistä. Tutkimuksessa vain bipolaaripotilailla ilmeni kielellisen oppimisen ja muistin vaikeuksia, ja ne olivat yleisimpiä potilailla, joiden perheessä esiintyi vain bipolaari I tyypin häiriötä. Muistitoiminnot eivät olleet korkeasti periytyviä ominaisuuksia. Prosessointinopeus vaikutti merkittävästi potilailla havaittujen muiden kognitiivisten vaikeuksien taustalla ja vaikutti selittävän osan potilailla havaituista kognitiivisista muutoksista.

Kognitiivisten toimintojen, myös prosessointinopeuden, hyödyllisyyttä endofenotyyppeinä on kokeiltu ja hyödynnetty jo useissa bipolaarihäiriön alttiusgeenejä tutkivissa sekä suomalaisissa että kansainvälisissä tutkimuksissa. Tieto bipolaarihäiriöön liittyvistä kognitiivisista muutoksista, niiden yhteydestä sairauden puhkeamiseen, kulkuun ja geneettiseen alttiuteen on tärkeä osa bipolaarihäiriön tutkimusta ja myös hoitoa. Kognitiivisten muutosten mahdollisuus olisi tärkeää huomioida potilaiden hoidossa sekä tutkia myös niiden kuntouttamisen mahdollisuuksia.

Avainsanat: bipolaarihäiriö, endofenotyyppi, kaksisuuntainen mielialahäiriö, kognitiiviset toiminnot, muisti, neuropsykologia, perhetutkimus, prosessointinopeus, tarkkaavaisuus, toiminnanohjaus, väestöpohjainen otos

Contents

List of original papers

I Antila, M.[1], Tuulio-Henriksson, A.[1], Kieseppä, T., Eerola, M., Partonen, T. & Lönnqvist, J. (2007). Cognitive functioning in patients with familial bipolar I disorder and their unaffected relatives. Psychological Medicine, 37, 679-687.

II Antila, M., Tuulio-Henriksson, A., Kieseppä, T., Soronen, P., Palo, O. M., Paunio, T., Haukka, J., Partonen, T. & Lönnqvist, J. (2007). Heritability of cognitive functions in families with bipolar disorder. American Journal of Medical Genetics Part B: Neuropsychiatry Genetics, 144B, 802-808.

III Antila, M., Partonen, T., Kieseppä, T., Suvisaari, J., Eerola, M., Lönnqvist, J. & Tuulio-Henriksson, A. (2009). Cognitive functioning of bipolar I patients and relatives from families with or without schizophrenia or schizoaffective disorder. Journal of Affective Disorders, 116, 70-79.

IV Antila, M., Kieseppä, T., Partonen, T. Lönnqvist, J. & Tuulio-Henriksson, A. (2011). The effect of processing speed on cognitive functioning in patients with familial bipolar I disorder and their unaffected relatives. Psychopathology, 44, 40-45.

[1] These authors contributed equally to this work.

Abbreviations

ACC	Anterior cingulate cortex
ADHD	Attention-deficit/hyperactivity disorder
BDNF	Brain-derived neurotrophic factor
COWAT	Controlled Oral Word Association Test
CPT	Computerized Continuous Performance Test
CVLT	California Verbal Learning Test
GAF	Global Assessment of Functioning scale
GEE	Generalized estimating equation model
DISC1	Disrupted-in-Schizophrenia-1 gene
DRS	Dementia Rating Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
FAST	Functioning Assessment Short Test
fMRI	Functional magnetic resonance imaging
GWAS	Genome-wide association studies
h^2	Heritability estimate
IQ	General cognitive ability
ICD	International Classification of Disorders
MCI	Mild Cognitive Impairment
MRI	Magnetic resonance imaging
NOS	Not otherwise specified
PET	Positron emission tomography
p, p-value	Significance probability
RAVLT	Rey's Auditory Verbal Learning Test
SCID	Structured Clinical Interview for DSM
SD	Standard Deviation
SNP	Single nucleotide polymorphism
TMT	Trail Making Test
TMT-A	Trail Making Test Part A
TMT-B	Trail Making Test Part B
WAIS-R	Wechsler Adult Intelligence Scale – Revised
WCST	Wisconsin Card Sorting Test
WMS-R	Wechsler Memory Scale – Revised

1 INTRODUCTION

Bipolar I disorder is a severe psychiatric disorder, characterized by episodes of depressive and manic behavior. Bipolar I disorder affects approximately 1 % of the world's population (Rihmer & Angst, 2005). Although twin, family, and adoption studies show that bipolar I disorder is highly heritable (McGuffin et al., 2003; Kieseppä et al., 2004) the search for the genetic loci of the disorder has been impeded by its complexity. Like other severe psychiatric disorders bipolar disorder is regarded to be multifactorial in etiology, and to show a complex mode of transmission (Craddock & Jones, 2001). Indicators of processes that mediate between genes and phenotype, so called endophenotypes (Gottesman & Gould, 2003), may be helpful for molecular genetic studies searching for genes predisposing to bipolar disorder (Lenox et al., 2002). Linkage and association studies focusing to map quantitative endophenotypes rather than dichotomic phenotypes would allow studying the transmission of bipolar disorder -related traits in extended pedigrees, including healthy family members. One possible type of endophenotypes of bipolar disorder may be cognitive functions (Glahn et al., 2004; Savitz et al., 2005; Hasler et al., 2006; Kravariti et al., 2009a). To be considered as an endophenotype, the trait or function in question must fulfill certain criteria. According to Gottesman and Gould (2003), the endophenotypes should be: (1) significantly heritable, (2) associated with the illness in the population, (3) manifest in an individual whether or not the illness is active (being state-independent), (4) in families with the illness, many of the unaffected relatives have the same endophenotypic trait, and (5) the endophenotype that is present in the affected, is more prevalent in the unaffected in the family than in the general population.

The presence of variable, state-dependent alterations in cognitive functioning during symptomatic phases of bipolar disorder has long been recognized. Moreover, recent studies focusing on asymptomatic, euthymic bipolar disorder patients have demonstrated impairments particularly on measures of executive functions and verbal learning and memory (Quraishi & Frangou, 2002; Robinson et al., 2006; Bora et al., 2009a). Thus, cognitive impairment in some patients with bipolar disorder may be enduring, thus presenting a trait rather than state variable. However, little is known whether such dysfunctions occur as a consequence of the disease or whether they are etiologically significant vulnerability markers for bipolar disorder. Unlike studies of bipolar disorder patients, studies of their relatives are not confounded by medication, psychopathology, or by other acute or chronic effect of illness. Therefore, assessing the level of impairment in both affected and unaffected family members of bipolar disorder may aid to ascertain whether the cognitive impairments could be considered as endophenotypes of bipolar disorder. In

relatives of patients with schizophrenia cognitive deficits similar to schizophrenia have been demonstrated, although less attenuated (Tuulio-Henriksson et al., 2003; Sitskoorn et al., 2004; Kuha et al., 2007). The comparatively few studies of first-degree relatives of bipolar disorder have revealed less evidence of impairment, and the findings are somewhat controversial as others have found learning and memory impairments (Keri et al., 2001; Ferrier et al., 2004; Kieseppä et al., 2005), impairments of attention and psychomotor performance (Sobczak et al., 2003; Frantom et al., 2008), impairments in executive functions (Zalla et al., 2004; Bora et al., 2008; Juselius et al. 2009), and others have failed to find such impairments (Kremen et al. 1998; Clark et al., 2005a). The discrepancies can result from methodological differences or relatively small sample sizes of these studies. So far, certain measures of verbal memory and certain executive tasks appear to best meet the established criteria for endophenotypic markers of bipolar disorder (Glahn et al., 2004; Robinson et al., 2006; Bora et al., 2009a).

The present study investigated cognitive functioning, possible impairments, and the heritability of cognitive functions in bipolar I disorder patients and in their unaffected first-degree relatives. The specific aim was to identify possible neuropsychological endophenotypes for bipolar I disorder in this bipolar I family sample by exploring the endophenotype criteria defined by Gottesman and Gould (2003). The framework of the study was in neuropsychology, in psychiatry and in psychiatric genetics.

1.1 Bipolar I disorder

Bipolar I disorder is a severe psychiatric disorder with life-time prevalence varying from 0.1 to 4.8 percent in the general population (Rihmer & Angst, 2005). In Finland, lifetime prevalence of bipolar I disorder is estimated at 0.24 percent in persons 30 years and older (Perälä et al., 2007), and 0.53 percent in adults aged 19 to 34 years (Suvisaari et al., 2009). Bipolar disorder is typically characterized by recurrent manic and depressive episodes, often accompanied with periods of normal mood or sub-threshold mood symptoms between the episodes. The disorder is often chronic, and the patients can spend half of their time in a symptomatic state (Post et al., 2003; Joffe et al., 2004). The age of onset is usually around 20 years of age (Rihmer & Angst, 2005). The disorder causes great disability on functional outcome, psychosocial factors, and quality of life for the patients (Vos & Mathers, 2000). Studies also show that bipolar patients have increased rates in mortality (Goodwin & Jamison, 2007). Probability of biological component for bipolar disorder is strong with environmental factors playing a role in the exacerbation of symptoms (Alloy et al., 2005).

According to the Diagnostic and Statistical Manual of Mental Disorders, fourth version (DSM-IV) (American Psychiatric Association, 1994), a person must have at least one manic episode to fulfill the diagnosis of bipolar I disorder (Table 1). Mania is sometimes referred to as the other extreme to depression, and it is an intense high where the patients feel euphoric, almost indestructible in areas such as personal finances, business dealings, or relationships. Patients may have an elevated self-esteem, be more talkative than usual, have flight of ideas and reduced need for sleep, and to be easily distracted. This will often lead to serious difficulties in several areas of life, such as in spending much more money than intended, making extremely rash business and personal decisions, involvement in dangerous sexual behavior, and/or in excessive use of drugs or alcohol. Depression usually follows as the high quickly fades, and as the consequences of activities during the mania episode become apparent, the depressive episode can be exacerbated (Table 1).

Severity of bipolar I disorder varies, and many patients have psychotic symptoms in mania, mainly grandiose or paranoid. Depressive episodes can vary from mild mood decrease to severe major depressive episodes with psychotic symptoms. Patients can also have mixed episodes, which can mean 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 (Rosa et al., 2010b).

1.2 Bipolar II disorder

In bipolar II disorder, there are periods of highs as described above and often followed by periods of depression. Bipolar II disorder, however, is different in that the highs are hypomanic, rather than manic. In other words, they have similar symptoms but they are not severe enough to cause marked impairment in social or occupational functioning and typically do not require hospitalization in order to assure the safety of the person. The depressive episodes of bipolar II disorder, however, may include psychotic features.

Table 1. DSM-IV Diagnostic criteria for bipolar I disorder manic and depressive episodes (American Psychiatric Association, 1994)

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 presented 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, or light therapy) should not count toward a diagnosis of bipolar I disorder.

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 due 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., feel 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. 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 feeling 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 every 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.

1.3 Cognitive functions: attention, processing speed, executive functioning and memory functions

Cognitive functioning refers to individual's information processing functions which can conceptually be divided into different discrete classes but which are inextricably bound together (Lezak et al., 2004). Attention refers to several processes that are related to how individual becomes receptive to stimuli. Attention can be divided into focused and selective attention, sustained attention, divided attention, and alternating attention (Lezak et al., 2004). Information processing speed refers to the rapidity of performing different types of cognitive processes (Salthouse, 1996). Executive functioning includes processes that are responsible for planning, cognitive flexibility, abstract thinking, and rule acquisition, initiating appropriate actions and inhibiting inappropriate actions, and selecting relevant sensory information (Lezak et al., 2004).

Memory is a complex system, and can be classified in several ways. Generally, short-term memory includes immediate and working memory, and long-term memory includes declarative (explicit) and nondeclarative (implicit or procedural) memory, comprising both verbal and visual memory domains. Memory is made up of encoding or registering, storing, and accessing or retrieving information (Lezak et al., 2004). Memory can be classified further on the basis of the time span of memory processing, the level of processing, consciousness of the learning, the modality through which the material is presented or the content of the material. Storage is achieved by the two interactive systems comprising short-term and long-term memory. Once information has been encoded and stored in memory, it must be retrieved in order to be used. There are different ways in which information can be pulled from long-term memory, for example by recall or recognition (Lezak et al., 2004).

Working memory refers to a system that provides temporary storage and manipulation of the information necessary for complex cognitive tasks. Working memory can be divided into the following three subcomponents: 1) the central executive, which is assumed to be an attentional-controlling system, and two slave systems, 2) the visuospatial sketch pad, which manipulates visual images and 3) the phonological loop, which stores and rehearses speech-based information (Baddeley, 1992).

1.4 Cognitive functioning in bipolar disorder

The most studied cognitive functions in bipolar disorder involve attention and information processing speed, executive functions, memory and learning, and working memory. Usually basic receptive and expressive functions are unimpaired in bipolar patients. However, these functions have been less studied.

The diagnostic criteria of bipolar I disorder include many symptoms that can by definition be considered as cognitive impairments (see Table 1). It has been long assumed that in bipolar disorder cognitive deficits are somewhat mild, transient and limited to acute phases of mania and/or depression. However, during the last decade, research has consistently evidenced that several cognitive dysfunctions persist during euthymia, too, and can be rather stable in chronic patients (Balanza-Martinez et al., 2005). Recent meta-analyses of cognitive functioning in euthymic bipolar disorder patients have found impairments especially in the domains of attention/processing speed, and executive functions, including cognitive flexibility, inhibitory control, working memory and verbal fluency and verbal learning/memory (Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008; Bora et al., 2009a). In these meta-analyses, magnitude of cognitive impairments were calculated using effect sizes (small, medium and large), which is a statistical concept that measures the strength of the relationship between two variables, that is independent of sample size. There is a wide array of formulas used to measure effect sizes, but in aforementioned meta-analyses, they were measured as the standardized difference between two means (Cohen's d or Hedge's g) (see e.g. Cohen 1988).

1.4.1 Attention, processing speed and executive functioning

There is evidence that bipolar disorder patients have impairments in tasks assessing sustained attention (e.g. Clark et al., 2005a; Fleck et al., 2001; Kieseppä et al., 2005; Bora et al., 2006; Martino et al., 2008a, Ancin et al. 2010) and psychomotor processing speed (e.g. Krabbendam et al., 2000; Kieseppä et al., 2005; Thompson et al., 2005; Frantom et al., 2008; Martino et al., 2008a). However, not all studies have found evidence of impairments in task assessing sustained attention (e.g. Bozikas et al., 2005; Frantom et al., 2008). In the attention/psychomotor processing speed domain, meta-analyses have shown medium effect sizes for three variables (response latency in sustained attention task, Digit Symbol test and Trail Making Test Part A (TMT-A)) (Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008).

Several studies have shown that euthymic bipolar disorder patients have dysfunctions in the various aspects of executive functioning (e.g. Ferrier et al., 1999; Krabbendam et al., 2000; Zubieta et al., 2001; Zalla et al., 2004; Frangou et al.,

2005; Martinez-Aran et al., 2005; Thompson et al., 2005; Goswami et al., 2006; Mur et al., 2007; Frantom, et al., 2008; Jamrozinski et al., 2009; Juselius et al., 2009; Kravariti et al., 2009b), while some studies have not (e.g. Rubinsztein et al., 2000; Olley et al., 2005). In recent meta-analyses of cognitive functioning of studies of euthymic bipolar disorder patients, the effect sizes in the executive domain have usually been the largest. In the meta-analysis of Robinson et al. (2006), there were large effect sizes in the executive domain in tasks assessing fluency (categories), and working memory (Digit Span Backward task). Inability to inhibit inappropriate actions and responses (Stroop performance) and impairments in set-shifting and abstraction (Wisconsin Card Sorting Test (WCST)) showed medium effects. In the study by Torres et al. (2007), the functions that appear to be the most affected in the executive domain, included cognitive flexibility⁄set shifting ability (WCST) as well as response inhibition (Stroop test) (see also Juselius et al., 2009).

In the study by Arts et al. (2008), the largest effect sizes were evidenced in task assessing executive control (Trail Making Test Part B (TMT-B)), concept shifting (WCST perseverative errors), fluency (categories) and mental speed (Digit Symbol task). The meta-analysis of Bora et al (2009a) found largest effect sizes in executive control (TMT-B), in sustained attention (Continuous Performance Test (CPT) omissions), response inhibition (Stroop) and attention. Digit Symbol tasks, and nearly all tasks assessing executive functioning and attention/psychomotor speed showed medium to large effect sizes.

1.4.2 Memory

Large effect sizes have been found in immediate verbal learning and recall assessed with list learning tasks (usually CVLT or RAVLT) in all recent meta-analyses on cognition in bipolar disorder (e.g. Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008; Bora et al., 2009a). In general, short- and long-delay free recalls have shown medium effect sizes, except in Arts et al. (2008) in which the effect sizes were large in these functions. There are still some controversies in different studies, as some have found impairments in verbal learning and memory and/or delayed recall (Krabbendam et al., 2000; Zubieta et al., 2001; Deckersbach et al., 2004; Kieseppä et al., 2005; Martinez-Aran et al., 2005; Thompson et al., 2005; Goswami et al., 2006; Quraishi et al., 2009), while others have not found deficits in learning or recall (e.g. Mur et al., 2007; Frantom et al., 2008; Martino et al., 2008b). Large effect sizes have also been found in task assessing working memory (Digit Span Backward) (Robinson et al., 2006; Arts et al., 2008; Bora et al., 2009a). However, tasks assessing short-term immediate verbal memory (usually Digit Span Forward) and verbal recognition memory have shown small effects sizes in all above meta-analyses.

Visual learning and memory functions have been less studied, and only Art et al. (2008) and Bora et al. (2009a) have included these functions in their meta-analyses evidencing small or medium effect sizes for delayed visual memory. Some studies have found that there is impairment in visual learning and memory also in euthymic bipolar patients (Rubinsztein et al., 2000; Deckersbach et al., 2004; Kieseppä et al., 2005; Martinez-Aran et al., 2005; Thompson et al., 2005; Frantom et al., 2008), although not all (Zubieta et al., 2001; Quraishi et al., 2009). There are only few studies that have assessed procedural memory, and it may indeed be unaffected in bipolar disorder patients (van Gorp et al., 1999).

Verbal memory functioning in euthymic bipolar disorder patients has generally been assessed with list-learning tasks, which are known to involve the ability of strategic organization and to be especially sensitive to executive dysfunction (Tremont et al., 2000). It may be that executive deficits affects effective memory performance by introducing inefficiency in encoding and/or retrieval processes. It has been reported that memory and executive function share 50–60% of variance (Duff et al., 2005). Robinson and Ferrier (2006) suggest that future studies should attempt to better separate memory performance from executive functioning, and to investigate whether the cognitive impairment associated with bipolar disorder arises from a single core deficit or from multiple deficits in cognition.

Meta-analysis of Bora et al. (2009a) found no association between verbal memory and executive function impairments, but only few studies have tried to assess directly the relationship of different cognitive functioning in bipolar disorder. There is some evidence that bipolar patients´ episodic memory problems, both in verbal and visual memory, may be partly secondary to difficulties using organizational strategies (difficulties using semantic clustering strategies) during encoding (Deckersbach et al., 2004), even when instructed to do so (Deckersbach et al., 2005). However, another study did not find similar deficits in semantic clustering (Bearden et al., 2006), but this study included also bipolar II disorder patients. In addition, information processing speed can have a significant effect on encoding and learning efficiency in bipolar I disorder patients, and controlling the effect of processing speed have made the difference between bipolar patients and controls disappear in working memory and immediate memory tasks (Kieseppä et al., 2005). However, differences remained in some delayed recall tasks.

1.5 The effect of illness phase on cognitive functioning

Cognitive impairments are present in acute phases of bipolar disorder, and they also may remain among euthymic bipolar patients, although generally being less severe in euthymia (Clark & Goodwin, 2004; Dixon et al., 2004; Martinez-Aran et

al., 2004b; Bora et al., 2006; Gruber et al., 2007; Malhi et al., 2007; Kurtz & Gerraty, 2009; Langenecker et al., 2010). There are only few studies that have assessed the effect of different affective phases of bipolar disorder on cognitive functioning, and most of these studies are cross-sectional (Martinez-Aran et al., 2002b; Clark & Goodwin, 2004; Martinez-Aran et al., 2004b; Gruber et al., 2007; Malhi et al., 2007; Kurtz & Gerraty, 2009; Langenecker et al., 2010). One longitudinal study that assessed neuropsychological performance across illness phases (Malhi et al., 2007) evidenced that impairment in verbal memory, including also recognition memory, became more pronounced during episodes of hypomania or depression. A recent study by Langenecker et al. (2010) showed that of the eight neuropsychological factor scores included in the study, the control group outperformed the euthymic group in three (processing speed with interference resolution, visual memory, and fine motor dexterity), and the depressed group in seven (auditory memory, visual memory, processing speed with interference resolution, verbal fluency and processing speed, conceptual reasoning and set-shifting, emotion processing, and fine motor dexterity), and the hypomanic/mixed patients in four (inhibitory control, processing speed with interference resolution, fine motor dexterity, and auditory memory). In this study, the depressed group was most affected, and the profile looked very similar to the profile observed in major depressive disorder (Burt et al., 1995; Rogers et al., 2004).

Although all patients, irrespective of acute phase, have impairments in executive functioning, the impairment seems to be more widespread in manic/hypomanic patients (Dixon et al., 2004; Larson et al., 2005; Langenecker et al., 2010). Recent meta-analytic investigation (Kurtz & Gerraty, 2009) about neuropsychological deficits in bipolar disorder in different phases showed that patients tested during a manic/mixed or depressed phase of illness showed exaggerated impairment on measures of verbal learning, and patients tested during a depressed phase showed greater decrement on measures of phonemic fluency. Moreover, the meta-analysis showed that there are impairments across all neuropsychological domains in euthymic bipolar patients, with effect sizes (Cohen's d) in the moderate-to-large range for vast majority of measures (Kurtz & Gerraty, 2009). There is also evidence that some subclinical affective symptoms may remain in euthymic patients and can partly account for cognitive dysfunctions in this phase of the illness (Clark et al., 2002; Ferrier & Thompson, 2002; Martinez-Aran et al., 2002b).

1.6 Confounding factors on cognitive functioning in bipolar disorder

Although the evidence about most typical cognitive dysfunctions in bipolar disorder is accumulating, there is no specific neuropsychological profile of bipolar disorder that could differentiate it from other neuropsychiatric disorders, and there is inter-individual variability of cognitive functioning among patients with bipolar disorder (Burdick et al., 2006; Depp et al., 2008; Martino et al., 2008b). In addition to the acute clinical phase, there are many other potential confounding clinical, medical and comorbid conditions that may affect cognitive functioning and cause variability on cognition in bipolar patients. Of clinical factors, the most consistent evidence is that lifetime episodes, particularly manic episodes, number of hospital admissions, and illness duration are negatively associated with cognition in bipolar disorder (Donaldson et al., 2003; Robinson et al., 2006). For example the amount of manic episodes is negatively correlated with verbal learning and memory (Cavanagh et al., 2002). In addition, there is evidence that the duration of inpatient admission predicts cognitive functioning at discharge in patients with bipolar I disorder (Levy et al., 2009). Patients with longer admissions have more severe deficits particularly in executive functioning at discharge after controlling of residual mood symptoms and previous number of psychiatric admissions (Levy et al., 2009). However, the direction of causality is unclear: it may be that cognitive disability worsens with illness progression, or that a poorer course is the consequence of cognitive problems. Even though there is correlative evidence that cognitive impairments are associated with the number of manic episodes and psychosis, the few follow-up studies of cognitive functioning of bipolar disorder show no clear cognitive decline over periods of 1 to 3 years (Balanza-Martinez et al., 2005; Depp et al., 2008; Mur et al., 2008a, 2008b; Pavuluri et al., 2009). Thus, at least in short term, the cognitive dysfunctions are rather stable, but there are still too few follow-up studies to confirm this in long-term.

In addition to above mentioned clinical factors, bipolar disorder patients can have rapid cycling episodes (Bauer et al., 2008), sleep abnormalities, circadian rhythm abnormalities and seasonal changes (Hakkarainen et al., 2003; Murray & Harvey, 2010), but the relationship with these and cognitive dysfunctions in bipolar disorder is largely unknown. There is evidence that inconvenience in seasonal effects on mood and behavior among patients and relatives from bipolar families may affect on performance in visuoconstructional functions, auditory attention and working memory, as well as in verbal memory (Rajajärvi et al., 2010). Sleep deprivation may also associate with impaired cognitive performance in healthy subjects, but there are also individual differences in the degree of their cognitive vulnerability to sleep loss which may be based on genetic differences in regulating sleep homeostasis and circadian rhythms (Goel et al., 2009; Ratcliff & Van Don-

gen, 2009). Bipolar disorder is also associated with high comorbid medical burden, for example cardiovascular diseases and other diseases, including diabetes mellitus (Kupfer, 2005), which can also had their own effect on cognitive functioning.

1.6.1 Medication

Psychotropic medications are among potential factors that can affect cognitive functioning in bipolar disorders. In most neuropsychological studies, bipolar patients are typically assessed while taking a combination of mood stabilizers (lithium or anticonvulsants), antipsychotics, antidepressants, and/or benzodiazepines. According to Balanza-Martinez et al. (2010) the contribution of medications to cognitive impairment in bipolar disorder is very complicated to be controlled for, and very few studies have addressed the issue. The most usually assessed and administered medication in bipolar I disorder patients, lithium, is associated with mild and transient impairments, especially in verbal memory and psychomotor speed (Honig et al., 1999; Pachet & Wisniewski, 2003), but recent studies have shown that lithium may also have neurotrophic and neuroprotective effects (Schloesser et al., 2008). There are no randomized studies especially targeted to test the cognitive effects of lithium in bipolar disorder patients, but there is evidence that there are no differences between patients treated with lithium and those without lithium in cognitive functioning (Clark et al., 2002; Altshuler et al., 2004; Lopez-Jaramillo et al., 2010). In another study, lithium plasma levels were not associated with cognitive performance in bipolar patients (van Gorp et al., 1998). One study assessing cognitive functioning of euthymic bipolar patients treated with lithium monotherapy found no association of lithium doses and neuropsychological functioning, and impairments in executive functioning and processing speed were stable over a 2-year period (Mur et al., 2008a). It is still unclear whether the lithium treatment is neuroprotective or neurotoxic (Fountoulakis et al., 2008), and it has been suggested that acute lithium treatment is detrimental, whereas chronic treatment is beneficial for the central nervous system, yet not enough to overcome the cognitive deficits in bipolar patients (Balanza-Martinez et al., 2010).

Anticonvulsants such as valproate, carbamazepine and lamotrigine, are common in the treatment of bipolar disorder. Polytherapy and high-dose treatment with anticonvulsants may increase the risk for cognitive impairment, and older anticonvulsants are related with a worse cognitive profile than the new (Meador, 2003; Balanza-Martinez et al., 2010). The doses of anticonvulsants in bipolar disorder are typically lower than those used to treat epilepsy, and more research focused specifically on bipolar disorder is needed.

Some studies suggests that antipsychotic medication may associate with impaired cognitive function among bipolar patients, particularly in psychomotor processing speed, verbal memory and different executive processing tasks (Frangou et al., 2005; Jamrozinski et al., 2009; Balanza-Martinez et al., 2010). However, effects on cognition have not been related to exposure to antipsychotics in other reports (e.g. Martinez-Aran et al., 2004a; Martino et al., 2008b). Some authors have suggested that use of antipsychotics rather than psychotic symptoms may contribute to cognitive dysfunctions in bipolar disorder (Donaldson et al., 2003; Frangou et al., 2005; Jamrozinski et al., 2009), although not all agree (Glahn et al., 2007; Martinez-Aran et al., 2008). According to Bora et al. (2009a) medication effects (and earlier age of onset) contribute partly to slowness in psychomotor processing speed. However, the result of psychomotor processing speed association to medication was assessed by higher percentage of antipsychotic usage. Therefore, slowness in psychomotor speed may also be related to psychotic symptoms, not medication usage per se. Another issue is whether atypical antipsychotics confer more benefit than conventional antipsychotics in terms of cognitive performance, but the evidence is still relatively sparse in bipolar disorder patients (see Balanza-Martinez et al., 2010).

The knowledge on the effect of psychotropic medication on cognitive functions in bipolar disorder is not unambiguous. However, even unmedicated bipolar patients may have similar cognitive impairments that are seen in patients with psychotropic treatment (Macqueen & Young, 2003; Pavuluri et al., 2006; Goswami et al., 2009) implicating that medication does not explain all dysfunctions observed in patients.

1.6.2 Psychotic symptoms

About two thirds of bipolar patients have a lifetime history of psychotic symptoms (Goodwin & Jamison, 2007). It has been proposed that ´psychotic bipolar disorder´ would be a distinct subtype (Glahn et al., 2007) of bipolar disorder, in which the cognitive impairments may resemble those typically seen in schizophrenia. Previous studies have shown that a history of psychosis in bipolar patients may indeed further worsen cognitive performance compared to bipolar patients without psychosis (Glahn et al., 2007; Martinez-Aran et al., 2008).

Lifetime history of a psychotic disorder may also associate with the severity of cognitive impairments. Patients with bipolar disorder with past history of psychotic symptoms have showed a more severe impairment in verbal memory and working memory/executive tasks than those without such a history (Bora et al., 2007; Glahn et al., 2007; Martinez-Aran et al., 2008; Levy & Weiss, 2010), although other authors found no overall differences between these groups (Selva et al., 2007; Lahera et al., 2008; Szöke et al., 2008; Sanchez-Morla et al., 2009; Savitz et

al., 2009). Moreover, patients with bipolar I disorder or schizophrenia with positive family history of psychosis have been found to be more impaired than patients without family history of psychosis on visual-motor processing and attention domain (Tabares-Seisdedos et al., 2003). In that study, the only predictor of belonging to the group with positive family history of psychosis was poor performance on task assessing psychomotor processing speed (the Digit Symbol task).

1.6.3 Alcohol disorders and other comorbid psychiatric conditions

Comorbid conditions in bipolar disorder can cause an extra cognitive burden. Among the Axis I psychiatric disorders, bipolar disorder has the highest lifetime prevalence (approximately 50%) of alcohol and other substances use disorders (Sbrana et al., 2005), which may exert some negative impact on cognitive function (van Gorp et al., 1998; Sanchez- Moreno et al., 2009). Yet, only a few studies have assessed neuropsychological functioning in bipolar disorder patients with comorbid substance misuse. In the study by van Gorp et al. (1998), executive dysfunction was found only in bipolar patients with comorbid alcohol dependence. This group had also a more severe memory impairment than patients without past alcohol dependence. In another study, patients with current alcohol dependence were more impaired than those without past history of alcohol dependence in measures of visual memory, verbal recall and executive functioning (Levy et al., 2008). In that study, bipolar disorder patients in full remission from alcohol dependence showed similar executive dysfunction than those with current alcohol dependence which implicates that prior alcohol misuse may have neuropsychological consequences also in the long-term. In particular, patients with bipolar disorder with previous alcohol consumption have been found to be more impaired in the Stroop interference task, which may indicate that difficulties of inhibitory control may be related to higher impulsivity and probably to higher risk of other addictive behaviors (Sanchez-Moreno et al., 2009).

There is evidence that attention-deficit/hyperactivity disorder (ADHD) is highly comorbid especially with pediatric bipolar disorder (Faraone et al., 1997), and there is also comorbity with ADHD in adult patients (Krishnan, 2005; Klassen et al., 2010). Both disorders overlap also in their profile of cognitive impairments, and comorbid symptoms of ADHD can potentially have a significant effect on cognitive functioning in young bipolar patients (McClure et al., 2005; Rucklidge, 2006; Henin et al., 2007). No studies on adults patients with comorbid ADHD and bipolar disorder exist, but young bipolar patients with comorbid ADHD have been found to perform significantly worse than those without comorbid ADHD on verbal memory (McClure et al., 2005) and attention and executive tasks (Pavuluri et al., 2006). However, there are also studies that have not found evidence that comorbid ADHD in bipolar patients have an effect on cognitive functioning (Dickstein

et al., 2004; Bearden et al., 2007), or that patients with both bipolar disorder and ADHD have more impairment than ADHD patients only in processing speed (Henin et al., 2007). Usually verbal memory impairment is quantitatively more severe in bipolar disorder than in ADHD, and is likely to be more specific to bipolar disorder (Joseph et al., 2008).

