

On cognition and personality in bipolar disorder

Doctoral thesis

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To my beloved family Nicholaus, Nemo, Alma & Zoe

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Abstract

Even though the hallmark of bipolar disorder is recurrent episodes of elevated or depressed mood, mounting evidence suggests that cognitive impairment is a prominent characteristic of bipolar disorder. The heterogeneity and longitudinal trajectory of cognitive functioning are, however, poorly understood. Additionally, certain personality traits may play a role in psychopathological processes along with cognitive impairments.

This thesis is based on six studies. Data were collected within the framework of St. Göran bipolar project, which is a longitudinal study of patients with bipolar disorder. *Study I* examined the clinical relevance of cognitive impairments and examined if cognitive abilities differ between bipolar disorder subtypes and healthy controls. *Study II* examined whether the correlation structure between various cognitive abilities differs between individuals with bipolar disorder and healthy controls. *Study III* examined if cognitive abilities differ between individuals with bipolar disorder with and without attention-deficit hyperactivity disorder (ADHD). *Study IV* examined if long-term changes in cognitive functioning in individuals with bipolar disorder differ from normal aging. *Study V* examined if personality traits differ between individuals with bipolar disorder and healthy controls, as well as the association between personality traits and illness course. *Study VI* examined if the cognition/personality interface is altered in bipolar disorder, and if combining cognitive predictors with personality measures would enhance the understanding of the illness course.

Results showed that cognitive impairments approached clinical significance for substantial minority of the patients on certain cognitive tests measuring, e.g., set shifting and inhibition (I). While the majority of bipolar disorder patients performed on par with healthy controls, a subgroup (30%) showed impairments concerning memory (II). Comorbid ADHD in bipolar disorder could not explain the cognitive heterogeneity in bipolar disorder (III). The cognitive trajectory over a 6-year period did not differ between individuals with bipolar disorder patients and healthy controls (IV). The personality profile differed between patients and healthy controls but had no prognostic value (V). However, differences in personality traits explained some of the variation in cognitive performance in individuals with bipolar disorder (VI).

Keywords: bipolar disorder, cognition, cognitive function, impairment, neuroticism, personality, personality inventory, psychometrics, and multivariate data analysis.

Sammanfattning på svenska

Bipolär sjukdom kännetecknas av återkommande kraftiga förskjutningar i stämningsläge och aktivitetsnivå. Sjukdomen som drabbar ungefär 2 procent av befolkningen orsakar stort lidande. Bipolär sjukdom är episodiskt förlöpande men förloppet varierar mycket mellan individer. Med adekvat behandling kan dock många leva symtomfria. Flertalet studier har emellertid påvisat varaktiga kognitiva nedsättningar hos individer med bipolär sjukdom. De flesta studier visar på stor heterogenitet avseende svårighetsgrad och omfattning av kognitiva nedsättningar vid bipolär sjukdom. Det är inte fastställt i vad mån kognitiva nedsättningar påverkar risken för återinsjuknande och sjukdomsprognos. Inte heller om kognitiva nedsättningar progredierar och i så fall vilka riskfaktorerna är. Vissa personlighetsegenskaper utgör en sårbarhet för utvecklingen av olika psykiatriska tillstånd. Personlighet kan även ha prognostisk betydelse för sjukdomens skiftande förlopp. Det finns olika uppfattningar om hur personlighet och kognitiv funktion samvarierar.

Den här avhandlingen bygger på sex delstudier. Data är insamlade inom ramen för St. Görans bipolärprojekt, en longitudinell, prospektiv studie av patienter med bipolära syndrom. I *studie I* undersöktes skillnader avseende kognitiv funktionsförmåga mellan bipolär sjukdom typ I, typ II och friska kontroller. Därutöver undersöktes om de kognitiva nedsättningar man finner hos individer med bipolär sjukdom har någon klinisk relevans. I *studie II* undersöktes om korrelationsstrukturen mellan deltest i ett kognitivt testbatteri skilde sig åt mellan individer med bipolär sjukdom och friska kontrollindivider. I *studie III* undersöktes om individer som har både bipolär sjukdom och ADHD har annan kognitiv profil än individer med endast bipolär sjukdom. I *studie IV* undersöktes hur kognitiv funktion hos personer med bipolär sjukdom och friska kontrollpersoner förändrats efter sex år. I *studie V* undersöktes eventuella skillnader mellan patienter och kontroller avseende personlighetsegenskaper. Vidare undersöktes om utfallet i patientgruppen hade någon betydelse för sjukdomsförloppet de kommande två åren. I *studie VI* undersöktes gränssnittet mellan personlighet och kognition och huruvida det skiljde sig åt mellan individer med bipolär sjukdom och friska individer.

