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ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN BIPOLAR DISORDER

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To Göran, Johannes, and Simon

ABSTRACT

Attention-deficit hyperactivity disorder (ADHD) is a developmental disorder, i.e., it is by definition present from childhood. The main features characterizing ADHD are the difficulties to regulate attention, activity level, and impulses. The hallmark of bipolar disorder is episodic mood alterations with restitution between episodes. Although debut in childhood may occur, bipolar disorder typically debuts in late adolescence or early adulthood. The overarching aim with this thesis was to study the importance of ADHD symptoms in adult bipolar disorder.

The first study assessed the prevalence of childhood and current ADHD in a cohort of adult bipolar patients. Childhood ADHD was a significant predictor for more frequent hypomanic, depressive, and mixed episodes, as well as more violent incidents, regardless of whether ADHD criteria were fulfilled in adulthood or not. It is suggested that bipolar disorder with a history of childhood ADHD might represent a developmental subtype of bipolar disorder.

The second study examined adult personality traits and affective regulation in euthymic bipolar patients with and without a history of childhood ADHD, as well as in a group of pure ADHD patients. Those with childhood ADHD had more affective dysregulation than bipolar patients without childhood ADHD. Childhood ADHD was a significant predictor for the development of affective dysregulation in terms of anxiety, stress-susceptibility, irritability, aggression, and impulsivity in bipolar patients. Whereas the personality profile in bipolar patients with childhood ADHD differed from pure bipolar patients, it closely resembled patients with pure ADHD.

The third study compared the levels of cerebrospinal fluid monoamine metabolites in euthymic patients with bipolar disorder type 1, with and without a history of childhood ADHD. The results demonstrated significantly lower levels of dopamine (HVA) and serotonin metabolites (5-HIAA) in those with a history of childhood ADHD, compared to those without ADHD. This lends biological support for the notion that bipolar disorder type 1 with childhood ADHD represents a specific subtype of bipolar disorder.

The fourth population-based study examined the risk for bipolar disorder and schizophrenia in ADHD probands and their relatives in comparison with matched controls. The aim was to test the hypothesis that ADHD is familially associated to bipolar disorder, but not to schizophrenia. The results showed that persons with ADHD were at considerably increased risk for bipolar disorder, and more importantly, so were their parents and siblings. Contrary to the hypothesis, however, persons with ADHD, along with their parents and siblings, had an equally increased risk for schizophrenia. Our results suggest that ADHD is familially associated with both bipolar disorder and schizophrenia.

LIST OF PUBLICATIONS

This thesis is based on the following communications, which will be referred to in the text by their Roman numerals:

I. Rydén E, Thase M.E, Stråht D, Åberg-Wistedt A, Bejerot S, Landén M (2009).
A history of childhood attention deficit hyperactivity disorder impacts clinical outcome in adult bipolar patients regardless of current ADHD.
Acta Psychiatrica Scandinavica, 120(3): 239-46

II. Rydén E, Rydén G, Bejerot S, Landén M.
A history of childhood ADHD is associated with affective dysregulation and specific personality traits in bipolar disorder.
Manuscript

III. Rydén E, Johansson C, Blennow K, Landén M (2009).
Lower CSF HVA and 5-HIAA in bipolar type 1 with a history of childhood ADHD.
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IV. Rydén E, Boman M, Långström N, Lichtenstein P, Landén M.
Bipolar disorder and schizophrenia in relatives of individuals with attention-deficit hyperactivity disorder: National nested case-control study
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LIST OF ABBREVIATIONS

ADD	Attention Deficit Disorder
ADE	Affective Disorder Evaluation
ADHD	Attention-Deficit Hyperactivity Disorder
ANOVA	Analysis of Variance
A-TAC	Autism-Tics, ADHD, and other Co-morbidities Questionnaire
BP	Bipolar Disorder
BP I	Bipolar Disorder Type 1
BP II	Bipolar Disorder Type 2
CI	Confidence Interval
CSF	Cerebrospinal fluid
DAT	Dopamine Transporter
DR	Dopamine Receptor
DSM-II-IV	Diagnostic and Statistical Manual of Mental Disorders, Second-Fourth Edition
fMRI	functional Magnetic Resonance Imaging
HDR	Hospital Discharge Register
HVA	Homovanillic Acid
MADRS	Montgomery-Åsberg Depression Rating Scale
MBD	Minimal Brain Dysfunction
NOS	Not Otherwise Specified
IQ	Intelligence Quotient
OR	Odds Ratio
PET	Positron Emission Tomography
SBP	S:t Göran Bipolar Project
SCID	Structured Clinical Interview for DSM Disorders
SCID II PQ	Structured Clinical Interview for Axis II Disorders, Patient Questionnaire
SD	Standard Deviation
SNAP-25	Synaptosome Associated Protein of 25000 Daltons
SSP	Swedish Universities Scales of Personality
STEP-BD	Systematic Treatment Enhancement Program for Bipolar Disorder
WURS-25	Wender Utah Rating Scale
5-HIAA	5-Hydroxyindoleacetic Acid
5-HT	5-Hydroxytryptamine
5-HTT	5-Hydroxytryptamine Transporter

INTRODUCTION

ADHD

Historical Aspects

In 1798, the Scottish physician Alexander Crichton (1763-1856) published "An inquiry into the nature and origin of mental derangements, on attention and its diseases", in which he describes what we today call Attention-Deficit Hyperactivity Disorder, ADHD (Crichton, 2008). He argued that the readiness with which we attend to subjects and objects depends on two principles: a constitutional proneness and a proneness acquired. He described the constitutional deficit of attention as an "incapacity of attending with a necessary degree of constancy to any one object, arising from unnatural or morbid sensibility of the nerves" and that this becomes evident very in life. Crichton argued that education should be adapted for each person's constitution.

The British pediatrician George Still (1868-1941) described in a series of lectures in 1902 children from his clinical practice (Still, 1902). The children were "aggressive, defiant, resistant to discipline, excessively emotional or passionate, showed little inhibitory volition, had serious problems with sustained attention and could not learn from the consequences of their actions". Still suggested that the deficits in inhibitory volition, moral control, and sustained attention had the same underlying neurological deficit. These children would today be conceptualized as having ADHD in association with oppositional defiant disorder or conduct disorder (Barkley, 2006).

Stimulant medication was noted to improve attention and disrupted behavior in the late 1930s, and confirmed in later studies (Laufer & Denhoff, 1957). During the 1960s and 1970s, the term used to describe these symptoms was Minimal Brain Dysfunction (MBD), which implied an underlying neurological dysfunction. Paul Wender included the following dysfunctions in MBD: motor function, attention-perception, cognition, learning, impulse control, interpersonal relations and emotions (Wood et al., 1976). The disorder was labeled Hyperkinetic Disorder in the second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (APA, 1968). In the 1970s, the importance of inattention as the hallmark of the syndrome was established by means of neuropsychological testing (Sykes et al., 1973). In the DSM-III, MBD was replaced by the term Attention Deficit Disorder (ADD) (APA, 1980). The diagnostic criteria used in current clinical practice and research was introduced in the DSM-IV (APA, 1994) and labeled ADHD.

Definition

ADHD is defined as a childhood onset developmental disorder with a disability in regulating attention, activity-level, and impulsivity (Table 1). These features are normally distributed in the population, and the developmental disorders, like ADHD, describe deviations from normality (Angold et al., 1999). Deficits in attention, activity-level, and impulsivity tend to occur together, which means that ADHD is a valid construct (Barkley, 2002).

Table 1. *DSM-IV criteria for ADHD*

A. Either (1) or (2):
(1) Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
Inattention

a. Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
b. Often has difficulty sustaining attention to tasks or play activities
c. Often does not seen to listen when spoken to directly
d. Often does not follow through on instructions and fail to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
e. Often has difficulties organizing tasks and activities
f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
g. Often looses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books or tools)
h. Is often easily distracted by extraneous stimuli
i. Is often forgetful in daily activities

(2) Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
Hyperactivity

a. Often fidgets with hands and feet or squirms in seat
b. Often leaves seat in classroom or in other situations in which remaining seated is expected
c. Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or in adults, may be limited to subjective feelings of restlessness)
d. Often has difficulty in playing or engaging in leisure activities quietly
e. Is often "on the go" or often acts as of " driven by a motor"
f. Often talks excessively

Impulsivity

g. Often blurts out answers before questions have been completed
h. Often has difficulty awaiting turn
i. Often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before the age of 7 years
C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).
D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning
E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorders, and are not better accounted for by another mental disorder (i.e., Mood Disorder, Anxiety Disorder, Dissociative disorder, or a Personality Disorder)

Subclassification of ADHD in DSM-IV
1.The combined subtype (A+B criteria)
2.The inattentive subtype (A criteria)
3.The hyperactive-impulsive subtype (B criteria)

Prevalence

The worldwide prevalence of ADHD in the general population is estimated to be 5-10% in children (Faraone et al., 2003) and 4.5% in adults (Kessler et al., 2006). The prevalence in males is six times higher than in females (Lahey et al., 1994). The prevalence is much higher in a psychiatric population; at one Swedish adults' psychiatric outpatient unit, 40% of patients had possible ADHD in childhood and 22% fulfilled the criteria for current ADHD (Nylander et al., 2009).

Classification Considerations

Even though the classification systems DSM and ICD (International Classification of Diseases) use a categorical (all-or-none) model, a dimensional view of ADHD is more consistent with available evidence (August & Garfinkel, 1989; Chen et al., 1994; Crawford et al., 2006; Edelbrock et al., 1984; Kadesjö & Gillberg, 2001; Levy et al., 1997; Sherman et al., 1997).

Only few children with ADHD have full functional and symptomatic remission when followed into adulthood, but more than half reach syndromal remission, i.e., they no longer meet the DSM criteria in adulthood (Biederman et al., 2000). This is, however, partly explained by the fact that the DSM-IV criteria were developed for children, not for adults (Lahey et al., 1994). Follow-up studies commonly use self-reports, which also underestimates the prevalence of ADHD associated problems in adulthood (Barkley et al., 2002). Moreover, the DSM-IV criteria are also male-referenced, since the majority of individuals in the DSM-IV field trials were boys (Lahey et al., 1994). This can partly explain the higher prevalence in males. Consequently, the present criteria fail to identify adults and females who might benefit from treatment (McGough & Barkley, 2004).

Heritability

Family studies lend credence to the importance of genetic factors in ADHD (Faraone & Doyle, 2000). A review of 20 twin studies estimated the mean heritability to 0.76, which is comparable to schizophrenia and bipolar disorder (Faraone et al., 2005; Levy et al., 1997; Thapar et al., 1995).

Co-occurrence of Other Developmental Disorders and Psychiatric Disorders

Patients with ADHD have in 60-100% one or more co-occurring disorder (Gillberg et al., 2004), the most frequent being oppositional defiant disorder and/or conduct disorder (Gillberg et al., 2004; Thapar et al., 2001), followed by autistic traits, motor coordination problems, anxiety and reading problems (Rommelse et al., 2009). Results of multivariate twin analyses suggest that ADHD shares most of its genetic liability with conduct disorder, oppositional defiant disorder, and executive functional deficits (Coolidge et al., 2000). A

higher co-existance of these disorders in childhood has significant influence on cognition, behavior and everyday functioning (Crawford et al., 2006). Adults with ADHD also have a high prevalence of co-occurring psychiatric disorders, e.g., mood disorder (40%) including 20% bipolar disorder, anxiety disorders (50%), and substance use disorders (15%) (Kessler et al., 2006).

Neuropsychology and ADHD

Executive processes are higher mental processes that direct thought, action, and emotion, particularly during active problem solving (Pennington & Ozonoff, 1996). A meta-analysis of 83 neuropsychological studies (Willcutt et al., 2005) showed that the ADHD groups exhibited significant impairment on all executive functions tasks; the strongest and most consistent effects were obtained on measures of response inhibition, vigilance, working memory, and planning. A 7-year follow up study of children showed that executive dysfunctions are stable over time (Biederman, Petty et al., 2007). Importantly, impairments of executive functions in subjects with ADHD as detected by standardized neuropsychological testing are related to performance difficulties in real-world activities (Lawrence et al., 2004).

Affective Regulation, Temperament, and Personality in ADHD

During childhood and adolescence, behavior normally changes in the direction of working towards long-term goals, ignoring irrelevant information that distracts us from our goals, and controlling our impulses (Bunge & Wright, 2007). Self-regulation defines the ability to control inner states and responses of emotions, along with the ability to control thoughts, attention, and performance (Bell & Deater-Deckard, 2007). The suggested mechanism of early developing self-regulation for both cognitive and emotional domains is *attention control*, which also is called effortful control, cognitive control, or conscientiousness (Nigg, 2000). Working memory is one neuropsychological executive component correlating to self-regulation (Bell & Deater-Deckard, 2007). Several magnetic resonance imaging (MRI) studies have examined the developmental changes in brain structure and function that underlie improvements in working memory and cognitive control over the course of development, and it has been established that the increased recruitment of task-relevant regions in the prefrontal cortex, parietal cortex, and striatum is associated with better performance in a range of cognitive tasks (Bunge & Wright, 2007).

In ADHD, there are impaiments in both *cognitive executive functions* that include self-regulation, working memory, planning, and cognitive flexibility, associated with the dorsolateral prefrontal cortex; and in *affective executive functions* like behavioral inhibition and attention, associated with ventral and medial regions of the prefrontal cortex, including the anterior cingulate cortex (Emond et al., 2009).

"Affective dysregulation", "emotion dysregulation", or "emotional instability" implies brief, temporally instable mood changes (Siever, 2005; Wagner & Linehan, 1999). Affective dysregulation is common in ADHD and was previously part of the MBD conceptualization, although it is not part of the current DSM-IV criteria for ADHD (Barkley, 1997; Nigg & Casey, 2005; Reimherr et al., 2005; Wood et al., 1976). Affective dysregulation is in the DSM-IV, however, a hallmark of borderline personality disorder.