In addition to alcohol disorders and ADHD, comorbid anxiety is common among patients with bipolar I disorder (McElroy et al., 2001; Mantere et al., 2006). Patients with anxiety have shown impairments in tests of attention, memory, information processing speed and executive functions (Ruiz-Caballero & Bermudez, 1997; Peretti, 1998), and comorbid anxiety may have an exacerbating effect on the cognitive impairments related to bipolar disorder.

1.7 Cognitive functioning in bipolar I disorder compared to bipolar II disorder

Not all studies on cognitive functioning in bipolar disorder have included merely type I bipolar patients, and only few studies have directly compared neuropsychological performance between patients with bipolar I or bipolar II disorder. Moreover, the results of these studies are inconsistent. Some of the studies have suggested that cognitive deficits are more severe and pervasive in bipolar II than bipolar I disorder patients (Harkavy-Friedman et al., 2006; Summers et al., 2006). Others have reported that patients with bipolar I disorder performed significantly poorly than bipolar II disorder patients especially on tasks of verbal memory, psychomotor processing speed and executive function, and that bipolar II patients have intermediate level of performance compared to bipolar I disorder patients and controls (Torrent et al., 2006; Simonsen et al., 2008; Hsiao et al., 2009). Also an overall similar pattern of cognitive deficits in both types of bipolar disorder have been found (Dittmann et al., 2008), and specifically in working memory, attention and visual memory (Torrent et al., 2006; Hsiao et al., 2009). Some of these inconsistent results may be due to different sampling methodology, and some patients may not have been euthymic in all of these studies.

In some studies, the bipolar II patients may have had more a severe illness than in other studies (Harkavy-Friedman et al., 2006; Summers et al., 2006; Simonsen et al., 2008). As patients with bipolar II disorder may spend long periods in depression, it may be that their neuropsychological impairments and clinical profile may be more similar to those of patients with major depressive disorder. Bipolar I disorder patients have also been observed to show a similar pattern of functional impairment than patients with bipolar II disorder, with the exception of the cognitive domain of the Functioning Assessment Short Test (FAST), in which bipolar II

patients scored even worse than bipolar I patients (Rosa et al., 2010a). However, after controlling for age, subsyndromal depressive symptoms and the number of depressive episodes, this statistical difference between the groups disappeared.

1.8 Cognitive functioning in bipolar disorder compared to other psychiatric disorders

As previously stated, there is no specific neuropsychological profile of bipolar disorder that could differentiate it from other psychiatric disorders. Comparing different psychiatric disorders is methodologically very challenging, as there are many confounders that are difficult to control and match for, for example psychotropic medications and the severity of illness. Some authors have suggested that instead of comparing these categorically different disorders, it may be more useful to investigate how for example psychotic or affective symptoms contribute to the cognitive deficits found in patients with severe mental disorders.

1.8.1 Bipolar disorder compared to major depressive disorder

Patients with unipolar or major depressive disorder have impairments in several cognitive functions including attention, psychomotor processing speed, executive functioning, verbal and visual short- and long-term memory (Zakzanis et al., 1998; Austin et al., 2001; Marazziti et al., 2010). Thus, cognitive dysfunction in major depressive disorder seems to be comparable and overlapping with bipolar disorder. However, there are only few studies that have actually compared directly these two patient groups, and there are inconsistent findings partly because of methodological differences and small samples in these studies. According to the present evidence, acutely ill as well as remitted patients with bipolar disorder are usually more impaired in cognitive functioning than those with major depressive disorder (e.g. Wolfe et al., 1987; Borkowska & Rybakowski, 2001; Smith et al., 2006; Gruber et al., 2007).

Some studies that have compared neuropsychological performance in depressed bipolar and unipolar patients have found that unipolar patients outperform bipolar patients in verbal learning and fluency (Wolfe et al., 1987; Borkowska & Rybakowski, 2001), and in visuospatial and visuomotor abilities, visuospatial working memory and executive functioning (Borkowska & Rybakowski, 2001). However, not all studies have found differences between these patients (Sweeney et al., 2000; Gruber et al., 2007; Hermens et al., 2010).

In the study by Sweeney et al. (2000) bipolar patients in manic and mixed phases of illness where more impaired than unipolar and bipolar depressed patients in episodic and working memory, spatial attention and problem solving compared to

controls. In addition, compared to unipolar depressed patients, bipolar patients in mixed and manic phase have impairments in spatial working memory and recognition memory (Sweeney et al., 2000). Another study comparing neuropsychological functioning in 30 patients with major depression, 15 manic and 22 depressed bipolar patients at three different times during and after their psychiatric hospitalization, found that manic bipolar patients were more impaired in measures of selective attention and speed of responding than other patient groups (Gruber et al., 2007). However, there were no differences between the groups in memory and executive functioning. After being tested six to eight weeks after discharge all groups showed substantial improvement of neuropsychological performance, although some deficits especially in executive functions remained, and the manic group was found to be most impaired as compared with the others (Gruber et al., 2007).

Euthymic young adults with bipolar spectrum disorder have been found to be significantly more impaired than both major depressive patients and controls in tasks of executive function and verbal memory, whereas patients with major depression were impaired only in tests of executive function compared to controls (Smith et al., 2006). Recently a study using different methods than those in the study of Smith et al. (2006), found that only depressed bipolar and unipolar patients, but not euthymic bipolar patients, had impairments in executive functioning (Maalouf et al., 2010). Impairments in sustained attention appeared to be specific to bipolar disorder patients, as both euthymic and depressed bipolar patients were impaired in this function compared to controls. However, the patient groups did not differ from each other in these functions. In a study comparing neuropsychological dysfunction in first-episode psychotic patients with unipolar depression, bipolar disorder, and schizophrenia, quite similar profiles of generalized neuropsychological deficits were observed in the two groups of psychotic affective disorders, being however less severe than those in schizophrenia (Hill et al., 2009).

1.8.2 Bipolar disorder compared to schizophrenia

There is evidence that bipolar disorder and schizophrenia patients share some neuropsychological deficits (Hoff et al., 1990; Martinez-Aran et al., 2002a; Dickerson et al., 2001; Zalla et al., 2004; McIntosh et al., 2005a; Maier et al., 2006), but differences are also found for example in spatial working memory, reaction times, and sustained attention that seem to be more impaired in schizophrenia than in bipolar disorder (Goldberg, 1999; Fleck et al., 2001; Badcock et al., 2005; Bozikas et al., 2005; McIntosh et al., 2005a; Pirkola et al., 2005; Daban et al., 2006). Moreover, the impairments are usually the severest in schizophrenia (Martinez-Aran et al., 2002a; Dickerson et al., 2004a; Burdick et al., 2006; Jabben et al., 2010). According to most studies, patients with schizophrenia show more genera-

lized impairments than bipolar disorder patients (Dickerson et al., 2004a; Krabbendam et al., 2005; Jabben et al., 2010). However, although neuropsychological deficits are less severe in psychotic affective disorders, some studies show that they can be similarly generalized than in schizophrenia (Seidman et al., 2002; Schretlen et al., 2007; Hill et al., 2009), and in psychotic bipolar disorder, the neuropsychological profile may resembles that of schizophrenia patients (Albus et al., 1996; Tabares-Seisdedos et al., 2003; Glahn et al., 2006; Jabben et al., 2009).

Contrary to the meta-analysis by Krabbendam et al. (2005), another meta-analytic study comparing cognitive differences between schizophrenia and affective psychosis (both schizoaffective and bipolar disorder patients) found very minimal differences in both inpatient and outpatients samples, although patients with schizophrenia performed more poorly in general (Bora et al., 2009b). In both meta-analyses (Bora et al., 2009b; Krabbendam et al., 2005) the distribution of effect sizes showed substantial incoherence indicating heterogeneity in individual studies. In the study of Bora et al. (2009b), the between-group differences resulted from a higher percentage of males, more severe negative symptoms and younger age at onset of illness in the schizophrenia sample. The meta-analysis by Bora et al. (2009b) did not include non-psychotic bipolar disorder patients as did the study of Krabbendam et al. (2005), which may partly explain the differences.

Impairments in memory and attention appear to be common among first-episode patients with psychotic illnesses, regardless of diagnosis (McClellan et al., 2004). Schizophrenia patients in their first episode may have greater global and premorbid cognitive deficits than first episode bipolar patients. Similar findings have been found in other studies (McIntosh et al., 2005a). In another population-based study of patients with first-episode psychosis, deficits in patients with bipolar disorder or mania were less pervasive than in other psychotic disorders, but differences between the four patient groups and controls were attenuated after controlling for differences in general cognitive ability (IQ) (Zanelli et al., 2010). In that study, bipolar disorder patients performed better than schizophrenia patients on measures of current and estimated premorbid IQ, vocabulary and comprehension, in processing speed (Digit Symbol), working memory (Letter-number span), and visuospatial reasoning (Block Design task), but after controlling for the effect of current IQ, there were no statistically significant differences between these two patient groups. Therefore, the evidence of studies showing patients with schizophrenia manifesting more severe neuropsychological impairments than bipolar patients may be at least partly due to differences in general ability, or differences in included populations (for example non-psychotic versus psychotic bipolar disorder patients). Schizophrenia patients have often low premorbid IQ, which is less general in bipolar disorder (Toulopoulou et al., 2006). However, another study com-

paring first-admission schizophrenia and psychotic affective disorder patients (both bipolar disorder and major depressive disorder patient groups) found that schizophrenia patients performed worse even after adjusting the results of differences in demographical characteristics and general intellectual functioning (Mojtabai et al., 2000).

1.9 The effect of cognitive dysfunctions on psychosocial functioning

Contrary to prior assumptions about relatively good functional recovery of bipolar disorder, recent research has shown that many bipolar patients may show a quite poor prognosis and outcome. Cognitive dysfunctions associate with a lower functional outcome and poor psychosocial functioning in bipolar patients (Dickerson et al., 2004b; Martinez-Aran et al., 2004a; Martinez-Aran et al., 2007; Martino et al., 2008b; Wingo et al., 2009; Yen et al., 2009). Impaired immediate verbal memory in patients with bipolar disorder has been found to be associated with current unemployment status (Dickerson et al., 2004b; Burdick et al., 2010), and impaired verbal recall with poor psychosocial functioning (Atre-Vaidya et al., 1998; Martinez-Aran et al., 2007). In addition, impairments in executive functions have direct effect of worse psychosocial adjustment in bipolar patients (Yen et al., 2009). Tabares-Seisdedos et al. (2008) found that impairment evaluated with a global index of cognition was more predictive of functional outcome than clinical factors in both schizophrenia and bipolar disorder. Interestingly, improvements in cognitive status predicted positive changes in functional outcome, but only in bipolar subjects.

Longitudinal reports (Jaeger et al., 2007; Gruber et al., 2008; Tabares-Seisdedos et al., 2008; Martino et al., 2009) have indicated that cognitive disturbances may predict a poorer psychosocial adjustment in the long-term as well. Specifically, baseline deficits in fluency and attention/psychomotor speed (Jaeger et al., 2007), and in verbal memory, executive and attentional functions (Martino et al., 2009) seemed to be independent predictors of functional recovery one year later. In addition, there is association between time to recover and performance on a measure of the interference condition of the Stroop test in first episode bipolar patients, and patients who performed better on the Stroop required fewer days to return to a baseline level of function as defined by self report (Gruber et al., 2008). Baseline subclinical depressive symptoms together with impairments related to verbal memory and working memory predict poor overall psychosocial and occupational functioning among bipolar I and II disorder patients, also in a 4 year follow-up (Bonnin et al., 2010).

In a 15 years follow-up after the first hospitalization of bipolar I disorder patients, recent depressive symptoms, a greater number of hospitalizations, and processing speed (Digit Symbol) deficits appeared to be related to impaired functional outcome (Burdick et al., 2010). In contrast, recent mania did not significantly influence functional outcome in any of the domains assessed (work, social, and global). Processing speed deficits contributed to poor global functioning and social adaptation, while verbal learning and memory impairment influenced occupational status even after controlling for recent affective symptoms, course of illness features, other cognitive measures, and medication.

1.10 Structural and functional brain abnormalities in bipolar disorder

Although there are several studies that have assessed structural and functional brain abnormalities in bipolar disorder patients, their results have been inconsistent and conflicting. As in neuropsychological studies, there are many confounding factors that can affect the heterogeneous findings in structural and functional brain anatomy studies in bipolar patients (Bearden et al., 2001; McDonald et al., 2004b; Kempton et al., 2008).

1.10.1 Structural brain abnormalities and cognitive dysfunctions in bipolar disorder

Studies have evidenced both significantly larger or smaller volumes of the amygdala (Altshuler et al., 1998; Strakowski et al., 1999; Altshuler et al., 2000; Blumberg et al., 2003a; Chen et al., 2004; Chang et al., 2005; Rosso et al., 2007; Foland et al., 2008; Usher et al., 2010), hippocampus (Blumberg et al., 2003a; Beyer et al., 2004; Frazier et al., 2005; Strasser et al., 2005; Bearden et al., 2008), thalamus (Dupont et al., 1995a; Frazier et al., 2005; Radenbach et al., 2010), and cerebellum (DelBello et al., 1999) among patients with bipolar disorder. These abnormalities have been found to be related with cognitive dysfunctions found among patients (Coffman et al., 1990; Sax et al., 1999; Ali et al., 2000; Krabbendam et al., 2000; Zimmerman et al., 2006; Killgore et al., 2009).

Meta-analyses of structural brain changes in bipolar disorder have shown increased rates of white matter hyperintensities (Altshuler et al., 1995; Videbech, 1997; Kempton et al., 2008) and lateral ventricular enlargement (Elkis et al., 1995; McDonald et al., 2004b; Kempton et al., 2008). A recent meta-analysis found that bipolar patients had gray matter reduction in left rostral anterior cingulate cortex (ACC) and right fronto-insular cortex (Bora et al., 2010). In early phase of the illness, there was no evidence of fronto-insular cortex abnormality, and in chronic patients, longer duration of illness was associated with increased gray matter in

basal ganglia, subgenual ACC, and amygdala. Lithium treatment was associated with enlargement of ACC gray matter volumes. According to Bora et al. (2010), the most robust gray matter reductions occurring in anterior limbic regions may be related to the executive control and emotional processing abnormalities seen in this patient population. Hyperintensities are especially found in the deep white matter and subcortical gray matter (Beyer et al., 2009).

Gray matter abnormalities may not always be present in bipolar patients, and they are more clearly observed in schizophrenia patients (McDonald et al., 2005). Inconsistent findings about gray matter abnormalities may be related to medication effects, especially lithium and its possible neurotrophic, increasing effect on gray matter volume (Moore et al., 2000; Kempton et al., 2008). In addition, in first-episode bipolar patients, there are reductions for total intracranial and white matter volumes, but not for gray matter and whole brain volumes (Vita et al., 2009). Findings of this meta-analysis support the hypothesis of different patterns of changes in brain morphology over the time course of bipolar disorder. A pilot study, evidenced that only psychotic bipolar patients have increased ventricle volumes and a trend toward smaller hippocampal volumes as observed in schizophrenia patients (Strasser et al., 2005).

1.10.2 Functional brain abnormalities and cognitive dysfunctions in bipolar disorder

Functional imaging studies of bipolar patients have found that several prefrontal subregions are abnormally activated at rest and during cognitive tasks compared with healthy subjects (Keener & Phillips, 2007). In general, during depression there seems to be a generalized decrease in prefrontal activation, which is also present during mania (Strakowski et al., 2005b). However, during mania increased activation is observed in the anterior cingulate (Blumberg et al., 2003b).

Euthymic bipolar disorder patients have demonstrated poor task performance on executive measures (such as the Stroop task), with reduced activity in dorsal and ventral prefrontal cortical (Blumberg et al., 2003b; Gruber et al., 2004; Malhi et al., 2005; Kronhaus et al., 2006) and anterior cingulate (Gruber et al., 2004) areas compared to controls. In the Stroop tasks, patients have shown also relatively greater activation in the medial occipital cortex compared to increased activation in temporal cortical regions, middle frontal gyrus, putamen, and midline cerebellum seen in controls (Strakowski et al., 2005a), and also hypoactivation in right inferior and medial frontal gyri, as well as number of posterior brain regions (Roth et al., 2006). Decreased activity in the right inferior frontal gyrus and increased activity in the anterior cingulate has also been observed during another decision making task in manic patients (Rubinsztein et al., 2001). In manic patients, hy-

poactivation has been observed in right orbitofrontal area also during a go/no go task (Elliott et al., 2004; Altshuler et al., 2005), and in the right rostral and orbital prefrontal cortices during a word fluency task (Blumberg et al., 1999). However, there is also evidence of increase prefrontal cortical activation (Curtis et al., 2001), and no differences of frontal activation (Dye et al., 1999) in bipolar patients compared to controls during a verbal fluency task. In addition, during an emotional go/no go task there is fronto-striatal overactivation in euthymic bipolar patients (Wessa et al., 2007).

Euthymic bipolar patients have shown impairment during working memory tasks compared to controls, and demonstrated significantly greater activation in several brain regions including the fronto-polar prefrontal cortex, temporal cortex, basal ganglia, thalamus, and posterior parietal cortex (Adler et al., 2004). The same has been observed also in another study in similar areas (especially frontopolar and insula) (Thermenos et al., 2010). In addition, euthymic bipolar patients have shown impairment in a verbal learning task which is associated with abnormalities in brain areas involved in learning, in the left dorsolateral prefrontal cortex (Deckersbach et al., 2006). It has been suggested that disruption in fronto-temporal neural circuitry may underlie memory difficulties frequently observed in patients with bipolar disorder (Robinson et al., 2009).

The somewhat inconsistent results of activation and deactivation in frontal areas of bipolar patients can result from several reasons. Comparisons of functional brain studies are hampered by differences in the cognitive tasks used in the studies. Moreover, brain activation may also vary during a specific mood state. For example, in study by Blumberg et al. (2003b) there was decreased activation in ventral prefrontal cortical areas in all patients independently of their active mood state compared to controls, but manic patients showed decreased right ventral cortex activation, whereas depressed patients showed an increased activation compared to euthymic patients. While euthymic, unmedicated bipolar patients perform similarly to controls on sustained attention task (the CPT test), and first-episode, manic patients in response inhibition task, they may show significantly different patterns of functional magnetic resonance imaging (fMRI) brain activation (Strakowski et al., 2004; Strakowski et al., 2008). So, despite the similar behavioral data, bipolar and healthy subjects exhibit different patterns of brain activation, which may, according to Strakowski et al. (2008) reflect that different brain areas are activated during similar behavioral performance; patients may be using compensatory brain areas and methods in task performance, or they may inappropriately activate emotional brain areas during nonemotional tasks (Strakowski et al., 2004; Thermenos et al., 2010).

Neuroimaging findings indicate that there are orbitofrontal, cingulate and lateral frontal changes in patients with bipolar disorder using a variety of cognitive and affective tasks (Keener & Phillips, 2007; Clark & Sahakian, 2008). These brain areas are usually involved in emotional processing (Phillips, 2003), and in executive functioning (Robbins, 1998), and are closely interconnected with striatal regions involved in response selection and the hippocampus, a key node in memory encoding and retrieval (Zola-Morgan et al., 1991).

Strakowski et al. (2005b) have proposed a neuroanatomical model of bipolar disorder that involves dysfunction within striatal-thalamic-prefrontal networks and associated limbic regions (amygdala, midline cerebellum). They propose that diminished prefrontal modulation of subcortical and medial temporal structures within the anterior limbic network (amygdale, anterior striatum and thalamus) underpin the mood dysregulation found in bipolar disorder, and may also be behind the cognitive dysfunctions (Strakowski et al., 2005b).

1.11 Cognitive functioning in relatives of bipolar disorder patients

Recent meta-analyses of cognitive functioning in unaffected first-degree relatives of bipolar disorder patients have shown similar, although milder, deficits, especially in verbal memory and some aspects of executive functions to those observed in patients with bipolar disorder (Arts et al., 2008; Balanza-Martinez et al., 2008; Bora et al., 2009a). There are some controversies in different studies, as some have found impairments in verbal learning and memory (Gourovitch et al., 1999; Keri et al., 2001; Sobczak et al., 2003; Kieseppä et al., 2005; McIntosh et al., 2005a; Quraishi et al., 2009; Kulkarni et al. 2010), while others have not (Kremen et al., 1998; Ferrier et al., 2004; Clark et al., 2005b; Bora et al., 2008; Jabben et al., 2009). In one study, verbal learning and memory was the only function that did not demonstrate an intermediate pattern of performance in the unaffected relatives compared to patients and controls (Frantom et al., 2008).

Impairments in tasks assessing executive functions have been found in relatives of bipolar patients (Sobczak et al., 2002; Zalla et al., 2004; Clark et al., 2005b; Bora et al., 2008; Trivedi et al., 2008 Juselius et al., 2009; Kulkarni et al. 2010), but these results have also been somewhat inconsistent and variable. Response inhibition deficits have shown to have the largest and second largest effect sizes in relatives of bipolar disorder patients in two recent meta-analyses (Arts et al., 2008; Bora et al., 2009a), although some individual studies have indicated that first-degree relatives have intact performance in task requiring response inhibition (Sobczak et al., 2002; Ferrier et al., 2004; Kravariti et al., 2009b; Kulkarni et al.,

2010). Findings of no impairment exist for cognitive flexibility (Gourovitch et al., 1999; Ferrier et al., 2004; Zalla et al., 2004; Frantom et al., 2008; Kulkarni et al. 2010) and working memory (Gourovitch et al., 1999; Keri et al., 2001; Pirkola et al., 2005), although some studies have found impairments among unaffected relatives in cognitive flexibility and working memory (Ferrier et al., 2004; Szoke et al., 2006; Bora et al., 2008; Glahn et al., 2010).

In addition, impairments have been found in attention, psychomotor performance and information processing speed (Pierson et al. 2000; Sobczak et al., 2003; Frantom et al., 2008; Glahn et al., 2010), although there are contrasting results, too (Ferrier et al., 2004; Kieseppä et al., 2005; McIntosh et al., 2005a). Visual functions and memory are less studied, and there is evidence both for impaired (Frantom et al., 2008; Glahn et al., 2010; Kulkarni et al. 2010), but mostly for spared (Kremen et al., 1998; Gourovitch et al., 1999; Kieseppä et al., 2005; Quraishi et al., 2009) visuospatial and constructional abilities, and visual learning and memory in unaffected relatives. Usually, the general ability or verbal IQ is not impaired compared to controls (Arts et al., 2008; Bora et al., 2009a).

These discrepancies in different studies may result from methodological and sampling differences, such as different exclusion criteria. They may also be caused by between-study differences in the degree of genetic closeness in the relatives, for example including first-degree (parents, siblings, children) or second-degree relatives (cousins, aunts, uncles). Also the family type may be critical: some studies include families with one sporadic patient in the family, while some represent familial type of the disorder with several affected family members. Also relatively small sample sizes may be reflected in substantial heterogeneity as to effect sizes (Arts et al., 2008; Bora et al., 2009a). Among the majority of studies including neuropsychological measures that support evidence of impairment in unaffected relatives, there are also studies with negative results. Some cognitive functions, for example verbal learning and memory and executive functions are also more frequently investigated than others (see Kravariti et al., 2009a).

Most studies of unaffected relatives have been conducted among adult participants, and less attention has been given to cognitive functioning in high-risk offspring of parents with bipolar disorder. In one study, 43 adolescent offspring (average age of 15 years) of bipolar disorder mothers were found to have deficits in executive functions and attention, but not in verbal memory compared to controls (Klimes-Dougan et al. 2006). Another high-risk study of offspring having parents with schizophrenia or bipolar disorder (average age of 17.3 years) descending from densely affected kindreds, found that both subgroups displayed impairments in verbal and visual memory and in executive functions compared to

controls (Maziade et al., 2009). In addition, both groups had lower IQ than controls. In a study of 8-12 years old children of bipolar I disorder parents, there were no differences between high-risk offprings and controls in general, verbal or performance IQ, but there were discrepancies between performance IQ and verbal IQ in children at-risk (McDonough-Ryan et al., 2002). Children at-risk had lower performance IQ compared to verbal IQ, and they also performed more poorly than controls on reading, spelling and arithmetic.

Direct comparisons of unaffected relatives with schizophrenia and bipolar patients have shown that relatives with schizophrenia perform worse than both controls and relatives with bipolar patients in spatial working memory (Keri et al., 2001), and in verbal and visual memory and auditory attention (Kremen et al., 1998). However, verbal working memory, verbal learning and executive functions were found to be spared in both groups, while long-delay verbal recall was impaired in both groups (Keri et al., 2001). In line with these results, similar impairments were found in memory in both unaffected groups, and relatives did not differ from each other in these functions, although current and verbal IQ was impaired only in relatives with schizophrenia (McIntosh et al., 2005a). One study of 32 unaffected co-twins with schizophrenia patients and 16 unaffected co-twins with bipolar disorder patients found that only unaffected co-twins of schizophrenia patients performed significantly worse than control subjects on the spatial working memory task (Pirkola et al., 2005).

1.12 Structural and functional brain abnormalities in relatives of bipolar disorder patients

There are only few structural and functional brain studies of relatives of bipolar disorder patients, and the results of these studies have been somewhat inconsistent. In studies of structural brain abnormalities, risk for bipolar disorder has been found to be associated with local gray matter deficits in the right anterior cingulate gyrus and ventral striatum (McDonald et al., 2004a) and reduced anterior thalamic gray matter (McIntosh et al., 2004). However, there is conflicting evidence with studies that found no gray matter deficit in unaffected relatives (Kieseppä et al., 2003; McIntosh et al., 2006). White matter hyperintensities and volume deficits are reported in unaffected relatives and twins of bipolar patients (Kieseppä et al., 2003; Hajek et al., 2005; McDonald et al., 2005; Chaddock et al., 2009), although not in all studies (McIntosh et al., 2005b). Studies have also found that unaffected relatives have reduced left hemispheric white matter volume (Kieseppä et al., 2003), especially in the left prefrontal and temporoparietal regions (McDonald et al., 2004a). Significant differences in ventricular, hippocampal, anterior cingulated or strital volumes between bipolar disorder relatives and controls have not been

consistently found (McIntosh et al., 2004; McDonald et al., 2006; Hajek et al., 2008; Hajek et al., 2009), and there are contrasting findings of increased caudate volume in healthy co-twins of bipolar disorder patients compared with controls (Noga et al., 2001).

In fMRI studies, relatives of bipolar patients have demonstrated hyperactivation in left frontal pole/ventrolateral gyrus during impaired working memory performance and deactivation in retrosplenial cortex and reduced activation of left prefrontal cortex during verbal fluency task (Allin et al., 2010). In a positron emission tomography (PET) study of an emotional challenge task, hyperactivation was evidenced in the insula and medial frontal cortex in relatives of bipolar patients (Kruger et al., 2006). Largely in line with these results, a recent fMRI study of relatives of bipolar patients suggested that frontopolar and insula (and possibly orbitofrontal cortex) regions are involved in failure to suppress emotional arousal during working memory task which may interfere the role of frontopolar cortex in cognitive coordination and task learning (Thermenos et al., 2010).

1.13 Etiology of bipolar disorder and cognitive dysfunctions

The pathogenesis and etiology of bipolar disorder is still unknown. Although bipolar disorder is a highly genetic disorder (McGuffin et al., 2003; Kieseppä et al., 2004), there are also environmental risk factors that increase the risk of developing the disorder (Alloy et al., 2005). It is most likely that bipolar disorder is multifactorial and complex in etiology (Craddock & Jones, 2001). There is no single gene that predisposes the development of any psychiatric disorders, and there are no measurable laboratory parameters that could verify diagnosis of a given psychiatric disorder (Tsuang & Faraone, 2000). Etiological research on psychiatric disorders, including bipolar disorder, is complicated by their multifactorial background. The search for potential measurable parameters associating with bipolar disorder, for example cognitive functions, may help also identifying etiological factors behind these complex disorders, and provide a link between neurobiology and observed symptoms and behaviors.

1.13.1 Early course of cognitive impairments in bipolar disorder

The mechanism leading to cognitive disabilities in bipolar disorder is probably a combination of neurodevelopmental and neurodegenerative/progressive processes (Goodwin et al., 2008). Bipolar disorder is not usually associated with premorbid intellectual decline contrary to schizophrenia (Reichenberg et al., 2002; Zammit et al., 2004; Goodwin et al., 2008). However, these studies have concentrated on intellectual functioning and infrequently to other cognitive functions, for example attention, executive or memory functions. Adult bipolar disorder patients have

also usually preserved intellectual functioning (Robinson et al., 2006; Arts et al., 2008; Bora et al., 2009a). One conscript study found evidence that particularly good performance on an arithmetic reasoning task associated with future bipolar disorder (Tiihonen et al., 2005).

Pediatric bipolar disorder with illness onset before age 18 may represent a distinct and highly genetic form of the disorder (Lin et al., 2006). In children and adolescents with bipolar disorder, there are impairments in executive functioning, memory, attention and processing speed as well as differences in IQ testing results and academic functioning compared to controls (Lagace et al, 2003; Doyle et al., 2005; McClure et al., 2005; Bearden et al., 2007) which are similar evidenced in adult patients (Robinson et al., 2006; Arts et al., 2008). A qualitative review of pediatric bipolar patients suggests that impairments in attention, decision-making, and response inhibition are particularly common in this population (Kyte et al., 2006). A recent meta-analysis found the largest differences between pediatric bipolar disorder patients and controls in measures of verbal memory, whereas moderate differences were found in attention, executive functioning, working memory, visual memory and visual perceptual skills (Joseph et al., 2008). In addition, there were small differences for measures of reading, motor speed and measures of IQ, but there was also heterogeneity of effect sizes across studies.

Although findings are consistent with previous studies with adult patients (Cahill et al., 2009), there are no direct comparisons between children and adults with bipolar disorder, and one can question whether findings with very early onset bipolar disorder are generable to whole bipolar population (Carlson & Meyer, 2006). At a 3-year follow-up, developmental progress in executive functions and verbal memory has been found to be significantly slower in the patients with pediatric bipolar patients than in controls, and cognitive functioning remains compromised in patients despite symptom remission with optimal pharmacotherapy (Pavuluri et al., 2009). In addition, one study that assessed pediatric bipolar disorder patients and their unaffected siblings showed that the patients have impairments in processing speed, verbal learning, working memory, interference control and abstract problem solving. The siblings were impaired in measures of abstract problem solving, working memory and interference control (Doyle et al., 2009). Similar dysfunctions are also found in unaffected relatives of adult bipolar populations (Arts et al., 2008; Balanza-Martinez et al., 2008; Bora et al., 2009a).

1.13.2 Later course of cognitive impairments in bipolar disorder

Even though there may be some cognitive deficits before the onset of illness or in first-degree relatives, the deficits are more severe in patients with full blown bipolar disorder. Goodwin et al. (2008) discuss potential neurodegenerative processes

of cognitive dysfunctions, and potential loss of function and underlying functional neuropathology subsequent to the onset of bipolar disorder. In a cross-sectional study of cognitive performance between first- and multi-episode patients, first-episode patients performed generally more poorly than controls or multi-episode patients, but the latter group performed worst on tasks assessing memory and one task assessing cognitive flexibility (WCST) (Nehra et al., 2006). Another study using this same task found out that most cognitive capabilities assessed with the WCST are spared during euthymic first-episode patients, but are impaired during acute manic or mixed states in both first- and multiepisode bipolar patients compared to controls (Fleck et al. 2008). However, in some other tasks assessing executive functioning there are deficits even in early course of illness in euthymic patients (Nehra et al. 2006; Gruber et al., 2008). Studies of first-episode patients are still relatively rare. It is possible that some mild problems with executive dysfunction exist in the early course of the illness, possibly before the onset of illness and in genetically high-risk individuals, but these impairments are more pronounced with the outbreak of the illness. One problem in these first-episode studies are that there is commonly some latency before the diagnosis of bipolar disorder, particularly when the first episode is depressive, and the timing of the first episode may not be correct (Bowden, 2001).