Resultaten i *studie I* visade att kognitiva nedsättningar inte skiljer sig nämnvärt åt mellan bipolär sjukdom typ I och II. Nedsättningar avseende kognitiv flexibilitet, inhiberingsförmåga och processhastighet var kliniskt signifikanta för en minoritet av patienterna. *Studie II* visade att majoriteten av patienterna presterar i nivå med kontrollerna men att en betydande undergrupp har nedsättningar inbegripande olika aspekter av minne. *Studie III* visade att det

inte med hjälp av kognitiv testning går att särskilja patienter som har både bipolär sjukdom och ADHD från dem som endast har bipolär sjukdom. Resultaten i *studie IV* visade att kognitiv funktion inte försämras under en sex-årsperiod hos individer med bipolär sjukdom relativt friska individer. *Studie V* visade att personer med bipolär sjukdom kännetecknas av övergenomsnittliga medelvärden på nästan alla delskalor i personlighetsinventoriet jämfört med friska individer, men att variation i personlighet saknade prognostiskt värde för sjukdomsförloppet två år framåt. Personlighetsegenskaper skilde sig inte åt mellan bipolär sjukdom typ I och II. Slutligen visade *studie VI* att sambandet mellan Neuroticism och prestation på en rad kognitiva tester var starkare hos individer med bipolär sjukdom än hos friska individer.

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List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals:

- I. Sparding, T., Silander, K., Pålsson, E., Östlind, J., Sellgren, C., Ekman, C. J., Joas, E., Hansen, S., & Landén, M. (2015). Cognitive functioning in clinically stable patients with bipolar disorder I and II. *PLoS One*, 10(1): e0115562.
- II. Sparding, T., Silander, K., Pålsson, E., Östlind, J., Ekman, C. J., Sellgren, C. M., Joas, E., Hansen, S., & Landén, M. (2017). Classification of cognitive performance in bipolar disorder. *Cognitive Neuropsychiatry*, 22(5), 407-421.
- III. Salarvan, S., Sparding, T., Clements, C., Rydén, E., & Landén, M. Neuropsychological profiles of adult bipolar disorder patients with and without comorbid attention-deficit hyperactivity disorder. Manuscript.
- IV. Sparding, T., Joas, E., Clements, C., Sellgren, C., Pålsson, E., & Landén, M. Long-term trajectory of cognition in bipolar disorder and controls: a 6-year follow-up study. Manuscript.
- V. Sparding, T., Pålsson, E., Joas, E., Hansen, S., & Landén, M. (2017). Personality traits in bipolar disorder and influence on outcome. *BMC Psychiatry*, 17(1), 159.
- VI. Sparding, T., Pålsson, E., Sellgren, C., Landén, M., & Hansen, S. Different relationship between cognition and personality in bipolar disorder and healthy controls. Manuscript.

Abbreviations

ADE	Affective Disorder Evaluation
ADHD	Attention deficit hyperactivity disorder
ANOVA	Analysis of variance
AQ	Autism Spectrum Quotient
AUDIT	Alcohol Use Disorders Identification Test
BD	Bipolar disorder
Brown-ADD	Brown Attention-Deficit Disorder Scales
CD VLT	Claeson-Dahl Verbal Learning (and Retention) Test
CGI	Clinical Global Impressions
CPT II	Conners' Continuous Performance Test II
CSCI	Clinically Significant Cognitive Impairment
CSCI	Cognitive Behavior Therapy
CWIT	Color-Word Interference Test
DFT	Design Fluency Test
DModXs'	Observations' model distances
DSC IL	Digit-Symbol-Coding-Incidental Learning
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition, Text Revision
DSST	Digit symbol substitution test
DUDIT	Drug Use Disorders Identification Test
FSIQ	Full Scale Intelligence Quotient
g'	General intelligence
GDS	Global Deficit Score
GWAS	Genome-wide association study
HC	Healthy controls
IPR	Individual Profile Rating
M.I.N.I	Mini International Neuropsychiatric Interview
MADRS	Montgomery-Åsberg Depression Rating Scale
MANCOVA	Multivariate analysis of covariance
MHC	Martino et al., Hard Criteria
MSC	Martino et al., Soft Criteria
NART	National Adult Reading Test
NEO PI-R	NEO Personality Inventory – Revised
NOS	Not otherwise specified
OPLS-DA	Orthogonal partial least squares discriminant analyses
ψ'	General Psychopathology Factor
PC1	First principal component
PC2	Second principal component
PCA	Principal component analysis

PLS	Projection to latent structures by means of partial least squares
PGWB	Psychological general wellbeing
Q^2X	Predicted variation
R^2X	Explained variation
RAADS	Ritvo Autism Asperger's Diagnostic Scale
RCFT	Rey Complex Figure Test and Recognition Trial
SBP	St. Göran bipolar project
SCID	Structured Clinical Interview for DSM-IV
SD	Standard deviation
SDS	Sheehan Disability Scale
SS	Symbol Search
SSP	Swedish universities Scales of Personality
STEP-BD	Systematic Treatment Enhancement Program for Bipolar Disorder
TMT	Trail Making Test
VFT	Verbal Fluency Test
WAIS -III	Wechsler Adult Intelligence Scale - Third Edition
WHO	World Health Organization
WURS	Wender Utah Rating Scale
YMRS	Young Mania Rating Scale

Introduction

Studies on psychiatric conditions have traditionally focused on emotional symptoms, delusions, and abnormal behavior, but less on cognitive functioning despite the close relationship between cognition and psychopathology (Millan et al., 2012). For example, lower childhood IQ predicts several psychiatric disorders, e.g., schizophrenia and anxiety disorders, and greater psychiatric comorbidity in adulthood (Koenen et al., 2009). In fact, cognitive impairments are part and parcel of psychiatric disorders that may impact quality of life and psychosocial functioning (Fourrier, Singhal, & Baune, 2019; Millan et al., 2012). Many severe psychiatric conditions are treated with drugs to alleviate some of the symptoms, e.g., anxiety or hallucinations. Yet, associated cognitive impairments do not improve to the same extent and may even worsen (Hill, Bishop, Palumbo, & Sweeney, 2010; Millan et al., 2012).