In terms of personality traits, adults with ADHD have high rates of borderline-, antisocial-, and depressive personality disorders, and are characterized by high novelty seeking (impulsive, disorderly), high harm avoidance (pessimistic and anxious), and extremely low self-directedness (Anckarsäter et al., 2006; Cloninger & Svrakic, 1997; Faraone et al., 2009; First, 1997; Jacob et al., 2007). ADHD subjects also have higher neuroticism (i.e., emotion/affective instability/dysregulation) and lower conscientiousness (less self-disciplined, careful, organized and deliberate) (Jacob et al., 2007; McCrae & Costa, 1997). Because of this specific personality profile, personality traits have even been used to validate ADHD (Faraone et al., 2009).

Neurotransmission and ADHD

Dopamine

In 1974, Wender proposed a catecholamine theory of MBD (Wender, 1974) and in 1991, Levy launched the dopamine theory of ADHD (Levy, 1991). Dopamine is a member of the catecholamine family and a precursor to noradrenaline. The dopamine circuits include neuronal cellbodies in the midbrain structures substatia nigra and the ventral tegmental area that projects via the tuburoinfundibular, nigrostriatal, mesolimbic, and mesocortical pathways (Swanson et al., 2007). These pathways are involved in the motor system, impulsivity control, attention, reward seeking, emotional processing, working memory, and executive functions (Cousins et al., 2009), i.e., both non-emotional cognitive processes and emotional processes. The dopamine system is involved in encoding the *salience* of events in the external world, in other words, the importance of a specific stimulus over another stimulus.

Several lines of evidence suggest altered dopamine transmission in ADHD. First, an important piece of evidence rests in the fact that stimulant drugs like metylphenidate (Ritalin®, Concerta®) and dexamphetamin (Metamina®) that facilitate catecholamine transmission are highly effective in the treatment of ADHD (Arnsten & Li, 2005; Shaywitz et al., 2001; Wender et al., 2001; Volkow et al., 2005). Positron emission tomography (PET) studies suggest that blocking the dopamine transporter (DAT) is the mechanism by which the stimulant drug methylphenidate increases the availability of synaptic dopamine in the striatum (Swanson & Volkow, 2003; Volkow et al., 1998; Volkow et al., 2002; Volkow et al., 2005;).

Second, morphological MRI studies of ADHD subjects have demonstrated smaller brain regions in areas that contain a large density of dopamine receptors compared to controls, including the caudate nucleus and globus pallidus (Swanson et al., 2007), and the anterior regions, including dorsolateral prefrontal cortex and anterior cingulate (Seidman et al., 2006; Valera et al., 2007). Studies using functional MRI (fMRI) have found hypoactivation in the dopamine cortico-striatal-thalamic-cortical loop in children with ADHD during task activation (Durston et al., 2003; Rubia et al., 1999; Vaidya et al., 1998).

Third, in a PET study visualizing the dopamine reward system in subjects with ADHD, a reduction in dopamine synaptic markers associated with symptoms of inattention was shown (Volkow et al., 2009).

Fourth, the dopamine metabolite homovanillic acid (HVA) has been measured in the cerebrospinal fluid (CSF) of subjects with ADHD. The concentration of HVA in CSF gives insight into the turnover of dopamine in the mesolimbic and mesostriatal areas, and may be used as an indirect marker of the dopaminergic neurotransmission (Marin-Valencia et al., 2008). In children with MBD, CSF HVA was found to be lower compared to controls (Shaywitz et al., 1977). In another study of ADHD children, however, impulsivity and hyperactivity was positively correlated to CSF HVA, although these subjects were not compared to controls (Castellanos et al., 1994). In adults with ADHD, the literature on CSF HVA is scarce and inconclusive. One study found a trend towards lower CSF HVA in adult patients with ADD that had responded to methylphenidate, compared to controls (Reimherr et al., 1984). Another study found an inverse correlation between CSF HVA levels and WURS-25 (Wender Utah Rating Scale, measuring childhood ADHD) in substance abusers (Gerra et al., 2007). In a study of adult violent offenders, CSF HVA did not correlate to ratings of attention deficit or hyperactivity disorder in childhood (Söderström et al., 2003).

Fifth, there is genetic evidence of dopamine involvement in ADHD. Based on the dopamine theory of ADHD, the first candidate genes for ADHD described were the dopamine transporter gene (DAT), and the dopamine receptor type 4 (DRD4) genes (Cook et al., 1995; LaHoste et al., 1996). In a meta-analysis, statistically significant evidence of association with ADHD was shown with respect to variants of the DRD4, DRD5, DAT1, dopamine beta hydroxylase (DBH), the serotonin transporter (5-HTT), serotonin receptor 1B (HTR1B), and the synaptosomal-associated protein 25 (SNAP-25) genes (Faraone et al., 2005). DBH catalyzes the synthesis of noradrenalin from dopamine, which is crucial for catecholamine regulation (Cubells & Zabetian, 2004), and SNAP-25 is a multifunctional protein that plays essential roles in neurotransmitter release (Corradini et al., 2009). The serotonin receptor 1B (5-HTR1B) is a presynaptic heteroreceptor that control the release of dopamine (Sarhan et al.,

2000). The 5-HTT is the enzyme that constrains serotonin production, and variants are associated with individual differences in anger, fear, anxiety, depression, and trait neuroticism (i.e., affective/emotion dysregulation) (Pezawas et al., 2005; Rujescu et al., 2002; Thapar et al., 2005).

Serotonin

As illustrated above by genetic evidence, variants of serotonin receptors and transporters are also associated to ADHD. Serotonin is an important regulator of morphogenetic activities during early central nervous system development, including cell proliferation, migration, and differentiation (Peroutka, 1994). The serotonin and dopamine systems are closely related and there is a functional interaction between serotonergic and dopaminergic neurons in the brain (Di Matteo et al., 2008). Serotonergic neurons exert an inhibitory effect on midbrain dopamine cell bodies and influence dopamine release in terminal regions; this modulation is reciprocal (Di Giovanni et al., 2008; Oades, 2008).

Although few studies have focused on serotonin and ADHD, there are circumstantial evidence to suggest a role for the serotonin system in ADHD (Malmberg et al., 2008; Oades, 2007; Ribases et al., 2009): There are abundant support for the involvement of serotonin in impulsivity and aggression, which are common features in ADHD (Frankle et al., 2005; Retz & Rosler, 2009; Witte et al., 2009; Young et al., 1999; Zepf et al., 2008). The final product in the metabolism of serotonin is 5-HIAA, and low levels of CSF 5-HIAA has repeatedly been found to correlate with violence, aggression, and low impulse control (Åsberg et al., 1976; Brown et al., 1979; Jokinen et al., 2009; Linnoila et al., 1983; Stanley et al., 2000; Åsberg, 1997). Low CSF 5-HIAA is also a consistent finding in studies of suicide attempters (Åsberg et al., 1976; Brown et al., 1979; Jokinen et al., 2009; Linnoila et al., 1983; Nordström et al., 1994; Stanley et al., 2000; Träskman et al., 1981; Åsberg, 1997).

As opposed to dopaminergic drugs, however, drugs that affect the serotonin system are generally not concidered helpful for core features of ADHD in adults in the abscence of depression or dysthymia (Wender et al., 2001).

Environmental factors in ADHD

Although a substantial part of the etiology of ADHD is explained by genetic factors, there is evidence to support that environmental factors also increase the risk for ADHD, e.g., cigarette and alcohol exposure during pregnancy, premature or low birth weight, and lead exposure (Banerjee et al 2007). Traumatic brain injuries in childhood can also yield ADHD symptoms (Max et al., 2002). Most likely, there is also a gene-environment interaction (Caspi & Moffitt,

2006). As an example one study showed an association of DAT1 genotypes to ADHD and to maternal use of alcohol during pregnancy (Brookes et al., 2006).

Bipolar Disorder

Historical Aspects

Please consult Jules Angst for extensive account of the historical aspects of bipolar disorder (Angst & Marneros, 2001). In summary, Emil Kraepelin (1856-1926) launched in 1889 a unitary concept of affective disorders, including all clinical forms of melancholia and circular psychosis in "manic-depressive insanity". He included both manic and depressive episodes, as well as recurrent depression alone. Kraepelin's system put an emphasis on the patterns of features of the illness that differentiated it most clearly from dementia praecox (schizophrenia): the periodic and episodic course, the more benign prognosis, and a family history of manic-depressive illness. The distinction between bipolar disorder and unipolar disorder was reintroduced in the 1960 s (Leonhard, 1968; Perris, 1966). In the 1970s the concept of Bipolar Disorder type 1 (BP I) and type 2 (BP II) was introduced, distinguishing depression with mania from depression with hypomania (Dunner et al., 1976). In 1980, these concepts were incorporated into the DSM–III.

Cyclothymia dates back to a publication by Ewald Hecker (1843-1909) in 1877, describing periodic changes of depression and exaltation. Emil Kraepelin accepted this to be a mild form of bipolar disorder in 1899. In the 1920s, Ernst Kretchmer (1888-1964) argued that cyclothymia is rather a constitutional temperament. Kurt Schneider (1887-1967) rejected a continuous transition from temperament to psychosis and saw cyclothymia as part of a disease state (Brieger & Marneros, 1997). Cyclothymia was included in the DSM-III under the mood disorder chapter (APA, 1980).

Mixed state emerges from a concept used by Kraepelin in 1886. He described six different types including depressive or anxious mania, exited or agitated depression, mania with thought poverty, manic stupor, depression with flight of ideas, and inhibited mania subdivided into transition or autonomic forms. It has been suggested that a mixing of manic and depressive symptoms with cyclothymic, hyperthymic, or depressive temperament creates different mixed states (Akiskal & Pinto, 1999). These authors described that the most common symptoms of hypomania found in major depressive disorder are irritability, racing/crowded thoughts, distractibility, psychomotor agitation, and pressured speech. They also concluded that there is a close relation between BP II (see below) and depressive mixed state, and between cyclothymic and hyperthymic temperaments.

Diagnostic criteria

Bipolar Disorder Type 1

The essential feature of BP I is a clinical course characterized by the occurrence of one or more manic episodes or mixed episodes (Table 2). Often individuals have also had one or more depressive episodes. Episodes of substance mood disorder (due to the direct effect of medication, or other somatic treatments for depression, drug abuse, or toxin exposure) or of mood disorder due to a general medical condition, are not considered in the diagnosis of BP I.

Bipolar Disorder Type 2

The essential feature of BP II is the occurrence of one or more major depressive episodes, accompanied by at least one hypomanic episode (Table 2). Episodes of substance-induced mood disorder (due to the direct effects of a medication, or other somatic treatments for depression, a drug of abuse, or toxin exposure) or of mood disorder due to a general medical condition do not count toward a diagnosis of BP II.

Table 2. *DSM-IV Criteria for Bipolar Disorder Episodes*

Criteria for Manic Episode (DSM-IV)

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

- inflated self-esteem or grandiosity
- decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
- more talkative than usual or pressure to keep talking
- flight of ideas or subjective experience that thoughts are racing
- distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
- increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
- excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

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, a medication, or other treatments) or a general medical condition (e.g., hyperthyroidism).

Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder.

Criteria for Mixed Episode (DSM-IV)

A. The criteria are met both for a Manic Episode and for a Major Depressive Episode (except for duration) nearly every day during at least a 1-week period.

B. 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.

Criteria for Hypomanic Episode (DSM-IV)

A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual non-depressed mood.

B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

- inflated self-esteem or grandiosity
- decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
- more talkative than usual or pressure to keep talking
- flight of ideas or subjective experience that thoughts are racing
- distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
- increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
- excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.

F. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Note: Hypomanic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar II Disorder.

Cyclothymia

The DSM-IV defines cyclothymia as chronic fluctuating mood disturbance, involving numerous periods of hypomanic symptoms and numerous periods of depressive symptoms. The hypomanic symptoms are of insufficient number, severity, pervasiveness, or duration to meet the full criteria for a hypomanic episode. During a 2-year period (1-year for children and adolescents), any symptom-free intervals last no longer than two months and the 2-year period of cyclothymia symptoms must be free from major depressive, manic, and mixed episodes. After the initial two years of the cyclothymic disorder, manic or mixed episodes may be superimposed on the cyclothymia disorder, in which case both cyclothymia and BP I are diagnosed, and if major depressive episode is superimposed both cyclothymia and BP II are diagnosed .

Bipolar Disorder Not Otherwise Specified

BP NOS is also called sub-threshold bipolar disorder and indicates bipolar illness in a patient who does not meet the criteria for one of the subtypes of the formal DSM-IV bipolar diagnostic categories (BP I, BP II, or cyclothymia).

Rapid Cycling

Rapid cycling is characterized by four or more affective episodes per year (Coryell et al., 2003; MacKinnon et al., 2003; Perugi et al., 1997).

Prevalence

In epidemiological studies the estimated lifetime prevalence of BP I is 0.3-1.2%, BP II 1%, and cyclothymia 0.4-6% (Depue 1981; Placidi 1998, Chiaroni 2005, Akiskal 1998).

Classification Considerations

Bipolar disorder is described as a categorical disorder in DSM-IV, although a bipolar spectrum has also been proposed (Table 3) (Akiskal, 2007; Angst, 2007; van Valkenburg et al., 2006). In the bipolar spectrum, the authors place "full-blown" manic-psychotic symptoms in the hard end, and cyclothymia and subsyndromal conditions in the milder end of the spectrum. Akiskal has argued that the 20% of the population that have marked affective temperaments should be included in the bipolar spectrum (Angst et al., 2003; Rihmer et al., 2009). This includes depressive, cyclothymic and anxious temperaments that is more frequent in women, and hyperthymic and irritable temperaments predominating in men.