As described previously, there are only few longitudinal studies of neuropsychological functioning in bipolar disorder patients, and the follow-up times are usually rather short to allow any definite conclusions to be drawn of the course of cognitive functioning in these patients. In a follow-up study on brain structure of bipolar disorder patients and age matched controls, patients with bipolar disorder showed a larger decline in hippocampal, fusiform, and cerebellar gray matter density over 4 years than controls, and reductions in temporal lobe gray matter correlated with decline in intellectual function and with the number of intervening mood episodes over the follow-up period (Moorhead et al., 2007). The result of this study implies a progressive and neurodegenerative aspect to bipolar disorder.

Epidemiologic studies have suggested that bipolar disorder may be associated with increased risk of developing dementia (Kessing & Nilsson, 2003; Kessing & Andersen, 2004). Euthymic older adults (mean age 69.7) with bipolar disorder have been shown to have more cognitive dysfunction assessed with the Dementia Rating Scale (DRS) at baseline and more rapid cognitive decline over three-year prospective follow-up than a mentally healthy comparison group (Gildengers et al., 2009). Another study that compared older (mean age 63.8) bipolar patients (with recent cognitive complaints) to patients with Mild Cognitive Impairment (MCI) found distinct profiles of cognitive impairments in these groups (Silva et al., 2009). However, using discriminant analysis, about half of the bipolar group

was classified as belonging to the MCI group, this group showing similar deficits in episodic memory, and potentially suffering a concomitant incipient neurodegenerative condition. Some studies have found similar impairments in cognitive functioning in euthymic elderly bipolar patients than in younger patients, which were not related to chronicity measures such as age at onset, length of illness, or number of hospital admissions (Gildengers et al., 2004; Martino et al., 2008a; Delaloye et al., 2009).

1.13.3 Environmental factors and cognitive functioning

Some evidence has emerged that some environmental risk factors may be associated also with cognitive impairments seen in bipolar disorder. These may be associated with obstetric complications (Martino et al., 2008b), and early traumatic adversity (Savitz et al., 2008). In a study by Savitz et al. (2008), self-reported history of sexual or emotional abuse during childhood was associated with poorer cognitive performance in bipolar patients, particularly on verbal fluency, cognitive flexibility, and visual and verbal memory, but the experienced childhood trauma did not explain all deficits.

1.13.4 Genetic factors and cognitive functioning

In genome-wide linkage analyses in bipolar disorder, the strongly supported chromosomal regions have been in 6q16–q22, 8q12q23–q24, 13q32–q34, 16p12–p13, 22q11–q22 and Xq24–26 (Craddock & Jones, 1999; Ekholm et al., 2003; Craddock et al., 2005). In Finnish linkage studies of bipolar disorder, significant linkage has been found in locus Xq24–27.1 (Pekkarinen et al., 1995) and in locus 4q32 and 16p12 (Ekholm et al., 2003).

In addition to chromosomal findings in linkage analyses, there are a number of functional candidate genes that are suggested to be involved in the biological processes implicated in bipolar disorder. Genome-wide association studies (GWAS) (e.g. Baum et al., 2008; Sklar et al., 2008) have revealed some promising association signals, but the mechanism by which these genes increase susceptibility has remained unresolved. GWAS studies of Finnish bipolar families have found evidence that supports the previous findings of six associating single nucleotide polymorphisms (SNPs) in the DFNB31 (CASK-interacting protein CIP98 isoform 1), in the SORCS2 (Sortilin-related VPS10 domain containing receptor 2), in the SCL39A3 (Solute carrier family 39) and in the DGKH (Diacylglycerol kinase, eta) genes (Ollila et al., 2009), and in the CDH7 (cadherin 7, type 2) gene with bipolar disorder (Soronen et al., 2010). In the latter study, SNPs in the CDH7 gene were also associated with circadian rhythm and seasonality, and with better performance in visual attention and visual working memory (Soronen et al., 2010). Interestingly, the CDH7 genes regulate, for example, brain development in several

ways by cell sorting, migration and axon outgrowth (Luo & Redies, 2004), and it is expressed in the developing eye and in the retina of mice (Faulkner-Jones et al., 1999). In this study, alleles that predisposed to bipolar disorder were associated also with functions related to neurons using visual information, and indicating possible susceptibility genes that might have an effect on the brain functions affected in bipolar disorder (Soronen et al., 2010).

In addition, other studies have also found that some executive impairment seen in bipolar disorder patients might be explained on genetic or neurodevelopmental grounds. BDNF (Brain-derived neurotrophic factor) gene has been associated with abnormal performances of bipolar patients in task assessing cognitive flexibility/set shifting ability (WCST) (Rybakowski et al., 2006), and COMT (cathecol O-methyltransferase) in prefrontal aspects of learning (Burdick et al., 2007). In addition, BDNF Val66Met genotype and differential gray matter ratio in brain structures may be associated, and the variation in this gene may play a prominent role in brain structure differences in bipolar disorder patients, and affect verbal learning (Matsuo et al., 2009).

In addition, the haplotypes at the 5' end of the DISC1 (Disrupted-in-Schizophrenia-1) gene have been found to be associated with memory perseverations and auditory attention, while the variants at the 3' end have associated with several cognitive functions including verbal fluency and psychomotor processing speed in bipolar families (Palo et al., 2007). DAOA (d-amino acid oxidase activator) gene also may play a role in predisposing individuals to a mixed phenotype of psychosis and mania, and to impairments in related neuropsychological traits as impaired performance in visuospatial ability (Soronen et al., 2008).

1.14 Potential neuropsychological endophenotypes in bipolar disorder

Although heritability estimates of bipolar disorder have been shown to be around 80% (McGuffin et al., 2003; Kieseppä et al., 2004), the genetic basis and underlying etiology of this complex disease has remained poorly understood. Although many candidate genes and linkage loci associated with bipolar disorder have been suggested (Craddock & Jones, 2001; Hayden & Nurnberger, 2006), no genes have definitively been identified, and the replication of findings has been difficult. The multifactorial character of the disorder and heterogeneity in clinical phenotype, as well as possible differences in applying the diagnostic criteria may stand behind these difficulties. Thus, using the clinical diagnosis of bipolar disorder as the only phenotype in etiological studies may not be optional (Tsuang, 2001; Szatmari et al., 2007).

1.14.1 The concept and criteria of endophenotypes

One potential strategy for decreasing phenotypic heterogeneity in the etiological studies on complex disorders is the use of endophenotypes (Gottesman & Shields, 1973; Gottesman & Gould, 2003). Endophenotypes are traits or intermediate phenotypes that mediate between genes and phenotype, and it is assumed that they could be used as quantitative trait measures in linkage and association studies instead of the categorical diagnostic variables. According to Gottesman and Gould (2003) the endophenotypes should be: (1) significantly heritable, (2) associated with the illness in the population, (3) manifest in an individual whether or not the illness is active (being state-independent), (4) in families with the illness, many of the unaffected relatives have the same endophenotypic trait, and (5) the endophenotype that is present in the affected, is more prevalent in the unaffected in the family than in the general population.

Using endophenotypes is assumed to provide an increase in statistical power as the undiagnosed relatives can also be included in the genetical analysis. At present, it is not clear whether an endophenotype needs to be specific to a given psychiatric condition, such as schizophrenia or bipolar disorder, and some endophenotypes seem to be shared by two (or more) conditions (Berrettini, 2005; Hill et al., 2008; Thaker, 2008a). In bipolar disorder, several neurophysiological, biochemical, endocrinological, neuroanatomical, and neuropsychological endophenotypes have been proposed (Lenox et al., 2002; Glahn et al., 2004; MacQueen, et al., 2005; Savitz et al., 2005; Hasler et al., 2006; Thaker, 2008b).

1.14.2 Neuropsychological endophenotypes

The scores derived from neuropsychological assessment may provide informative cognitive endophenotypes for severe mental illnesses, including bipolar disorder. The neuropsychological impairments associate closely with the clinical status of the disorders but may also be present without acute illness. Moreover, they may be present also among unaffected relatives. According to present knowledge, executive functioning and verbal memory meet best the criteria for neuropsychological endophenotypes of bipolar disorder as there are impairments in these functions both in euthymic bipolar patients and their unaffected family members (Glahn et al., 2004; MacQueen et al., 2005; Hasler et al., 2006; Robinson & Ferrier, 2006; Balanza-Martinez et al., 2008; Kravariti et al., 2009a; Tuulio-Henriksson et al., 2009). However, the evidence of the usability of neuropsychological endophenotypes in genetic analyses is still controversial and limited.

1.14.3 The heritability of cognitive functions

Heritability defines how much of the total phenotypic variation in a certain population is attributable to variation among individual genotypes compared to the variation in their environment. It does not quantify the extent to which genes and environment actually determine a phenotype. Most of the research of genetic factors and cognitive functions has focused on the heritability of general intelligence, which seems to be highly heritable (Devlin et al., 1997; McClearn et al., 1997; Bouchard, 1998; Wright et al., 2001; Plomin & Spinath, 2004). The heritability of more specific cognitive processes has been less studied and documented, but there is some evidence that individual variation in more discrete functions such as attention, executive functioning, spatial and verbal working memory, verbal memory, and processing speed are influenced substantially by genetic effects (Finkel et al. 1995; Ando et al., 2001; Fan et al., 2001; Luciano et al., 2001; Wright et al., 2001). In these studies, with variation of the heritability estimates in different populations, the 65-80% of individual variation in adult intelligence test performance, and 50-80% in measures of processing speed and memory may be due to genetic factors.

Twin and family studies have also found significant heritabilities in neuropsychological functions in schizophrenia, particularly in working memory (Cannon et al., 2000; Tuulio-Henriksson et al., 2002). The fundamental criterion of heritability for neuropsychological endophenotypes in bipolar disorder has thus far been only scarcely studied. One recent study found that processing speed, working memory, and declarative (facial) memory were significantly heritable in bipolar disorder patients and their relatives (Glahn et al., 2010).

2 AIMS OF THE STUDY

The general aim of the present study was to identify possible neuropsychological endophenotypes for bipolar I disorder in families with this disorder by investigating the endophenotype criteria presented by Gottesman and Gould (2003).

The specific aims of the study were:

1. To assess cognitive functioning in relatively asymptomatic bipolar I disorder patients and their unaffected first-degree relatives, and compare them to healthy population-based control group with no family history of psychotic disorders. This aim focused on the endophenotype criteria 2, 3, 4 and 5 described on section 1.14.1, to study whether there are any cognitive dysfunctions in bipolar I disorder patients (criterion 2), who are relatively euthymic (criterion 3). Furthermore, and whether these cognitive dysfunctions are present in relatives with bipolar I disorder patients (criterion 4) more generally than in population-based controls (criterion 5) (Study I).

2. To estimate the heritability of different cognitive functions in families with bipolar I disorder. This aim focused on the endophenotype criterion 1 to study whether cognitive functions are heritable in bipolar disorder families (Study II).

3. To examine cognitive functioning in bipolar I disorder patients and their unaffected relatives in a group of families affected with bipolar I disorder only (bipolar families) and another group of families affected both with bipolar I disorder and schizophrenia or schizoaffective disorders (mixed families). In addition, the aim was to estimate the heritability of cognitive functions in these two types of families. This aim focused on endophenotype criteria 1, 2, 3, 4, and 5 (Study III).

4. To investigate the effect of the processing speed (potential cognitive endophenotype in bipolar I disorder) on other cognitive functions in this population of familial bipolar I disorder patients, their first-degree relatives and controls.

3 METHODS

3.1 Study

The present study is part of the project "The Genetic Epidemiology and Molecular Genetics of Severe Mental Disorders in Finland" originally launched by professors Leena Peltonen-Palotie and Jouko Lönnqvist at the Department of Mental Health and Substance Abuse Services, National Institute for Health and Welfare, Helsinki, Finland (formerly Department of Mental Health and Alcohol Research and the Department of Molecular Medicine at the National Public Health Institute). The Ministry of Social Affairs and Health and the Ethics Committee of the National Public Health Institute approved the study. After complete description of the study to all subjects, they gave written informed consent to participation.

3.2 Subjects

The search for the study participants began with the Finnish Nationwide Hospital Discharge Register, which was used to identify all patients who were hospitalized due to bipolar disorder between 1969 and 1991 (ICD-8 codes 296.10 or 296.30 before year 1987, or DSM-III-R codes 296.4, 296.5 or 296.6 1987-1991). Parents and siblings of these patients were identified from the national Population Information System which is maintained by the Population Register Centre and local register offices. Information on family relations was linked back to the Hospital Discharge Register to obtain data on family members' hospital admissions, if any. After this identification process, families with at least two members diagnosed either with bipolar disorder or schizoaffective disorder, bipolar type, were targeted for a detailed phenotypic investigation (n = 57). All available medical records of the whole family (parents and siblings) were collected. Probands were contacted through their treating psychiatrist, and, if the proband gave permission other family members were contacted for the detailed investigation.

Totally, there were 57 nuclear families including 115 probands. Of the probands, 40 refused to participate to the study and 17 were deceased. Of the remaining family members, 153 (58 probands) were interviewed and a neuropsychological test battery was administered.

Because the present study was planned to focus on bipolar I disorder, the following exclusion criteria were applied. One family (2 affected and 3 other family members) was excluded, because it did not have the bipolar I disorder proband based on the final consensus diagnosis. 4 families were excluded because the

family members fulfilled some of the exclusion criteria. The exclusion criteria included other disorders that could be related to neuropsychological impairment (severe significant physical or neurological illness, brain injury, current substance abuse or dependence (3 probands and 2 other family members), or mental retardation (1 proband)). In addition, subjects over 70 years of age (2 probands and 14 other family members) were excluded because of increasing risk that high age could have confounded cognitive performance (Ylikoski et al., 1998). Altogether 6 probands and 10 other family members did not complete the neuropsychological tests, and were thus excluded from the present study.

The final study sample of the present study thus included 110 persons (44 probands) from 52 families with bipolar disorder. In all families of the present study, there were at least two bipolar I disorder relatives, or one bipolar I disorder relative and another family member with schizoaffective disorder, bipolar type. Of the included non-proband family members (n = 72), 59 were first-degree relatives and 13 were second-degree relatives for the probands.

The demographic and clinical characteristics and the diagnostic distribution of the study sample are presented in Table 2. Of the 72 subjects that had any lifetime axis I diagnosis altogether 44 had a lifetime psychotic disorder. Three bipolar I disorder patients (all having a depressive episode) and two depressive disorder patients were acutely ill. 32 bipolar I patients were currently medicated, often with more than one psychotropic drug. Among the remaining subjects with lifetime diagnosis (n = 34), 15 had current psychoactive drug treatment (Table 2).

All subjects were interviewed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) (First et al., 1997). The final consensus diagnosis was made based on all available data, including case notes records from hospital and outpatient treatments, and the face-to-face interview. Psychiatrists assigned all the diagnoses. Psychosocial functioning status was assessed using the Global Assessment of Functioning scale (GAF, DSM-IV). The same day a comprehensive neuropsychological test battery designed to assess the central cognitive functions was administered in a fixed order to all subjects.

Table 2. Demographic and Clinical Characteristics of Participants in the Study

Characteristics	Mean	SD
Age (years)	50.8	(8.0)
	N	%
Sex		
Men	55	50
Women	55	50
Primary axis I diagnosis (lifetime)		
Bipolar I disorder (with psychosis n = 31)	38	34.5
Bipolar disorder not otherwise specified	2	1.8
Schizoaffective disorder (bipolar type)	6	5.5
Major depressive disorder, recurrent (with psychosis n = 3)	5	4.5
Major depressive disorder with single episode	6	5.5
Depressive disorder not otherwise specified	3	2.7
Dysthymic disorder	2	1.8
Schizophrenia	4	3.6
Alcohol dependence (not current)	4	3.6
Adjustment disorder	2	1.8
None	38	34.5
Medication* (current)	47	42.7
Lithium	19	17.3
Antipsychotics	34	30.9
Other psychoactive medication	28	25.5
None	62	56.4

* The information of current medication is missing for one person with schizophrenia.

The four studies comprising the present thesis apply different inclusion and exclusion criteria and subsamples which were derived from the above mentioned final sample. These subsamples are described below.

3.2.1 Studies I and IV

Of the 52 families, altogether 41 families fulfilled the inclusion criteria of the Studies I and IV, and 11 families were excluded because all interviewed and tested family members had some of the exclusion criteria. Of the bipolar I patients, five acutely ill patients were excluded from Studies I and IV. In addition, first-degree relatives fulfilling DSM-IV criteria for a lifetime diagnosis of bipolar II disorder (n = 1), bipolar disorder not otherwise specified (NOS) (n = 2), cyclothymia (n = 1), recurrent major depressive disorder (n = 5), or any psychotic disorder (n = 20) or for any current diagnosis of psychiatric disorder (n = 4), or currently treated with psychotropic medication were also excluded (n =1).

The final study samples of Studies I and IV thus included 32 bipolar I disorder patients (23 were in full remission and 9 in partial remission according to the DSM-IV criteria). Of the included 32 patients, seven had comorbid lifetime but not current Axis I diagnosis. 26 patients were currently medicated. In addition, Studies I and IV included 40 relatives without a lifetime psychotic disorder, or any current mental disorder. Eight relatives had lifetime psychiatric diagnoses as-

signed at the SCID-based interview. In addition, 55 controls with no personal or family history of psychotic disorder were also included (described in detail in section 3.3).

3.2.2 Study II

The sample in Study II included all 110 persons from the 52 families with bipolar disorder described in section 3.2. Of the 72 subjects that had some lifetime axis I diagnosis, altogether 44 had a lifetime psychotic disorder. Three bipolar I disorder patients (all having a depressive episode) and two depressive disorder patients were acutely ill. Thirty-two bipolar I patients were currently medicated, often with more than one psychotropic drug. Among the remaining subjects with lifetime diagnosis (n = 34), 15 had current psychoactive drug treatment. The descriptives of the study sample is presented in Table 2.

3.2.3 Study III

The sample of Study III was derived from three different population-based genetic epidemiological samples including families with bipolar disorders, families with schizophrenia spectrum disorders and families with at least one member with schizophrenia originating from a genetic isolate in the north-eastern part of Finland (described in detail by Tuulio-Henriksson et al., 2003).

For Study III, two groups of families were formed. In these groups, there were 1) families with a proband with bipolar I disorder, and at least one family member with bipolar I disorder, but no schizophrenia spectrum disorders in the family, or 2) there was a proband with bipolar I disorder, and at least one family member with schizophrenia or schizoaffective disorder. Of the 57 families originating from the sample with bipolar disorder, 41 families fulfilled the inclusion criteria for Study III.

The search for study participants of the schizophrenia families began with three Finnish nationwide computerized health care registers (the Hospital Discharge, Medication Reimbursement, and Disability Pension Registers), which were used to identify all patients with diagnosis of schizophrenia between 1969 and 1998. Two samples were targeted for collection. The first sample consisted of families with at least two siblings with schizophrenia, and their first-degree family members. The other sample comprised of families from an isolated region in the northern part of Finland with at least one member with schizophrenia, and their first-degree relatives. The data collection of relatives from schizophrenia families was otherwise similar to the bipolar disorder study, but information from the Medication Reimbursement and Disability Pension Register was collected as well. From these two schizophrenia family samples we identified all families including also at

least one family member with bipolar I disorder. We found 11 patients with bipolar I disorder from 10 schizophrenia families and included them into Study III.

After this process, the two study groups of families included 30 families with bipolar I disorder only (bipolar families) and 21 families with both bipolar and schizophrenia or schizoaffective disorders (mixed families).

For the comparisons of neuropsychological performance of bipolar I disorder patients originating from bipolar vs. mixed families, we excluded six bipolar I disorder patients (four of them were acutely ill, one had current co-morbid alcohol abuse, and one had mild mental retardation). When comparing neuropsychological performance in unaffected relatives originating from bipolar vs. mixed families, nine relatives over 70 years of age, one relative with psychotropic medication, one with bipolar II disorder, ten with schizoaffective disorder (bipolar type), ten with schizophrenia, two with other psychotic disorder, nine with recurrent depressive disorder, and six with other current diagnosis of psychiatric disorder were excluded.

The final sample of bipolar families included 20 bipolar I disorder patients and 36 first-degree relatives without a lifetime psychotic disorder, or any current mental disorder. Fourteen patients were in full remission and six in partial remission according to the DSM-IV criteria. Four patients had a co-morbid lifetime Axis I diagnosis. Of the 36 included relatives, 10 had lifetime history of psychiatric disorder.

The final mixed family sample included 19 bipolar I disorder patients and 28 first-degree relatives without a lifetime psychotic disorder, or any current mental disorder. Sixteen patients were in full remission and three were in partial remission. Three patients had a co-morbid lifetime Axis I diagnosis. Of the 28 included relatives, 9 had a lifetime history of psychiatric disorder.

For the heritability estimation analyses, we included all patients irrespective of their diagnoses, and relatives with valid neuropsychological test performance. The subjects were not allowed to have current substance abuse or dependence, severe significant physical or neurological illness, brain injury, or mental retardation, and all were under 70 years of age. For the heritability estimation analyses of the bipolar families, 68 persons (23 probands) from 30 families were included. The analyses of the mixed families included 68 persons (20 probands) from 21 families.

3.3 Control group

A population-based control group screened negative for psychotic or manic symptoms was recruited from a national health survey (Aromaa & Koskinen, 2004; Perälä et al., 2007). The subjects were interviewed with the Structured Clinical Interview for DSM-IV (SCID-I), and a neuropsychological test battery was administered. The same exclusion criteria as for the relatives of bipolar I patients were used, plus excluding individuals with family history of mental disorder according to self-report at interview, leaving altogether 55 subjects in the control group. For 17 control subjects, a lifetime Axis I diagnosis (not current, except for specific phobia) was assigned at the SCID interview. These included major depressive disorder with single episode (n = 6), depressive disorder NOS (n = 5), eating disorder NOS (n = 1), panic disorder (n = 1), alcohol abuse (n = 1), alcohol dependence (n = 3), adjustment disorder with depressed mood (n = 1), and specific phobia (n = 2). None of the subjects suffered from a current mental disorder, except the two with specific phobia. The control group was included in Studies I, III and IV.

3.4 Neuropsychological assessment

The study participants completed a comprehensive neuropsychological test battery administered in fixed order on the study day. All examiners were psychologists or advanced psychiatric nurses extensively trained and supervised with the test battery. Psychologists scored all the tests. The test battery for the controls was slightly narrower than that for the bipolar families.

Four subtests from the Finnish version of the Wechsler Adult Intelligence Scale – Revised (WAIS-R) (Wechsler, 1981) were used to assess verbal and non-verbal ability. Verbal abilities were assessed with the Vocabulary and Similarities subtests from the WAIS-R. The Vocabulary is considered the best single measure of both verbal and general abilities (Lezak et al., 2004), and the Similarities subtest is a measure of verbal abstraction and concept formation. Non-verbal abilities were assessed with the Block Design and Digit Symbol subtests. The Block Design is a measure of visuoconstructional functions and visuospatial reasoning. The Digit Symbol measures psychomotor and information processing speed. Both Block Design and Digit Symbol tests are timed and have a component of motor performance.

Three tests were used to assess executive functioning, complex attention and mental flexibility. Visual scanning, attention and mental flexibility were assessed with the Trail Making Test parts A and B (Reitan, 1958). Part A of the test assessed simple attention. Part B reflects the ability to shift strategy (Lezak et al., 2004).

Both parts are timed, and the difference score (time B- time A) was used as a measure of executive functioning. Whether the subject performed correctly or not was used as a variable of performance quality in both parts A and B. Performance quality in Part B was also used as a measure of executive functioning. Study II included selective attention and executive function that were assessed with The Stroop Color and Word Test (Golden, 1978). The Interference trial of the test was used to measure subject ability to name words of colors that are written in an incongruent manner. The interference score, which measures 'resistance to interference', was calculated using the formula provided by Golden (Golden, 1978). The higher score implicates more susceptibility to interference. Controlled Oral Word Association test (COWAT) (Benton & Hamsher, 1989) was used to assess verbal fluency. In this test, subjects are asked to generate as many words as they can think in one minute beginning with a given letter (S and K), or within a given semantic category (animals). This test is also a sensitive measure of executive functioning because it requires the subject to generate his or her own strategy.

The Digit Span Forward task and the Digit Span Backward task of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987) were used to assessed auditory attention and verbal working memory, respectively. Visual attention was measured with the Visual Span Forward task of the WMS-R, and the Visual Span Backward task of the WMS-R was used as a measure of visual working memory.

Verbal learning and memory were assessed with the California Verbal Learning Test (CVLT) (Delis et al., 1987) which examines both recall and recognition of word lists over a number of trials. Verbal memory was also measured using the Logical Memory subtest of WMS-R (Wechsler, 1987). The Visual Reproduction subtest from the WMS-R (Wechsler, 1987) was used as a measure of visual memory.

The assessed cognitive functions and neuropsychological test variables used in Studies I-IV are summarized in Table 3.

Table 3. Neuropsychological test variables and assessed cognitive functions in Studies I-IV

Neuropsychological tests	Variables	Studies
Verbal ability		
Vocabulary (WAIS-R)	Total raw score	I-IV
Similarities (WAIS-R)	Total raw score	II
Visuoconstructional functions		
Block Design (WAIS-R)	Total raw score	II
Psychomotor and information processing speed		
Digit Symbol (WAIS-R)	Total raw score	I-IV
Attention and working memory		
Digit Span Forward (WMS-R)	Total raw score	I-IV
Digit Span Backward (WMS-R)	Total raw score	I-IV
Visual Span Forward (WMS-R)	Total raw score	I-IV
Visual Span Backward (WMS-R)	Total raw score	I-IV
Verbal learning and memory		
Immediate learning and recall		
Learning trials 1-5 (total) (CVLT)	Total number of words in trials 1-5	I-IV
Learning slope (CVLT)	Increment in words recalled per trial	I, IV
Free short-delay recall (CVLT)	Immediate total score	I, III, IV
Clued short-delay recall (CVLT)	Immediate cued total score	I, III, IV
Short-delay retention /Interference (CVLT)	Ratio (%) of total score in short-delay free recall vs. total score of trial 5 of list A	I-IV
Logical memory (WMS-R)	Immediate total score	II
Delayed memory recall		
Free delayed recall (CVLT)	Delayed total score	I, III, IV
Cued delayed recall (CVLT)	Delayed cued total score	I, III, IV
Long-delay retention (CVLT)	Ratio (%) of total score in short-delay free recall vs. long-delay free recall	II
Recognition memory (CVLT)	Discriminability index of CVLT (%)	I-III
Logical memory (WMS-R)	Delayed total score	II
Learning strategies and errors		
Semantic clustering (CVLT)	Semantic clustering ratio (%)	I-IV
Perseverations (CVLT)	Total number of perseveration errors in CVLT	I-III
Intrusions (CVLT)	Total number of intrusion errors in CVLT	I-III
Visual memory immediate and delayed		
Visual reproduction (WMS-R)	Immediate total score	II
Visual reproduction (WMS-R)	Delayed total score	II
Attention and executive functions		
Trail Making Part A	Time and ratio of correct performances (%)	I, III, IV
Trail Making Part B	Time and ratio of correct performances (%)	I, III, IV
Trail Making Part B – Part A	Time B – time A	I-IV
Stroop Interference Score	Interference score calculated by formula provided by Golden (1978)	II
Category fluency	Total number of animal names	II
Phonemic fluency	Total number of words beginning with S and K	II

WAIS-R = Wechsler adult Intelligence Scale - Revised, WMS-R= Wechsler Adult Memory Scale - Revised, CVLT = California Verbal Learning Test, TMT=Trail Making Test.

3.5 Statistical analyses

In Studies I, III and IV, neuropsychological test performance between the groups was compared using the generalized estimating equation (GEE) model, which estimates population-averaged regression coefficients while controlling for the correlation due to family data (Zeger & Liang, 1986). In Studies I and III, analyses were done using the Stata statistical software, version 8.2 (StataCorp, 2003), and in Study IV using the program R (Team RDC, 2008). All models were adjusted for age and sex.

In Studies II and III, the additive genetic heritability of cognitive traits was estimated using the Solar computer package (Almasy & Blangero, 1998). Heritability measures the relative contributions of differences in genetic and non-genetic factors to the total phenotypic variance in a population. The heritability estimate (h^2) in the additive genetic model is proportion of variance due to the additive effect. The continuous raw scores from the neuropsychological tests were considered as the phenotypes, instead of the dichotomous affected vs. unaffected diagnosis. Variables that were not normally distributed were transformed to approximate normality. Age, sex, and a lifetime history of psychotic symptoms were used as covariates.

In Studies I, III and IV, statistical differences were considered significant under p-value ≤ 0.01. P-value ≤ 0.05 was considered as indicative of significance. In Study II, we counted a conservative Bonferroni correction ($p = 0.05/23$), and considered $p < 0.002$ significant. Results at $p < 0.05$ to $p > 0.002$ were considered as indicative of significance.

3.5.1 Study I

In the Study I, neuropsychological test performance was compared with GEE model between the three groups (patients, relatives and controls). The analyses were also done without 9 patients in partial remission to control for the effect of residual mood effects.

3.5.2 Study II

In Study II, the additive genetic heritability of cognitive traits was estimated in bipolar I disorder families. As 25 families out of the 52 were part of altogether six larger pedigrees rich in bipolar I disorder, pedigree structure was included in all analyses. The ascertainment correction, which considered all bipolar I disorder patients as probands, was incorporated in the analyses.

As five subjects were on acute episodes during the assessment, the analyses were also done adding acute illness status as a covariate in the above mentioned models.

Moreover, the effects of psychotropic medication on heritability estimates were analyzed separately adding lithium use and antipsychotics use as covariates in models.

3.5.3 Study III

In Study III, in first phase, neuropsychological test performance was compared between the five groups (bipolar I disorder patients and relatives from bipolar families, bipolar I disorder patients and relatives from mixed families, and controls) using the GEE model. As nine patients were in partial remission during the assessment, additional analyses were done without these patients to control for the effect of residual mood symptoms. In addition, as three bipolar families had family members with other psychotic disorders, additional analyses were done without these families. In second phase, the additive genetic heritability of cognitive functions was estimated separately in bipolar families and in mixed families.

3.5.4 Study IV

In Study IV, neuropsychological test performance between the patients, relatives and controls was compared using the GEE model. All models were adjusted for the raw score in the Digit Symbol test. In the first phase, the effect of processing speed on other cognitive functioning was analyzed in between group comparisons. In the second phase, the effect of processing speed on other cognitive functions was analyzed separately within the groups.

4 RESULTS

4.1 Cognitive functioning in patients with bipolar I disorder and their relatives (Study I)

The groups did not differ significantly in age, sex and education (Study I, Table 1, page 682). Means and standard deviations of the neuropsychological variables are shown in Table 4.

In GEE models with age and sex as covariates, patients and relatives did not differ significantly from controls in verbal ability while relatives scored slightly better than patients (Table 3, and see also Study I, Table 3, page 684). Both patients and relatives performed worse than the controls in psychomotor processing speed. In addition, patients performed worse than relatives in task assessing psychomotor processing speed.

In the TMT, patients were slower than controls in completing both Parts A and B, and also in the measures of executive functioning (Part B minus Part A time and performance quality in TMT Part B) (Table 3). The relatives performed worse than controls in the performance quality of TMT Part B, and patients were slower than relatives in TMT Part B, but these differences were only indicative of significance.

No differences were detected between the groups in tests of attention and working memory.

In the CVLT, patients performed worse than controls in all other measures of verbal learning and memory except in the number of recall errors (perseverations and intrusions) or in the forgetting/retroactive interference score (Table 3, and Study I, Table 3, page 684). Patients performed worse than relatives in total learning, learning slope, cued short recall, free and cued delayed recall. In semantic clustering the difference between patients and relatives was indicative of significance. Relatives did not differ significantly from controls in any of the CVLT measures.

In subsequent analyses of euthymic patients (n = 23) only, the results remained similar to those concerning the whole sample (n = 32), although the statistical significances decreased.

Table 4. Neuropsychological test performance of patients with bipolar I disorder, first-degree relatives and controls

	Patients (N = 32)	Relatives (N=40)	Controls (N =55)	Statistical differences in neuropsychological tests (adjusted with age and sex)
Variables	Mean (SD)	Mean (SD)	Mean (SD)	
Verbal ability and psychomotor processing speed (WAIS-R)				
Vocabulary	38.4 (13.4)	43.0 (12.1)	41.0 (10.7)	R > B*
Digit Symbol	36.2 (15.5)	43.4 (13.8)	49.7 (14.5)	B < C***, R*** R < C**
Attention and working memory (WMS-R)				
Digit Span forward	7.5 (2.2)	7.3 (2.1)	7.4 (1.7)	NS
Digit Span backward	5.7 (2.4)	5.7 (1.9)	6.0 (1.8)	NS
Visual Span forward	7.7 (1.9)	7.7 (1.5)	8.2 (1.9)	NS
Visual Span backward	6.9 (2.5)	7.1 (1.8)	7.8 (1.7)	NS
Verbal Learning (CVLT)	(N = 32)	(N = 39)	(N = 54)	
Learning trials 1-5 (total)	41.1 (10.7)	47.7 (10.5)	49.0 (10.2)	B < C***, R***
Learning slope	1.0 (.49)	1.4 (.59)	1.3 (.59)	B < C*, R**
Free short recall	8.7 (3.3)	9.9 (3.2)	10.5 (3.2)	B < C**
Cued short recall	9.4 (2.8)	11.2 (2.4)	11.4 (2.7)	B < C***, R***
Free delayed recall	8.5 (3.2)	10.6 (3.1)	10.9 (3.3)	B < C***, R***
Cued delayed recall	9.0 (3.1)	11.5 (2.6)	11.4 (3.0)	B < C***, R***
Interference	-.13 (.30)	-.17 (.18)	-.11 (.23)	NS
Recognition	89.8 (6.9)	92.4 (8.1)	94.4 (5.7)	B < C***
Semantic clustering	10.4 (6.5)	14.1 (8.4)	15.7 (9.2)	B < C***, R*
Perseverations	2.0 (1.9)	1.9 (2.1)	2.2 (2.4)	NS
Intrusions	.53 (1.0)	.64 (1.3)	.80 (1.3)	NS
Attention and Executive functions				
Trail Making Test				
	(N = 30)	(N = 36)	(N = 53)	
Part A (time)	44.0 (15.2)	38.8 (17.6)	34.6 (13.6)	BP < C***
Part A (% correct)	65.6	72.5	80.0	NS
	(N = 25)	(N = 35)	(N = 53)	
Part B (time)	120.0 (57.5)	99.8 (41.7)	89.0 (41.9)	BP < C***, R*
Part B (% correct)	37.5	47.5	69.1	BP < C**; R< C*
Part B-A (time)	77.0 (48.9)	62.5 (35.6)	55.0 (39.1)	BP < C**

Values are means (standard deviations) of neuropsychological raw scores.
B = bipolar I disorder patient, R = relatives, C = controls.
WAIS-R = Wechsler adult Intelligence Scale - Revised, WMS-R= Wechsler Adult Memory Scale - Revised, CVLT = California Verbal Learning Test, TMT=Trail Making Test.
* $p \leq 0.05$ = indicative, ** $p \leq 0.01$ = significant, ***$p \leq 0.001$ = very significant

4.2 Heritability of cognitive functions in bipolar families (Study II)

4.2.1 Heritability

In the additive models with age, sex and lifetime psychosis as covariates (Study II, Table III, page 806), significant heritability was found in the Vocabulary task ($h^2 = 0.96$, $p = 0.000002$), in the Digit Symbol task ($h^2 = 0.72$, $p = 0.0008$), in the Visual Span Backward task ($h^2 = 0.69$, $p = 0.0009$), in the Digit Span Backward task ($h^2 = 0.69$, $p = 0.001$), in the delayed recall of visual memory ($h^2 = 0.65$, $p = 0.001$), and in the Stroop Color and Word Test interference score ($h^2 = 0.58$, $p = 0.0004$).

4.2.2 Effect of current affect status and medication

After adding the current affect status (in remission vs. acute) as an additional covariate in the above mentioned models the results remained similar (data not shown), except that the heritability in the Digit Span Backward task slightly diminished ($h^2 = 0.59$, $p = 0.005$).

After adding also lithium use as a covariate in the models the results remained unchanged. However, adding antipsychotic use as covariate, a slight decrease in the heritability estimates was observed in the Visual Span Backward task ($h^2 = 0.52$, $p = 0.003$) and in the delayed recall of visual memory ($h^2 = 0.44$, $p = 0.006$). Otherwise the results remained similar.

4.3 Cognitive functioning and their heritability in patients and their relatives from bipolar and mixed families (Study III)

4.3.1 Neuropsychological test comparisons in bipolar and mixed families

In Study III, the unaffected relatives from mixed families were significantly younger than the unaffected relatives from bipolar families and controls (Study III, Table 2, page 72). There were no statistically significant differences between the groups in education and sex distribution, and the two patient groups did not differ in the assessed clinical characteristics. Both patient groups had lower global functioning as assessed using the GAF than unaffected relatives and controls. In addition, patients from mixed families had lower GAF ratings than patients from families with bipolar disorder only.

Means and standard deviations of the neuropsychological variables are shown in Table 5.

Table 5. Neuropsychological performances of patients with bipolar I disorder, relatives and controls in bipolar and mixed families

	B1 (N = 20)	R1 (N = 36)	B2 (N = 19)	R2 (N = 28)	Controls (N = 55)	Statistical differences[1]
Variable	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Verbal ability and psychomotor processing speed (WAIS-R)						
Vocabulary	41.7 (12.7)	43.3 (12.6)	37.4 (13.7)	42.5 (8.8)	41.0 (10.7)	NS
Digit Symbol	38.5 (14.0)	40.9 (13.7)	36.5 (16.6)	47.6 (11.3)	49.7 (14.5)	B1, B2 < C***; R1, R2 < C**
Attention and working memory (WMS-R)						
Digit Span forward	7.4 (2.2)	7.3 (2.0)	7.2 (2.5)	7.1 (1.7)	7.4 (1.7)	NS
Digit Span backward	6.0 (2.4)	5.6 (1.8)	5.2 (2.3)	5.9 (2.0)	6.0 (1.8)	NS
Visual span forward	7.8 (1.7)	7.6 (1.5)	8.0 (2.0)	8.5 (1.8)	8.2 (1.9)	B2 < C*
Visual span backward	7.8 (1.9)	7.1 (1.6)	6.8 (3.0)	7.8 (2.0)	7.8 (1.7)	NS
Verbal Learning (CVLT)	(N = 20)	(N = 35)	(N = 19)	(N = 28)	(N = 54)	
Learning trials 1-5 (total)	40.8 (9.1)	46.4 (11.0)	44.7 (11.5)	50.8 (7.8)	49.1 (10.3)	B1 < C***; B2 < C*
Free short recall	8.5 (3.2)	9.5 (3.5)	9.5 (2.9)	11.1 (2.1)	10.5 (3.2)	B1 < C**
Cued short recall	9.0 (2.8)	10.9 (2.7)	10.2 (2.4)	12.2 (1.8)	11.4 (2.7)	B1 < C***; B2 < C*
Free delayed recall	8.3 (3.1)	10.3 (3.1)	9.5 (2.9)	11.9 (2.1)	10.9 (3.3)	B1 < C***; B2 < C**
Cued delayed recall	9.0 (2.5)	11.2 (2.8)	9.6 (3.3)	12.5 (2.0)	11.3 (3.0)	B1 < C***; B2 < C*
Interference	- 0.2 (0.3)	- 0.2 (0.2)	- 0.03 (0.3)	- 0.1 (0.1)	- 0.1 (0.2)	NS
Recognition memory	0.89 (0.1)	0.92 (0.1)	0.92 (0.01)	0.96 (0.03)	0.94 (0.1)	B1 < C**; B2 < C*; R1 < R2*
Semantic clustering (ratio)	1.4 (0.4)	1.6 (0.8)	1.6 (0.8)	2.0 (0.6)	1.8 (0.7)	B1 < C**; R1 < R2*
Perseverations	2.0 (2.0)	2.3 (2.4)	2.0 (1.8)	2.8 (3.4)	2.2 (2.4)	NS
Intrusions	0.8 (1.2)	0.8 (1.3)	0.6 (1.1)	0.8 (1.4)	0.8 (1.3)	NS
Attention and Executive functions (TMT)	(N = 19)	(N = 33)	(N = 17)	(N = 27)	(N = 53)	
Part A (time)	42.2 (13.7)	41.0 (20.0)	44.2 (14.7)	33.5 (9.7)	34.6 (13.6)	B1 < C***; B2 < C***
Part A (% correct)	78.9	84.8	58.8	81.5	83.0	B2 < C**
	(N = 18)	(N = 31)	(N = 13)	(N = 27)	(N = 52)	
Part B (time)	117.6 (54.2)	106.2 (51.9)	122.5 (67.0)	95.2 (38.9)	89.0 (41.9)	B1 < C**; B2 < C**; R2 < C*
Part B (% correct)	52.6	51.6	29.4	70.4	71.7	B2 < C***; R1 < C**
Part B-A (time)	77.3 (49.4)	67.9 (42.0)	79.5 (57.6)	61.6 (37.6)	55.0 (39.1)	B1 < C*; B2 < C**

Values are means (standard deviations) of neuropsychological raw scores, [1]adjusted with age and sex, B1 = bipolar I patients from bipolar families, R1 = relatives from bipolar families, B2 = bipolar I patients from mixed families, R2 = relatives from mixed families, WAIS-R = Wechsler Adult Intelligence Scale – Revised, WMS-R = Wechsler Adult Memory Scale – Revised, CVLT = California Verbal Learning Test, TMT = Trail Making Test, * $p \leq 0.05$ = indicative, ** $p \leq 0.01$ = significant, ***$p \leq 0.001$ = very significant

In GEE models with age and sex as covariates, there were no significant differences between the groups in verbal ability assessed with the Vocabulary test (Table 5, and see also Study III, Table 4a and 4B pages 74 and 75). Both groups of patients and relatives were significantly slower in psychomotor processing speed than controls measured with the Digit Symbol test. However, neither the patient groups nor the groups of relatives differed from each other.

There were no significant group differences in tasks assessing verbal and visual attention or verbal and visual working memory (Table 5).

Bipolar patients from families with only bipolar I disorder performed significantly worse than controls in nearly all measures of verbal learning and memory (Table 5). Bipolar patients from mixed families were significantly worse than controls in free delayed recall of the CVLT. In total learning, cued short and delayed recalls, and recognition, bipolar patients from mixed families scored lower than controls, but the difference was only indicative of significance. There were no significant differences between the two patient groups in any measures of verbal learning and memory.

There were no significant differences between the relative groups and controls in any measures of verbal learning and memory (Table 5). Relatives from bipolar families performed significantly worse than relatives from mixed families in recognition memory, and they used fewer semantic categories as learning strategies than relatives from mixed families, although these statistical differences were indicative of significance only.

Both patient groups were significantly slower than controls in both parts A and B of TMT (Table 5). Bipolar patients from mixed families made significantly more errors than controls in both parts A and B, and were also slower in the TMT part-B-minus-part-A score. The difference between patients from bipolar families and controls in the latter part was indicative of significance. The relatives from bipolar families made more errors than controls in TMT part B while the relatives from mixed families were slower than controls (Table 5). Neither the patient groups nor the groups of relatives differed from each other.

In subsequent analyses of euthymic bipolar patients only, the results remained similar to those from the whole sample, although the statistical significance weakened due to smaller samples (data not shown).

In subsequent analyses without bipolar families that had family members with other psychosis (three families with two bipolar I patients and two unaffected

relatives) results remained essentially similar to those from the whole sample (data not shown).

4.3.2 Heritability of cognitive functions in bipolar and mixed families

In the additive model with age, sex and lifetime psychosis as covariates (Study III, Table 5, page 76), in bipolar families, significant heritability was estimated in perseverative recall errors in the CVLT ($h^2 = 0.84$, $p = 0.002$) and in TMA time score ($h^2 = 0.88$, $p = 0.006$). In addition, indicative significance in heritability estimates was evidenced in the Vocabulary task ($h^2 = 0.60$, $p = 0.02$), in the Digit Symbol task ($h^2 = 0.48$, $p = 0.05$), in the Visual Span ($h^2 = 0.38$, $p = 0.05$) and in the Digit Span Backward tasks ($h^2 = 0.49$, $p = 0.03$), and in the free and cued delayed recalls of the CVLT task ($h^2 = 0.49$, $p = 0.05$; $h^2 = 0.47$, $p = 0.05$, respectively).

In mixed families, significant heritability estimates were detected in the Vocabulary task ($h^2 = 0.82$, $p = 0.0001$), in the Visual Span ($h^2 = 1.0$, $p < 0.0001$) and in the Digit Span Backward ($h^2 = 0.68$, $p = 0.001$) tasks, and in the long-delay cued recall of the CVLT task ($h^2 = 0.65$, $p = 0.007$). In addition, indicative significances were found in the Digit Symbol task ($h^2 = 0.38$, $p = 0.05$) and Visual Span Forward task ($h^2 = 0.42$, $p = 0.03$).

4.4 The effect of processing speed on cognitive functioning in patients and their relatives (Study IV)

4.4.1 Effect of processing speed in between group comparisons

The effect of processing speed in the GEE models was significant on most of the other neuropsychological test scores (Study IV, Table 2, page 42). In these models, differences indicative of significance between patients and controls were detected in short-delay cued recall ($p \leq 0.05$), long-delay free and cued recalls (both p values ≤ 0.05) with the patients scoring lower than the controls, and in auditory attention ($p \leq 0.05$) in which the patients outperformed the controls (Study IV, Table 3, on page 43). The patients performed worse than their relatives in short-delay cued recall ($p \leq 0.01$), in long-delay free and cued recalls (both p values ≤ 0.01), and in the learning slope ($p \leq 0.05$). In verbal ability, the relatives scored better than the controls ($p \leq 0.01$).

4.4.2 Effect of processing speed in within group comparisons

In the models separately in each group, the effect of processing speed differed by group being most extensive in patients, then in relatives and smallest in controls (Study IV, Table 2, page 42).

In patients, the effect of processing speed was significant in verbal ability ($p < 0.0001$), in verbal working memory ($p = 0.001$), in visual attention ($p = 0.009$), in verbal learning ($p < 0.0001$), in short-delay free recall ($p < 0.0001$), in long-delay free ($p < 0.0001$) and cued ($p = 0.0002$) recalls, in semantic clustering ($p = 0.0005$), in timed measures of TMT Part A ($p < 0.0001$), TMT Part B ($p < 0.0001$) and TMT Part B-A ($p < 0.0001$), and performance quality in TMT Part B ($p = 0.01$).

In relatives, the effect of processing speed was significant in verbal attention ($p < 0.0001$) and working memory ($p < 0.0001$), in visual attention ($p = 0.003$), in learning ($p = 0.004$), in short-delay free recall ($p = 0.008$), in semantic clustering ($p = 0.004$), in timed measures of TMT Part A ($p < 0.0001$), TMT Part B ($p < 0.0001$) and TMT Part B-A ($p = 0.004$). In addition, the effect of processing speed was indicative of significance in verbal ability ($p = 0.04$), in visual working memory ($p = 0.03$) and in cued short-delay recall ($p = 0.02$).

In controls, the effect of processing speed was significant in verbal ability ($p = 0.002$), verbal working memory ($p = 0.008$), in timed measures of TMT Part A ($p < 0.0001$), TMT Part B ($p = 0.0003$) and TMT Part B-A ($p = 0.009$). In addition, the effect of processing speed was indicatively significant in learning ($p = 0.04$).

5 DISCUSSION

The aim of the present study was to investigate cognitive functioning and its heritability in bipolar I disorder patients and their unaffected first-degree relatives originating from families affected by more than one bipolar patient, focusing on identifying possible neuropsychological endophenotypes for bipolar I disorder. First, cognitive functioning was compared with a neuropsychological test battery in population-based samples of bipolar I disorder patients, their first-degree relatives, and healthy control group with no family history of psychotic disorders. Then, the heritability of different cognitive functions in bipolar disorder families was estimated. After this, cognitive functioning and its heritability was assessed in bipolar I disorder patients and their unaffected relatives in a group of families affected with bipolar I disorder only (bipolar families) and another group of families affected both with bipolar I disorder and schizophrenia or schizoaffective disorders (mixed families). The final aim was to investigate the effect of the potential endophenotype, processing speed, on other cognitive functions in bipolar disorder patients, their relatives and controls.

5.1 Cognitive functioning in bipolar I disorder patients and their relatives

In Study I, both the bipolar I disorder patients and their unaffected relatives from familial population-based sample were found to be impaired in the task measuring psychomotor processing speed. In addition, both patients and relatives performed worse than controls in the executive task, although this difference was only indicative of significance in the relatives. In the task assessing verbal learning and memory (CVLT), relatives were not impaired. However, bipolar I disorder patients were found to have deficits in nearly all measures of verbal learning and memory compared with both their unaffected first-degree relatives and the controls. There were no difference between the groups in the simple attention and working memory tasks.

The results of Study I suggested that the impairment of psychomotor processing speed may indicate an association with vulnerability to the illness, and to be a potential endophenotype of bipolar disorder. The results are in line with previous study of Pierson et al. (2000), who found that relatives of multiple affected bipolar families had slower sensory-motor processing speed than controls, although contrasting results are found in another study of relatives of familial bipolar disorder (McIntosh et al., 2005a). In addition, there is evidence that processing speed is

highly heritable (Luciano et al., 2001), and slowness in processing speed is associated with changes in white matter volume of the brain (Gunning-Dixon & Raz, 2000), which are often found in bipolar disorder patients (Bearden et al., 2001; Kempton et al., 2008) and also in their unaffected relatives (Kieseppä et al., 2003; McDonald et al., 2004a).

The finding that executive functioning may also be a potential endophenotype accords with some previous studies that have found that unaffected relatives are impaired in some measures of executive functions (Ferrier et al., 2004; Clark et al., 2005b; Zalla et al., 2004; Juselius et al., 2009), but not all (Keri et al., 2001; Kremen et al., 1998; Kravariti et al., 2009b).

According to Study I, verbal learning and memory impairments seemed to be more related to the fully developed disorder, as only bipolar I disorder patients were affected in these functions compared also with their relatives. In contrast with this study, some previous studies have found evidence in verbal learning and memory impairment also in relatives (Gourovitch et al., 1999; Keri et al., 2001; Sobczak et al., 2003; Kieseppä et al., 2005; McIntosh et al., 2005a; Quraishi et al., 2009), although not all (Kremen et al., 1998; Ferrier et al., 2004; Clark et al., 2005b; Bora et al., 2008; Jabben et al., 2009). Moreover, there is still some controversy whether the impairment in verbal learning and memory in patients is more related to other illness factors (Robinson & Ferrier, 2006), executive or working memory problems (Deckersbach et al., 2004) or impairment in processing speed (Kieseppä et al., 2005). Still, many previous studies have found verbal learning and memory problems in bipolar I disorder patients (Arts et al., 2008; Bora et al., 2009a), according with Study I.

Results of the Study I suggested that, psychomotor processing speed and possibly executive functioning may represent endophenotypes of bipolar I disorder. Impairments in both cognitive functions were associated with the illness, and these impairments were state independent as the patients were mainly euthymic. Impairments in these functions were also found in non-affected family members at a higher rate than in the general population. In Study I, the impairment in processing speed and in executive function seemed to support the endophenotype criteria 2, 3, 4 and 5. In turn, verbal memory impairment seemed to be more related to the fully developed disease.

5.2 Heritability of cognitive functions in bipolar families

In Study II, the aim was to assess the fundamental criterion for neuropsychological endophenotypes, their heritability, which has remained relatively unstudied in bipolar disorder. This was done by estimating additive heritability of cognitive functions in a population-based sample of Finnish families with bipolar I disorder. The aim was to investigate the heritability of functions (verbal memory, executive functions) where previous studies have evidenced impairments in both affected and unaffected relatives of bipolar disorder (Keri et al., 2001; Ferrier et al., 2004; Sobczak et al., 2003; Zalla et al., 2004; Clark et al., 2005b; Kieseppä et al., 2005; McIntosh et al., 2005a; Robinson & Ferrier, 2006; Quraishi et al., 2009), and to investigate whether these impairments are heritable in bipolar disorder families. As the Study I showed that both affected and unaffected family members were impaired in psychomotor processing speed and both scored lower than controls in executive functioning, these functions were expected to be highly heritable. In line with the expectations, the significant additive heritabilities were found for verbal ability, psychomotor processing speed, and executive functioning (sensitivity to interference). Moreover, heritability was significant for verbal and visual working memory and for delayed visual memory.

Measures that assessed verbal learning, learning strategy, and short-delay or long-delay retention of verbal material did not show significant genetic effects in this population. This result is in line with Study I in which only patients were impaired in these functions compared both with their unaffected relatives and with controls, suggesting that verbal learning and memory impairments might be more an illness state than a genetic trait variable. In addition, there is evidence that impairment in verbal memory may be related to various illness factors, for example number of manic episodes and the length of illness while for example executive dysfunctions are less consistently related to illness features (Cavanagh et al., 2002; Robinson & Ferrier, 2006). In other studies, long-delay memory has been found to be impaired among unaffected relatives (Gourovitch et al., 1999; Keri et al., 2001; Kieseppä et al., 2005; Quraishi et al., 2009), but in this population, the heritability estimate of it was non-significant. The result is in line with a previous study of schizophrenia in which components of verbal learning and memory reflected non-genetic influences (Tuulio-Henriksson et al., 2002). In addition, although a recent study of bipolar disorder population found that verbal learning and memory performance (CVLT) was heritable and impaired in individuals with bipolar disorder, nonbipolar first-degree relatives did not statistically differ from healthy subjects in this task (Glahn et al., 2010).

The finding of significant additive heritability in psychomotor processing speed agrees with previous studies in which a substantial genetic component in this func-

tion has been found among individuals without psychiatric disorders (Posthuma et al., 2003; Finkel et al., 2005), and also in bipolar disorder families (Glahn et al., 2010). Processing speed has been suggested to be genetically related to white matter volume, and part of the genes that influence axonal myelination are likely to be common to the genes that influence processing speed (Posthuma et al., 2003). So far, only few studies have investigated associations between slowed processing speed and white matter abnormalities in bipolar disorder, and evidence from those is still somewhat controversial and preliminary. One study found that patients with bipolar disorder with more pronounced white matter lesions are more impaired in cognitive functioning, including psychomotor speed (Dupont et al., 1995b), but this was not evidenced in another study (Krabbendam et al., 2000).

In Study II, executive functioning, especially vulnerability to interference, showed a marked genetic contribution. Furthermore, all tasks reflecting executive functioning showed heritabilities at least indicative of significance. In recent meta-analytic studies, most pronounced impairments in euthymic bipolar patients have been reported in executive functioning. However, not all executive functions are equally impaired, and patients do not seem to have a broad dysexecutive syndrome (Robinson & Ferrier, 2006). In addition, unaffected relatives of bipolar disorder have been found to have deficits in executive functioning, especially in the Stroop task assessing response inhibition (Arts et al., 2008; Bora et al., 2009a; Juselius et al., 2009), which was also found to show large heritability in Study II. In Study I, both bipolar I disorder patients and their unaffected relatives had some impairment in the task assessing executive functioning (TMT B).

In addition to psychomotor processing speed and executive functioning, visual and verbal working memory showed a significant genetic contribution in Study II. Previously, these functions have been found to be significantly genetic in general population (Ando et al., 2001), and deficits in these functions have high heritabilities in schizophrenia (Cannon et al., 2000; Tuulio-Henriksson et al., 2002), and also in bipolar disorder (Glahn et al., 2010). Although there is one study, that has found visual working memory to be highly heritable in bipolar disorder, and impaired both in bipolar patients and their nonbipolar relatives (Glahn et al., 2010), the evidence about the genetic influence and working memory impairment is still relatively sparse and controversial. Moreover, in unaffected relatives of bipolar disorder, only few studies have found impairment in these functions (Ferrier et al., 2004; Bora et al., 2009a), while others have not (Keri et al., 2001; Kieseppä et al., 2005). Working memory functions have a high component of executive processes, and may therefore reflect more the deficit and heritability of executive functioning than storage and working memory per se (Thompson et al., 2006). Thus, more

studies are required before the question of whether working memory impairment is associated with the risk for bipolar disorder can be addressed.

Long-delay visual memory also showed a marked heritability in this population, which partly agrees with the study by Glahn et al. (2010) that found that declarative (facial) memory was heritable, impaired in individuals with the illness and in their unaffected relatives, and genetically correlated with affection status. However, previous studies that examined this function in unaffected twins of bipolar patients with the same task did not found impairment in this function or any implication of the genetic effect (Gourovitch et al., 1999; Kieseppä et al., 2005). Very few studies have measured visual memory of patients with bipolar disorder, and their relatives, and more studies are needed to draw conclusions of this question.

The influence of genetic factors on general intelligence is rather well established in previous studies on general populations (Devlin et al., 1997; Plomin & Spinath, 2004). Intelligence as measured using the Vocabulary task, considered to be the best single measure of both verbal and general mental abilities (Lezak et al., 2004), and showed a significant heritability in the present study. However, intelligence involves many discrete cognitive processes and a range of genetic and environmental influences, and therefore, it may not be an effective endophenotype. Moreover, general intelligence has not usually been found to be impaired among patients with bipolar disorder or their relatives (McIntosh et al., 2005a; Arts et al., 2008; Kumar & Frangou, 2010).

Results of the Study II suggested that there is a strong genetic contribution to verbal ability, psychomotor processing speed, and executive functions in bipolar disorder families. In Study I, impairments in these functions, particularly in executive functions and psychomotor processing speed, were found in both bipolar patients and in their unaffected first-degree family members. The Study I and II, therefore, implicate that these may be traits with major genetic component. In contrast, verbal learning and memory did not show a genetic component. Current knowledge of the functioning of working memory and visual long-term memory among subjects with vulnerability to bipolar disorder is limited, and more studies need to be conducted for evaluating the genetic contribution of these functions.

5.3 Are cognitive functioning and its heritability different depending on the other severe mental disorders in the families?

In Study III, the aim was to examine cognitive functioning and their heritability in bipolar I disorder patients and their unaffected relatives in a group of families affected with bipolar I disorder only (bipolar families) and another group of families affected both with bipolar I disorder and schizophrenia or schizoaffective disorders (mixed families). The expectation was that bipolar I disorder patients and unaffected relatives from mixed families would show a more generalized cognitive impairment than those from bipolar families implicating some genetical loading from schizophrenia. Contrary to the expectations, bipolar I disorder patients from mixed families scored worst only in executive functioning, and bipolar I disorder patients from bipolar families were impaired in executive functioning as well. In addition, the two patient groups did not differ significantly from each other in this function. Both groups of relatives performed slightly worse than controls in executive functioning, but the groups did not differ from each other.

The finding of impairment in executive functioning in both patient groups as well as in both relative groups, although to a lesser degree, is in accordance with the recent meta-analytic studies (Arts et al., 2008; Bora et al., 2009a). These results, along with Studies I, II and III, support the potential role of executive dysfunction as an endophenotype of bipolar disorder. Moreover, our finding of more pronounced abnormalities in executive functioning in patients belonging to mixed families may reflect vulnerability to psychotic disorders in general, as bipolar patients with history of psychosis have been found to be more impaired on executive functioning compared with non-psychotic bipolar patients (e.g. Glahn et al., 2007; Martinez-Aran et al., 2008).

The results concerning verbal learning and memory were contrary to our expectation, as bipolar I patients from families affected both by schizophrenia or schizoaffective disorder and bipolar I disorder were impaired only in delayed free verbal recall, while bipolar I patients from families with bipolar I disorder were impaired in nearly all verbal learning and memory variables. Unaffected relatives from bipolar and mixed families did not differ from controls in any measure of verbal learning and memory. Our results are in line with recent meta-analysis that have shown that bipolar patients have verbal memory impairments (Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008; Bora et al., 2009a). However, the results of Study III, partly confirms the results of Studies I and II that verbal memory impairment in bipolar patients may be more related to other factors than genetic effects of bipolar disorder as the two patients groups had somewhat differing profile in impairment of verbal learning. Both patients groups had impairment in

long-delay memory and particularly delayed verbal memory has been found to be impaired also among unaffected relatives of bipolar disorder patients (Gourovitch et al., 1999; Keri et al., 2001; Kieseppä et al., 2005; Arts et al., 2008).

Bipolar I disorder patients and relatives performed worse than controls in the psychomotor processing speed irrespective of psychopathology within the family. This is partly in accordance with previous findings of schizophrenia and bipolar disorder patients and their unaffected relatives belonging to families affected by schizophrenia and bipolar disorder alone and from families affected by both disorders (McIntosh et al., 2005a). In that study, psychomotor processing speed was impaired in all patients regardless of diagnoses in the family. However, in that study only unaffected relatives from schizophrenia families were impaired in this function. In line with these results, independently of the specific diagnosis, bipolar I disorder and schizophrenia patients with positive family history of psychosis have been found to be more impaired than patients without family history of psychosis on visual motor processing and attention domain (Tabares-Seisdedos et al., 2003). In that study, the only predictor of belonging to the group with positive family history of psychosis was poor performance on task assessing psychomotor processing speed (the Digit Symbol task) (Tabares-Seisdedos et al., 2003). However, our findings somewhat contradict with the recent meta-analysis of neuropsychological deficits in euthymic bipolar disorder patients and their first-degree relatives (Bora et al., 2009a), in which impairments in psychomotor processing tasks were relatively large among patients with bipolar disorder, while first-degree relatives were mostly unimpaired in this function.

In bipolar families, significant heritability was estimated in the recall errors of the verbal memory task and simple attention task assessed with the TMA. In mixed families, significant heritability estimates were found in tasks assessing verbal ability, visual and verbal working memory, and long-delayed cued recall. In Study II, executive functioning was found to be highly heritable in bipolar disorder families. As a result of the small samples and the lack of normality and adequate variation of some measures, heritability could not be estimated for all the tasks, unfortunately including the task assessing executive functioning. Due to rather small samples in Study III, the heritability estimates here are considered as indicative only. Basically, however, compared with Study II, the heritability of cognitive functions was here generally similar irrespective of psychopathology in the family. There were, however, greater genetic effects in several cognitive tasks in mixed families. In these families, particularly visual and verbal working memory showed significant genetic effects, possibly reflecting liability for schizophrenia spectrum disorders, as previous studies have indicated significant genetic effects in these functions in schizophrenia (Cannon et al., 2000; Tuulio-Henriksson et al., 2002).

In Study III, only bipolar I disorder patients from mixed families scored lower than controls in verbal working memory. Previous studies have shown that working memory impairment appears to discriminate patients between schizophrenia and bipolar disorder (Goldberg, 1999).

Study III suggest that impaired psychomotor processing speed and executive function may represent vulnerability markers of bipolar I disorder irrespective of psychopathology in the family confirming the results of Studies I and II. However, those patients with family members suffering from schizophrenia or schizoaffective disorders had a more pronounced dysfunction in executive functioning, suggesting that the presence of a more severe psychotic disorder in the family may have an effect on this cognitive function. Generalized impairment in verbal memory, in turn, may associate more with bipolar disorder than to vulnerability to other psychotic disorders.