Table 3. *The Bipolar Spectrum, Akiskal's bipolar subtypes (Akiskal & Pinto, 1999)*

Bipolar I: full-blown mania
Bipolar I ½: depression with protracted hypomania
Bipolar II: depression with hypomanic episodes
Bipolar II ½: cyclothymic disorder
Bipolar III: hypomania due to antidepressant drugs
Bipolar III ½: hypomania and/or depression associated with substance use
Bipolar IV: depression associated with hyperthymic temperament
Bipolar V: recurrent depressions that are admixed with dysphoric hypomania
Bipolar VI: late onset depression with mixed mood features, progressing to a dementia-like syndrome

Heritability

The heritability of bipolar disorder is high. The estimated heritability of BP I is 0.73- 0.93 (Cardno et al., 1999; Edvardsen et al., 2008; Kendler et al., 1995; Kieseppa et al., 2004); of BP I and BP II combined 0.77, and of BP I, BP II, and Cyclothymia 0.71 (Edvardsen et al., 2008).

Childhood Bipolar Disorder

Althought an increasing number of children and adolescents are diagnosed with bipolar disorder, it is still a rare condition (Baroni et al., 2009). The characteristics of childhood onset is a disorder that is more chronic than episodic, more irritable, more mixed, more rapid cycling, and with co-occurring ADHD and conduct disorder to a high degree (Geller & Luby, 1997; Masi et al., 2006). In an 8-year follow up of children with BP I, 44% still fulfilled the criteria for bipolar disorder (Geller et al., 2008). It has been suggested that childhood bipolar disorder is a severe developmental subtype of bipolar disorder (Biederman et al., 2004).

Pathophysiology of Bipolar Disorder

No specific associated genes have been established in bipolar disorder, although it is known to be a highly heritable disorder, established by family and twin studies (Bertelsen et al., 1977; Reich et al., 1969). The strongest suggested candidate genes for bipolar disorder are also candidate genes for schizophrenia, schizoaffective disorder and major depressive disorder (Barnett & Smoller, 2009; Kato, 2007). The conclusion is that the limited understanding of pathogenesis in bipolar disorder, and the genetic and phenotypic complexity of the syndrome, has complicated the search for genes influencing bipolar disorder.

There is also remaining uncertainty of whichbrain areas that are crucial for the pathogenesis of bipolar disorder (Ellison-Wright & Bullmore, 2010). A meta-analytic review shows that bipolar disorder is characterised by whole brain and prefrontal lobe volume reductions, and by increases in the volume of the globus pallidus and lateral ventricles (Arnone et al., 2009). Meta-analysis has further identified four regions of gray matter decrease in bipolar subjects compared to controls, including the right insula, perigenual anterior cingulate, left insula and subgenual anterior cingulate (Ellison-Wright & Bullmore, 2010). Although the authors concluded that the brain volume differed significantly from healthy controls, most changes did not seem to be diagnostically specific, compared to patients with schizophrenia.

Dopamine

Dopamine has been a prime candidate in the pathogenesis of bipolar disorder. A vast literature has shown that neuroleptic drugs, dopamine antagonists, are efficient in preventing manic episodes (Beynon et al., 2009; Smith et al., 2007) and treating acute mania (Smith et al., 2007). Pretreatment plasma HVA has been shown to predict neuroleptic treatment response in manic psychosis, where those with higher HVA responded better (Mazure & Bowers, 1998). Lithium, being the first line treatment in BP I, has been shown to decrease dopamine formation (Friedman & Gershon, 1973). Agents that increase dopamine availability, on the other hand, have been shown to trigger hypomania-mania, exemplified by amphetamine (Gerner et al., 1976; Jacobs & Silverstone, 1986), the dopamine precursor L-dopa (Bunney et al., 1970), and dopamine agonist bromocriptine (Silverstone, 1984). Dopamine excess has therefore been a theoretical construct of mania and a deficiency of dopamine has been suggested in depression, taken from disease models of Parkinson's disease, a degenerative disorder of dopaminergic cells (Lieberman, 2006) where the dopamine deficiency leads to decreased motivation and drive and psychomotor slowing. A dopamine deficiency in depression has been supported by consistent findings of a reduction of the CSF HVA in depressed subjects (Åsberg et al., 1984; Roy et al., 1985; Träskman-Bendz et al., 1984).

Compared to ADHD, fewer imaging studies of bipolar disorder and dopamine have been performed. One PET study found increased binding potential for striatal D2 receptors in psychotic bipolar patients compared to non-psychotic bipolar patients, which was similar to patients with schizophrenia (Pearlson et al., 1995). In a SPECT (single photon emission computed tomography) study where euthymic bipolar patients and healthy controls were subjected to an amphetamine challenge, there was a significantly greater behavioral response in bipolar patients than in healthy subjects, but no difference in striatal binding (Anand et al., 2000). The authors concluded that they did not find evidence for increased striatal dopamine release but suggested that the data was consistent with enhanced postsynaptic dopamine responsivity in patients with bipolar disorder.

Although these data point at an important role of dopamine in bipolar disorder, there is not considered to be a primary dopaminergic abnormality in bipolar disorder in euthymia, but a defect in the system of dampening and fine-tuning (Goodwin, 2007).

Serotonin

There are several lines of evicence supporting a role for serotonin in depression (Goodwin, 2007). Earlier studies have concluded that low CSF 5-HIAA is associated with depression (Åsberg & Träskman, 1981; Träskman-Bendz et al., 1984). In post-mortem studies, a low concentration of serotonin and 5-HIAA has been found in the brain stem of depressed patients who completed suicide (Träskman-Bendz et al., 1984). In CSF, levels of HVA, 5-HIAA, and the noradrenalin metabolite methoxyhydroxyphenylglycol (MHPG) have been found to be inversely correlated with the lethality of suicide attempts in bipolar disorder (Sher et al., 2006). Agents that increase intrasynaptic serotonin are effective antidepressant agents and can trigger manic episodes, although to a lesser degree than dopaminergic drugs (Goodwin, 2007).

ADHD and Bipolar Disorder

In 1981, the first suggested relation between hyperactivity in childhood and manic-depressive illness in adulthood was presented (Dvoredsky & Stewart, 1981). In 1987, a family study showed that major affective disorders were significantly more common in ADHD probands than in normal controls (Biederman et al., 1987). The association between ADHD and bipolar disorder has been established in child– and adolescent psychiatry, and it is concluded that this is not a pure artifact of overlapping symptoms (Biederman et al., 1991; Milberger et al., 1995). Epidemiological and clinical studies of children and adolescents with bipolar disorder has shown a prevalence of co-occurring ADHD in up to 85% of children, and in 50% of adolescents (Geller & Luby, 1997).

Family studies suggest that ADHD and bipolar disorder co-segregate, e.g., are inherited together, and that ADHD/bipolar disorder is a distinct form of ADHD (Faraone et al., 1997; Faraone et al., 2001). A recent study showed that children of subjects with bipolar disorder have an elevated risk of ADHD, and have greater levels of subthreshold manic and depressive symptoms than children of comparison parents (Birmaher et al, 2010).

Twin studies also indicate an association of ADHD and bipolar disorder in children and adolescents examined by the Child Behaviour Checklist (CBCL) (Althoff et al., 2006; Hudziak et al., 2005; Reich et al., 2005). The rate of developing prepubertal and early adolescent BP I in children with ADHD has been estimeted to 28% in a prospective study (Tillman & Geller, 2006). ADHD has also been shown to be a specific risk factor for the transition from unipolar to bipolar disorder in a prospective study of youth (Biederman et al., 2009).

Studies of adults with co-occurring ADHD and bipolar disorder have only lately started to evolve. The first systematic assessment of the association of ADHD and bipolar disorder in adults was conducted in a large multicenter study, the Systematic Treatment Enhancement Program for Bipolar Disorder, STEP-BD (Nierenberg et al 2005). The prevalence of lifetime ADHD (current ADHD) was estimated to 9.5 %, representing the combined subtype of ADHD. In other studies, where all subtypes of ADHD were included, the prevalence of lifetime ADHD in bipolar disorder has been estimated to 15.9-20.2% (Kessler et al., 2006; Tamam et al., 2006) (Table 4).

Table 4. *Previous studies of the prevalence of ADHD in bipolar disorder in adults, modified from Wingo and Ghaemi (2007)*

Author	Study	Year	Population	Diagnostic method bipolar disorder	Diagnostic method ADHD	ADHD Criteria	% Current ADHD	% Child-hood ADHD
Nierenberg	STEP-BD	2005	Bipolar subjects; outpatients (N=919)	DSM-IV based on MINI	MINI DSM- IV criteria	Combined subtype	9.5	-
Kessler	National Co-morbidity survey	2006	Population representatives of 9282 household residents (N=3199)	DSM- IV based on CIDI	Adult ADHD Clinical Diagnostic Scale DSM- IV criteria	All subtypes	21.2	-
Tamam		2006	BP I; outpatients (N=44)	DSM-IV based on SCID I	WURS-25 DSM-IV criteria	All subtypes	15.9	34.1
Tamam		2008	Bipolar subjects; outpatients (N=159)	DSM- IV based on SCID I	WURS-25 K-SADS-PL DSM- IV criteria	All subtypes	16.3	27.2

Differences and Similarities between ADHD and Bipolar Disorder in Adults

The hallmark of bipolar disorder is distinct episodes of mania, hypomania and depression, typically with regained function between episodes. It is not defined as existing from childhood, although it may exist (Geller & Luby, 1997). ADHD, on the other hand, is a developmental disorder present from childhood, characterized by a chronic dysregulation of certain aspects of cognition, impulsivity and emotions. In adults, current psychiatric symptoms can be difficult to interpret, since many symptoms and factors often co-occur, including developmental function disabilities, personality factors, traumatic experiences, subclinical/clinical affective symptoms, anxiety, alcohol and drug use/abuse, and different life-events. Current mood states can mimic ADHD, with executive dysfunctions, concentration problems, restlessness, irritability and hyperactivity. Therefore, a developmental history can distinguish trait function from current state. Mood alterations can be separated from ADHD traits by the presence of episodes that are qualitatively different from "everyday" functioning.

Biological correlates to the difference between ADHD and bipolar disorder in adults is scarce (Wingo & Ghaemi, 2007). One MRI volumetric study compared three groups, subjects with

ADHD only, subjects with bipolar disorder only, and subjects with both bipolar disorder and co-occurring ADHD (Biederman, Makris et al., 2007). The results showed that ADHD was selectively associated with smaller neocortical, including superior prefrontal cortex and anterior cingulated cortex volumes, and cerebellar gray matter volume. Bipolar disorder was associated with significantly larger thalamic volumes, and smaller left orbital prefrontal volumes, independently of the co-occurrence of ADHD. The combined group with ADHD and bipolar disorder had elements of each disorder's neuroanatomic deviations. The authors concluded that this pattern of syndrome-congruent neuroanatomic findings suggests that ADHD and bipolar disorder contribute relatively selectively to brain volume alterations.

Clinical Importance

In 2000, it was shown that bipolar patients with a history of childhood ADHD had an earlier onset of affective disorder (Sachs et al., 2000). In the STEP-BD study, patients with co-occurring ADHD had a worse course of bipolar disorder, with more episodes of mania and depression, and fewer remissions (Nierenberg et al., 2005). These subjects were also more likely to suffer from co-occurring anxiety disorders, post- traumatic stress disorder, abuse, violence and suicide-attempts. These findings imply more rapid cycling and a more chronic than episodic course, compared to patients without co-occurring ADHD, and highlighted the importance of ADHD in bipolar disorder.

Rationale of Thesis

Although there are available treatments for bipolar disorder, the prognosis is very dismal. One reason for this is that the DSM diagnostic categories are insufficient tools to guide individual treatment desicisons, which means that there are no instruments to predict whether an individual will respond to a particular treatment or not. Therefore, we urgently need to define more homogenous diagnostic groups that enable us to individually tailor treatment. Moreover, valid homogenous diagnostic groups are a prerequisite for pathophysiological research, which in turn is key for developing novel treatment strategies. This thesis revolves around the notion that some - but far from all - bipolar patients have ADHD symptoms in addition to their mood disturbance, and the question whether making a diagnostic distinction between these groups would faciliate prognostic judgement, pathophysiological research, and individual treatment decisions.

Since there are scarce assessments of ADHD in bipolar disorder, the first aim was to meticulously survey ADHD symptoms in bipolar patients and their impact on the course of illness. To this end, we extended the ADHD assessment to include an interview with a parent and added specific assessment tools to address inattentive problems that are more common in adults and females, to increase the diagnostic validity of ADHD. We also wanted to explore

the specific importance of having childhood ADHD, since many subjects with ADHD have ADHD-related problems in adulthood without fulfilling the DSM-IV criteria. Since ADHD subjects have affective dysregulation, we wanted to explore if ADHD accounts for the affective dysregulation that has been found in bipolar disorder. Elucidating this question has implications for our conceptualisation of, e.g., mixed states, rapid cycling, cyclothymia and the notion of a bipolar spectrum. One way to test the validity of a specific subphenotype of bipolar disorder with ADHD is to study biological markers. We chose to assess monoamine metabolites i CSF in euthymia since there is strong support of monoaminergic dysfunction in ADHD. Finally, we hypothesized that ADHD might share basic etiologic mechanisms and hence familiality with bipolar disorder, but not with schizophrenia. In order to circumvent the problems that diagnostic criteria for different psychiatric syndromes include overlapping symptoms and individual differences in how disorder manifests itself, we studied the occurrence of schizophrenia and bipolar disorder in relatives of probands with ADHD, in addition to ADHD probands themselves in a population-based study.

AIMS

The overarching aim of this thesis was to study the developmental disorder ADHD in relation to bipolar disorder.

The specific aims were:

Paper I

- to assess the prevalence of ADHD in adult bipolar patients using more valid assessment tools than had previously been done;
- to study how childhood and adult ADHD impacts the course of illness in bipolar patients;

Paper II

- to test the hypothesis that affective dysregulation in bipolar disorder is more prevalent in the group with co-occurring ADHD than in pure bipolar patients;
- to test the validity of the ADHD subgroup of bipolar disorder by comparing personality measures with a contrast group containing pure ADHD patients;

Paper III

- to test the hypothesis that the levels of monoamine metabolites in CSF differ between pure bipolar patients and bipolar patients with a history of childhood ADHD;

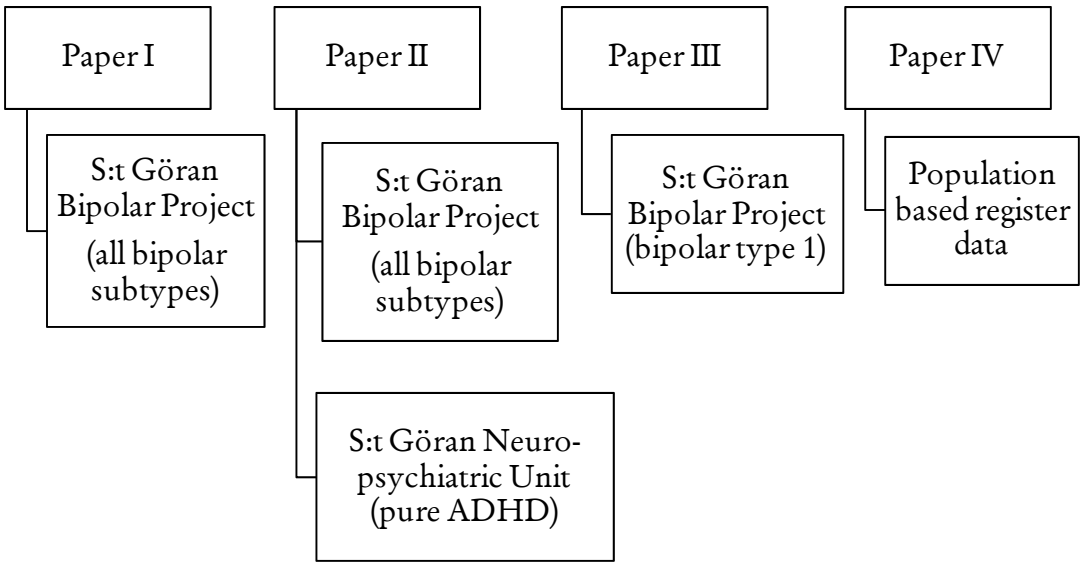
Paper IV

- to test the hypothesis that ADHD is familially coupled to bipolar disorder, but not to schizophrenia.

MATERIALS AND METHODS

Materials from three different cohorts were used in this thesis. Details of these cohorts are outlined below (Figure 1).

Figure 1. *Cohorts studied in Paper I-IV*



S:t Göran Bipolar Project

The S:t Göran Bipolar Project is a prospective, longitudinal study that was launched in 2005 aiming to provide early identification, assessment, treatment, and follow-up of patients with bipolar disorder, and is built as a clinical program intertwined with the regular health care system. Baseline and follow-up variables include brain imaging, neurochemistry, genetics, and laboratory blood work in combination with meticulous clinical diagnostic assessments and neuropsychological testing. This broad scope of clinical data in conjunction with biological data enables research about the biological underpinnings of bipolar disorder, as well as about predictive factors for the outcome of bipolar disorder.

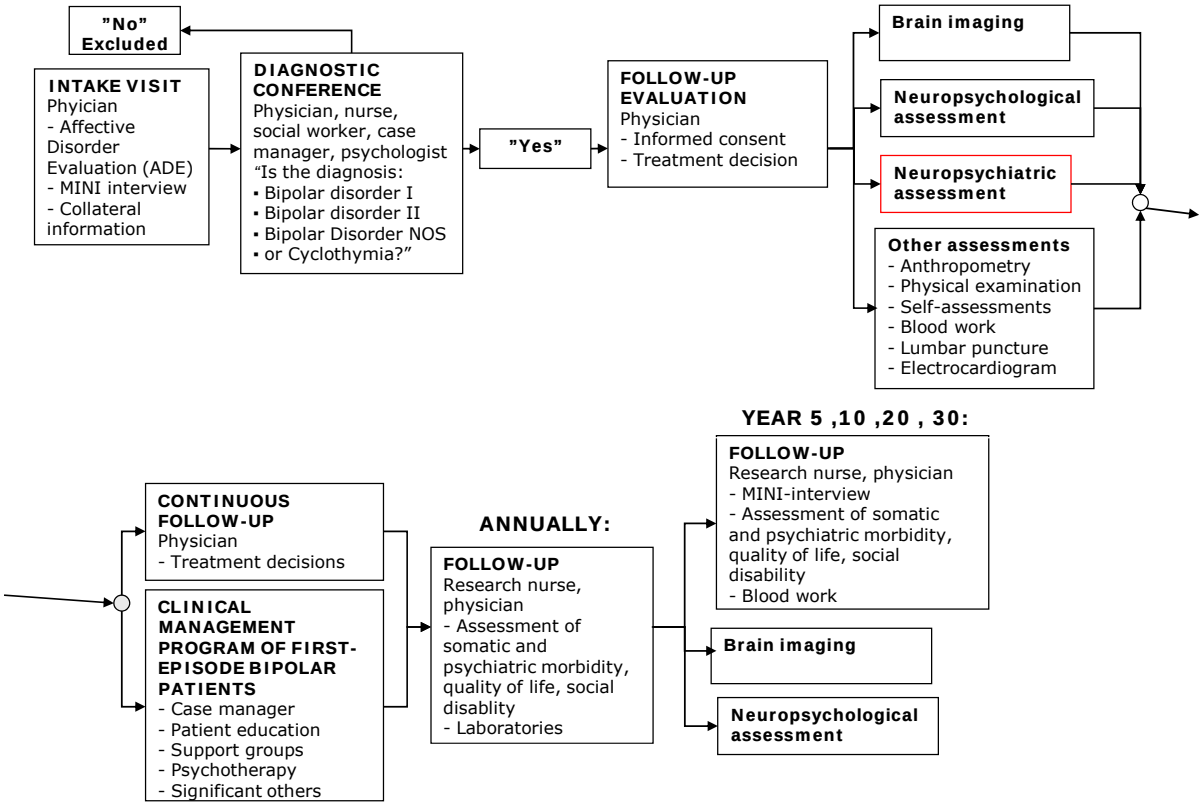
Patients diagnosed with bipolar disorder are enrolled from the Bipolar clinics at the Northern Stockholm psychiatry and the Sahlgrenska university hospital/Mölndal, Sweden. The baseline investigations are carried out when the patients are in remission, i.e., they do not currently have a depressive, manic, or mixed episode. Tests are taken under standardised conditions: the patient arrives fasting at the clinic at 8 a.m., where a somatic status will be taken followed by blood work and a lumbar puncture. For ethical reasons, treatment is not affected by participation in the study.

All subjects in this thesis were enrolled from the Bipolar Clinic at the Northern Stockholm

psychiatry clinic. The catchment area for this clinic includes 320 000 persons over 18 years of age who live in neighbourhoods ranging from affluent inner city to working class suburbs or impoverished areas with high numbers of immigrants and welfare benefit recipients. The Bipolar Clinic is a tertiary outpatient unit that treats the vast majority of all known bipolar patients in the catchment area.

Board-certified psychiatrists working at the Bipolar Unit, or residents in psychiatry completing their psychiatric training at this unit, conduct the intake interview. The assessments make use of all available sources of information, including patient records, and interviews with next of kin where feasible. A consensus panel of experienced board-certified psychiatrists specialized in bipolar disorder makes a "best estimate" diagnosis. Those that are included in the study are at least 18 years of age and meet the DSM-IV criteria for any bipolar disorder (BP I, BP II, NOS, cyclothymia, or schizoaffective syndrome manic type), and consent to participate. Patients are excluded if they are unable to complete the standard clinical assessment, or if they are incapable of providing informed consent. The study flow is depicted below (Figure 2).

Figure 2. *Flow-chart of events in the S:t Göran Bipolar Project*



Assessments

Bipolar Assessment

The baseline clinical diagnostic instrument for bipolar disorder is the Affective Disorder Evaluation (ADE), translated and modified to suit Swedish conditions, after permission from the originator Gary S. Sachs. The ADE was the diagnostic instrument used in the STEP-BD study (Sachs et al., 2003). It starts with a social anamnesis, followed by the affective module of the Structured Clinical Interview for DSM-IV Axis I (Spitzer et al., 1992). It documents the number of lifetime affective episodes and their characteristics.

ADHD Assessment (Neuropsychiatric assessment)

After the bipolar diagnosis is established, the patient is referred for ADHD assessment. This assessment is done when the patient is not suffering from an acute affective episode. The ADHD assessments were initially conducted by two independent, board-certified psychiatrists working at the S:t Göran Neuropsychiatric Unit (see below). They are now carried out at the Bipolar Unit. The ADHD clinical assessment requires approximately 1.5 hours. All rating

scales and self-report questionnaires, except the parental interview, are completed during the same session. The structured parental interview (A-TAC, see below) takes approximately 30 minutes to complete. We use the following instruments to assess various aspects of ADHD:

Childhood ADHD

- The Wender Utah Rating Scale (WURS-25) is a self-rating scale that retrospectively assesses ADHD-relevant childhood behaviors and symptoms (Ward et al., 1993).
- The Autism-Tics, ADHD, and Other Co-morbidities Inventory (A-TAC) is a comprehensive screening telephone interview conducted with a parent, particularly suited for ADHD, autistic spectrum disorder, tics, learning disorders, and developmental co-ordination disorder. The interview comprises 178 items, and covers all symptoms listed in the DSM-IV criteria of childhood-onset neuropsychiatric disorders. The ADHD score is based on 3 of the 18 subscales, measuring attention, impulsivity/activity, and planning/organizing problems (Hansson et al., 2005).

Current ADHD

- The World Health Organization Adult ADHD Self-Report Scale (ASRS) is an 18-item self-rating scale based on the DSM-IV criteria for ADHD (Kessler et al., 2005).
- The BROWN ADD Scales includes 40 items that assesses five clusters of ADHD-related executive dysfunctions, including "organizing, prioritizing and activating to work", "sustaining attention and concentration" (i.e. attention regulation), "sustaining energy and effort" "managing frustration and modulating emotions" (i.e. affective regulation) and "utilizing working memory and accessing recall" (Brown, 2008). These subscales are normed. The scale is especially useful in the assessment of the predominantly inattentive type of ADHD (Rucklidge & Tannock, 2002).
- The DSM-IV criteria for ADHD, including all subtypes (Table 1).

Personality Assessments

The following self-assessments of personality traits are used:

- The Swedish Universities Scale of Personality (SSP) is based on the Karolinska Scales of Personality, KSP (af Klinteberg, 1986; Gustavsson et al., 2000). SSP is a revised version of KSP with increased reliability and validity (Gustafsson, 2000). The SSP includes 91 items divided into 13 normed subscales. There are four response alternatives ranging from disagreeing completely to agreeing completely. The KSP was developed to explore the relation between personality traits and biological markers, and does not cover the whole aspect of personality.
- The self-rated version of the Structured Clinical Interview for DSM-IV Axis II personality disorders, the SCID-II Patient Questionnaire (SCID II PQ), was

administered to assess axis II personality disorder traits and disorders (Beneke & Rasmus, 1992). Originally the screening version of the SCID-II interview, this is a self-report instrument with questions in a simple yes-or-no format.

When estimating personality disorders by means of the SCID II PQ, we increased the cut-off level for a personality disorder by one score. This maneuver has been shown to give an acceptable agreement with the SCID II interview (Ekselius et al., 1994). Along with categorical assessment we present personality traits as a total score, since personality traits are usually perceived as dimensional traits (Siever, 2005).

Lumbar Puncture and Assessment of Monoamine Metabolites

Patients fasted overnight before the CSF collection, which occurred between 9 a.m. and 11. Most spinal taps were performed with the patient leaning forward. The spinal needle was inserted into the L4/L5 interspaces and a volume of 12 mL of CSF was collected, gently inverted to avoid gradient effects, divided into 1.6 mL aliquots, and sent to the laboratory.

Levels of monoamine metabolites were determined with high performance liquid chromatography (HPLC) with electrochemical detection, as described by Blennow and co-workers (Blennow et al., 1993). The interpretation of lumbar CSF levels of monoamine metabolites is complicated by a ventriculo-lumbar concentration gradient along the spinal cord (Blennow et al, 1993) resulting in a correlation between body height/spine length and lumbar CSF HVA/5-HIAA. We therefore also calculated height-corrected values for the monoamine metabolites (Blennow et al., 1993).

Assessment of Intelligence Quotient (IQ)

The Wechsler Adult Intelligent Scale (WAIS III-R) was administered by a trained psychologists (Wechsler, 1981). In this thesis, WAIS III-R was used to provide information about mental retardation. In those few cases where the patients were not tested, mental retardation was excluded by educational level and/or other historical facts.

Assessment of Current Mood

Depressive symptom severity and manic symptom severity was measured in conjunction with the spinal tap by the Montgomery Åsberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (Montgomery, 1979; Young et al., 1978).

Study at the Neuropsychiatric Unit

The Neuropsychiatric Unit, at Northern Stockholm Psychiatry, served the same catchment area as the Bipolar Clinic. It was at the time the largest tertiary unit in Sweden assessing adult

patients with suspected ADHD or autism spectrum disorders. No other unit in the catchment area performed these assessments at the time. From 2001, all consecutively assessed patients at this unit were included in a descriptive study, and in Paper II patients included from 2001-dec 2007 were included.