5.4 Effect of processing speed on other cognitive functions

Studies I, II and III showed that processing speed was the only function that both bipolar patients and relatives were significantly impaired compared to controls irrespective of psychopathology in the families, and it was also highly heritable function. Therefore, we set out to investigate the effect of this function on other cognitive functions in this same population in Study IV. In line with our expectations, we found that processing speed had a significant effect on nearly all other assessed cognitive functions among patients with bipolar I disorder, their unaffected relatives, and controls, all from population-based samples. In all groups, the effect of processing speed was significant on attention and executive functions, and on verbal working memory.

Study IV showed that the effect of processing speed was partly dissimilar depending on the group. Interestingly, the effect of processing speed in memory scores reflecting learning or retrieval was most notable in patients and less so in relatives, and absent in controls. In addition, the effect of processing speed was significant on long-delay recall only in bipolar patients. This may be due to the fact that the impairment in processing speed was greatest in the patients. The effect of processing speed on verbal learning and retrieval has been found also among schizophrenia patients (Brebion et al., 2007), twins with bipolar I disorder (Kieseppä et al., 2005), as well as among healthy (Salthouse, 1994). In our study, processing speed had no effect on memory storage, this result being in line with previous studies.

After adjustment for the effect of processing speed no significant differences were detected between patients and controls. Previously, similar findings have been detected among first-episode schizophrenia-spectrum disorder patients (Rodriguez-Sanchez et al., 2007), and in bipolar I disorder twins and their siblings (Kieseppä et al., 2005). In study of Kieseppä et al. (2005), adjusting for processing speed made the difference between the study groups disappear in working memory and immediate memory tasks, but remain in some delayed recall tasks. In our study, however, there were only differences indicative of significance in short-delay cued recall and long-delay memory. Significant differences between patients and relatives were found in short-delay cued recall and long-delay recall. These results suggest that in bipolar I disorder, short-term memory and learning may be more sensitive to processing speed impairment than long-term memory, in which the impairment may be more independent of processing speed.

The results of Study IV further confirm that impaired processing speed may be a potential endophenotype in bipolar I disorder, and it may contribute to a range of other cognitive dysfunctions seen in bipolar disorder.

5.5 Methodological considerations

5.5.1 Strengths

The study sample was population-based and nationally representative, including familial bipolar I disorder patients, and their unaffected relatives and controls. Results drawn from this study sample offer a strong contribution to the endophenotype literature searching for the genetic etiological factors of bipolar I disorder. Including patients also outside the clinical settings offered this study to represent also less severe types of bipolar I disorder. Including only bipolar I disorder patients in neuropsychological group comparisons allowed assessing homogeneous samples, as many previous studies have included heterogeneous samples of all bipolar spectrum disorders.

The diagnostic procedure was careful and detailed; the subjects were assessed with the SCID on the study day, and all available psychiatric case-notes were collected for the subjects to make the diagnostic procedure more reliable.

5.5.2 Limitations

Several methodological limitations should be considered when evaluating the results of these studies. The study samples included only familial type of bipolar I disorder, and most of the patients suffered from psychotic symptoms in their illness history. This may limit the generalizability of the results of the Studies I-IV

to all patients with bipolar I disorder. In addition, although the samples were larger than those in most previous bipolar disorder high-risk studies, the sample sizes were still small. The power limitations and type II error should therefore be taken into account when interpreting the results. In Studies I, III and IV, we chose not to use multiple corrections because diminishing power in an already low power analysis (relatively small sample size) may have increased the risk of not detecting a true difference. In addition, we used a p value 0.01 as the limit of statistical significance. In Study II, where the sample was a bit larger, we computed a conservative Bonferroni correction, and considered $p < 0.002$ significant.

Another limitation of the study is that current mood state was not assessed with mania or depression rating scales, which would have allowed more careful controlling of current mood state. However, the current and lifetime diagnoses using the SCID were made on the same day as the neuropsychological assessment. In Studies, I, III and IV, all patients with acute conditions were excluded. We included patients who were in partial remission, but additional analyses excluding them did not affect significantly on the results. In Study II, we controlled the acute illness status (in remission vs. acutely depressive) as an additional covariate in the models, and the results remained similar.

In Studies I, III and IV the possible effects of medication on the test performance were not controlled for, and the medication could have effect on cognitive functioning and their heritability estimates. However, there is no consensus about the effect of psychotropic medication on cognition, and similar neuropsychological findings have been found in unmedicated bipolar patients (Macqueen & Young, 2003; Pavuluri et al., 2006). Medication did not confound the comparisons between relatives and controls, and in Study III, the two patients groups did not differ in medication. In Study II, we adjusted the analyses separately for lithium use and found no significant effect on the heritability estimates. After controlling for the use of antipsychotics, the heritability of visual memory functions diminished, but remained indicative of significance.

Concerning relatives and controls, we included some persons with a lifetime, non-psychotic Axis I disorder. However, all persons with current diagnoses were excluded. There is no general consensus, whether to allow some psychopathology that is relatively common in the general population, and reducing psychopathology to near zero rates may lead to selection to atypical samples, with deflated degrees of genetic susceptibility in relatives, and super-normal controls.

The neuropsychological test selection was limited in the present study as no tests of sustained attention were used. In addition, we could not compare long-term

visual memory, visual functions and most of the executive functions with controls as their test battery did not include these measures. In tests of sustained attention, deficits have previously been found in euthymic bipolar patients (Clark & Goodwin, 2004; Thompson et al., 2005), but the evidence is still relatively scarce. In group comparisons, executive functioning was measured using only the TMT. Using more sensitive and different measures in assessing this function, a better vision of executive functioning would have been attained particularly among the unaffected relatives. Another limitation is that the only measure of processing speed was the Digit Symbol task. Processing speed may have been more accurately measured using a computerized method for assessing speed and reaction time. However, in a previous study of twins with bipolar I disorder, the computerized measure of processing speed showed similar effects on memory tasks as the Digit Symbol test (Kieseppä et al., 2005).

6 CONCLUSIONS

The present study investigated neuropsychological endophenotypes of bipolar I disorder in families with bipolar I disorder. The results suggest that particularly executive functioning and psychomotor processing speed fulfill the endophenotype criteria: impairments in these functions were found in bipolar I disorder patients and also in their unaffected relatives, and these cognitive functions were highly heritable in these families. In addition, the results of the study showed that these impairments may represent vulnerability markers or endophenotypes of bipolar I disorder irrespective of psychopathology in the family. Finally, the most potential endophenotype, psychomotor processing speed, seemed to contribute to a range of other cognitive dysfunctions seen in bipolar disorder patients.

The present study also shows that bipolar I disorder patients with family members suffering from schizophrenia or schizoaffective disorders may also have a more pronounced dysfunction in executive functioning, suggesting that the presence of a more severe psychotic disorder in the family may have an effect on this cognitive function. Generalized impairment in verbal memory, in turn, may associate more with bipolar disorder than to vulnerability to other psychotic disorders, and be more related to fully developed disease as the impairments in verbal learning and memory are found only in patients, and were not found to be highly heritable.

This study showed that the executive dysfunction and psychomotor processing speed may be valid endophenotypic traits for genetic studies of bipolar disorder. We have already explored these results in several genetic association studies of bipolar disorder in Finland. These studies have shown that DISC1 risk haplotypes at the 5’ end is associated with memory errors (perseverations) and poorer long-term memory, and for presence of psychotic disorder in Finnish bipolar families (Palo et al, 2007). In addition, several haplotypes at the 3’end of DISC1 gene were associated to bipolar spectrum disorders, and with neuropsychological test performance, particularly in verbal fluency, visuospatial ability, and psychomotor processing speed. In addition, in searching other candidate genes for bipolar and psychotic disorders and their endophenotypes, we found that the COMT gene showed an association for bipolar spectrum disorders, and COMT and DAOA genes were associated with visuospatial ability (Soronen et al, 2008). DAOA showed also association to general ability, psychomotor speed, auditory attention and visual memory. In addition, SNPs in the CDH7 gene have been found to associate with circadian rhythm and seasonality, and with better performance in visual attention and visual working memory (Soronen et al., 2010).

7 FUTURE IMPLICATIONS

Cognitive functions as endophenotypes in complex disorders, including bipolar disorder, have already been tested in genetic association analyses with some evidence of their potential. This work should continue with more homogeneous and statistically more powerful samples than what the present study included. Neuropsychological endophenotype approach may have some advantages compared to another potential endophenotypes (Kravarati et al., 2009), but other well evaluated endophenotypes, such as those drawn from neuroimaging studies, may also prove to be effective in investigating the complex etiology of the highly heritable psychiatric disorders, such as bipolar disorder.

The present study emphasizes also the clinical significance of neuropsychological assessment of bipolar patients. It has been increasingly shown that bipolar disorder patients have neuropsychological impairments affecting their functional outcome, working capacity and psychosocial functioning (Kumar & Frangou, 2010). Although bipolar patients may not suffer from subjective cognitive incapacity, they may still have measurable objective cognitive impairment (Martinez-Aran et al., 2005) that may associate with general functioning. Neuropsychological assessment is suggested to be a part of the clinical evaluation of patients with bipolar disorder, and it would have implications for treatment planning, including psychosocial support and rehabilitation.

In addition, more longitudinal studies need to be constructed to establish whether cognitive impairments in bipolar disorder are stable or whether deterioration in the cognitive functioning occurs. Since recurring episodes in the course of the disorder may worsen cognitive functioning, it is important to prevent episodes for example using psychoeducational methods together with medication treatment. In future, psychosocial interventions and neuropsychological rehabilitation may also be considered more often as an adjunct treatment convention among bipolar patients alongside with optimal psychotrophic treatment. Randomized controlled trials would be helpful in order to establish their efficacy as well as the need to implement these strategies in clinical settings to help these persons with bipolar disorder to better cope with their disorder.

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Cognitive functioning in patients with familial bipolar I disorder and their unaffected relatives

MERVI ANTILA[1]*†, ANNAMARI TUULIO-HENRIKSSON[1]†, TUULA KIESEPPÄ[1,2], MERVI EEROLA[1,3], TIMO PARTONEN[1] AND JOUKO LÖNNQVIST[1,2]

[1] *Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland*; [2] *Department of Psychiatry, University of Helsinki, Finland*; [3] *Department of Mathematics and Statistics, University of Helsinki, Finland*

ABSTRACT

Background. Impairments in verbal learning and memory, executive functions and attention are manifest in some euthymic patients with bipolar disorder (BPD). However, evidence is sparse on their putative role as aetiologically important genetic vulnerability markers for the disorder. This population-based study examined the cognitive functions of affected and unaffected individuals in families with BPD. The aim was to discover whether any cognitive function would indicate genetic liability to the disorder and could thus be regarded as endophenotypes of BPD.

Method. A diagnostic interview and a neuropsychological test battery were administered to 32 familial bipolar I disorder patients, 40 of their unaffected first-degree relatives and 55 controls, all representing population-based samples.

Results. Unaffected first-degree relatives showed impairment in psychomotor performance speed and slight impairment in executive function. Bipolar patients were impaired in verbal learning and memory compared with unaffected relatives and controls. They also differed from controls in tasks of executive functions. There were no difference between the groups in simple attention and working memory tasks.

Conclusions. Impaired psychomotor performance speed and executive function may represent endophenotypes of BPD, reflecting possible underlying vulnerability to the disorder. Verbal memory impairments appear to be more related to the fully developed disorder.

INTRODUCTION

The presence of variable, state-dependent alterations in cognitive functioning during symptomatic phases of bipolar disorder (BPD) has long been recognized. Moreover, recent studies focusing on euthymic BPD patients have demonstrated impairments in measures of executive functions, verbal learning and memory, and sustained attention (Bearden *et al.* 2001; Quraishi & Frangou, 2002; Clark & Goodwin, 2004; Thompson *et al.* 2005). Thus, cognitive impairment may be enduring in some bipolar patients and may present a trait rather than a state variable. However, little is known about the putative role of these dysfunctions as aetiologically important genetic vulnerability markers for BPD.

Although BPD has been shown to be highly heritable in twin, family and adoption studies from various populations (McGuffin *et al.* 2003; Kieseppä *et al.* 2004), the search for the genetic loci of the disorder has been impeded by its complexity. Like other psychiatric disorders, BPD is thought to involve more than one gene and a complex mode of transmission (Craddock & Jones, 2001). Indicators of processes that mediate between the genotype and phenotype,

* Address for correspondence: Mervi Antila, M.Psych., Department of Mental Health and Alcohol Research, National Public Health Institute, Mannerheimintie 166, 00300 Helsinki 30, Finland.
(Email: mervi.antila@ktl.fi)
† These authors contributed equally to this work.

the so-called endophenotypes (Gottesman & Gould, 2003), may aid molecular genetic studies in searching for genes predisposing to BPD (Lenox *et al.* 2002; Gottesman & Gould, 2003). Variables derived from neuropsychological test data may be one type of endophenotype in BPD (Glahn *et al.* 2004). For a cognitive function to be considered as an endophenotype, it must have the following characteristics: (1) heritable, (2) associated with illness, (3) primarily state-independent, (4) impairments and illness co-segregate within families, and (5) the impairment found in affected family members occurs in non-affected members at a higher rate than in the general population (Gottesman & Gould, 2003).

Unlike studies of bipolar patients, studies of their relatives are not confounded to that degree by medication, psychopathology or by other acute or chronic effects of illness. Therefore, assessing the level of impairment in both affected and unaffected family members of BPD may help to ascertain whether the cognitive impairments seen in patients could be considered as endophenotypes of BPD. Relatives of schizophrenia patients have been found to have cognitive deficits similar to schizophrenia patients themselves, differing only in degree (Tuulio-Henriksson *et al.* 2003; Sitskoorn *et al.* 2004). However, there are fewer studies and less evidence of impairments among relatives of bipolar patients, and the findings have been controversial. Some studies have found impairments in learning and memory (Kéri *et al.* 2001; Ferrier *et al.* 2004; Kieseppä *et al.* 2005; McIntosh *et al.* 2005), attention, psychomotor performance and information processing speed (Pierson *et al.* 2000; Sobczak *et al.* 2003), and executive function (Sobczak *et al.* 2002; Zalla *et al.* 2004; Clark *et al.* 2005*b*), while others have not (Kremen *et al.* 1998; Clark *et al.* 2005*a*). The discrepancies may result from methodological differences and the relatively small sample sizes in these studies. So far, impairments in verbal memory and certain executive functions appear to best meet the criteria for endophenotypes of BPD (Glahn *et al.* 2004; Hasler *et al.* 2006; Robinson & Ferrier, 2006).

In the present study, neuropsychological functioning was evaluated in population-based groups of familial bipolar I disorder patients, their non-affected family members and healthy controls. Among this familial bipolar sample, we hypothesized that subjects at high genetic risk would show some level of cognitive disruption compared with the controls, but in an attenuated form as compared with the patients.

METHOD

All patients who were hospitalized due to BPD between 1969 and 1991 (ICD-8 codes 296.10 or 296.30 before 1987, or DSM-III-R codes 296.4, 296.5 or 296.6 from 1987 to 1991) were identified from the Nationwide Hospital Discharge Register of Finland. Data on relatives were gathered from the National Population Register, and linked back to the records of the hospital discharge register to obtain information on their possible hospital treatments. All available medical records of the whole family (siblings and parents) were collected. After this identification process, only families with at least two members diagnosed with either BPD or schizoaffective disorder, bipolar type, were included in the study. Probands were contacted through their treating psychiatrist and, if the proband gave permission, other family members were contacted. In total, 153 family members from 57 nuclear families were interviewed and tested. Blood samples were collected for genetic analyses (Ekholm *et al.* 2002, 2003).

The Ministry of Social Affairs and Health and the Ethics Committee of the National Public Health Institute approved the study. After complete description of the study to all subjects, they gave written informed consent to participation.

All subjects were interviewed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First *et al.* 1997) during 1999–2004. Experienced psychiatrists made the final consensus diagnoses, based on all available data, including case-note records from hospital and out-patient treatments, and the SCID.

Of the 57 families, six families were excluded from the present analyses because there were no bipolar I disorder probands based on the final consensus diagnosis. In addition, 10 families were excluded because all interviewed and tested family members had some of the exclusion criteria. These included severe physical or neurological illness, brain injury, current psychiatric disorder, current substance abuse or dependence, or mental retardation. Furthermore, all persons over 70 years of age ($n=16$) were

excluded from the analyses based on the possible effect of ageing on cognitive performance (Ylikoski *et al.* 1998). Five acutely ill patients were excluded as well. First-degree relatives were excluded if they met DSM-IV criteria for a lifetime diagnosis of bipolar II disorder ($n=1$), bipolar disorder not otherwise specified (NOS) ($n=2$), cyclothymia ($n=1$), recurrent major depressive disorder ($n=5$), or any psychotic disorder ($n=20$), or for any current diagnosis of psychiatric disorder ($n=4$). Relatives currently being treated with psychotropic medication were also excluded ($n=1$).

Of the 41 families included, 28 represented the familial form of the disorder, having at least two first-degree members with bipolar I disorder. In a further six families, at least one member had bipolar I disorder and another family member had schizo-affective disorder, bipolar type. In the remaining seven families, there was only one bipolar I disorder first-degree family member but at least two second-degree relatives with bipolar I disorder.

The final study sample thus included 32 persons who met DSM-IV criteria for bipolar I disorder. Twenty-three of them were in full remission and nine in partial remission according to the DSM-IV criteria. Seven patients had a comorbid lifetime but not current Axis I diagnosis (alcohol dependence, obsessive-compulsive disorder, or sedative dependence). Twenty-six patients were currently medicated.

Forty first-degree relatives were included. Eight of them had lifetime psychiatric diagnoses: one had a major depressive disorder with a single episode, one had depressive disorder NOS, one had dysthymia, three had alcohol abuse and one alcohol dependence, and two had adjustment disorder with depressed mood.

A population-based control group with no history of any psychotic disorder was recruited from a national health survey (Aromaa & Koskinen, 2004), randomly selected from all the 8028 participants. Altogether, 114 individuals were interviewed and tested. Using the same exclusion criteria as for the relatives of bipolar I patients, plus excluding individuals with family history of mental disorder according to self-report at interview, a total of 55 control subjects were included. For 17 control subjects, a lifetime Axis I diagnosis was assigned at the SCID-based interview. These included major depressive disorder with a single episode ($n=6$), depressive disorder NOS ($n=5$), eating disorder NOS ($n=1$), panic disorder ($n=1$), alcohol abuse ($n=1$), alcohol dependence ($n=3$), adjustment disorder with depressed mood ($n=1$), and specific phobia ($n=2$). None of the subjects suffered from a current mental disorder, except the two with specific phobias.

In summary, the final study sample included 41 families comprising 32 bipolar I patients and 40 relatives without a lifetime psychotic disorder, or any current mental disorder, and 55 controls with no personal or family history of psychotic disorder.

Neuropsychological assessment

Subjects completed a comprehensive neuropsychological test battery administered in fixed order. All examiners were psychologists or advanced psychiatric nurses extensively trained and supervised with the test battery. Psychologists scored all the tests. The test battery for the controls was slightly narrower than that for the families. This study reports results from the tests that were administered to all subjects.

Verbal ability was assessed with the Vocabulary subtest from the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1981). Psychomotor performance speed was assessed with the Digit Symbol subtest of the WAIS-R. The Trail Making Test (TMT; Reitan, 1958) measured visual scanning, attention and mental flexibility. Part A of the test assesses simple attention. Part B reflects the ability to shift strategy (Lezak *et al.* 2004). Both parts are timed, and the difference score (time B − time A) was used as a measure of executive functioning (Lezak *et al.* 2004). Whether the subject performed correctly or not was used as a variable of performance quality in both parts A and B. Performance quality in part B was also used as a measure of executive functioning.

Auditory attention and verbal working memory were assessed with the Digit Span Forward and Backward tasks of the Wechsler Memory Scale – Revised (WMS-R; Wechsler, 1987) respectively. Visual attention and visual working memory were measured with the Visual Span Forward and Backward tasks of the WMS-R respectively.

Verbal learning and memory were assessed with the California Verbal Learning Test

Table 1. *Demographic and clinical characteristics of participants*

Characteristic	Patients ($n=32$)	Relatives ($n=40$)	Controls ($n=55$)	Analysis
Age (years), mean (S.D.)	51·4 (7·2)	51·4 (9·1)	51·3 (10·4)	$F=0·001$, N.S.
Education (years), mean (S.D.)	10·5 (2·6)	10·7 (2·7)	11·9 (3·4)	$F=3·335$, N.S.
Age of onset (years), mean (S.D.)	25·0 (7·0)			
Number of episodes (hospitalizations), mean (S.D.)	6·7 (7·3)			
Gender, *n* (%)				$\chi^2=0·233$, N.S.
Male	14 (54)	19 (47)	27 (48)	
Female	18 (56)	21 (53)	28 (51)	

S.D., Standard deviation; N.S., not significant.

(CVLT; Delis *et al*. 1987), which measures both recall and recognition of word lists over a number of trials. The following variables were analysed in the present study: total recall from trials 1 to 5 (verbal learning) and increment in words recalled per trial (learning slope), short-delay free and cued recall (immediate memory), long-delay free and cued recall (long-term memory), discriminability index (recognition memory), semantic clustering (learning strategy), recall errors (perseverations and intrusions) and short-delay free recall *versus* trial 5 of list A (short-delay retention and retroactive interference).

Statistical analysis

Neuropsychological test performance between the three groups was compared using the generalized estimating equation (GEE) model, which estimates population-averaged regression coefficients while controlling for the correlation due to family data (Zeger & Liang, 1986) as some subjects belonged to the same family. All models were adjusted for age and sex. As nine patients were in partial remission during the assessment, the analyses were also performed without these patients to control for the effect of residual mood effects. Because of multiple tests, statistical differences were considered significant at p value $\leqslant 0·01$. A p value $\leqslant 0·05$ was considered as indicative of significance. All analyses were performed using Stata statistical software, version 8.2 (StataCorp, 2003).

RESULTS

The groups did not differ significantly in age, sex and education (Table 1). Means and standard deviations of the neuropsychological variables are shown in Table 2.

Patients and relatives did not differ significantly from controls in verbal ability measured with the Vocabulary test while relatives scored slightly better than patients (Table 3). Both patients and relatives performed worse than the controls, and patients worse than relatives in psychomotor performance speed measured with the Digit Symbol test.

In the TMT, patients were slower than controls in completing both parts A and B and also in the measures of executive functioning (part B minus part A time and performance quality in TMT part B). The relatives performed worse than controls in the performance quality of TMT part B, and patients were slower than relatives in TMT part B, but these differences were only indicative of significance.

No differences were detected between the groups in tests of attention and working memory (Table 3). However, relatives scored slightly below the controls in the visual working memory task (the Visual Span Backward task).

In the CVLT, patients performed worse than controls in all measures of verbal learning and memory except in the number of recall errors (perseverations and intrusions) or in the forgetting/retroactive interference score. Patients performed worse than relatives in total learning, learning slope, cued short recall, free and cued delayed recall. In semantic clustering the difference between patients and relatives was indicative of significance. Relatives did not differ significantly from controls in any of the CVLT measures (Table 3).

In subsequent analyses of euthymic patients ($n=23$) only, the results remained similar to

Table 2. *Neuropsychological test performance of patients with bipolar disorder, first-degree relatives and controls*

Variables	Patients	Relatives	Controls
General intellectual functioning (WAIS-R)	($n=32$)	($n=40$)	($n=55$)
Vocabulary	38·4 (13·4)	43·0 (12·1)	41·0 (10·7)
Digit Symbol	36·2 (15·5)	43·4 (13·8)	49·7 (14·5)
Attention and working memory (WMS-R)			
Digit Span forward	7·5 (2·2)	7·3 (2·1)	7·4 (1·7)
Digit Span backward	5·7 (2·4)	5·7 (1·9)	6·0 (1·7)
Visual Span forward	7·7 (1·9)	7·7 (1·5)	8·2 (1·9)
Visual Span backward	6·9 (2·5)	7·1 (1·8)	7·8 (1·7)
Verbal learning (CVLT)	($n=32$)	($n=39$)	($n=54$)
Learning trials 1–5 (total)	41·1 (10·7)	47·7 (10·5)	49·0 (10·2)
Learning slope	1·0 (0·49)	1·4 (0·59)	1·3 (0·59)
Free short recall	8·7 (3·3)	9·9 (3·2)	10·5 (3·2)
Cued short recall	9·4 (2·8)	11·2 (2·4)	11·4 (2·7)
Free delayed recall	8·5 (3·2)	10·6 (3·1)	10·9 (3·3)
Cued delayed recall	9·0 (3·1)	11·5 (2·6)	11·4 (3·0)
Interference	−0·13 (0·30)	−0·17 (0·18)	−0·11 (0·23)
Recognition	89·8 (6·9)	92·4 (8·1)	94·4 (5·7)
Semantic clustering	10·4 (6·5)	14·1 (8·4)	15·7 (9·2)
Perseverations	2·0 (1·9)	1·9 (2·1)	2·2 (2·4)
Intrusions	0·53 (1·0)	0·64 (1·3)	0·80 (1·3)
Executive functions (TMT)	($n=30$)	($n=36$)	($n=53$)
Part A (time)	44·0 (15·2)	38·8 (17·6)	34·6 (13·6)
Part A (% correct)	65·6 (21)	72·5 (29)	80·0 (44)
	($n=25$)	($n=35$)	($n=53$)
Part B (time)	120·0 (57·5)	99·8 (41·7)	89·0 (41·9)
Part B (% correct)	37·5 (12)	47·5 (19)	69·1 (38)
Part B − A (time)	77·0 (48·9)	62·5 (35·6)	55·0 (39·1)

Values are means (standard deviations) of neuropsychological test raw scores.
WAIS-R, Wechsler Adult Intelligence Scale – Revised; WMS-R, Wechsler Memory Scale – Revised; CVLT, California Verbal Learning Test; TMT, Trail Making Test.

those for the whole sample ($n=32$), although the statistical significances decreased.

DISCUSSION

Among this familial population-based bipolar I disorder sample, we found that both the unaffected relatives and patients were impaired in the task measuring psychomotor performance speed. This function is relatively unaffected by intellectual ability, memory and learning (Lezak *et al*. 2004). According to Lezak *et al*. (2004) this task is also more sensitive to brain damage than other WAIS-R tasks, even when the damage is minimal. However, it is not a specific test, as the performance in it tends to be affected regardless of the locus of the lesion.

Our finding of psychomotor processing speed impairment in unaffected relatives is in line with the study of Pierson *et al*. (2000), who found that relatives of multiple affected bipolar families (at least two members with a bipolar diagnosis) had slower sensory-motor processing speed than controls. However, they task was different from ours as they used an auditory oddball task. Conversely, our finding contrasts with those of Kieseppä *et al*. (2005), who did not detect this impairment in unaffected non-bipolar co-twins. The discrepancy may be due to the fact that in our study the relatives were from families in which BPD was present in at least two affected relatives, and therefore the level of genetic susceptibility to the disorder may have been higher in our sample as compared with the twin sample of Kieseppä *et al*. (2005).

The impairment of psychomotor processing speed in unaffected relatives indicates an association with vulnerability to the illness, and thus it may be a potential endophenotype of BPD. There is evidence that processing speed is highly heritable (Luciano *et al*. 2001). Moreover, slowness in processing speed is associated with changes in white matter volume of the brain (Gunning-Dixon & Raz, 2000), which are often

Table 3. *Population-averaged regression coefficients (GEE) of differences on neuropsychological tests, adjusted with age and sex, and the 95% confidence intervals*

Variables	Patients *versus* controls	Relatives *versus* controls	Relatives *versus* patients
Intellectual functioning (WAIS-R)			
Vocabulary	−2·5 (−7·9 to 2·8)	3·8 (−0·95 to 8·5)	6·3 (1·1 to 11·5)*
Digit Symbol	−15·1 (−20·6 to −9·6)***	−5·3 (−9·5 to −1·1)**	9·8 (4·7 to 14·9)***
Attention and working memory (WMS-R)			
Digit Span forward	−0·06 (−0·7 to 0·8)	−0·09 (−0·9 to 0·8)	−0·1 (−1·1 to 0·8)
Digit Span backward	−0·4 (−1·2 to 0·5)	−0·3 (−1·0 to 0·4)	0·05 (−0·7 to 0·8)
Visual Span forward	−0·4 (−1·1 to 0·3)	−0·3 (−0·9 to 0·3)	0·1 (−0·5 to 0·8)
Visual Span backward	−0·9 (−2·0 to 0·2)	−0·7 (−1·4 to 0·02)	0·2 (−0·9 to 1·4)
Verbal learning and memory (CVLT)			
Learning trials 1–5	−8·1 (−12·3 to −3·9)***	−0·5 (−4·5 to 3·5)	7·6 (3·3 to 11·9)***
Learning slope	−0·2 (−0·4 to −0·0)*	0·2 (−0·1 to 0·4)	0·4 (0·1 to 0·6)**
Free short recall	−1·8 (−3·0 to 0·6)**	−0·5 (−1·8 to 0·7)	1·3 (−0·1 to 2·6)
Cued short recall	−2·0 (−3·0 to 1·0)***	−0·2 (−1·2 to 0·9)	1·9 (0·8 to 3·0)***
Free delayed recall	−2·5 (−3·7 to −1·2)***	−0·3 (−1·5 to 0·9)	2·2 (0·9 to 3·4)***
Cued delayed recall	−2·4 (−3·7 to −1·1)***	0·09 (−1·0 to 1·2)	2·5 (1·3 to 3·7)***
Interference	−0·01 (−0·08 to 0·07)	−0·03 (−0·09 to 0·04)	−0·02 (−0·09 to 0·06)
Recognition	−0·05 (−0·08 to −0·02)***	−0·02 (−0·04 to 0·01)	0·03 (−0·00 to 0·07)
Semantic clustering	−5·4 (−8·6 to −2·2)***	−1·6 (−5·2 to 2·1)	3·8 (0·5 to 7·2)*
Perseverations	0·05 (−0·2 to 0·3)	0·05 (−0·2 to 0·3)	0·0 (−0·2 to 0·2)
Intrusions	0·6 (−0·6 to 1·8)	1·0 (−0·8 to 1·4)	−0·3 (−1·8 to 1·2)
Executive functions (TMT)			
Part A (time)	−0·01 (−0·01 to −0·0)***	−0·0 (−0·01 to 0·0)	0·0 (−0·0 to 0·01)
Part A (% correct)	0·8 (−0·2 to 1·8)	0·4 (−0·6 to 1·5)	−0·4 (−1·3 to 0·6)
Part B (time)	−0·0 (−0·01 to −0·0)***	−0·0 (−0·0 to 0·0)	0·0 (0·0 to 0·0)*
Part B (% correct)	1·5 (0·4 to 2·5)**	1·0 (0·1 to 1·9)*	−0·5 (−1·6 to 0·6)
Part B−A (time)	−0·01 (−0·01 to −0·0)**	−0·0 (−0·01 to 0·0)	0·0 (−0·0 to 0·01)

GEE, Generalized Estimation Equation; WAIS-R, Wechsler Adult Intelligence Scale−Revised; WMS-R, Wechsler Memory Scale−Revised; CVLT, California Verbal Learning Test; TMT, Trail Making Test.
* $p \leqslant 0{\cdot}05$ = indicative, ** $p \leqslant 0{\cdot}01$ = significant, *** $p \leqslant 0{\cdot}001$ = very significant.

found in BPD patients (Bearden *et al*. 2001) and also in their unaffected relatives (Kieseppä *et al*. 2003; McDonald *et al*. 2004).

In addition to impairment in psychomotor processing speed, relatives performed slightly worse in the executive task, although this difference was only indicative of significance. Some previous studies have found that unaffected relatives are impaired in some measures of executive functions (Ferrier *et al*. 2004; Zalla *et al*. 2004; Clark *et al*. 2005*b*), but not all (Kremen *et al*. 1998; Kéri *et al*. 2001). In our study, unaffected relatives did not differ from controls in timed measures of TMT, which are the usual variables derived from this test. We considered the performance quality in TMT part B as a measure of executive functioning as well, and found it impaired among both patients and relatives.