Assessments

Neuropsychiatric Assessments

Psychiatrists trained in diagnosing neurodevelopmental disorders, including ADHD and autism spectrum disorders, made the assessments. The assessments included reports and questionnaires with the subject and relatives, and a review of previous medical charts. A trained psychologist performed the neuropsychological testing. The time spent with the patient was 6-9 hours with a psychiatrist and 6-9 hours with a psychologist. Patients did not have significant symptoms of affective or psychotic disorder, or alcohol/drug abuse at the time of assessment.

ADHD Assessment

Childhood ADHD

- The Five–to–fifteen (FTF) is a structured interview with a parent, and covers eight different domains of childhood functions: memory, learning, language, executive functions, motor skills, perception, social skills, and emotional/behavioral problems (Kadesjö et al., 2004).
- The WURS-25 was included from August 2001 and more regularly used since June 2005 (see above).

Current ADHD

- The World Health Organization Adult ADHD Self-Report Scale (ASRS), (see above) was included from October 2004.
- The Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) is a structured interview that measures the severity of ADHD core symptoms of adults, using the Wender Utah criteria (Stein et al., 1995). It measures symptoms relating to current difficulties from seven categories: attention difficulties, hyperactivity/ restlessness, temper, affective lability, emotional over-reactivity, disorganization, and impulsivity.
- The DSM-IV criteria for ADHD, including all subtypes (Table 1).

Assessment of Bipolar Disorder

- The affective module of the Structured Clinical Interview for DSM-IV Axis I (Spitzer et al., 1992).

- Reviewing information from previous medical charts.

Assessment of Personality, IQ and Current Mood

- The same assessments as in S:t Göran Bipolar Project (see above).

Subjects and Study Designs, Paper I-III

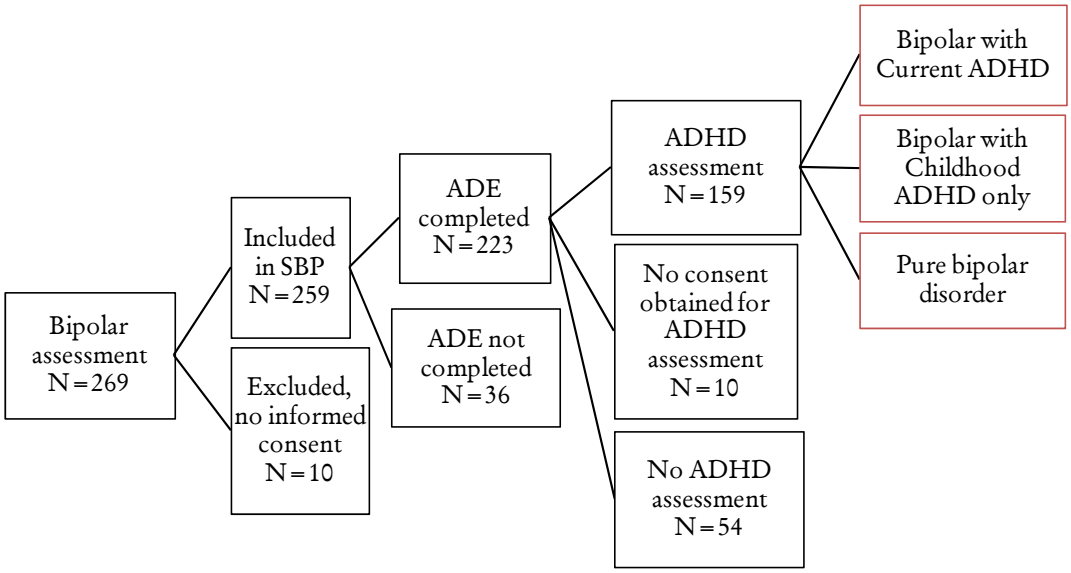
Papers I-III are cross-sectional studies based on retrospective and current data from the S:t Göran Bipolar Project.

Paper I determined the prevalence of ADHD with more valid methods by using specific ADHD rating instruments and conducting a parental interview. Three subgroups of bipolar patients were compared (Figure 3):

1) bipolar patients with a history of childhood ADHD, fulfilling the criteria for current ADHD;
2) bipolar patients with a history of childhood ADHD, not fulfilling the criteria for current ADHD;
3) bipolar patients without a history of childhood ADHD (pure bipolar).

We explored whether ADHD impacts age of onset of affective disorder, frequency of affective episodes, suicide-attempts, interpersonal violence and psychotic episodes in bipolar patients, when confounding factors were adjusted for. Finally, we examined whether a mere history of childhood ADHD influences these clinical parameters.

Figure 3. *Subjects in Paper I*

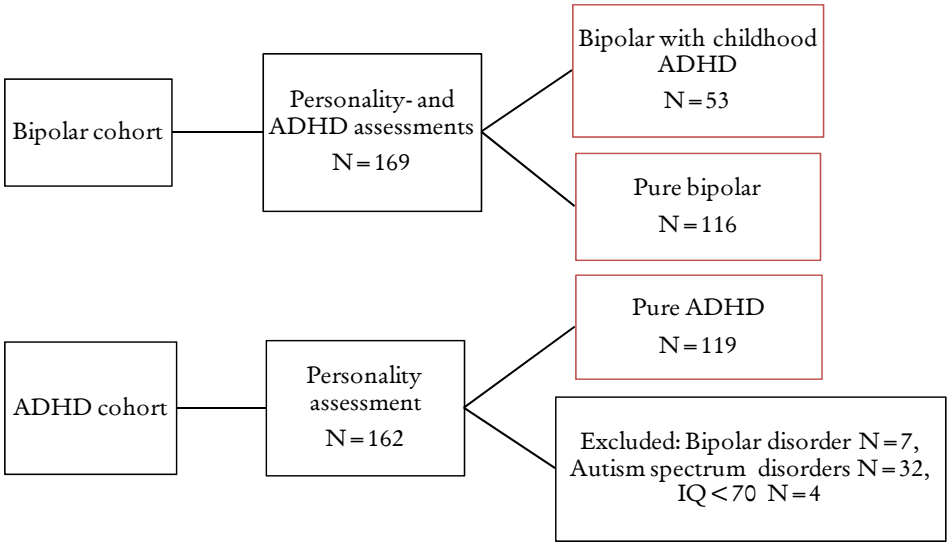


Paper II explored whether a history of childhood ADHD accounts for affective dysregulation in adult bipolar patients. Results from Paper I showed that a mere history of ADHD is important for the outcome of important clinical parameters in bipolar disorder, which prompted us to dichotomize the bipolar patients as childhood ADHD or not. Three groups were compared (Figure 4):

1) bipolar patients with a history of childhood ADHD;
2) bipolar patients without a history of childhood ADHD (pure bipolar);
3) ADHD without bipolar disorder (pure ADHD).

We compared the different groups with respect to affective regulation and other personality traits, and explored the predictive value of childhood ADHD on these personality traits in the bipolar cohort using regression analyses.

Figure 4. *Subjects in Paper II*

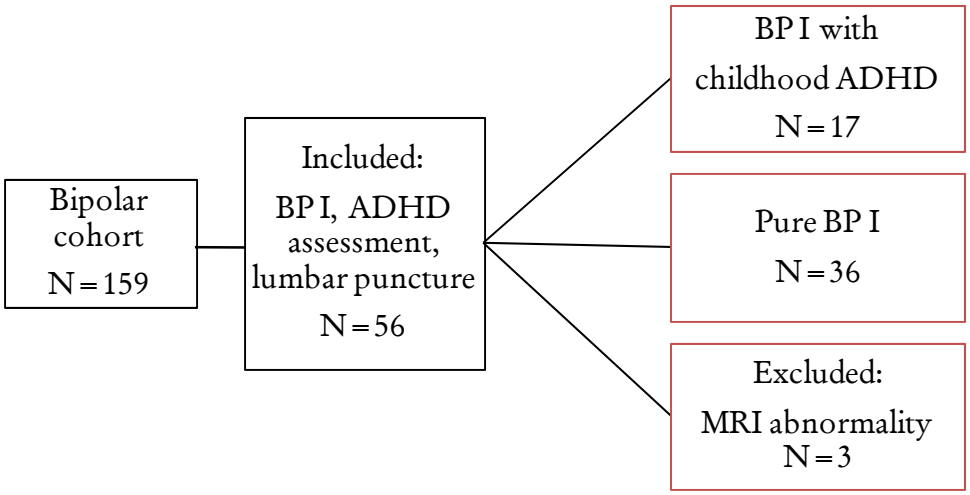


Paper III compared monoamine metabolite levels in CSF in the following groups of euthymic bipolar patients (Figure 5):

1) bipolar disorder without a history of childhood ADHD (pure bipolar);
2) bipolar disorder with a history of childhood ADHD.

We also correlated monoamine metabolites in CSF to measures of attention and affective regulation, as assessed by the BROWN ADD subscales.

Figure 5. *Subjects Paper III*



Methodological Considerations, Paper I, II and III

Study Populations and Representativity

During the recruitment period, virtually all new patients with bipolar disorder in the specific catchment area were referred to and evaluated at the bipolar outpatient unit. We invited both new consecutive and continuing outpatients to participate in the study provided that they had a bipolar disorder diagnosis. The catchment area includes inhabitants from all socio-economic classes. This representative population is thus likely to be generalizable for bipolar patients in general. The ADHD cohort includes all patients that were assessed for ADHD at the Northern Stockholm Psychiatry clinic during this period. The cohort is hence representative with respect to subjects with ADHD in psychiatric care, but not with respect to subjects with ADHD outside psychiatric care.

Study Design

The fact that the bipolar patients - based on the findings in Study I - was subdivided based on a history of childhood ADHD rather than based on current ADHD, served to reduce the risk that current symptoms that might mimic ADHD confound the results. A limitation with

Studies I-III is the lack of a healthy control group since our aim was to study differences between subtypes of bipolar disorder. Hence, caution is advised with respect to whether the results in Study II and III would differ from healthy controls.

Assessments

A strength of this study was the bipolar assessment that included not only an extensive structured interview but also a diagnostic conference which served to minimize inter-rater variability. This in turn reduces the risk that the bipolar patients would in fact be misclassified ADHD patients.

Likewise, the ADHD assessment is a strength of the study. We used our experience from the extensive ADHD assessment performed in the neuropsychiatric study (page 35) and designed a condensed, but clinically valid ADHD assessment. In particular, we made an effort to properly assess the developmental aspect of ADHD by both subjective and objective means. Moreover, the ADHD assessment was designed to capture all subgroups of ADHD, not only the combined subgroup. This was accomplished by the use of the BROWN-ADD scale, which is especially useful in the assessment of the predominantly inattentive type of ADHD (Rucklidge & Tannock, 2002). The recall bias of childhood history was minimized by adding a parental interview to the self-assessment. The cut-off for subjective ADHD related problems in childhood assessed by WURS was set higher than when assessing a normal population in order to increase the specificity for ADHD. Those that did not reach the criteria for childhood ADHD were classified as pure bipolar disorder, which could introduce some misclassification, although this would decrease rather that increase the possibility of detecting differences between the groups.

A limitation was that personality measures in Study II were self-evaluations. However, raising the cut-off (page 35) for SCID II PQ has been shown to yield an acceptable agreement with the SCID II interview (Ekselius et al., 1994). Since the aim was to compare the groups, we considered self-evaluation sufficient.

In Study III, a limitation is that patients were on their prescribed medication due to ethical reasons. This confounder was, however, possible to adjust for in the statistical analyses.

Subjects and Study Design Paper IV

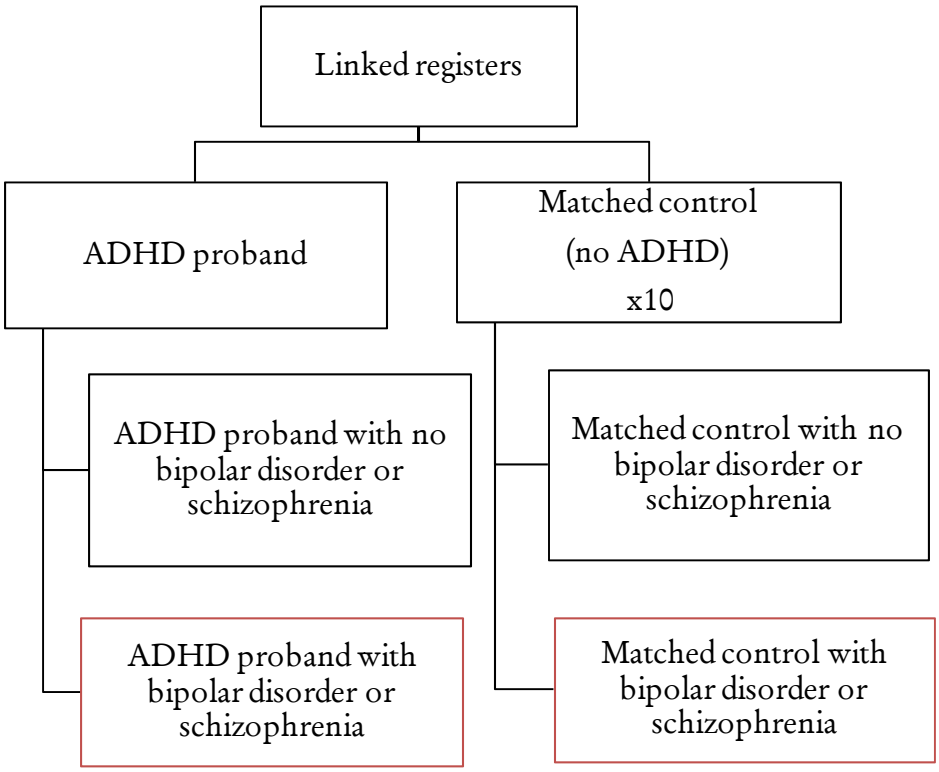
In Paper IV a database linking several Swedish national registers were used: the Total Population Register, the Multi-Generation Register, the Hospital Discharge Register (HDR), the Cause of death register, and the Migration register. This linking is possible by using the unique civic national registration number. All psychiatric discharges during 1973-2004 were

included in this study. We identified 3,067 individuals with ADHD, 46,006 individuals with bipolar disorder, and 47,693 with schizophrenia. We used a nested case-control design in the two different parts of the study:

1. Probands vs. Controls

In the first part, we compared the risk for bipolar disorder and schizophrenia in probands affected by ADHD to matched controls. For each case, 10 control subjects matched by birth year and gender were randomly selected. The matched controls were alive and living in Sweden and not affected by ADHD at the time of the first ADHD diagnosis of the proband (Figure 6).

Figure 6. *Subjects in First Part of Paper IV*

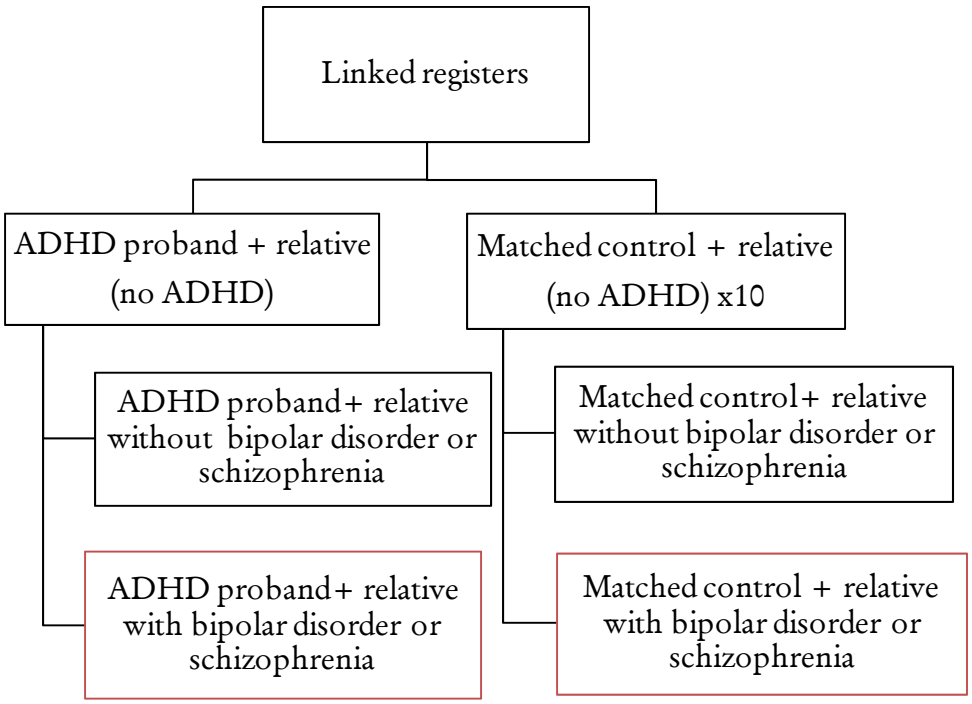


2. Relatives of Probands vs. Relatives of Controls

We also compared the risk for bipolar disorder and schizophrenia in relatives (children, parents, full siblings, and half-siblings) to probands with ADHD with the relatives of matched non-ADHD controls. For each proband-relative pair, 10 randomly selected control-relative pairs were matched by birth year and gender of both the proband and the relative. To avoid spurious associations due to comorbidity, we excluded probands and controls with

schizophrenia or bipolar disorder, as well as relatives to probands or controls with ADHD (Figure 7).

Figure 7. *Subjects in Second Part of Paper IV*



Methodological considerations, Paper IV

Study Population, Representativity, and Design

A major strength is that the HDR coverage of psychiatric inpatient episodes in Sweden is excellent. An additional strength is that the Multi-Generation Register provides the possibility to study first-, and second-degree relatives of probands and controls. With this approach, we circumvented the obstacles associated with assessing psychiatric co-morbidity on an individual level. Finally, the study was powered to yield robust, unambiguous results.

Diagnosis

A limitation with Study IV is the use non-standardized register diagnoses. However, validation studies of schizophrenia register diagnoses have found a high proportion of"true"cases of schizophrenia in the Swedish HDR (Dalman et al., 2002; Ekholm et al., 2005). No validation study of bipolar disorder or ADHD diagnosis in the HDR has yet been published, but can be assumed to be similar to schizophrenia. Notably, persons with ADHD would not usually require inpatient assessment and care, and an HDR diagnosis of ADHD is

therefore likely to be a highly specific but less sensitive caseness measure capturing more severe cases of ADHD.

Statistical Analysis

The computer software STATISTICA Version 7 was used in the statistical analyses in Paper I-III. When comparing two or more parametric variables, the student t-test or Analysis of Variance (ANOVA) was used. Mann–Whitney U-Test or Kruskal-Wallis ANOVA was used when the variables were non-parametric. For cross-tabulation analyses, the Fisher Exact test was used. Pearson correlation was used if the data weres continuous or normed. Spearman correlation was used in all other correlation analyses. Regression analyses were used to adjust for possible confounding factors. In Paper I, multiple regression analysis was used to investigate if a history of childhood ADHD was a significant predictor for the frequency of total affective episodes, depressive- and hypomanic episodes, when adjusted for gender, age and bipolar subgroup. These outcome variables were used as dependent variables with gender, age, bipolar subgroup (BP I or BP II) and childhood ADHD as independent variables.

In Paper II, a logistic regression analysis was used to estimate the associated risk of childhood ADHD and personality disorders by the odds ratio (OR) and 95% confidence interval. Multiple regression analysis was used to calculate whether childhood ADHD was a significant predictor of personality traits in SSP and for attention and affective regulation as measured by the BROWN ADD. The regression analyses were adjusted for, age, gender, bipolar subgroup, and MADRS score.

In Paper III, multiple regression analyses were computed to adjust for potential confounding factors found both in our study and in other studies that may influence group differences in monoamine metabolite levels. CSF HVA and 5-HIAA were used separately as dependent variables, while childhood ADHD, gender, MADRS score, antipsychotic and antidepressant treatments were independent variables. For HVA, age was also used as an independent variable, since this is not included in the corrected HVA value. For 5-HIAA, the variable interpersonal violence was also added (Virkkunen, Nuutila et al. 1987).

In all analyses, a 2-sided p-value of less than 0.05 was regarded as statistically significant, if not otherwise specified.

In Paper IV, the measure of association was the OR and 95% confidence interval, which was calculated using conditional logistic regression models in PROC PHREG in SAS version 9.2 (Inc., 2008). First we compared the association between ADHD and bipolar disorder or schizophrenia, by comparing probands with controls. Second, we compared relatives in

probands' extended families (children, parents, full siblings or half-siblings) with relatives of controls. This method avoids bias because of individuals in the population registries entering the study at different time points (i.e., left truncation) and allows equal follow-up times of probands, controls, and the relatives of both (Lichtenstein et al., 2006; Lichtenstein et al., 2009). When studying associations within families, confidence intervals were obtained through a robust sandwich estimator in order to adjust for the non-independence of probands.

Ethical Aspects

Patients obtained detailed written and oral information about the S:t Göran Bipolar Project, and written information about the study at the S:t Göran Neuropsychiatric Unit. Written informed consent was obtained from each patient included in the S:t Göran Bipolar Project. Patients from the S:t Göran Neuropsychiatric Unit cohort obtained written information about the study, and those that did not consent to the use of collected clinical data for research purposes, were excluded from this study. The Ethics Committe at Karolinska Institutet in Stockholm approved the S:t Göran Bipolar Project. The study at the S:t Göran Neuropsychiatric Unit was reviewed by the Regional Ethics Committee in Stockholm that gave an advisory statement. The Ethics Committe at Karolinska Institutet in Stockholm approved the method in Paper IV.

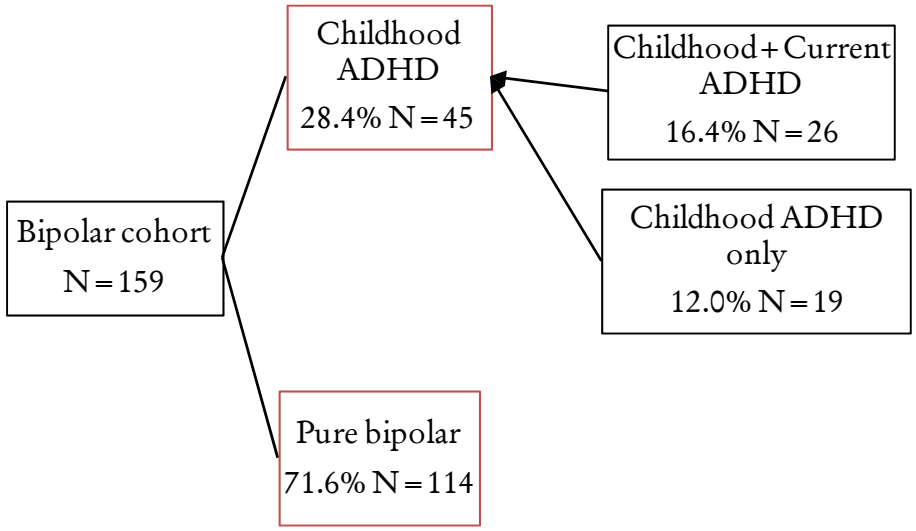
RESULTS AND COMMENTS

Paper I: Prevalence and Impact of Childhood ADHD in Adult Bipolar Disorder

Results

The prevalence of co-occurring ADHD in the cohort of patients with bipolar disorder was 16.4% (N=26). An additional 12.0% (N=19) met criteria for childhood ADHD without meeting DSM-IV criteria for current ADHD; the latter group did, however, score significantly higher on current ADHD symptoms compared to the group without a history of ADHD. Both groups with a history of childhood ADHD had significantly earlier onset of the first affective episode, more frequent affective episodes (except mania), and more interpersonal violence compared to bipolar patients without a history of ADHD (Figure 8). It was significantly more common with suicide-attempts in the childhood+current ADHD group compared to the pure bipolar group. A history of childhood ADHD was significantly more common in the BP II than BP I subgroup, and increased the mean number of total affective episodes 15 times calculated by a multiple regression analysis adjusted for age, gender, and bipolar subgroup. A history of psychosis was, however, significantly *less* common in patients with a history of childhood ADHD.

Figure 8. *Prevalence of Childhood and Current ADHD*



Comments

A history of childhood ADHD was common in adult bipolar patients and these patients had a different clinical course of illness compared to pure bipolar patients. Childhood ADHD was the best predictor of the number of affective episodes and a history of interpersonal violence, which suggest that this is a risk group of bipolar patients. Interestingly, a mere history of childhood ADHD influenced the courses in bipolar disorder, regardless of whether the patients met the ADHD-criteria in adulthood or not. More current ADHD symptoms seemed to be an additional risk for suicide attempts. Hence, the adult bipolar patients with a history of childhood ADHD are similar to children with bipolar disorder, who have a high co-occurrence with ADHD and conduct disorder, a chronic rather than episodic course, rapid mood cycling, and frequent mixed episodes. This is suggestive of a childhood onset developmental subtype of bipolar disorder with a specific set of symptoms and course of illness that remains in adulthood.

Based on this notion, we suggest that an assessment and understanding of childhood function is important to understand current state in adult bipolar patients. It is not farfetched to speculate that bipolar subjects with a history of childhood ADHD might benefit from additional treatment to remedy ADHD dysfunction. Future clinical trials are warranted to evaluate, for example, central stimulant treatment of bipolar patients with co-occurring ADHD.

Paper II: Impact of ADHD on Affective Regulation in Adult Bipolar Disorder

Results

Whereas the personality profile of the bipolar subtype with childhood ADHD was similar to the pure ADHD group, it differed from pure bipolar group (Table 5). In particular, personality traits corresponding to affective dysregulation were significantly more common in bipolar patients with childhood ADHD, as well as in pure ADHD patients, compared to pure bipolar patients. Within the bipolar group, childhood ADHD was a significant predictor for aspects of affective dysregulation, including anxiety, stress-susceptibility, irritability, impulsivity, and aggression, adjusted for age, gender, bipolar subgroup and MADRS-score. Bipolar patients with childhood ADHD also had significantly higher prevalence of personality disorders, and childhood ADHD was a significant predictor for borderline, depressive, obsessive-compulsive, and narcissistic personality disorder.

With respect to attention and affective regulation as measured with BROWN-ADD, pure bipolar patients did not deviate from the norm while bipolar patients with ADHD deviated

close to 2 SD. Interestingly, BROWN-ADD measures of attention and affective regulation were significantly positively correlated in bipolar patients ($r = 0.60$, $p < 0.001$).

Table 5. *Comparison of self-assessed personality traits measured with SCID II PQ in three patient groups: 1) pure bipolar disorder, 2) bipolar disorder with childhood ADHD, and 3) pure ADHD.*

	Significant differences of total score in SCID II PQ, between three groups ($p < 0.05$)		
Personality trait	pure bipolar (1) vs. bipolar + childhood ADHD (2)	pure bipolar (1) vs. pure ADHD (3)	bipolar + childhood ADHD (2) vs. pure ADHD (3)
Avoidant	1 < 2	1 < 3	2 = 3
Obsessive-compulsive	1 < 2	1 < 3	2 = 3
Depressive	1 < 2	1 < 3	2 = 3
Schizotypal	1 < 2	1 < 3	2 = 3
Histrionic	1 = 2	1 < 3	2 = 3
Borderline	1 < 2	1 < 3	2 = 3
Dependent	1 < 2	1 < 3	2 < 3
Passive-aggressive	1 < 2	1 < 3	2 = 3
Paranoid	1 < 2	1 < 3	2 = 3
Schizoid	1 < 2	1 < 3	2 = 3
Narcissistic	1 < 2	1 < 3	2 = 3
Antisocial	1 < 2	1 < 3	2 = 3

Comments

These findings imply that affective dysregulation in euthymic bipolar patients is highly accounted for by co-occurring ADHD. Indeed, bipolar patients without a history of ADHD do not deviate from the norm with respect to personality and affective regulation. This means that affective dysregulation is not linked to the "amplitude" of bipolar disorder per se, but to deficits with respect to cognitive affective control, e.g., co-occurring ADHD. Affective dysregulation might nevertheless influence the expression and severity of bipolar disorder; the specific course of illness in bipolar patients with childhood ADHD with more frequent affective episodes, i.e., a more rapid cycling pattern, could be explained by this affective dysregulation. The interesting observation that affective regulation and attention regulation were highly correlated begs the question of whether treatment with central stimulants has the possibility to remedy, not only attention, but also affective dysregulation in subjects with

bipolar disorder with ADHD.