We found no deficits in verbal learning and memory of the relatives as measured with CVLT. This result conflicts with some previous findings that have evidenced impairments in verbal memory in unaffected relatives of BPD patients (Gourovitch *et al*. 1999; Kéri *et al*. 2001; Sobczak *et al*. 2002, 2003; McIntosh *et al*. 2005), but are in accordance with three other high-risk studies (Kremen *et al*. 1998; Ferrier *et al*. 2004; Clark *et al*. 2005*b*). The study of Kieseppä *et al*. (2005) found no evidence of impairment in verbal memory in the total sample of non-BPD co-twins. In their study, female co-twins had impairment in CVLT total recall and long-delay free recall. The inconsistencies in results may be a consequence of differences in methodology and the relatively small samples. Moreover, the inclusion criteria of the unaffected relatives varied between studies. For example, in the study of Gourovitch *et al*. (1999), the unaffected twins were young adults, and as the researchers point out, it is possible that some of the unaffected twins may later develop

BPD. In our study, all except two unaffected relatives were above 40 years of age, so it is likely that the risk of developing BPD had already passed. We also excluded all relatives with any psychotic and recurrent depressive disorders in order to diminish the risk that we would include participants who might later develop BPD.

Although unaffected relatives had no deficit in verbal memory, bipolar I disorder patients were found to have deficits in verbal learning and memory compared with both their unaffected first-degree relatives and the controls. Patients, all at least partially euthymic at the assessment, performed worse than controls in most measures of verbal learning and memory, except in short-delay retention and recall errors. They also scored worse than controls in psychomotor speed and in executive measures. However, patients were not impaired in simple attention and working memory tasks.

Our results accord with several other studies that have shown deficits in verbal learning and memory in bipolar I disorder patients (Bearden *et al.* 2001; Quraishi & Frangou, 2002; Deckersbach *et al.* 2004; Kieseppä *et al.* 2005; Thompson *et al.* 2005). The finding that only patients were impaired in verbal learning and memory task suggests that particularly verbal learning and memory deficits may be more related to the fully developed disease, and thus be a state rather than a trait marker (Clark *et al.* 2005*b*).

One limitation of the study is that current mood state was not assessed with mania or depression rating scales. However, the current and lifetime diagnoses were made on the same day as the neuropsychological assessment, and all patients with acute conditions were excluded. We included patients who were in partial remission, but when the analyses were made excluding them, the results remained similar. Furthermore, we did not control for possible effects of medication on the test performance. However, there is no consensus about the effect of psychotropic medication on cognition (MacQueen & Young, 2003; Pavuluri *et al.* 2006). Moreover, medication did not confound the comparisons between relatives and controls. Another limitation is that some relatives and controls had a lifetime, non-psychotic Axis I disorder. However, all persons with current diagnoses were excluded.

The neuropsychological test selection was limited in the present study as no tests of sustained attention and visuospatial memory were used. In these functions, deficits have previously been found in euthymic bipolar patients (Clark & Goodwin, 2004; Thompson *et al.* 2005). Moreover, executive functioning was measured using only the TMT. Using more sensitive measures in assessing this function, a better picture of executive functioning among the unaffected relatives, in particular, would have been attained.

Although our study sample was larger than those in most previous BPD high-risk studies, the sample size was still small. The power limitations and type II error should therefore be taken into account when interpreting the results. We chose not to use multiple corrections because diminishing power in an already low-power analysis (relatively small sample size) may have increased the risk of not detecting a true difference. In addition, we used a p value $\leqslant 0{\cdot}01$ as the limit of statistical significance.

To our knowledge, this is the first study on cognitive functioning of population-based samples of familial bipolar I disorder and controls. The diagnostic procedure was careful and detailed; the subjects were assessed with SCID on the study day, and all available psychiatric case-notes were collected for the subjects.

In conclusion, impairment in psychomotor performance speed and possibly in executive functioning as well may represent endophenotypes in bipolar I disorder. Both measures were associated with the illness, and the impairments were state independent as the patients were mainly euthymic. The impairments in these functions were also found in non-affected family members at a higher rate than in the general population, as relatives performed worse than the population-based controls. In turn, verbal memory impairment may be more related to the fully developed disease.

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DECLARATION OF INTEREST

None.

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II

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Heritability of Cognitive Functions in Families With Bipolar Disorder

Mervi Antila,[1]* Annamari Tuulio-Henriksson,[1,2] Tuula Kieseppä,[1,4] Pia Soronen,[3] Outi M. Palo,[3] Tiina Paunio,[3,4] Jari Haukka,[1] Timo Partonen,[1] and Jouko Lönnqvist[1,4]

[1]*Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland*
[2]*Department of Psychology, University of Helsinki, Finland*
[3]*Department of Molecular Medicine, National Public Health Institute, Helsinki, Finland*
[4]*Department of Psychiatry, Helsinki University Central Hospital, Helsinki, Finland*

Bipolar disorder is highly heritable. Cognitive dysfunctions often observed in bipolar patients and their unaffected relatives implicate that these impairments may be associated with genetic predisposition to bipolar disorder and thus fulfill the criteria of a valid endophenotype for the disorder. However, the most fundamental criterion, their heritability, has not been directly studied in any bipolar population. This population-based study estimated the heritability of cognitive functions in bipolar disorder. A comprehensive neuropsychological test battery and the Structured Clinical Interview for DSM-IV were administered to a population-based sample of 110 individuals from 52 families with bipolar disorder. Heritability of cognitive functions as assessed with neuropsychological test scores were estimated using the Solar package. Significant additive heritabilities were found in verbal ability, executive functioning, and psychomotor processing speed. Genetic contribution was low to verbal learning functions. High heritability, in executive functioning and psychomotor processing speed suggest that these may be valid endophenotypic traits for genetic studies of bipolar disorder.

KEY WORDS: bipolar disorder; endophenotype neuropsychology; cognition; heritability

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INTRODUCTION

Heritability can be defined as the proportion of phenotypic variance attributable to genetic variance across a particular population. Heritability estimates may vary as a function of the type of population under study at a specific time. Heritability estimates of bipolar disorder have been shown to be around 80% [McGuffin et al., 2003; Kieseppä et al., 2004], but the genetic basis and underlying etiology of this complex disease has remained poorly understood. Many candidate genes and linkage loci associated with bipolar disorder have been found [Craddock and Jones, 2001; Hayden and Nurnberger, 2006], but no genes have been identified definitively, and the replication of findings has been difficult. Heterogeneity in clinical phenotype, etiology, or possible differences in applying the diagnostic criteria may stand behind these difficulties. Thus, using only the clinical diagnosis of bipolar disorder in linkage studies may be too vague. Various strategies to overcome methodological difficulties associated with identification of genes in complex disorders have therefore been suggested.

One potential strategy for decreasing heterogeneity is the use of endophenotypes [Gottesman and Gould, 2003]. Endophenotypes are traits that mediate between genotype and phenotype, and it is assumed that they could be used as quantitative trait measures in linkage and association studies instead of the categorical diagnostic variables. Several criteria for a trait to be considered as a useful endophenotype have been suggested: (1) heritability; (2) association with the illness in the population; (3) manifestation in an individual whether or not the illness is active (being state-independent); (4) cosegregation of the endophenotype and illness within families; (5) the impairment found in affected family members occurring in non-affected members at a higher rate than in general population [Gottesman and Gould, 2003]. In bipolar disorder, some neurophysiological, biochemical, endocrinological, neuroanatomical, and neuropsychological endophenotypes have been proposed [Glahn et al., 2004; MacQueen et al., 2005; Savitz et al., 2005; Hasler et al., 2006]. Presently, of the neuropsychological endophenotypes, executive functioning, and verbal memory meet best the criteria for endophenotypes of bipolar disorder as there are impairments in these functions both in bipolar patients and their unaffected family members [Glahn et al., 2004; Hasler et al., 2006; Robinson and Ferrier, 2006]. However, the evidence of these and possible other dysfunctions is still controversial and limited, and the fundamental criterion for neuropsychological endophenotypes, their heritability, has remained unstudied in bipolar disorder.

Most of the research of genetic factors and cognition has focused on the heritability of general intelligence, which seems to be highly heritable [Devlin et al., 1997; McClearn et al., 1997; Plomin and Spinath, 2004]. The heritability of more specific cognitive processes has been less studied and documented, but there is some evidence that individual variation in more discrete functions such as attention, executive functioning, spatial and verbal working memory, verbal memory, and processing speed are influenced substantially by genetic effects [Finkel et al., 1995; Ando et al., 2001; Fan et al., 2001; Luciano et al., 2001]. In schizophrenia, for instance, significant heritability has been found in

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*Correspondence to: Mervi Antila, M.Psych., Department of Mental Health and Alcohol Research, National Public Health Institute, Mannerheimintie 166, 00300 Helsinki 30, Finland.
E-mail: mervi.antila@ktl.fi

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neuropsychological dysfunctions, particularly in working memory [Cannon et al., 2000; Tuulio-Henriksson et al., 2002].

The aim of the present study was to estimate the heritability of cognitive functions in a population-based sample of Finnish families with bipolar I disorder. The aim was to investigate the heritability of functions (verbal memory, executive functions) where previous studies have evidenced impairments in both affected and unaffected relatives of bipolar disorder [Keri et al., 2001; Sobczak et al., 2003; Ferrier et al., 2004; Zalla et al., 2004; Clark et al., 2005; Kieseppä et al., 2005; McIntosh et al., 2005; Robinson and Ferrier, 2006; Robinson et al., 2006], and to investigate whether these impairments are heritable in bipolar disorder families. In our previous study of the families under study, bipolar I disorder patients were found to be impaired in verbal learning and memory compared with both their unaffected relatives and population-based controls [Antila et al., 2007]. In addition, both affected and unaffected family members were impaired in psychomotor processing speed and both scored lower than controls in executive functioning. Based on these findings as well as on previous results from other studies, we hypothesized that heritability would be high in these functions.

MATERIALS AND METHODS

The search for study participants began with the Nationwide Hospital Discharge Register of Finland, which was used to identify all patients who were hospitalized due to bipolar disorder between 1969 and 1991 (ICD-8 codes 296.10 or 296.30 before year 1987, or DSM-III-R codes 296.4, 296.5, or 296.6 1987–1991). Data on relatives were gathered from the National Population Register, and linked back to the records of the hospital discharge register to construct families, and to detect possible hospital treatments of the family members. After this identification process, families with at least two members diagnosed either with bipolar disorder or schizoaffective disorder, bipolar type, were targeted for a detailed phenotypic investigation. All available medical records of the whole family (siblings and parents) were collected. Probands were contacted through their treating psychiatrist, and if the proband gave permission, other family members were contacted for the detailed investigation.

The Ministry of Social Affairs and Health and the Ethics Committee of the National Public Health Institute approved the study. After complete description of the study to all subjects, they signed the written informed consent to participation.

Subjects

Totally, there were 57 nuclear families including 115 probands. Of the probands, 40 refused to participate to the study and 17 were deceased. Of the remaining family members, 153 (58 probands) were interviewed and tested with a neuropsychological test battery. Because of our focus on bipolar I disorder, we applied the following exclusion criteria. One family (two probands and three other family members) was excluded, because it did not have any bipolar I disorder proband based on the final consensus diagnosis. Four families were excluded because the family members fulfilled some of the exclusion criteria. The exclusion criteria included other disorders that could be related to neuropsychological impairment (severe significant physical or neurological illness, brain injury, current substance abuse or dependence (three probands and two other family members), or mental retardation (one proband)). In addition, subjects over 70 years of age (2 probands and 14 other family members) were excluded because of increasing risk that high age could have confounded cognitive performance [Ylikoski et al., 1998]. Altogether, 6 probands and 10 other family members did not complete the neuropsychological tests, and were thus excluded from the present study.

The final study sample of the present study included 110 persons (44 probands) from 52 families with bipolar disorder. This sample includes the subjects (n = 72) that were analyzed in our previous study [Antila et al., 2007]. In all families of the present study, there were at least two bipolar I disorder relatives, or one bipolar I disorder relative and another family member with schizoaffective disorder, bipolar type, but we could not interview and test them all due to the above mentioned reasons. Of the included non-proband family members (n = 72), 59 were first-degree relatives and 13 were second-degree relatives for the probands.

The demographic and clinical characteristics and the diagnostic distribution of the study sample are presented in Table I. Of the 72 subjects that had some lifetime axis I diagnosis, altogether 44 had a lifetime psychotic disorder. Three bipolar I disorder patients (all having a depressive episode) and two depressive disorder patients were acutely ill. Thirty-two bipolar I patients were currently medicated, often with more than one psychotropic drug. Among the remaining subjects with lifetime diagnosis (n = 34), 15 had current psychoactive drug treatment (Table I).

Diagnostic Procedure

The subjects were interviewed on the study day using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) [First et al., 1997]. The final consensus diagnosis was made based on all available data, including case notes records from hospital and outpatient treatments, and the face-to-face interview. Psychiatrists assigned all the diagnoses.

Neuropsychological Assessment

A comprehensive neuropsychological test battery designed to assess a variety of cognitive functions was administered in a fixed order to all subjects. All examiners were psychologists or advanced psychiatric nurses extensively

TABLE I. Demographic and Clinical Characteristics of Participants in the Study (Mean Age: 50.8 Years; SD: 8.0 Years)

Characteristics	N	%
Sex		
Men	55	50
Women	55	50
Primary axis I diagnosis (lifetime)		
Bipolar I disorder (with psychosis n = 31)	38	34.5
Bipolar disorder not otherwise specified	2	1.8
Schizoaffective disorder (bipolar type)	6	5.5
Major depressive disorder, recurrent (with psychosis n = 3)	5	4.5
Major depressive disorder with single episode	6	5.5
Depressive disorder not otherwise specified	3	2.7
Dysthymic disorder	2	1.8
Schizophrenia	4	3.6
Alcohol dependence (not current)	4	3.6
Adjustment disorder	2	1.8
None	38	34.5
Medication[a] (current)	47	42.7
Lithium	19	17.3
Antipsychotics	34	30.9
Other psychoactive medication	28	25.5
None	62	56.4

[a]The information of current medication is missing for one person with schizophrenia.

trained and supervised with the test battery. Experienced psychologists scored all the tests.

Four subtests from the Finnish version of the Wechsler Adult Intelligence Scale—Revised (WAIS-R) [Wechsler, 1981] were used to assess verbal and non-verbal ability. Verbal abilities were assessed with the Vocabulary and Similarities subtests from the WAIS-R. The Vocabulary is considered the best single measure of both verbal and general abilities [Lezak et al., 2004], and the Similarities subtest is a measure of verbal abstraction and concept formation. Non-verbal abilities were assessed with the Block Design and Digit Symbol subtests. The Block Design is a measure of visuoconstructional functions and visuospatial reasoning. The Digit Symbol measures psychomotor processing speed. Both tests are timed and have a component of motor performance.

Three tests were used to assess executive functioning, complex attention, and mental flexibility. Visual scanning, attention, and mental flexibility were assessed with the Trail Making Test (TMT) parts A and B [Reitan, 1958]. The variable that was used in the present study was the difference score (B – A) that removes the speed element from the test evaluation [Lezak et al., 2004]. Selective attention and executive function were assessed with The Stroop Color and Word Test [Golden, 1978]. The Interference trial of the test was used to measure subject ability to name words of colors that are written in an incongruent manner. The interference score, which measures "resistance to interference," was calculated using the formula provided by Golden [1978]. A higher score implicates more susceptibility to interference. Controlled Oral Word Association test (COWA) [Benton and Hamster, 1989] was used to assess verbal fluency. In this test, subjects are asked to generate as many words as they can think in 1 min, beginning with a given letter (S and K), or within a given semantic category (animals). This test is also a sensitive measure of executive functioning because it requires the subject to generate his or her own strategy.

The Digit Span Forward task and the Digit Span Backward task of the Wechsler Memory Scale—Revised (WMS-R) [Wechsler, 1987] were used to assess auditory attention and verbal working memory, respectively. Visual attention was measured with the Visual Span Forward task of the WMS-R, and the Visual Span Backward task of the WMS-R was used as a measure of visual working memory.

Verbal learning and memory were assessed with the California Verbal Learning Test (CVLT) [Delis et al., 1987] which examines both recall and recognition of word lists over a number of trials. In the present study, the following variables were used: verbal learning (total recall from trials 1–5), recognition memory (discriminability index), learning strategy (semantic clustering ratio), recall errors (perseveration and intrusion errors), short-delay retention (short-delay free recall vs. trial 5 of list A) and long-delay retention (short-delay free recall vs. long-delay free recall).

Verbal memory was also measured using the Logical Memory subtest of WMS-R [Wechsler, 1987]. The Visual Reproduction subtest from the WMS-R [Wechsler, 1987] was used as a measure of visual memory.

Statistical Methods

The additive genetic heritability of cognitive traits was estimated using the Solar computer package [Almasy and Blangero, 1998]. Heritability analyses estimate the relative contributions of differences in genetic and non-genetic factors to the total phenotypic variance in a population. The heritability estimate (h^2) in the additive genetic model is proportion of variance due to the additive effect. The continuous raw scores from the neuropsychological tests were considered as the phenotypes, instead of the dichotomous affected versus unaffected diagnosis. Five variables that were not normally distributed were transformed to approximate normality (logarithmic transformation for TMT B – A, perseverations and intrusions, square root transformation for semantic clustering and arcsine transformation for recognition memory), and two variables (short-delay and long-delay retention) were transformed to five different categories. As 25 families out of the 52 were part of altogether six larger pedigrees rich in bipolar I disorder, pedigree structure was included in all analyses. The ascertainment correction, which considered all bipolar I disorder patients as probands, was incorporated in the analyses. Age, sex, and a lifetime psychotic disorder during the illness history were used as covariates.

As five subjects were on acute episodes during the assessment, the analyses were also done adding acute illness status as a covariate in the above mentioned models. Moreover, the effects of psychotropic medication on heritability estimates were analyzed separately adding lithium use and antipsychotics use as covariates in models.

Because of multiple tests with 23 neuropsychological test variables, we counted a conservative Bonferroni correction ($P = 0.05/23$), and considered $P < 0.002$ significant. Results at $P < 0.05$ to $P > 0.002$ were considered as indicative of significance.

RESULTS

Means and standard deviations of the neuropsychological variables are shown in Table II.

In the additive model with age, sex, and lifetime psychosis as covariates (Table III), significant heritability was evidenced in the Vocabulary task ($h^2 = 0.96$, $P = 0.000002$), in the Digit Symbol task ($h^2 = 0.72$, $P = 0.0008$), in the Visual Span Backward task ($h^2 = 0.69$, $P = 0.0009$), in the Digit Span Backward task ($h^2 = 0.69$, $P = 0.001$), in the delayed recall of the Visual Reproduction test ($h^2 = 0.65$, $P = 0.001$), and in the Stroop Color and Word Test interference score ($h^2 = 0.58$, $P = 0.0004$).

After adding the acute illness status (in remission vs. acutely depressive) as an additional covariate in the above mentioned models the results remained similar (data not shown), except that the heritability in the Digit Span Backward task decreased and thereafter was indicative of significance ($h^2 = 0.59$, $P = 0.005$).

After adding lithium use as a covariate in the models the results remained similar. However, adding antipsychotic use as covariate, the significance for the Visual Span Backward task ($h^2 = 0.52$, $P = 0.003$) and in the delayed recall of visual memory ($h^2 = 0.44$, $P = 0.006$) was decreased to be indicative only. Otherwise the results remained similar.

DISCUSSION

To our knowledge (PubMed search: February 27, 2007), this is the first study that has estimated heritability of a set of cognitive functions in families with bipolar disorder. We found a significant additive heritability for verbal ability, psychomotor processing speed, and executive functioning (sensitivity to interference). Moreover, there was a significant heritability for verbal and visual working memory and for delayed visual memory.

Significant additive heritability in psychomotor processing speed agrees with previous studies in which a substantial genetic component in this function has been found among individuals without psychiatric disorders [Posthuma et al., 2003; Finkel et al., 2005]. Moreover, we found earlier that both bipolar I disorder patients and their unaffected relatives showed impairment in this particular function compared with controls, indicating an association with genetic predisposition to bipolar disorder [Antila et al., 2007]. In a study using similar

TABLE II. Neuropsychological Test Performance of Participants in the Study Sample (Means and Standard Deviations Are Untransformed Raw Scores)

Variables	Mean (SD)			
	Total sample (n = 110)	Probands (bipolar I disorder patients) (n = 38)	Other lifetime diagnosis (n = 34)	None lifetime diagnosis (n = 38)
General intellectual functioning (WAIS-R)				
Vocabulary	40.11 (12.29)	38.58 (12.78)	40.21 (13.05)	41.11 (11.46)
Similarities	24.55 (4.71)	23.84 (5.28)	24.56 (4.94)	25.00 (4.10)
Digit Symbol	39.26 (15.10)	35.13 (14.92)	37.18 (15.12)	45.18 (13.71)
Block Design	28.03 (12.22)	24.97 (13.35)	28.18 (14.12)	30.21 (9.31)
Attention and working memory (WMS-R)				
Digit span forward	7.29 (2.11)	7.58 (2.24)	7.00 (1.97)	7.26 (2.11)
Digit span backward	5.56 (2.00)	5.79 (2.30)	5.06 (1.67)	5.79 (1.93)
Visual span forward	7.55 (1.81)	7.68 (1.89)	7.44 (1.91)	7.50 (1.67)
Visual span backward	6.85 (2.23)	6.84 (2.54)	6.97 (2.37)	6.76 (1.78)
Verbal learning (CVLT)				
Learning trials 1–5 (total)	42.39 (12.70)	40.82 (10.35)	38.30 (14.39)	47.53 (11.83)
Short-delay retention[a] (%)	−0.14 (0.28)	−0.14 (0.29)	−0.15 (0.23)	−0.13 (0.31)
Long-delay retention[a] (%)	0.04 (0.24)	−0.03 (0.16)	0.09 (0.29)	0.06 (0.23)
Recognition memory[b] (%)	0.90 (0.08)	0.89 (0.07)	0.89 (0.09)	0.92 (0.09)
Semantic clustering[c]	1.51 (0.72)	1.39 (0.48)	1.41 (0.75)	1.73 (0.84)
Perseverations[d]	2.59 (3.08)	2.42 (2.51)	3.00 (3.69)	2.39 (3.05)
Intrusions[d]	2.87 (3.64)	2.63 (2.64)	3.64 (4.64)	2.45 (3.51)
Verbal memory (WMS-R)				
Immediate story recall	17.82 (8.17)	16.09 (6.78)	19.29 (8.47)	18.73 (9.57)
Delayed story recall	15.16 (8.15)	13.40 (6.70)	15.57 (8.39)	17.45 (9.57)
Visual memory (WMS-R)				
Immediate recall	26.80 (7.48)	25.08 (8.27)	26.56 (8.00)	28.83 (5.55)
Delayed recall	22.09 (10.35)	20.51 (11.89)	21.03 (11.12)	24.72 (7.20)
Executive functions				
Trail Making Test Part B – A[d]	59.59 (35.87)	62.55 (43.28)	58.95 (27.36)	57.96 (36.85)
Stroop interference score	82.09 (27.13)	93.48 (31.20)	76.13 (22.08)	76.13 (23.57)
Category fluency	19.27 (5.90)	18.50 (5.74)	18.12 (6.52)	21.03 (5.21)
Phonemic fluency	30.32 (11.25)	29.24 (13.70)	27.82 (10.41)	33.63 (8.40)

WAIS-R = Wechsler Adult Intelligence Scale—Revised; WMS-R = Wechsler Adult Memory Scale—Revised; CVLT = California Verbal Learning Test.
[a]Transformation to five different categories.
[b]Arcsine transformation.
[c]Square root transformation.
[d]Logarithmic transformation.

method in Finnish schizophrenia families, the heritability of psychomotor processing speed was low, only 9% [Tuulio-Henriksson et al., 2002]. This implicates that in schizophrenia, environmental factors and those related to illness state may contribute more than the genetic effects to the performance in tasks measuring psychomotor speed.

The impairment in psychomotor speed in bipolar disorder may be related to white matter abnormalities [Gunning-Dixon and Raz, 2000], that are potential endophenotypes in bipolar disorder [Hasler et al., 2006]. Processing speed has been evidenced to be genetically related to white matter volume, and part of the genes that influence axonal myelination are likely to be common to the genes that influence processing speed [Posthuma et al., 2003]. So far, there are only few studies that have investigated associations between slowed processing speed and white matter abnormalities in bipolar disorder, and evidence of those is still somewhat controversial and preliminary. One study found that patients with bipolar disorder with more pronounced white matter lesions are more impaired in cognitive functioning, including psychomotor speed [Dupont et al., 1995]. However, this was not evidenced in another study [Krabbendam et al., 2000]. Thus, more studies are needed to confirm whether there is any direct correlation with white matter abnormalities and slowed processing speed in bipolar disorder.

In line with our hypothesis, executive functioning, especially vulnerability to interference, showed a marked genetic contribution. Furthermore, all tasks reflecting executive functioning showed heritabilities at least indicative of significance. Most pronounced impairments in euthymic bipolar patients concern executive functioning, and verbal learning [Robinson et al., 2006]. However, not all executive functions are equally impaired, and patients do not have a broad dysexecutive syndrome [Robinson et al., 2006]. In a recent meta-analysis of cognitive deficits in bipolar patients, Robinson et al. [2006] propose that more selective tests or the use of a theoretically driven approach are needed to elucidate the picture of executive dysfunctions and their relationship to verbal memory impairment. This is noteworthy, given that executive function has been shown to share a substantial proportion of variance with memory test performance (55–60%) [Duff et al., 2005]. Recent studies in bipolar patients have reported abnormalities in prefrontal white matter tracts [Adler et al., 2004]. Robinson et al. [2006, on page 9] suggest that "abnormalities that disrupt communication between the prefrontal areas and other neural regions could explain both the existence of executive impairment and particular affective symptoms such as disinhibition, inattention, and impulsivity." In addition, unaffected relatives of bipolar disorder have been found to have deficits in executive functioning [Glahn et al., 2004; Robinson and Ferrier, 2006]. In accordance with the

TABLE III. Heritability of the Neuropsychological Variables from the Additive Genetic Model (Age, Sex, and Lifetime Psychosis as Covariates)

Variables	h^2	SD	*P*
General intellectual functioning (WAIS-R)			
Vocabulary	0.96	0.23	0.000002
Similarities	0.24	0.22	0.13
Digit Symbol	0.72	0.26	0.0008
Block Design	0.63	0.26	0.004
Attention and working memory (WMS-R)			
Digit span forward	0.15	0.26	0.27
Digit span backward	0.69	0.23	0.001
Visual span forward	0.64	0.28	0.006
Visual span backward	0.69	0.21	0.0009
Verbal learning (CVLT)			
Learning trials 1–5 (total)	0.16	0.27	0.25
Short-delay retention	0.27	0.25	0.12
Long-delay retention	0.24	0.29	0.20
Recognition memory	0.13	0.26	0.30
Semantic clustering	0.11	0.23	0.30
Perseverations	0.54	0.36	0.09
Intrusions	0.11	0.26	0.33
Logical verbal memory (WMS-R)			
Immediate recall	0.60	0.29	0.01
Delayed recall	0.33	0.34	0.15
Visual memory (WMS-R)			
Immediate recall	0.38	0.25	0.05
Delayed recall	0.65	0.24	0.001
Executive functions			
Trail Making Test Part B – A	0.60	0.32	0.02
Stroop interference score	0.58	0.17	0.0004
Category fluency	0.52	0.28	0.01
Phonemic fluency	0.62	0.25	0.006

WAIS-R = Wechsler Adult Intelligence Scale—Revised; WMS-R = Wechsler Adult Memory Scale – Revised; CVLT = California Verbal Learning Test.

present study, Zalla et al. [2004] who compared executive functioning in unaffected relatives of patients with bipolar disorder or schizophrenia, found that the unaffected relatives of bipolar disorder were impaired particularly in the interference score of the Stroop task. This task is a good measure of flexibility and ability to change demands while suppressing habitual response in favor of an unusual one.

Visual and verbal working memory showed a significant genetic contribution in the present study sample, similar to a previous twin study with general population, although it used different tasks [Ando et al., 2001]. In schizophrenia, deficits in these functions have high heritabilities [Cannon et al., 2000; Tuulio-Henriksson et al., 2002]. In contrast, evidence about the genetic influence and working memory impairment in bipolar disorder is relatively sparse and controversial. Moreover, in unaffected relatives of bipolar disorder, one study has found impairment in these functions [Ferrier et al., 2004], while others have not [Keri et al., 2001; Kieseppä et al., 2005]. Working memory functions have a high component of executive processes, and may therefore reflect more the deficit and heritability of executive functioning than storage and working memory per se. The method we used to assess working memory does not optimally allow separation of these functions. However, concerning visual working memory impairment in bipolar disorder, there is evidence that deficits in spatial span performance is not a result of impaired spatial memory but rather a consequence of impaired executive resources [Thompson et al., 2006]. Thus, more studies are required before the question of whether working memory impairment is associated with the risk for bipolar disorder can be addressed.

Long-delay visual memory also showed a marked heritability in this population. Previous studies that examined this function in unaffected twins of bipolar patients with the same task did not found impairment in this function or any implication of the genetic effect [Gourovitch et al., 1999; Kieseppä et al., 2005]. However, very few studies have measured visual memory of patients with bipolar disorder, and more studies are needed to address this question.

The influence of genetic factors on general intelligence is rather well established in previous studies [Devlin et al., 1997; Plomin and Spinath, 2004]. The Vocabulary task, considered to be the best single measure of both verbal and general mental abilities [Lezak et al., 2004], showed a significant heritability in this study. However, intelligence involves many discrete cognitive processes and a range of genetic and environmental influences, and therefore, it may not be an effective endophenotype. Moreover, general intelligence has not been found to be impaired among patients with bipolar disorder or their relatives [McIntosh et al., 2005].

Verbal learning, using semantic clustering as a learning strategy, and short-delay or long-delay retention of verbal material did not show significant genetic effects in this population. The result is in line with a previous study of schizophrenia population in which components of verbal learning and memory reflected non-genetic influences [Tuulio-Henriksson et al., 2002]. In our previous study, only patients were impaired in these functions compared both with their unaffected relatives and with population controls, suggesting that verbal learning and memory impairments might be more an illness state than a genetic trait variable [Antila et al., 2007]. There is evidence that impairment in verbal memory may be related to the number of manic episodes and the length of illness while executive dysfunction is less consistently related to illness features [Robinson and Ferrier, 2006]. Earlier, long-delay memory has been found to be impaired among unaffected relatives [Gourovitch et al., 1999; Keri et al., 2001; Kieseppä et al., 2005]. The heritability estimate of this function was, however, non-significant in the present study.

A limitation of the present study was the relatively small sample size and the inclusion of familial type of bipolar disorder only. However, our sample was population-based and nationally representative. In addition, we did control for the status of psychosis which would most likely affect cognitive functioning. Another limitation could be the effect of psychotropic medication on cognitive functioning and their heritability estimates. The effects of psychotropic and other medications on cognitive functions are unclear, and they may have influenced some of the cognitive functions in patients. However, we adjusted the analyses separately for lithium use and found no significant effect on the heritability estimates. After controlling for the use of antipsychotics, the heritability of visual memory functions diminished, but remained indicative of significance. We did not assess the current mood with mania or depression rating scales. However, the structured diagnostic interview, covering current and lifetime symptoms, was administered on the same day as the neuropsychological assessment, and after controlling for the acute illness status the results remained mainly similar.

CONCLUSIONS

Among families with bipolar disorder, there is a strong genetic contribution to verbal ability, psychomotor processing speed, and executive functions. Impairments in these functions, particularly in executive functions and psychomotor processing speed, have been found in bipolar patients and in their unaffected first-degree family members, implicating that these may be traits having a major genetic component. The present study shows that these functions were highly heritable, thus fulfilling the heritability criterion for a valid endophenotype. In contrast, verbal learning and memory had a

minor genetic component. Concerning working memory and visual long-term memory the current knowledge of the impairment of these functions in bipolar disorder is limited, and more studies need to be conducted. Our results suggest in accordance with previous studies that executive functioning and psychomotor processing speed, in particular, may be valid endophenotypic traits of bipolar disorder.

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Research report

Cognitive functioning of bipolar I patients and relatives from families with or without schizophrenia or schizoaffective disorder

Mervi Antila [a,*], Timo Partonen [a], Tuula Kieseppä [a,b], Jaana Suvisaari [a,c], Mervi Eerola [a,d], Jouko Lönnqvist [a,b], Annamari Tuulio-Henriksson [a,e]

[a] Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland
[b] Department of Psychiatry, University of Helsinki, Finland
[c] Department of Public Health, University of Tampere, Finland
[d] Department of Mathematics and Statistics, University of Helsinki, Finland
[e] Department of Psychology, University of Helsinki, Finland

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ABSTRACT

Background: Bipolar I disorder patients show cognitive impairments, and genetic vulnerability to other psychotic disorders may modify these impairments. We set out to assess cognitive functions and estimate their heritability in bipolar I disorder patients (bipolar families) and unaffected relatives in a group of families with bipolar I disorder only and in another group of families with both bipolar I disorder and schizophrenia or schizoaffective disorder (mixed families).
Methods: A neuropsychological test battery was administered to 20 bipolar patients and 36 relatives from bipolar families, 19 bipolar patients and 28 relatives from mixed families and 55 controls, all representing population-based samples.
Results: Irrespective of the family group, patients and relatives were impaired in psychomotor processing speed. Both patient groups were impaired in executive functioning, but the deficit was more severe in patients from mixed families. Patients from bipolar families scored lower than controls in nearly all measures of verbal memory. All relatives were slightly impaired in executive functioning. The heritability of cognitive functions was generally similar irrespective of psychopathology in the family. However, there were greater genetic effects in several cognitive tasks in mixed families.
Limitations: The small sample size and familial type of bipolar disorder could limit the generalizability of the results.
Conclusion: Impaired psychomotor processing speed and executive functions may represent markers of susceptibility to bipolar I disorder irrespective of psychopathology within the family. Generalized impairment in verbal memory, in turn, may associate more with bipolar disorder than to vulnerability to other psychotic disorders.

1. Introduction

Genetic vulnerability to psychotic disorders may modify cognitive impairments in patients with bipolar I disorder. Previous studies have shown that a history of psychosis in bipolar patients may have an effect on cognitive performance compared to bipolar patients without psychosis (Glahn et al., 2007; Martinez-Aran et al., 2008). Impairments in executive functioning, attention, processing speed, and verbal memory have been reported in euthymic bipolar patients (Arts et al., 2008; Bora et al., 2008; Hill et al., 2008; Robinson et al., 2006; Torres et al., 2007) and also to some extent in their unaffected relatives (Arts et al., 2008; Bora et al., 2008; Hill et al., 2008; Robinson and Ferrier, 2006). It is well established that generalized cognitive dysfunction is a core feature of

* Corresponding author. Department of Mental Health and Alcohol Research, National Public Health Institute, 00300 Helsinki 30, Finland. Tel.: +358 9 4744 8520; fax +358 9 4744 8478.
E-mail address: mervi.antila@ktl.fi (M. Antila).

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schizophrenia (Dickinson et al., 2007; Szoke et al., 2008), and some cognitive dysfunctions may be endophenotypic (Gottesman and Gould, 2003) features associated with genetic liability to the disorder (Faraone et al., 1999; Kuha et al., 2007; Tuulio-Henriksson et al., 2003).

There is evidence that patients with bipolar disorder suffer from cognitive deficits that are milder but qualitatively similar to those of patients with schizophrenia (Schretlen et al., 2007). It has been suggested that some cognitive endophenotypes may be shared between schizophrenia and affective disorders and that there may be genetic overlap between these two disorders (Bearden and Freimer, 2006; Hill et al., 2008). We set out to examine cognitive functioning in bipolar I disorder patients and their unaffected relatives in a group of families affected with bipolar I disorder only and another group of families affected both with bipolar I disorder and schizophrenia or schizoaffective disorders (mixed families), all representing population-based samples. In addition, we calculated estimates of additive heritability of cognitive functions in these two types of families. We expected that bipolar I patients and unaffected relatives from mixed families would show a more generalized cognitive impairment than those from families with bipolar I disorder only.

2. Methods

2.1. Sample

The study sample was derived from three different population-based genetic epidemiological samples including families with bipolar disorders (described in detail by Antila et al., 2007a,b), families with schizophrenia spectrum disorders and families with at least one member with schizophrenia originating from a genetic isolate in the north-eastern part of Finland (described in detail by Tuulio-Henriksson et al., 2003). The study protocol was approved by the Ethics Committee of the National Public Health Institute and by the Ministry of Social Affairs and Health. After complete description of the study a written informed consent to participation was received from all subjects.

The search for study participants of bipolar disorder families began with the Finnish nationwide Hospital Discharge Register, which was used to identify all patients who were hospitalized due to bipolar disorder between 1969 and 1991. Parents and siblings of these patients were identified from the national Population Information System which is maintained by the Population Register Centre and local register offices. Information on family relations was linked back to the Hospital Discharge Register to obtain data on family members' hospital admissions, if any. After this identification process, families with at least two members diagnosed either with bipolar disorder or schizoaffective disorder, bipolar type, were targeted for a detailed phenotypic investigation ($n=57$). All available medical records of the whole family (siblings and parents) were collected. Probands were contacted through their treating psychiatrist, and, if the proband gave permission, other family members were contacted for the detailed investigation. Of the 57 families, 41 families fulfilled the inclusion criteria of this study. In these families, there was a proband with bipolar I disorder, and at least one family member with bipolar I disorder, but no schizophrenia spectrum disorders in the family, OR there was a proband with bipolar I disorder, and at least one family member with schizophrenia or schizoaffective disorder.

The search for study participants of the schizophrenia families began with three Finnish nationwide computerized health care registers (the Hospital Discharge, Medication Reimbursement, and Disability Pension Registers), which were used to identify all patients with diagnosis of schizophrenia between 1969 and 1998. Two samples were targeted for collection. The first sample consisted of families with at least two siblings with schizophrenia, and their first-degree family members. The other sample comprised of families from an isolated region in the northern part of Finland with at least one member with schizophrenia, and their first-degree relatives. The data collection of relatives from schizophrenia families was otherwise similar to the bipolar disorder study, but information from the Medication Reimbursement and Disability Pension Register was collected as well. From these two schizophrenia family samples we identified all families including also at least one family member with bipolar I disorder. We found 11 patients with bipolar I disorder from 10 schizophrenia families and included them into the present study sample.

After this process, we divided the whole sample into families with bipolar I disorder only (bipolar families, $n=30$) and families with both bipolar and schizophrenia or schizoaffective disorders (mixed families, $n=21$) (Supplementary Tables 1a and 1b). Three bipolar families had family members with other psychotic disorders (brief psychotic disorder, psychotic disorder NOS, and delusional disorder) (Supplementary Table 1a).

When comparing neuropsychological performance of bipolar I disorder patients originating from bipolar vs. mixed families, we excluded six bipolar I disorder patients (four of them were acutely ill, one had current co-morbid alcohol abuse, and one had mild mental retardation). When comparing neuropsychological performance in unaffected relatives originating from bipolar vs. mixed families, nine relatives over 70 years of age, one relative with psychotropic medication, one with bipolar II disorder, ten with schizoaffective disorder (bipolar type), ten with schizophrenia, two

Table 1a
Samples included in the neuropsychological test comparisons.

Group	BP1 ($N=20$)	R1 ($N=36$)	BP2 ($N=19$)	R2 ($N=28$)	Controls ($N=55$)
	N	*N*	*N*	*N*	*N*
Axis I diagnosis (lifetime)					
Bipolar I disorder	20	–	19	–	–
Major depressive disorder with single episode	–	1	–	1	6
Depressive disorder NOS	–	1	–	2	5
Dysthymic disorder	–	1	–	1	–
Alcohol dependence or abuse (not current)	4 [a]	3	2 [a]	1	4
Adjustment disorder	–	2	–	–	1
Anxiety disorder	–	–	1 [a]	2	1
Specific phobia	–	2	–	1	2 [a]
Somatoform disorder NOS	–	–	–	1	–
Eating disorder NOS	–	–	–	–	1 [a]
None	–	26	–	19	38

BP1 = bipolar I patients from bipolar families, R1 = relatives from bipolar families, BP2 = bipolar I patients from mixed families, R2 = relatives from mixed families.
NOS = not otherwise specified.
[a] Co-morbid lifetime Axis I diagnosis.

Table 1b
Samples included in the additive heritability estimation analyses.

Group	Bipolar families ($N=30$)	Mixed families ($N=21$)
	$N=68$	$N=68$
Axis I diagnosis (lifetime)		
Bipolar I disorder	23 (3 acutely depressive)	20 (1 acutely depressive)
Major depressive disorder, recurrent	5	3
Schizoaffective disorder	–	4
Schizophrenia	–	9
Psychotic disorder	1	1
Major depressive disorder with single episode	1	1
Depressive disorder NOS	1	2
Dysthymic disorder	1	1
Alcohol dependence or abuse (not current)	3	1
Adjustment disorder	2	–
Anxiety disorder	–	2
Adjustment disorder	2	–
Specific phobia	2	1
Somatoform disorder NOS	–	1
Other current psychiatric disorder (not alcohol diagnosis)	2	3
Psychotropic medication	1	–
None	26	19

NOS = not otherwise specified.

with other psychotic disorder, nine with recurrent depressive disorder, and six with other current diagnosis of psychiatric disorder were excluded.

The final *bipolar disorder family* sample included 20 bipolar I disorder patients and 36 first-degree relatives without a lifetime psychotic disorder, or any current mental disorder. Fourteen patients were in full remission and six in partial remission according to the DSM-IV criteria. Four patients had a co-morbid lifetime Axis I diagnosis (Table 1a). Of the 36 included relatives, 10 had lifetime history of psychiatric disorder (Table 1a).

The final *mixed family* sample included 19 bipolar I disorder patients and 28 first-degree relatives without a lifetime psychotic disorder, or any current mental disorder. Sixteen patients were in full remission and three were in partial remission. Three patients had a co-morbid lifetime Axis I diagnosis (Table 1a). Of the 28 included relatives, 9 had a lifetime history of psychiatric disorder (Table 1a).

2.2. Control group

A population-based control group screened negative for psychotic or manic symptoms was recruited from a national health survey (Aromaa and Koskinen, 2004; Perälä et al., 2007). They were interviewed with the Structured Clinical Interview for DSM-IV (SCID-I), and a neuropsychological test battery was administered. We used the same exclusion criteria as for the relatives of bipolar I patients, plus excluding individuals with family history of mental disorder according to self-report at interview, leaving 55 subjects in the control group (described in detail by Antila et al., 2007a). For 17 control subjects, a lifetime Axis I diagnosis (not current, except for specific phobia) was assigned at the SCID interview (Table 1a).

2.2.1. Samples in the additive heritability estimation analyses

In the heritability estimation analyses, we included all patients irrespective of their diagnoses, and relatives with valid neuropsychological test performance. The subjects were not allowed to have current substance abuse or dependence, severe significant physical or neurological illness, brain injury, or mental retardation, and all were under 70 years of age. For the heritability estimation analyses of the bipolar disorder families, 68 persons (23 probands) from 30 families were included (Table 1b). The mixed family analysis included 68 persons (20 probands) from 21 families (Table 1b).

Table 2
Demographic and clinical characteristics of participants.

Characteristic	BP1 ($N=20$)	R1 ($N=36$)	BP2 ($N=19$)	R2 ($N=28$)	Controls ($N=55$)	Analysis	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*F*	*P*
Age (years)	51.60 (7.46)	52.0 (8.29)	47.94 (7.57)	44.69 (9.01)	51.33 (10.37)	3.555	**0.008**; R2<R1, C
Education (years)	11.55 (2.63)	10.61 (2.78)	9.89 (2.79)	11.46 (2.52)	11.98 (3.40)	2.347	0.06
Age of onset	25.00 (7.18)		24.37 (8.06)			0.067	0.797
Length of illness	26.33 (6.25)		23.19 (10.57)			1.284	0.264
GAF	65.58 (16.77)	80.36 (11.03)	53.88 (12.64)	84.07 (8.11)	83.35 (8.96)	31.05	<**0.001**; B1<R1, R2, C ; B2<B1, R1, R2, C
Proportion of diagnoses in the family (%)	48.6 (19.9)	29.4 (15.7)	40.8 (12.2)	30.7 (13.4)		8.050	<**0.001**; B1>R1, R2
	N^a (%)	N^a (%)	N^a (%)	N^a (%)	N^a (%)	*U*	*P*
Current medication	16 (80)	–	15 (78.9)	–	–	188.0	0.967
Lithium	9 (45)	–	5 (26)	–	–	154.5	0.322
Antipsychotics	12 (60)	–	9 (47)	–	–	166.0	0.513
						χ^2	*P*
None	4 (20)	0 (100)	4 (21.1)	0 (100)	0 (100)	–	–
Gender						0.453	0.978
Male	10 (50)	16 (44.4)	9 (47.4)	12 (42.9)	27 (49.1)		
Female	10 (50)	20 (55.6)	10 (52.6)	16 (57.1)	28 (50.9)		

BP1 = bipolar I patients from bipolar families, R1 = relatives from bipolar families, BP2 = bipolar I patients from mixed families, R2 = relatives from mixed families, C = controls.
GAF = The Global Assessment of Functioning.
[a] Total number of persons using medication (yes/no).

2.3. Diagnostic procedure

All subjects were interviewed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) (First et al., 1997). Experienced psychiatrists made the final consensus diagnoses, based on all available data, including case notes from hospital and outpatient treatments and the SCID. Psychosocial functioning status was assessed using the Global Assessment of Functioning scale (GAF, DSM-IV).

2.4. Neuropsychological assessment

A comprehensive neuropsychological test battery was administered in a fixed order to all subjects by psychologists or experienced psychiatric nurses extensively trained and supervised with the test battery. The following cognitive functions assessed with the respective neuropsychological test methods were included in the present study: *verbal ability* with the Vocabulary subtest from the Finnish version of the Wechsler Adult Intelligence Scale — Revised (WAIS-R) (Wechsler, 1981); *psychomotor processing speed* with the Digit Symbol subtest from the WAIS-R; *auditory attention and working memory* with the Digit Span Forward and Backward tasks of the Wechsler Memory Scale — Revised (WMS-R) (Wechsler, 1987); *visual attention and working memory* with the Visual Span Forward and Backward tasks of the WMS-R; *visual scanning and attention* with the Trail Making Test (TMT) part A (Reitan, 1958); *executive functioning* with the TMT part B and with the difference score TMT (B-A); *verbal learning and memory* with the California Verbal Learning Test (CVLT) (Delis et al., 1987). From the CVLT we included verbal learning (total recall from trials 1 to 5), immediate and delayed free and cued recalls, short-delay retention and interference (short-delay free recall versus trial 5 of list A), recognition memory (discriminability index), learning strategy (semantic clustering ratio), and recall errors (perseveration and intrusion errors). A higher score in these neuropsychological tests indicates better performance in all tests, except in the TMT timed scores and in recall errors. The test procedure has been described in more detailed by Antila et al. (2007a).

2.5. Statistical analysis

Neuropsychological test performance between the five groups was compared using the generalized estimating equation (GEE) model, which estimates population-averaged regression coefficients while controlling within-family correlation (Zeger and Liang, 1986). The Stata statistical software, version 8.2 (StataCorp, 2003), was used. All models were adjusted for age and sex. As nine patients were in partial remission during the assessment, additional analyses were done without these patients to control for the effect of residual mood symptoms. In addition, as three bipolar families had family members with other psychotic disorders, additional analyses were done without these families.

The additive genetic heritability of cognitive functions was estimated using the Solar computer package (Almasy and Blangero, 1998). Variables that were not normally distributed were transformed to approximate normality. Age, sex, and a lifetime history of psychotic symptoms were used as covariates.

Because of multiple tests, statistical differences with *p*-value $\leq$.01 were considered significant. *P*-value $\leq$.05 was considered as indicative of significance.

Table 3
Neuropsychological test performances of patients with bipolar I disorder, first-degree relatives and controls.

	BP1 ($N=20$)	R1 ($N=36$)	BP2 ($N=19$)	R2 ($N=28$)	Controls ($N=55$)
Variable	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Verbal ability and psychomotor processing speed (WAIS-R)					
Vocabulary	41.70 (12.70)	43.28 (12.60)	37.37 (13.71)	42.50 (8.84)	41.00 (10.74)
Digit Symbol	38.50 (14.04)	40.92 (13.67)	36.53 (16.60)	47.57 (11.26)	49.71 (14.50)
Attention and working memory (WMS-R)					
Digit Span forward	7.35 (2.16)	7.28 (2.04)	7.16 (2.52)	7.14 (1.69)	7.42 (1.69)
Digit Span backward	5.95 (2.39)	5.64 (1.78)	5.16 (2.27)	5.93 (2.04)	6.00 (1.78)
Visual span forward	7.75 (1.74)	7.58 (1.52)	8.00 (2.03)	8.54 (1.75)	8.15 (1.86)
Visual span backward	7.75 (1.92)	7.11 (1.63)	6.79 (2.95)	7.79 (1.97)	7.78 (1.66)
	($N=20$)	($N=35$)	($N=19$)	($N=28$)	($N=54$)
Verbal Learning (CVLT)					
Learning trials 1–5 (total)	40.75 (9.11)	46.43 (10.99)	44.74 (11.50)	50.79 (7.79)	49.07 (10.26)
Free short recall	8.50 (3.20)	9.51 (3.46)	9.47 (2.91)	11.11 (2.10)	10.46 (3.18)
Cued short recall	9.00 (2.83)	10.86 (2.70)	10.21 (2.39)	12.21 (1.79)	11.39 (2.71)
Free delayed recall	8.30 (3.11)	10.29 (3.11)	9.47 (2.89)	11.93 (2.09)	10.93 (3.30)
Cued delayed recall	9.00 (2.47)	11.17 (2.77)	9.63 (3.32)	12.50 (1.99)	11.33 (2.97)
Interference	−.18 (.25)	−.18 (.19)	−.03 (.29)	−.11 (.12)	-.11 (.23)
Recognition memory	.89 (.07)	.92 (.08)	.92 (.05)	.96 (.03)	.94 (.06)
Semantic clustering (ratio)	1.39 (.39)	1.55 (.80)	1.62 (.77)	2.01 (.61)	1.81 (.73)
Perseverations	1.95 (1.99)	2.34 (2.40)	1.95 (1.75)	2.79 (3.41)	2.22 (2.40)
Intrusions	0.75 (1.21)	0.83 (1.32)	0.58 (1.07)	0.75 (1.38)	0.80 (1.25)
Executive functions	($N=19$)	($N=33$)	($N=17$)	($N=27$)	($N=53$)
Trail Making Test A (time)	42.16 (13.72)	40.97 (19.99)	44.24 (14.74)	33.51 (9.65)	34.64 (13.64)
Part A (% correct)	78.9 ($N=15$)	84.8 ($N=28$)	58.8 ($N=10$)	81.5 ($N=22$)	83.0 ($N=44$)
	($N=18$)	($N=31$)	($N=13$)	($N=27$)	($N=52$)
Trail Making Test B (time)	117.56 (54.23)	106.16 (51.87)	122.54 (67.00)	95.15 (38.94)	89.02 (41.88)
Part B (% correct)	52.6 ($N=10$)	51.6 ($N=16$)	29.4 ($N=5$)	70.4 ($N=19$)	71.7 ($N=38$)
Trail Making Test Part B–A (time)	77.28 (49.35)	67.90 (42.03)	79.46 (57.64)	61.62 (37.64)	54.96 (39.12)

Values are means (standard deviations) of neuropsychological raw scores. BP1 = bipolar I patients from bipolar families, R1 = relatives from bipolar families, BP2 = bipolar I patients from mixed families, R2 = relatives from mixed families, WAIS-R = Wechsler Adult Intelligence Scale — Revised, WMS-R = Wechsler Adult Memory Scale — Revised, CVLT = California Verbal Learning Test, TMT = Trail Making Test.

3. Results

The demographic and clinical characteristics of the study sample are presented in Table 2. The unaffected relatives from mixed families were significantly younger than unaffected relatives from bipolar families and controls. There were no statistically significant differences between the groups in education and sex distribution. The two patient groups did not differ in the age of onset, length of illness, current medication, or proportion on persons with psychiatric diagnoses in the family. Both patient groups had lower GAF ratings than unaffected relatives and controls. In addition, patients from mixed families had lower GAF ratings than patients from families with bipolar disorder only.

Means and standard deviations of the neuropsychological variables are shown in Table 3.

There were no significant differences between the groups in verbal ability assessed with the Vocabulary test (Tables 4a and 4b). Both groups of patients and relatives were significantly slower in psychomotor performance speed than controls measured with the Digit Symbol test. However, neither the patient groups nor the groups of relatives differed from each other.

There were no significant group differences in tasks assessing verbal and visual attention or verbal and visual working memory (Tables 4a and 4b).

Bipolar patients from families with only bipolar I disorder performed significantly worse than controls in nearly all measures of verbal learning and memory (Table 3a) except in the number of recall errors and in the short-delay retention/interference score. Bipolar patients from mixed families were significantly worse than controls in free delayed recall of the CVLT. In total learning, cued short and delayed recalls, and recognition, bipolar patients from mixed families scored lower than controls, but the difference was only indicative of significance. There were no significant differences between the two patient groups in any measures of verbal learning and memory.

There were no significant differences between the relative groups and controls in any measures of verbal learning and memory (Table 4b). Relatives from bipolar families performed significantly worse than relatives from mixed families in recognition memory, and they used fewer semantic categories as learning strategies than relatives from mixed families, although these statistical differences were indicative of significance only.

Both patient groups were significantly slower than controls in both parts A and B of TMT (Table 4a). Bipolar patients from mixed families made significantly more errors than controls in both parts A and B, and were also slower in the TMT part-B-minus-part-A score. The difference between patients from bipolar families and controls in the latter part was indicative of significance. The relatives from bipolar families made more errors than controls in TMT part B while the relatives from mixed families were slower than controls (Table 4b). Neither the patient groups nor the groups of relatives differed from each other.

Table 4a
Population-averaged regression coefficients (GEE) of differences between bipolar I disorder patients and controls on neuropsychological tests, adjusted with age and sex, and the 95% confidence intervals.

Variables	BP1 vs. Controls		BP2 vs. Controls		BP1 vs. BP2	
	Coef. (95% interval)	*p*	Coef. (95% interval)	*p*	Coef. (95% interval)	*p*
Verbal ability and psychomotor processing speed (WAIS-R)						
Vocabulary	0.26 (−5.76–6.25)	0.936	−4.68 (−11.46–2.10)	0.174	4.93 (−3.08–12.93)	0.228
Digit Symbol	−11.67 (−18.15 to −5.19)	<**0.0001**	−16.29 (−22.84 to −9.75)	<**0.0001**	4.63 (−3.70–12.95)	0.276
Attention and working memory (WMS-R)						
Digit Span forward	−0.12 (−0.94–0.71)	0.782	−0.50 (−1.74–0.74)	0.427	0.39 (−0.98–1.76)	0.580
Digit Span backward	−0.16 (−1.19–0.86)	0.755	−1.17 (−2.32 to −0.02)	0.045	1.01 (−0.39–2.41)	0.158
Visual Span forward	−0.43 (−1.21–0.34)	0.275	−0.31 (−1.23–0.61)	0.513	−0.12 (−1.17–0.92)	0.817
Visual Span backward	−0.11 (−1.17–0.96)	0.845	−1.25 (−2.57–0.08)	0.06	1.14 (−0.47–2.75)	0.165
Verbal Learning and Memory (CVLT)						
Learning trials 1–5	−8.69 (−12.76 to −4.63)	<**0.0001**	−5.84 (−11.29 to −0.39)	0.036	−2.85 (−8.77–3.06)	0.345
Free short recall	−2.02 (−3.46 to −0.57)	**0.006**	−1.32 (−2.74–0.10)	0.069	−0.70 (−2.40–1.01)	0.423
Cued short recall	−2.41 (−3.50 to −1.31)	<**0.0001**	−1.43 (−2.67 to −0.19)	0.024	−0.98 (−2.33–0.38)	0.157
Free delayed recall	−2.60 (−3.99 to −1.22)	<**0.0001**	−1.86 (−3.25 to −0.48)	**0.008**	−0.74 (−2.33–0.85)	0.360
Cued delayed recall	−2.34 (−3.62 to −1.06)	<**0.0001**	−1.95 (−3.57 to −0.33)	0.018	−0.39 (−2.19–1.41)	0.669
Interference	−0.03 (−0.12–0.07)	0.618	0.03 (−0.05–0.11)	0.512	−0.05 (−0.16–0.05)	0.340
Recognition	−0.06 (−0.10 to −0.02)	**0.002**	−0.04 (−0.07 to −0.003)	0.035	−0.02 (−0.07–0.02)	0.305
Semantic clustering	−0.44 (−0.71 to −0.17)	**0.002**	−0.21 (−0.62–0.19)	0.301	−0.22 (−0.63–0.18)	0.274
Perseverations	0.05 (−0.22–0.32)	0.695	0.08 (−0.15–0.30)	0.510	−0.02 (−0.33–0.29)	0.892
Intrusions	0.08 (−0.86–1.02)	0.867	0.44 (−0.98–1.85)	0.545	−0.36 (−1.91–1.19)	0.653
Attention and Executive Functions (TMT)						
Part A (time)	−0.007 (−0.01 to −0.004)	<**0.0001**	−0.007 (−0.011 to −0.004)	<**0.0001**	0.00001 (−0.004–0.004)	0.995
Part A (% correct)	−0.75 (−1.97–0.47)	0.227	−1.60 (−2.81 to −0.39)	**0.009**	0.85 (−0.55–2.25)	0.235
Part B (time)	−0.003 (− 0.005 to −0.001)	**0.007**	−0.004 (−0.007 to −0.002)	**0.001**	0.001 (−0.002–0.004)	0.496
Part B (% correct)	−1.03 (−2.31–0.26)	0.117	−2.49 (−3.86 to −1.12)	<**0.0001**	1.46 (−0.13–3.05)	0.072
Part B–A (time)	−0.006 (−0.01 to −0.001)	0.025	−0.008 (−0.013 to −0.002)	**0.005**	0.002 (−0.004–0.008)	0.549

BP1 = bipolar I patients from bipolar families, BP2 = bipolar I patients from mixed families, WAIS-R = Wechsler Adult Intelligence Scale — Revised, WMS-R = Wechsler Adult Memory Scale — Revised, CVLT = California Verbal Learning Test, TMT = Trail Making Test.

Table 4b
Population-averaged regression coefficients (GEE) of differences between unaffected first-degree relatives and controls on neuropsychological tests, adjusted with age and sex, and the 95% confidence intervals.

Variables	R1 vs. controls		R2 vs. controls		R1 vs. R2	
	Coef. (95% interval)	*p*	Coef. (95% interval)	*P*	Coef. (95% interval)	*P*
Verbal ability and psychomotor processing speed (WAIS-R)						
Vocabulary	4.19 (−0.88–9.27)	0.105	0.70 (−4.06–5.46)	0.773	3.49 (−1.98–8.96)	0.211
Digit Symbol	−7.92 (−12.54 to −3.31)	**0.001**	−9.01 (−14.60 to −3.42)	**0.002**	1.08 (−5.10–7.27)	0.732
Attention and working memory (WMS-R)						
Digit Span forward	−0.008 (−0.83–0.81)	0.985	−0.15 (−1.13–0.83)	0.765	0.14 (−0.96–1.24)	0.801
Digit Span backward	−0.23 (−0.90–0.44)	0.498	−0.11 (−1.07–0.86)	0.830	−0.13 (−1.12–0.87)	0.805
Visual Span forward	−0.45 (−1.13–0.24)	0.202	−0.01 (−0.77–0.75)	0.978	−0.44 (−1.26–0.38)	0.297
Visual Span backward	−0.57 (−1.25–0.12)	0.104	−0.42 (−1.23–0.42)	0.336	−0.16 (−1.09–0.77)	0.734
Verbal Learning and Memory (CVLT)						
Learning trials 1–5	−2.26 (−6.78–2.26)	0.327	−1.20 (−4.62–2.22)	0.491	−1.06 (−5.50–3.37)	0.639
Free short recall	−0.84 (−2.25–0.57)	0.245	−0.19 (−1.28–0.91)	0.739	−0.65 (−2.08–0.78)	0.370
Cued short recall	−0.53 (−1.76–0.71)	0.405	0.29 (−0.69–1.28)	0.559	−0.82 (−2.10–0.46)	0.210
Free delayed recall	−0.66 (−1.98–0.67)	0.330	0.09 (−1.08–1.26)	0.879	−0.75 (−2.11–0.61)	0.280
Cued delayed recall	−0.25 (−1.47–0.97)	0.684	0.50 (−0.60–1.60)	0.374	−0.75 (−2.07–0.56)	0.261
Interference	−0.02 (−0.09–0.05)	0.563	−0.02 (−0.09–0.05)	0.533	0.001 (−0.08–0.08)	0.977
Recognition	−0.02 (−0.05 to −0.002)	0.074	0.01 (−0.008–0.03)	0.253	−0.03 (−0.06 to −0.01)	0.011
Semantic clustering	−0.29 (−0.64–0.07)	0.118	0.13 (−0.15–0.41)	0.376	−0.41 (−0.78 to −0.04)	0.029
Perseverations	−0.03 (−0.20–0.15)	0.781	−0.05 (−0.23–0.14)	0.608	0.02 (−0.18–0.23)	0.825
Intrusions	−0.01 (−0.83–0.80)	0.980	0.02 (−0.98–1.02)	0.963	−0.03 (−1.14–1.07)	0.952
Attention and Executive Functions (TMT)						
Part A (time)	−0.004 (−0.01–0.001)	0.153	−0.003 (−0.008–0.001)	0.138	−0.001 (−0.007–0.005)	0.816
Part A (% correct)	−0.03 (−1.28–1.21)	0.956	0.37 (−1.22–1.96)	0.647	−0.41 (−2.20–1.39)	0.657
Part B (time)	−0.002 (−0.004–0.0001)	0.057	−0.002 (−0.004–0.0001)	0.039	0.001 (−0.002–0.002)	0.968
Part B (% correct)	−1.26 (−2.22 to −0.31)	**0.009**	−0.86 (−2.04–0.31)	0.150	−0.40 (−1.53–0.73)	0.485
Part B–A (time)	−0.004 (−0.009–0.0007)	0.094	−0.004 (−0.01–0.0007)	0.090	0.0004 (−0.005–0.006)	0.878

R1 = relatives from bipolar families, BP2 = bipolar I patients from mixed families, R2 = relatives from mixed families, WAIS-R = Wechsler Adult Intelligence Scale − Revised, WMS-R = Wechsler Adult Memory Scale − Revised, CVLT = California Verbal Learning Test, TMT = Trail Making Test.

3.1. Euthymic patients

In subsequent analyses of euthymic bipolar patients only, the results remained similar to those from the whole sample, although the statistical significance weakened due to smaller samples (data not shown). The differences between the bipolar patients from mixed families and controls disappeared in CVLT measures of total learning ($p = 0.062$) and cued delayed recall ($p = 0.057$). In addition, the difference between patients from bipolar families and controls disappeared in TMT part B time ($p = 0.054$) and in the TMT part-B-minus-part-A score ($p = 0.080$). The significant difference between relatives disappeared in recognition memory ($p = 0.108$).

In subsequent analyses without bipolar families that had family members with other psychosis (three families with two bipolar I patients and two unaffected relatives) results remained essentially similar to those from the whole sample (data not shown).