There are other known conditions of affective dysregulation that deserve mentioning in this context, for example attachment disorders that are common in patients with a diagnosis of borderline personality disorder (Choi-Kain et al., 2009). The few bipolar patients who had affective dysregulation in the absence of ADHD could thus have disturbed affective regulation due to other conditions that might also be separate from bipolar disorder as such. Previous literature has not unambiguously distinguished patients with cyclothymia from patients with affective dysregulation due to ADHD or borderline personality disorder, who might therefore have been included in the soft end of a bipolar spectrum (Akiskal, 2004; Perugi & Akiskal, 2002). It is conceivable though, that cyclothymia with affective dysregulation might on occasion better be accounted for by a developmental disorder or an attachment disorder.

This line of reasoning challenges the concept of a unitary bipolar spectrum with affective dysregulation in one end and full-blown manic episodes in the other end. Instead, it is suggestive of a spectrum of cognitive control and correlating affective regulation. Euthymic bipolar patients without affective dysregulation do not belong in the disabled end of this spectrum. By contrast, bipolar subjects with ADHD have affective dysregulation not only during euthymia but across all mood states, which might give the impression of rapid cycling or mixed state. By taking into account both the history of affective regulation during childhood and affective regulation in euthymia, it is possible to disentangle affective dysregulation from mood disturbance.

Paper III: Monoamine Metabolites in Bipolar Patients with and without Childhood ADHD

Result

Compared to those with pure bipolar disorder, patients with a history of childhood ADHD had significantly lower mean CSF concentration (nmol/L$\pm$SD) of the dopamine metabolite HVA (89.0$\pm$32.5 vs. 116$\pm$47.1; $p = 0.039$), and the serotonin metabolite 5-HIAA (88.7$\pm$38.5 vs. 116$\pm$47.9; $p=0.021$). The results were adjusted for gender, age, and antipsychotic- and antidepressant medication. The CSF HVA correlated significantly to the BROWN ADD subscales measuring attention regulation ($r=-0.45$, $p=0.005$, Figure 9a) and affective regulation ($r=-0.38$, $p=0.005$, Figure 9b). Likewise, CSF 5 HIAA correlated significantly to attention regulation ($r=-0.43$, $p=0.002$, Figure 10a) and affective regulation ($r=-0.43$, $p=0.001$, Figure 10b).

Figure 9. *Correlation between CSF HVA levels and attention regulation (a), and affective regulation (b) as measured with BROWN-ADD.*

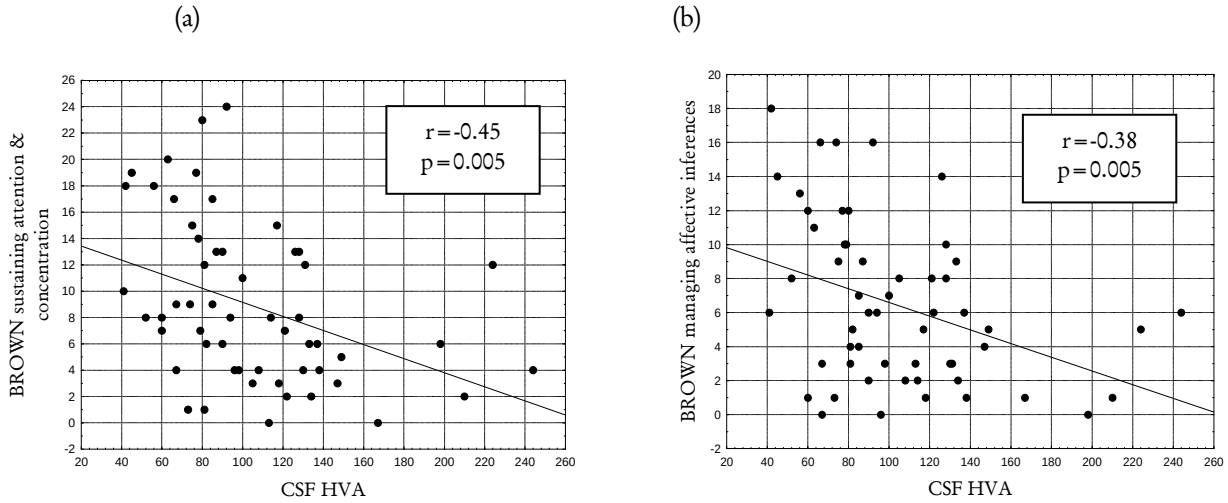
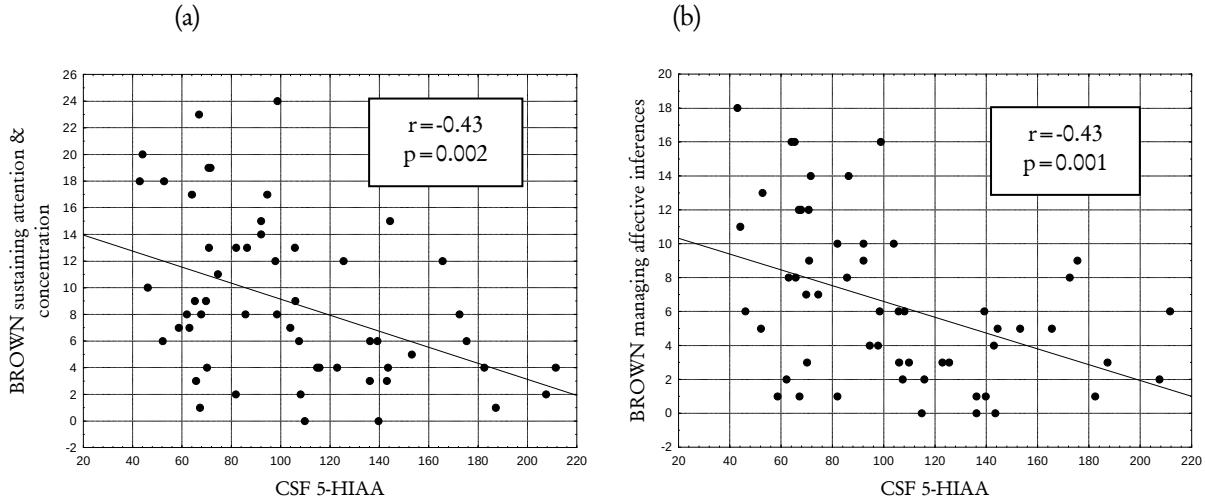


Figure 10. *Correlation between CSF 5-HIAA levels and attention regulation (a), and affective regulation (b) as measured with BROWN-ADD.*



Comments

The finding that bipolar patients with a history of ADHD have significantly lower CSF levels of HVA and 5-HIAA than bipolar patients without such history, suggests that these two groups have at least partially different biological underpinnings. Lower CSF dopamine level in euthymia in bipolar patients with ADHD is in unanimity with a lower dopamine level in patients with ADHD. By this means, the findings lend biological validity for the concept of a bipolar subphenotype with childhood ADHD. Tentatively, subdividing bipolar patients depending on the presence or absence of childhood ADHD might yield more homogeneous

subtypes, which could prove to be of importance in testing new treatment strategies and in further patophysiological studies.

In Paper I, we found that bipolar patients with current ADHD have more suicide attempts. It is therefore noteworthy that low CSF levels of HVA and 5-HIAA have previously been found to be a risk factor for more serious suicide attempts in bipolar disorder (Sher et al., 2006), and is also known to be coupled to suicide and suicide-attempts in general (Söderström et al., 2003). This highlights the bipolar subgroup with ADHD as a specific riskgroup.

Paper IV: Familial Association of ADHD, Bipolar Disorder, and Schizophrenia

Results

Probands with ADHD had a considerably increased risk of also being diagnosed with bipolar disorder compared to matched controls (OR=25, 95%CI 17-38). Importantly, bipolar disorder was also more common in parents (OR=2.0, 95%CI 1.5-2.9) and siblings (OR=3.3, 95%CI 1.7-6.5), but not in half-siblings of ADHD probands compared to corresponding control relatives. In a similar vein, ADHD probands were at increased risk of being diagnosed with schizophrenia compared to controls (OR=16, 95%CI 10-24), as were their parents (OR=4.1, 95%CI 2.9-5.8) and siblings (OR=3.7, 95%CI 1.8-7.3), but not half-siblings.

Discussion

As presumed, persons with ADHD were much more likely to have bipolar disorder than controls. In contrast to our hypothesis, ADHD probands were also much more likely to be diagnosed with schizophrenia. These findings could, however, be explained by diagnostic difficulties on an individual level; bipolar as well as schizophrenic symptoms might mimic ADHD symptoms and the findings might represent syndromal overlap rather than a true co-morbidity. It is therefore key that we also have access to first-degree relatives (parents and full siblings who were not diagnosed with ADHD) of the ADHD proband. Interestingly, first-degree relatives of ADHD probands had higher rates of both bipolar disorder and schizophrenia, compared to first-degree relatives of controls. Half-siblings who share only 25% of co-segregating genes with ADHD probands (compared to 50% in full siblings) were not at significantly higher risk for bipolar disorder or schizophrenia. This risk pattern across first- and second-degree relatives (half-siblings) is congruent with a genetic mechanism.

The strong association between ADHD and bipolar disorder is in agreement with previous family (Faraone et al., 1997; Faraone et al., 2001) and twin studies (Achenbach & Dumenci, 2001; Althoff et al., 2006; Hudziak et al., 2005; Reich et al., 2005), but the finding that ADHD and schizophrenia also co-segregated refuted our hypothesis that ADHD would be uniquely

linked to affective disorders. ADHD, being a developmental disorder, appears to cut across these diagnostic boundaries and might represent an unspecific early expression of a common vulnerability to all three disorders, or constitute a risk factor for the development of bipolar disorder and schizophrenia. In line with this, there is evidence to suggest that bipolar disorder and schizophrenia are not entirely separate disorders. Recent genetic studies have provided evidence for a genetic overlap between schizophrenia and bipolar disorder (Berrettini, 2003; Perlis et al., 2008; Tsuang et al., 2004). In a large population based study of bipolar disorder and schizophrenia, the familial co-occurrence of these disorders was shown to mainly be due to additive genetic effects common to both disorders (Lichtenstein et al., 2009).

The findings in Paper IV inform psychiatric nosology by highlighting the importance of developmental disorders in adult psychiatry. The results also suggest that children with ADHD and a family history of bipolar disorder or schizophrenia should be monitored with respect to early signs of bipolar disorder or schizophrenia. This would enable clinicians to intervene early and thereby hopefully improve long-term prognosis.

GENERAL DISCUSSION

It has been suggested that a psychiatric disorder may be considered a valid diagnostic entity if it can be shown to have i) evidence of familiality, ii) specific treatment response, and iii) a unique course of illness (Robins & Guze, 1970). Our data suggest that bipolar disorder and ADHD are familially linked and have a unique course of illness. Even though it remains to be proven in controlled trials that central stimulants in conjunction with mood stabilizers are effective for bipolar patients with ADHD, we have abundant positive clinical experience with this combination. Furthermore, the fact that bipolar patients with ADHD differed from pure bipolar patients with respect to monoamine patterns in CSF, lend biological support for the validity of this subphenotype. Needless to say though, independent studies confirming these findings are necessary to draw the conclusion that ADHD + bipolar disorder is indeed a biologically and clinically valid subphenotype. Until then, however, it might be worthwhile to re-assess previous bipolar literature from the ADHD vantage point.

It is not difficult to find descriptions of the impact of ADHD on bipolar disorder in the literature despite that few previous studies of adult bipolar disorder have considered ADHD explicitly. As an example, prospective studies have reported that early onset bipolar disorder is associated with greater risk of recurrence and chronicity of mood symptoms, as well as more functional impairment (Perlis et al., 2004; Perlis et al., 2009). It is not farfetched to suggest that Perlis and colleagues described a group with childhood ADHD, given that bipolar patients with co-occurring ADHD have earlier age of onset of affective disorder (Nierenberg et al., 2005; Sachs et al., 2000). Similarly, one study found an association between rapid cycling, younger age-of-onset, and a more chronic course in 1/3 of bipolar patients (Bader & Dunner, 2007). The authors conclude that early age of onset and a positive family history of bipolar illness are associated not only with BP I and BP II, but also with the 'softer' forms of bipolar illness, often referred to as bipolar spectrum disorder. As was shown in Paper II, affective dysregulation in bipolar disorder is to a considerable extent accounted for by ADHD. It has previously been noted that BP II patients score higher on neuroticism, i.e., affective instability (Akiskal, 2004; Akiskal et al., 2006), which might hence be explained by a higher prevalence of ADHD in BP II. With respect to pharmacological treatment, previous studies and case observations have suggested that dopamine agonists might be effective as adjunctive use in treatment-resistant BP II depression (Perugi et al., 2001). Since dopamine-stimulating agents are drugs of choice for ADHD, the symptoms treated could in fact be symptoms related to ADHD.

Depressive, cyclothymic, irritable, and anxious temperament has been found to be significantly higher in patients with mixed episodes (Rottig et al., 2007). This might be viewed

in light of our findings that bipolar patients with a history of childhood ADHD have a significantly higher incidence and frequency of mixed episodes (Paper I). A high incidence of mixed episodes has also been found in children with bipolar disorder, which is mostly co-occurring with ADHD (Geller & Luby, 1997). Mixed state may thus reflect a state of serious affective dysregulation and it is tempting to suggest that co-occurring ADHD could account for the affective dysregulation state described by Rotting.