3.2. The additive heritability of cognitive functions

The results in the models calculating additive heritability estimates with age, sex, and lifetime psychosis as covariates are shown in Table 5. In bipolar families, significant heritability was estimated in perseverative recall errors in the CVLT and in TMA time score. In addition, indicative significance in heritability estimates was evidenced in the Vocabulary task, in the Digit Symbol task, in the Visual Span and in the Digit Span Backward tasks, and in the free and cued delayed recalls of the CVLT task.

In mixed families, significant heritability estimates were detected in the Vocabulary task, in the Visual Span and in the Digit Span Backward tasks, and in the long-delay cued recall of the CVLT task. In addition, indicative significances were found in the Digit Symbol task and Visual Span Forward task.

4. Discussion

In this study of bipolar I disorder patients and their unaffected relatives from two different family populations, we expected that bipolar patients and unaffected relatives from families affected both by bipolar I disorder and schizophrenia or schizoaffective disorder would be more impaired in all cognitive functions as compared with patients and relatives from families affected by bipolar I disorder only. Contrary to our expectation about a more generalized cognitive impairment among the mixed families, bipolar I patients from mixed families scored worst only in executive functioning. In particular, they differed from controls in the TMT part-B-minus-part-A score that removes the motor speed element from the test evaluation and is considered as a good measure of mental flexibility and executive functioning (Lezak et al., 2004). However, bipolar I patients from families with only bipolar disorder were impaired in executive functioning as well, and the two patient groups did not differ significantly from each other in this function. Both

Table 5
Heritability of the neuropsychological variables (raw scores) from the additive genetic model (age, sex and lifetime psychosis as covariates) in bipolar families and in mixed families.

Variables	Bipolar families $N=68$		Mixed families $N=68$	
	H (SD)	*P*	H (SD)	*P*
Verbal ability and psychomotor processing speed (WAIS-R)				
Vocabulary	0.60 (0.29)	0.02	0.82 (0.26)	**0.0001**
Digit Symbol	0.48 (0.29)	0.05	0.38 (0.27)	0.05
Attention and working memory (WMS-R)				
Digit span forward	0.08 (0.23)	0.36	0.19 (0.22)	0.15
Digit span backward	0.49 (0.29)	0.03	0.68 (0.27)	**0.001**
Visual span forward	0.51 (0.36)	0.08	0.42 (0.26)	0.03
Visual span backward	0.38 (0.25)	0.05	1	<**0.0001**
Verbal learning (CVLT)				
Learning trials 1–5 (total)	0.35 (0.36)	0.16	NE	
Short-delay free recall	0	0.50	NE	
Short-delay cued recall	0.13 (0.32)	0.34	0.21 (0.26)	0.18
Long-delay free recall	0.49 (0.31)	0.05	0.20 (0.27)	0.20
Long-delay cued recall	0.47 (0.27)	0.05	0.65 (0.30)	**0.007**
Recognition memory	NE [a]		NE [a]	
Semantic clustering	NE [b]		0.06 (0.19)	0.36
Perseverations	0.84 (0.23) [c]	**0.002**	0.24 (0.22) [c]	0.08
Intrusions	0	0.50	NE [c]	
Attention and executive functions				
Trail Making Test Part A (time)	0.88 (0.26)	**0.006**	NE [c]	
Trail Making Test Part B (time)	NE [c]		NE [c]	
Trail Making Test Part B–A (time)	NE [c]		NE [c]	

WAIS-R = Wechsler Adult Intelligence Scale — Revised, WMS-R = Wechsler Adult Memory Scale — Revised, CVLT = California Verbal Learning Test, NE = heritability not estimated due to lack of normality of the variable and/or standard deviation is <0.5.
[a] Arcsine transformation.
[b] Square root transformation.
[c] Logarithmic transformation.

groups of relatives performed slightly worse than controls in executive functioning, but the groups did not differ from each other.

Our finding of impairment in executive functioning in both patient groups as well as in both relative groups, although to a lesser degree, is in accordance with the recent two meta-analytic studies (Arts et al., 2008; Bora et al., 2008). In both studies, measures of executive functioning demonstrated medium to large effect sizes in bipolar patients and small to medium effect sizes in unaffected relatives. These results, along with ours, support the potential role of executive dysfunction as an endophenotype of bipolar disorder. Moreover, our finding of more pronounced abnormalities in executive functioning in patients belonging to mixed families may reflect vulnerability to psychotic disorders in general. Bipolar patients with history of psychosis have been found to be more impaired on executive functioning compared with non-psychotic bipolar patients (Glahn et al., 2007). In that study, however, deficits in attention, psychomotor processing speed, and memory appeared to be part of the broader disease phenotype in all patients. In our study, the two patient groups did not differ statistically significantly in the task measuring executive functioning, although bipolar patients from mixed families scored lower. This may be explained by the fact that in both groups nearly all patients had history of psychosis, and the task in which our patients did not differ was the same in which patients in the Glahn et al study (2007) also scored similarly. In addition, the power limitations should be taken into account as well.

Moreover, results concerning verbal learning and memory were contrary to our expectation, as bipolar I patients from families affected both by schizophrenia or schizoaffective disorder and bipolar I disorder were impaired only in delayed free verbal recall, while bipolar I patients from families with bipolar I disorder were impaired in nearly all verbal learning and memory variables. Unaffected relatives from bipolar and mixed families did not differ from controls in any CVLT measure. In the study of McIntosh et al. (2005), memory was impaired in all patients and relatives, and the abnormalities in memory appeared to be related to an increased liability to psychotic disorders in the family. In our study, a more generalized impairment in verbal learning and memory was associated with presence of only bipolar I disorder in the family. In addition, there were no statistically significant differences between unaffected relative groups and controls. The discrepancy between the two studies may be due to the fact that the McIntosh study used more global measures of memory compared with our method assessing principally the process of verbal learning and memory.

However, irrespective of the psychopathology in the family, both bipolar patient groups in our study were impaired in delayed free verbal recall. This is in line with recent meta-analyses that have evidenced verbal memory impairment among euthymic bipolar patients ((Arts et al., 2008; Bora et al., 2008; Robinson et al., 2006; Torres et al., 2007). In the study by Kieseppä et al, the impairment in long-delay memory in bipolar I disorder patients remained after controlling for the effects of information processing speed, while the differences in verbal learning disappeared between patients and controls (Kieseppä et al., 2005). Concerning memory functions, particularly delayed verbal memory has been found to be impaired also among unaffected relatives of bipolar I disorder patients (Arts et al., 2008; Gourovitch et al., 1999; Keri et al., 2001; Kieseppä et al., 2005). However, these results conflicts with our study, as both groups of unaffected relatives were unimpaired in delayed verbal memory as well. It is possible, that particularly verbal learning and memory deficits may be more related to the fully developed disorder and to the symptoms of the disorder (Robinson and Ferrier, 2006).

Bipolar I disorder patients and relatives performed worse than controls irrespective of the psychopathology within the family in psychomotor processing speed. This is partly in accordance with previous findings of schizophrenia and bipolar disorder patients and their unaffected relatives belonging to families affected by schizophrenia and bipolar disorder alone, and bipolar disorder patients and their unaffected relatives that came from families affected by both disorders (McIntosh et al., 2005). In that study, psychomotor performance speed was impaired in all patients regardless of diagnoses in the family. However, in that study only unaffected relatives from schizophrenia families were impaired in this function which contradicts with our results. Our findings are however in line with a recent study in which bipolar I disorder patients and their unaffected relatives

demonstrated impaired performance in psychomotor processing speed, this being the only function that demonstrated a pure intermediate pattern (Frantom et al., 2008). The same finding was evidenced in our previous study (Antila et al., 2007a). In line with these results as well, independently of the specific diagnosis, bipolar I disorder and schizophrenia patients with positive family history of psychosis were found to be more impaired than patients without family history of psychosis on visual-motor processing and attention domain (Tabares-Seisdedos et al., 2003). In that study, the only predictor of belonging to the group with positive family history of psychosis was poor performance on the Digit Symbol task (Tabares-Seisdedos et al., 2003). In contrast, our findings somewhat contradict with the recent meta-analysis of neuropsychological deficits in euthymic bipolar disorder patients and their first-degree relatives (Bora et al., 2008) in which impairment in psychomotor tasks were relatively large among patients with bipolar disorder, while first-degree relatives were mostly unimpaired in this function.

The two bipolar I patient groups did not differ significantly in any demographic or clinical characteristics except that bipolar patients from mixed families had significantly lower GAF scores than those from families with only bipolar I disorder. In a recent study, low-functioning bipolar patients were cognitively more impaired than highly functioning patients in verbal recall and executive functions and the variable that best predicted psychosocial functioning was verbal memory (Martinez-Aran et al., 2007). This somewhat conflicts with our results, as bipolar I patients from mixed families scored significantly lower in executive functioning than in verbal learning and memory compared with controls.

4.1. Estimates of additive heritability of cognitive functions

In families affected by only bipolar I disorder, significant heritability was estimated in the recall errors of the CVLT task and simple attention task assessed with the TMA. In mixed families, significant heritability estimates were found in tasks assessing verbal ability, visual and verbal working memory, and long-delayed cued recall. As a result of small samples and the lack of normality and adequate variation of some measures, heritability could not be estimated for all the tasks, unfortunately including the task assessing executive functioning. In our previous study, executive functioning was found to be highly heritable in bipolar disorder families (Antila et al., 2007b).

Due to rather small samples in the present study, we consider the heritability estimates here as indicative only. Basically, however, compared with our previous study, the heritability of cognitive functions was here generally similar irrespective of psychopathology in the family. There were, however, greater genetic effects in several cognitive tasks in mixed families. In these families, particularly visual and verbal working memory showed significant genetic effects, possibly reflecting liability for schizophrenia spectrum disorders, as previous studies have indicated significant genetic effects in these functions in schizophrenia (Cannon et al., 2000; Tuulio-Henriksson et al., 2002). In addition, previous studies have shown that working memory impairment appears to discriminate between schizophrenia and bipolar disorder (Goldberg, 1999), and that spatial working memory differentiates patients with non-psychotic bipolar disorder patients from patients with psychosis (Glahn et al., 2007; Glahn et al., 2006). In the present study, bipolar I disorder patients from mixed families scored lower than controls in verbal working memory.

4.2. Study limitations

One limitation of our study was that the current mood state was assessed only with the SCID-I interview. Using specific rating scales for mania and depression would have allowed more careful controlling of current mood state. However, the current and lifetime diagnoses using the SCID were made on the same day as the neuropsychological assessment. All patients with acute conditions were excluded. We included patients who were in partial remission, but additional analyses excluding them did not affect the results. Possible effects of medication on the test performance were not controlled for. However, the two patient groups did not differ significantly in the amount or quality of medication and the medication did not confound the comparisons between relatives and controls. In addition, there is no consensus about the effect of psychotropic medication on cognition and similar neuropsychological findings have been found among unmedicated bipolar patients (Macqueen and Young, 2003; Pavuluri et al., 2006).

Moreover, inclusion of familial type of bipolar disorder limits the generalization of our results. In addition, in both patient groups, most of the patients had psychotic symptoms in illness history (85% in bipolar families vs. 95% in mixed families). In families with bipolar disorder only, we included three families that had one member with other psychotic disorder (not schizophrenia or schizoaffective disorder), but additional analyses excluding them did not affect the results.

Another limitation of our study was the small sample size with possible type II error consequences, as well as restrictions for estimating heritability. The power limitations should therefore be taken into account when interpreting the results. We chose not to use multiple corrections because diminishing power in an already low power analysis may have increased the risk not detecting a true difference. Instead, we decided that P values of .01 and below represent statistical significance.

4.3. The strengths of the study

To our knowledge, this is the first study that used population-based samples in studying neuropsychological functioning in familial bipolar I disorder and its association with other severe mental disorders within families. Moreover, only few studies have estimated the heritability of cognitive functioning in bipolar I disorder (Antila et al., 2007b). In our study, the diagnostic procedure was carefully conducted and detailed using all available psychiatric case notes for the final diagnostic assignment and the subjects were assessed with the SCID on the study day.

In conclusion, our findings suggest that impaired psychomotor processing speed and executive function may represent vulnerability markers of bipolar I disorder irrespective of

psychopathology in the family. Both groups of bipolar patients and their relatives were impaired in psychomotor processing speed and executive functioning. However, those patients with family members suffering from schizophrenia or schizoaffective disorders had a more pronounced dysfunction in executive functioning, suggesting that the presence of a more severe psychotic disorder in the family may have an effect on this cognitive function. On the other hand, verbal memory was impaired only among patients suggesting that this impairment may relate more to the symptoms of the disorder. Cognitive impairments may contribute to functional outcome of the patients (Martinez-Aran et al., 2007) and cognitive functioning of bipolar patients should be more routinely assessed in clinical practice.

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Conflict of interest

The Authors have no financial disclosures to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jad.2008.11.006.

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IV

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The Effect of Processing Speed on Cognitive Functioning in Patients with Familial Bipolar I Disorder and Their Unaffected Relatives

Mervi Antila[a, b] Tuula Kieseppä[a, c] Timo Partonen[a] Jouko Lönnqvist[a, c]
Annamari Tuulio-Henriksson[a, b, d]

[a]Department of Mental Health and Substance Abuse Services, National Institute for Health and Welfare, [b]Institute of Behavioral Sciences, and [c]Department of Psychiatry, University of Helsinki, and [d]Research Department, Social Insurance Institution, Helsinki, Finland

Key Words
Bipolar disorder · Cognitive · Neuropsychological · Endophenotype · Memory · Executive functions · Processing speed

Abstract
Background: Despite increasing evidence of cognitive dysfunctions in bipolar I disorder, there is no specific neuropsychological profile of the disorder. ***Sampling and Method:*** The aim of the present study was to investigate the effect of processing speed on other cognitive functions in a population-based sample of 32 familial bipolar I disorder patients, their 40 unaffected first-degree relatives and 55 controls. A neuropsychological test battery was administered to all participants, and the effect of processing speed on other cognitive functions was analyzed with the digit symbol subtest of the Wechsler Adult Intelligence Scale-Revised both in within- and between-group comparisons. ***Results:*** After adjusting for the effect of processing speed, only small differences were detected in short-delay cued recall and in long-delay memory between patients and controls, as well as between patients and relatives. Relatives scored better than controls only in verbal ability. Processing speed had a significant effect on nearly all scores, differing by group when patients, relatives and controls were examined separately, the effect being most extensive in patients. ***Conclusions:*** These results support the view that impaired processing speed in particular contributes to a range of cognitive dysfunctions in bipolar disorder. However, it may not be specific to bipolar I disorder and can possibly be considered a shared endophenotype with other mental disorders.

Introduction

Despite increasing evidence of cognitive dysfunctions in bipolar I disorder [1, 2], there is no specific neuropsychological profile of the disorder. While euthymic bipolar I disorder patients have shown impairments particularly in executive functioning and verbal memory, the findings across studies have been inconsistent [1–3]. These inconsistent results have partly made it difficult to specify a neuropsychological profile of bipolar I disorder. Similar cognitive dysfunctions are also found in first-degree relatives of bipolar patients, although to a lesser degree [1–3]. In addition, bipolar patients show large deficits

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Mervi Antila
Department of Mental Health and Substance Abuse Services
National Institute for Health and Welfare, Mannerheimintie 166
FI–00300 Helsinki (Finland)
Tel. +358 2 0610 8520, Fax +358 2 0610 7442, E-Mail mervi.antila@thl.fi

in processing speed [1, 2], which may be impaired also in relatives of familial bipolar I disorder [4, 5]. Robinson et al. [6] have suggested that further research is required to investigate whether the cognitive dysfunction associated with bipolar disorder arises from a certain deficit. Particularly memory performance may be affected by other cognitive functions including executive functioning [7] and processing speed [8]. The role of slowed processing speed in verbal memory has been evidenced in other mental disorders including schizophrenia [9–11] and depression [12] and also in a twin sample of bipolar I disorder patients [13]. According to our previous studies of bipolar I disorder patients and their first-degree relatives, processing speed may be a potential endophenotype [14] for bipolar disorder [4, 15]. In our previous study, we found that both the patients with familial bipolar I disorder and their unaffected first-degree relatives were significantly impaired compared to the controls in the task measuring processing speed (assessed with the digit symbol subtest of the Wechsler Adult Intelligence Scale-Revised, WAIS-R) [4]. In addition, the patients were more impaired in this function than their relatives. In this study, the relatives showed slight impairment in executive function compared to the controls, but there were no other significant differences between the relatives and controls. Bipolar patients were impaired in most tasks assessing verbal learning and memory compared with both the unaffected relatives and controls. They also differed from the controls in tasks of executive functions. Since the task assessing processing speed was the only function in which both the patients and relatives were significantly impaired compared to the controls, we set out to investigate the effect of this function on other cognitive functions in this same population-based sample of familial bipolar I disorder patients, their first-degree relatives and controls [4]. Based on previous studies, we hypothesized that processing speed would have a significant effect on other cognitive functions in bipolar I disorder.

Methods

The population-based study sample comprised families with at least 2 members with either bipolar disorder or schizoaffective disorder, bipolar type. Altogether 153 family members from 57 families were interviewed and tested. Of the 57 families, 41 fulfilled the inclusion criteria of this study. The excluded population has been described in detail elsewhere [4]. The final study sample included 41 families comprising 32 bipolar I patients (23 in full remission and 9 in partial remission according to DSM-IV criteria), and 40 relatives without a lifetime psychotic disorder, or any current mental disorder (8 had a lifetime axis I diagnosis; table 1).

Table 1. Demographic and clinical characteristics of participants

	Patients (n = 32)	Relatives (n = 40)	Controls (n = 55)
Age, years	51.4 ± 7.2	51.4 ± 9.1	51.3 ± 10.4
Education, years	10.5 ± 2.6	10.7 ± 2.7	11.9 ± 3.4
Age at onset, years	25.0 ± 7.0		
Episodes	6.7 ± 7.3		
Gender			
Male	14 (54)	19 (47)	27 (48)
Female	18 (56)	21 (53)	28 (51)
Axis I diagnosis (lifetime)			
Bipolar I disorder	32	–	–
Major depressive disorder with single episode	–	1	6
Depressive disorder NOS	–	1	5
Dysthymic disorder	–	1	–
Alcohol dependence or abuse (not current)	4[a]	3	4
Adjustment disorder	–	2	1
Anxiety disorder	–	–	1
Specific phobia	–	–	2[a]
Somatoform disorder NOS	–	–	–
Eating disorder NOS	–	–	1[a]
None	–	32	38

Figures are means ± SD or numbers of cases with percentages in parentheses. The groups did not differ statistically in age, sex, education and gender (data not shown). NOS = Not otherwise specified.

[a] Comorbid lifetime axis I diagnosis.

In addition, 55 controls without any personal or family history of psychotic disorder were recruited from a national health survey [16, 17]. For 17 control subjects, a lifetime axis I diagnosis (only specific phobia being current) was assigned at the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I). The groups did not differ in age, sex and education. The study protocol was approved by the Ethics Committee of the National Public Health Institute and by the Ministry of Social Affairs and Health. After a complete description of the study, a written informed consent was received from all subjects.

Clinical and Neuropsychological Assessments

All the participants were interviewed using the SCID I [18], and experienced psychiatrists made the final consensus diagnoses, based on all available data, including case note records from hospital and outpatient treatments, and the SCID. In addition, all the participants completed a neuropsychological test battery administered in fixed order. Processing speed was assessed using the digit symbol subtest of the WAIS-R [19]. Verbal ability was evaluated with the vocabulary subtest of the WAIS-R. Auditory attention and verbal working memory were assessed with the digit span forward and backward tasks, and visual attention and working memory with the visual span forward and backward tasks of

Table 2. Effect of processing speed on neuropsychological test values in within-group and between-group comparisons

	Bipolar patients		Relatives		Controls		Between-group comparisons	
Variables	estimate	p	estimate	p	estimate	p	estimate	p
Verbal ability (WAIS-R)								
Vocabulary	0.93 (0.10)	<0.0001	0.31 (0.15)	0.04	0.43 (0.13)	0.002	0.45 (0.07)	<0.0001
Attention and working memory (WMS-R)								
Digit span forward	0.06 (0.04)	0.11	0.13 (0.03)	<0.0001	0.01 (0.02)	0.59	0.06 (0.02)	<0.0001
Digit span backward	0.08 (0.02)	0.001	0.16 (0.03)	<0.0001	0.06 (0.02)	0.008	0.08 (0.01)	<0.0001
Visual span forward	0.05 (0.02)	0.009	0.06 (0.02)	0.003	0.03 (0.02)	0.13	0.05 (0.01)	<0.0001
Visual span backward	0.03 (0.02)	0.29	0.04 (0.02)	0.03	0.02 (0.02)	0.43	0.03 (0.01)	0.01
Verbal learning and memory (CVLT)								
Learning trials 1–5	0.43 (0.09)	<0.0001	0.34 (0.12)	0.004	0.27 (0.12)	0.04	0.37 (0.06)	<0.0001
Learning slope	0.01 (0.01)	0.33	0.01 (0.01)	0.16	0.01 (0.01)	0.47	0.01 (0.01)	0.04
Free short recall	0.13 (0.03)	<0.0001	0.09 (0.04)	0.008	0.03 (0.04)	0.47	0.08 (0.02)	<0.0001
Cued short recall	0.08 (0.37)	0.82	0.07 (0.03)	0.02	0.03 (0.04)	0.43	0.06 (0.02)	0.001
Free delayed recall	0.10 (0.02)	<0.0001	0.04 (0.04)	0.21	0.03 (0.04)	0.44	0.07 (0.02)	0.002
Cued delayed recall	0.12 (0.03)	0.0002	0.065 (0.03)	0.08	0.05 (0.04)	0.25	0.07 (0.02)	0.001
Short-delay free recall versus trial 5 of list A	0.002 (0.003)	0.58	0.002 (0.002)	0.40	0.0000003 (0.0002)	1.00	0.001 (0.001)	0.42
Semantic clustering	0.03 (0.01)	0.0005	0.02 (0.01)	0.004	0.02 (0.01)	0.08	0.02 (0.01)	<0.0001
Executive functions and attention (TMT)								
Part A (time)	–0.02 (0.003)	<0.0001	–0.03 (0.01)	<0.0001	–0.02 (0.004)	<0.0001	–0.02 (0.002)	<0.0001
Part A (% correct)	0.04 (0.03)	0.31	0.01 (0.03)	0.87	0.02 (0.04)	0.51	0.02 (0.02)	0.31
Part B (time)	–0.03 (0.004)	<0.0001	–0.02 (0.004)	<0.0001	–0.02 (0.01)	0.0003	–0.02 (0.002)	<0.0001
Part B (% correct)	0.12 (0.05)	0.01	0.03 (0.03)	0.41	0.04 (0.03)	0.19	0.05 (0.02)	0.001
Part B-A (time)	–0.03 (0.005)	<0.0001	–0.02 (0.01)	0.004	–0.02 (0.01)	0.009	–0.03 (0.004)	<0.0001

Figures in parentheses are standard errors. Analysis adjusted for age, sex and processing speed assessed with the digit symbol test of WAIS-R. WMS-R = Wechsler Adult Memory Scale-Revised; CVLT = California Verbal Learning Test.

the Wechsler Memory Scale-Revised [20]. The Trail Making Test (TMT) [21] part A was used to assess visual scanning and attention. TMT part B and the difference score TMT (B-A) were used to assess executive functioning. Correct performance (yes/no) was used as a variable of performance quality in both TMT parts. Verbal learning and memory was assessed with the California Verbal Learning Test [22]. Means and standard deviations of the neuropsychological raw test scores are described in detail by Antila et al. [4].

Statistical Analysis

Neuropsychological test performance between the patients, relatives and controls was compared using the generalized estimating equation model of the program R [23] estimating population-averaged regression coefficients while controlling for the correlation due to family data [24]. All models were adjusted for age and sex and the raw score in the digit symbol test. In the first phase, the effect of processing speed on other cognitive functioning was analyzed in between-group comparisons. In the second phase, the effect of processing speed on other cognitive functions was analyzed separately within groups. Because of multiple tests, statistical differences were considered as significant if $p \leq 0.01$ and as indicative of significance if $p \leq 0.05$.

Results

In the generalized estimated equation models, processing speed had a significant effect on most of the other neuropsychological test scores (table 2). Differences indicative of significance between patients and controls were detected in short-delay cued recall ($p \leq 0.05$), long-delay free and cued recalls (both p values ≤ 0.05) with the patients scoring lower than the controls, and in auditory attention ($p \leq 0.05$) in which the patients outperformed the controls (table 3). The patients performed worse than their relatives in short-delay cued recall ($p \leq 0.01$), in long-delay free and cued recalls (both p values ≤ 0.01), and in the learning slope ($p \leq 0.05$). In verbal ability, the relatives scored better than the controls ($p \leq 0.01$).

In the models in which the effect of processing speed was analyzed separately in each group, the effect was most extensive in the patients, less in the relatives and smallest in the controls (see p values of each group in table 2).

Table 3. Population-averaged model regression coefficients of differences on neuropsychological tests adjusted for processing speed

Variables	Patients vs. controls		Relatives vs. controls		Relatives vs. patients		Difference before adjustment[1]
	coef. (95% CI)	p	coef. (95% CI)	p	coef. (95% CI)	p	
Verbal ability (WAIS-R)							
Vocabulary	4.5 (–0.2 to 9.2)	0.063	6.1 (1.7 to 10.6)	0.007	1.7 (–2.6 to 6.0)	0.445	B < R*
Attention and working memory (WMS-R)							
Digit span forward	0.9 (0.2 to 1.6)	0.016	0.2 (–0.6 to –0.9)	0.643	–0.7 (–1.5 to 0.1)	0.098	
Digit span backward	0.8 (–0.03 to –1.6)	0.058	0.2 (–0.5 to –0.8)	0.625	–0.7 (–1.3 to 0.02)	0.056	
Visual span forward	0.2 (–0.5 to 0.9)	0.517	–0.04 (–0.6 to 0.6)	0.890	–0.3 (–0.9 to 0.3)	0.376	
Visual span backward	–0.4 (–1.4 to 0.6)	0.407	–0.5 (–1.2 to 0.2)	0.159	–0.1 (–1.1 to 1.0)	0.892	
Verbal learning and memory (CVLT)							
Learning trials 1–5	–2.6 (–6.5 to 1.4)	0.200	0.8 (–2.8 to 4.3)	0.670	3.4 (–0.6 to 7.3)	0.098	B < R***, C***
Learning slope	–0.1 (–0.3 to 0.2)	0.520	0.2 (–0.05 to 0.5)	0.107	0.3 (0.04 to 0.06)	0.024	B < R**, C*
Free short recall	–0.8 (–2.0 to –0.5)	0.231	–0.2 (–1.4 to 0.9)	0.693	0.5 (–0.6 to 1.7)	0.377	B < C**
Cued short recall	–1.2 (–2.3 to –0.1)	0.028	0.2 (–0.8 to 1.2)	0.696	1.4 (0.4 to 2.4)	0.005	B < R***, C***
Free delayed recall	–1.5 (–2.7 to –0.2)	0.020	0.09 (–1.1 to 1.2)	0.886	1.6 (0.4 to 2.7)	0.008	B < R***, C***
Cued delayed recall	–1.4 (–2.8 to –0.1)	0.040	0.5 (–0.6 to 1.5)	0.388	1.9 (0.7 to 3.1)	0.002	B < R***, C***
Short-delay free recall versus trial 5 of list A	0.004 (–0.09 to 0.09)	0.934	–0.02 (–0.09 to 0.04)	0.534	–0.02 (–0.1 to 0.05)	0.535	
Semantic clustering	–1.9 (–5.0 to 1.2)	0.236	–0.1 (–3.4 to 3.2)	0.938	1.8 (–1.4 to 4.9)	0.277	B < R*, C***
Executive functions and attention (TMT)							
Part A (time)	0.001 (–0.003 to 0.005)	0.567	–0.0002 (–0.004 to –0.003)	0.908	–0.001 (–0.004 to –0.002)	0.443	B < C***
Part A (% correct)	0.5 (–0.6 to 1.7)	0.373	0.3 (–0.7 to 1.4)	0.551	–0.2 (–1.2 to 0.8)	0.705	
Part B (time)	–0.001 (–0.002 to 0.001)	0.426	–0.0004 (–0.002 to 0.001)	0.654	0.0003 (–0.001 to 0.002)	0.722	B < R*, C***
Part B (% correct)	0.9 (–0.1 to 2.0)	0.089	0.7 (–0.3 to 1.6)	0.154	–0.2 (–1.3 to 0.9)	0.664	B < C**; R < C*
Part B–A (time)	–0.002 (–0.006 to –0.003)	0.434	–0.001 (–0.005 to 0.003)	0.671	0.001 (–0.003 to 0.005)	0.720	B < C**

Analysis adjusted for age, sex and processing speed assessed with the digit symbol test of WAIS-R. WMS-R = Wechsler Adult Memory Scale-Revised; CVLT = California Verbal Learning Test; B = bipolar I disorder patients; R = unaffected relatives; C = controls.

[1] The results of differences on neuropsychological tests between patients, relatives and controls before adjustment have been presented previously in Antila et al. [4]. * $p \leq 0.05$ = indicative; $p \leq 0.01$ = significant; $p \leq 0.001$ = very significant.

Discussion

We found that processing speed had a significant effect on nearly all other assessed cognitive functions among patients with bipolar I disorder, their unaffected relatives and controls, all from population-based samples. In all groups, processing speed had a significant effect on attention and executive functions, and on verbal working memory.

However, when the effect of processing speed was assessed separately within the groups, the effect was partly dissimilar depending on the group. In both bipolar patients and their relatives, processing speed had a significant effect on learning and strategies of learning, on short-delay free recall as well as visual attention. However, there was no association of processing speed with these functions in the control group. In addition, processing speed had a significant effect on long-delay recall only in the bipolar patients. Interestingly, the effect of processing speed in memory scores reflecting learning or retrieval was most notable in the patients, less so in the relatives and absent in the controls. This may be due to the fact that the impairment in processing speed was greatest in the patients. The effect of processing speed on verbal learning and retrieval has been evidenced also among schizophrenia patients [9], twins with bipolar I disorder [13] as well as among healthy people [8]. In our study, processing speed had no effect on memory storage, this result being in line with previous research [8, 9, 13].

After adjustment for the effect of processing speed no significant differences were detected between the patients and controls. This has also been found among first-episode schizophrenia spectrum disorder patients [10]. An earlier study assessing the effect of processing speed on memory functions in bipolar I disorder [13]

showed that adjustment for processing speed made the difference between the study groups disappear in working memory and immediate memory tasks. However, differences remained in some delayed recall tasks. In our study, however, there were no significant differences between the patients and controls after adjusting for processing speed apart from a variation indicative of significance in short-delay cued recall and long-delay memory. Significant differences between the patients and relatives were found in short-delay cued recall and long-delay recall. These results suggest that in bipolar I disorder, short-term memory and learning may be more sensitive to processing speed impairment than long-term memory, in which the impairment may be independent of processing speed.

This study has certain limitations. There was no measurement of residual mood symptoms which would have allowed for a more careful control of the current mood. We did, however, assess the current mood with the SCID-I interview on the study day. Another limitation is that the only measure of processing speed was the digit symbol test. Processing speed may have been more accurately measured using a computerized test method, such as the Continuous Performance Test. However, in a previous study of a twin sample of bipolar I disorder patients, using a computerized measure of processing speed, similar effects on memory tasks as when using the digit symbol test were detected [13].

In conclusion, impaired processing speed in particular contributes to a range of cognitive dysfunctions in bipolar disorder. Based on this and earlier evidence it may be a potential endophenotype of bipolar disorder. However, it may not be specific to bipolar I disorder, since it has been evidenced in other mental disorders including schizophrenia and depression. There is an overlap in genetic susceptibility to schizophrenia and mood disorders [25], and it is possible that some endophenotypes may be shared in both disorders [26].

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