Co-morbidity, Co-occurrence, or Spectrum?

To disentangle the relation between ADHD and bipolar disorder, a good start is to define the terms that describe the relationship. Kaplan and colleagues searched the literature for definitions and found that *co-morbidity* specifies an association in time without a causal relationship, suggesting that the disorders are independent. *Co-occurrence* describes two disorders that occur together, that may, or may not be casually related (Kaplan et al., 2006). The results in Paper IV suggest that ADHD and bipolar disorder are not independent disorders, and thus not co-morbid. Instead, childhood ADHD and bipolar disorder co-occur and have a causal heritable relation.

Kaplan and colleagues further describe that a continuum, or spectrum, is characterized by a progression of values by minute degrees that defines a linear relationship between the points. Developmental disorders, e.g., ADHD, exist along a continuum of severity (August & Garfinkel, 1989; Chen et al., 1994; Crawford et al., 2006; Edelbrock et al., 1984; Kadesjö & Gillberg, 2001; Kaplan et al., 2001; Levy et al., 1997; Sherman et al., 1997). They describe a gradual deviation from normality (Angold et al., 1999), where a categorical diagnosis is set at a certain defined point when the deviation is apparent and affects daily life functioning.

According to the notion of a *bipolar spectrum*, conditions with affective dysregulation residing at the soft end of the spectrum would continuously progress across hypomanic episodes to conditions with full-blown manic episodes at the hard end. The results in Paper II, however, suggest that pure bipolar patients do not deviate from normality with respect to affective regulation. Moreover, in Paper IV we found that ADHD was not uniquely linked to bipolar disorder, but was also linked to schizophrenia. This is in line with previous reports that ADHD is often found in early onset of schizophrenia (Mazzoni et al., 2009; Thaden et al., 2006) as well as in early onset bipolar disorder. Against this background, the notion of a bipolar spectrum might be misleading. Affective dysregulation at the soft end is not a light version of manic episodes, and manic episodes do not represent an extreme variant of affective dysregulation in most cases. A spectrum view is, however, applicable with respect to attention and affective regulation deficits, which continuously progress towards more disabling

symptoms, where more dysregulation is probably a risk factor for eliciting episodes of bipolar disorder or schizophrenia.

Limitations of Operational Criteria

The developmental disorder ADHD seems to cut across diagnostic boundaries. Since the diagnostic operational disorders in DSM-IV are constellations of symptoms and behaviors, they do not represent homogenous disorders with shared etiology but merely reflect a common manifestation of symptoms. This has hampered the search for genetic and other biological correlates of psychiatric disorders. The endophenotype concept in psychiatric research has therefore evolved to represent simpler clues to genetic underpinnings than the disease itself. Gottesman & Gould (2003) suggested the following criteria for an endophenotype:

1. the endophenotype is associated with illness in the population
2. the endophenotype is heritable
3. the endophenotype is primarily state-independent (manifests itself in an individual whether or not illness is active)
4. within families, endophenotypes and illness co-segregate

An additional criterion that may be helpful for identifying endophenotypes of diseases that display complex inheritance pattern is that:

5. the endophenotype is found in non-affected family members at a higher rate than in the general population

The ADHD construct is well suited for endophenotype study since the disorder represents stable traits. As an example, cognitive control has successfully been used in neuroimaging studies to investigate the role of dopamine in ADHD (Durston et al., 2009). Dimensions of the personality disorders also lend themselves to the study of corresponding endophenotypes including affective instability, impulsivity, aggression, emotional information processing (Siever, 2005), many of which are common traits in ADHD. As an example, novelty seeking that is a common personality trait in ADHD (Anckarsäter et al., 2006) has been found to be associated to polymorphisms in the dopamine genes DRD2 and DRD4 (Noble et al., 1998; Suhara et al., 2001). Aggression in general (Retz & Rosler, 2009; Vitiello & Stoff, 1997) and impulsive aggression in particular (Harty et al., 2009) is common in ADHD and has been associated with lower serotonergic innervations in the anterior cingulate cortex, a region that plays an important role in affective regulation (Frankle et al., 2005).

In bipolar disorder a meta-analysis of cognitive impairment in bipolar disorder and in first-degree relatives concluded that executive function and verbal memory are candidate bipolar endophenotypes, given large deficits in these domains in bipolar patients and intermediate

cognitive impairments in first-degree relatives (Arts et al., 2008). Personality traits and temperaments have also been suggested as endophenotypes for bipolar disorder, including irritable-aggressive subtypes of bipolar disorder associated to a DAT polymorphism (Savitz et al., 2008). These endophenotypes are possibly shared with ADHD.

Impaired ability to sustain attention has been found in ADHD (Balint et al., 2008; Shallice et al., 2002), bipolar disorder (Hasler et al., 2006; Kolur et al., 2006), and schizophrenia (Bergida & Lenzenweger, 2006), and might prove to be a shared endophenotype. That is to say, subgroups of patients with bipolar disorder and schizophrenia might share deficit in sustained attention with ADHD, while other subgroups might have no signs of sustained attention deficits. This line of reasoning accords the findings in Paper IV.

Clinical Implications

Findings in this thesis suggest that it is important to assess the developmental history in patients with bipolar disorder. Patients with ADHD have specific problems in attending at certain times, planning, remembering, following routines and create rhythms, which interfere with treatment. Specific ADHD psychoeducation and support is therefore warranted for bipolar patients with ADHD. From my own clinical experience, I have learned that bipolar patients with ADHD tolerate stimulant medication provided that mood stabilizers are given first. This has previously been shown to be an effective treatment strategy in children and adolescents (Findling et al., 2007). Our patients report that adding stimulants improve their ability to regulate attention, activity-level (easier to initiate as well as terminate an activity), impulses, and affective responses. Recognizing ADHD in bipolar disorder can possibly also give further guidance with respect to pharmacological strategies. Poor lithium response can, for example, be predicted by mixed episodes and rapid cycling (Backlund et al., 2009), which is common in bipolar patients with childhood ADHD. Moreover, a meta-analysis found that bipolar children and adolescence with co-occurring ADHD were less responsive to drugs commonly used to treat acute mania (Consoli et al., 2007).

Finally, Paper IV highlights a potential population at high risk for developing bipolar disorder or schizophrenia, i.e., children with ADHD and a family history of bipolar disorder and schizophrenia. This knowledge may prove to be of importance in terms of developing early intervention strategies.

MAIN FINDINGS AND CONCLUSIONS

Paper I

- Almost 30% of adult bipolar patients had a history of childhood ADHD.
- A history of childhood ADHD had significant impact on the course of bipolar disorder with earlier onset of the affective disorder, more frequent depressive, hypomanic, and mixed episodes, more violence of interpersonal character, but less psychotic features.
- Interestingly, a history of childhood ADHD impacts the course of bipolar disorder regardless of whether the criteria for ADHD is met in adulthood or not.
- These findings suggest that bipolar patients with a history of childhood ADHD might represent a specific developmental subphenotype of bipolar disorder.

Paper II

- Whereas bipolar subjects with childhood ADHD featured high affective dysregulation, pure bipolar patients had normal affective regulation as reflected by their personality profiles.
- Occurrence of affective dysregulation in bipolar disorder was highly accounted for by childhood ADHD.
- Patients with bipolar disorder and a history of childhood ADHD were similar to pure ADHD patients but differed from pure bipolar patients with respect to personality traits. This further validated ADHD in the bipolar subgroup.
- Attention regulation and affective regulation correlated in bipolar patients.

Paper III

- Euthymic bipolar patients with a history of childhood ADHD had lower levels of CSF HVA and CSF 5-HIAA, compared to those without an ADHD history.
- CSF levels of HVA and 5-HIAA correlated to measures of attention and affective regulation.
- These findings lend biological support to the notion that bipolar disorder with childhood ADHD represent a subphenotype of bipolar disorder.

Paper IV

- Probands with ADHD were at much higher risk of bipolar disorder and schizophrenia than controls.
- Relatives to probands with ADHD were also at higher risk of bipolar disorder and schizophrenia compared to relatives with controls.
- ADHD cosegregates with both bipolar disorder and schizophrenia, which refutes the

hypothesis that ADHD would cosegregate specifically with bipolar disorder.

- Hence, ADHD might be an unspecific early expression of a common vulnerability to ADHD, bipolar disorder, and schizophrenia. Alternatively, childhood ADHD might constitute a risk factor for the development of bipolar disorder and schizophrenia.

General conclusions:
Our findings suggest that bipolar disorder with a history of childhood ADHD represents a developmental subphenotype of bipolar disorder. Future studies of bipolar disorder should preferably account for co-occurring ADHD.

SVENSK SAMMANFATTNING

Denna studie är en del av ett större projekt som kallas S:t Görans bipolärstudie (SBP) som startade 2005. På Affektivt centrum vid Norra Stockholms psykiatri genomgår alla patienter en noggrann utredning för att kunna fastställa diagnosen bipolärt syndrom och kartlägga annan psykiatrisk samsjuklighet och personlighet. Patienterna genomgår även en neuropsykiatrisk utredning avseende utvecklingsrelaterade tillstånd som uppmärksamhetsstörning det vill säga *Attention-Deficit Hyperactivity disorder* (ADHD) och autismspektrumtillstånd samt en psykologtestning, magnetkameraundersökning av hjärnan och blodprovstagning för bland annat genetisk analys. Dessutom görs en lumbalpunktion för undersökning av ryggmärgsvätskan som avspeglar kemin i hjärnan. Studien är longitudinell vilket innebär att patienterna följs över tid med jämna intervall.

Bipolärt syndrom debuterar oftast i vuxen ålder eller sena ungdomsår och definieras som ett tillstånd av förhöjt stämningsläge som vid mani (bipolärt syndrom typ 1) eller hypomani (bipolärt syndrom typ 2), ofta följt av depression, med symptomfria perioder dess emellan. Bipolärt syndrom kan i debutera i barnaår och då förekommer samtidig ADHD i mycket hög utsträckning. ADHD skiljer sig från bipolärt syndrom genom att vara ett utvecklingsrelaterat tillstånd som förkommer från barndomen, karaktäriserat av ständiga svårigheter att reglera uppmärksamhet, aktivitetsnivå och impulser.

Syftet med denna avhandling var att undersöka det utvecklingsrelaterade tillståndet ADHD hos vuxna patienter med bipolärt syndrom. Specifikt ville vi:

- utforska förekomsten av ADHD bland vuxna med bipolärt syndrom med en mer utförlig utredning än vad som har gjorts tidigare, inkluderande bland annat en föräldraintervju.
- utforska hur ADHD påverkar den bipolära sjukdomens förlopp.
- klarlägga om det är förekomsten av ADHD i barndomen eller det faktum att man uppfyller kriterier för ADHD i vuxen ålder som är avgörande för förloppet.

Vi fann att ADHD i barndomen är vanligt vid bipolärt syndrom och förekommer i nästan 30 %. Dessa personer debuterade betydligt tidigare i sin affektiva sjukdom, hade 15 gånger fler affektiva skov och fler våldsincidenter än de utan ADHD. Drygt hälften av de med barndoms-ADHD, uppfyllde inte kriterier för ADHD i vuxen ålder, men hade ändå samma kliniska bild som de med ADHD i vuxen ålder. Således förefaller det som att de med bipolärt syndrom med ADHD i barndomen utgör en specifik undergrupp av bipolärt syndrom med tidiga regleringssvårigheter (Artikel I).

Vi undersökte vidare den känslomässiga regleringen och personlighetsdrag hos bipolära patienter med och utan barndoms-ADHD. Vi fann att bipolära patienter med ADHD hade mer ångest- och stresskänslighet, mer irritabilitet, aggressivitet och impulsivitet. Vi jämförde sedan dessa två grupper av patienter med bipolärt syndrom, med en grupp med ADHD utan bipolärt syndrom (ren ADHD). Gruppen med bipolärt syndrom och samtidig barndoms-ADHD liknade i hög grad gruppen med ren ADHD avseende dessa personlighetsdrag. Den känslomässiga regleringsförmågan samvarierade med förmågan att reglera uppmärksamheten hos patienter med bipolärt syndrom. Denna studie stödjer tanken att bipolärt syndrom med ADHD i barndomen utgör en specifik undergrupp av bipolärt syndrom (Artikel II).

I artikel III studerades signalsubstanserna dopamin, serotonin och noradrenalins nedbrytningsprodukter i ryggmärgsvätskan hos personer med bipolär sjukdom typ 1. Personer med BP I och ADHD i barndomen hade signifikant lägre nivåer av både dopamin- och serotoninnedbrytningsprodukter i ryggmärgsvätskan än de utan ADHD i barndomen. Dessa biologiska fynd väcker frågan om dessa grupper av bipolärt syndrom behöver olika behandling (Artikel III).

I artikel IV studerades den familjära kopplingen mellan bipolärt syndrom och ADHD i en populationsstudie. Vi undersökte hur hög risken var för en individ med ADHD att också ha diagnosticerats med bipolärt syndrom eller schizofreni. Denna risk jämfördes sedan med risken hos matchade kontroller utan ADHD. Vi jämförde vidare risken att ha bipolärt syndrom och schizofreni hos släktingar till personer med ADHD med matchade kontrollers släktingars risk för dessa sjukdomar. Förekomsten av bipolärt syndrom eller schizofreni hos de med ADHD diagnos var kraftigt ökad jämfört med kontroller. Släktingar till personer med ADHD hade också en ökad risk för både bipolärt syndrom och schizofreni jämfört med kontrollsläktingar, och risken minskade ju mer avlägsen släktingen var. Detta visar att ADHD är familjärt kopplat till såväl bipolärt syndrom som schizofreni.

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