I argue that cognitive functioning is a highly relevant dimension of psychiatric disorders that cuts across traditional diagnostic boundaries (Lai, Lombardo, & Baron-Cohen, 2014; Millan et al., 2012).

Ever since Kraepelin's diagnostic conceptions, remission without cognitive dysfunction has been considered the key feature separating manic-depressive illness from dementia praecox (i.e., schizophrenia) (Kraepelin, 1921). But we now know that individuals with bipolar disorder (BD) not only suffer from mood swings, but also struggle with impairments in cognitive functioning. Even though these cognitive deficits are most apparent during depression and mania, they might linger and contribute to functional deficits also during periods of remission (Kurtz & Gerraty, 2009; Martínez-Arán et al., 2004).

Kraepelin (1921) also proposed that “there are certain temperaments which may be regarded as rudiments of manic-depressive insanity” which form “the point of departure for a morbid process” (p. 118). These are the moody ‘depressive’ temperament, the hot-tempered ‘irritable’ temperament, and the impulsive ‘manic’ temperament. Moreover, he suggested that an individual's temperament type to some extent predicted the nature and course of the illness.

The standard classification of mental disorders used in current mental health services do not consider the notion that certain personality traits might impact illness course. The current categorical way of classifying psychopathologies

produces high incidence of ‘comorbid’ conditions. An alternative way of studying psychiatric conditions is based on dimensional models (Caspi et al., 2014). A General Psychopathology dimension has been proposed, characterized by personality traits that hinder coping with other people, the environment, and the self.

Personality and general cognitive ability are usually considered separate constructs (Maltby, Day, & Macaskill, 2007) and few attempts have been made to link them, in particular in the field of bipolar disorder.

Bipolar disorder

Conditions with clear fluctuations in mood states have been described ever since antiquity. Even though Jean Pierre Falret described ‘circular insanity’ in 1854 (Pichot, 2004), Emil Kraepelin is considered to be the father of the diagnosis ‘manic depressive illness’ (Kraepelin, 1921), which is called bipolar disorder (BD) in current diagnostic systems. A wealth of portrayals, stories, that put flesh on the bones enable us to better understand lived experiences of individuals with BD. Virginia Woolf writes in her diary: “And now today suddenly the weight of my head is lifted and I can think, reason, keep to one thing and concentrate. Perhaps this is the beginning of another spurt. Perhaps I owe it to my conversation with L. last night. I tried to analyze my depression: how my brain is jaded with the conflict of two types of thought, the critical, the creative; how I am harassed by the strife and jar and uncertainty without. This morning the inside of my head feel cool and smooth instead of strained and turbulent” (Woolf, 1977, p. 181). BD is associated with a great deal of suffering and should not be romanticized, but nuances are warranted. There is a disproportionate rate of BD in creative individuals (Koutsantoni, 2012; Kyaga et al., 2011), which is important to keep in mind when examining individuals from the psychiatric vantage point.

Subtypes of bipolar disorder

There are subtypes of bipolar disorder. The essential features of *bipolar I disorder* is the occurrence of one or more manic or mixed episodes (DSM-IV-TR, 2000). More often than not, afflicted individuals also suffer one or more major depressive episodes during the course of illness. Manic episodes are characterized by abnormally elevated mood and increased motor drive and approximately 75% of all patients show psychotic symptoms during an acute manic episode (Grande, Berk, Birmaher, & Vieta, 2016). Mixed episodes can

also be present in BD I and are characterized by a combination of depressive and manic symptoms that occur every day for a week.

Bipolar II disorder is characterized by the occurrence of one or more major depressive episodes, accompanied by at least one hypomanic episode (DSM-IV-TR, 2000). A hypomanic episode presents with persistently elevated, expansive, or irritable mood during at least four days, but hypomanic symptoms do not cause severe impairments in every day functioning. A history of a full blown manic or mixed episode precludes the diagnosis of bipolar II disorder.

Both subtypes of BD present with symptoms that taken together cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. Mood episodes induced by medication, drug-use, or toxin exposure do not count towards a diagnosis of BD. Also, the episodes should not be better explained by schizoaffective disorder, schizophrenia, or other psychotic disorders.

BD not otherwise specified (NOS) includes disorders with bipolar features that do not meet criteria for any specific BD mentioned above, e.g., recurrent hypomanic episodes without depressive symptoms, or periods with hypomanic symptoms that do not meet the duration requirement of a minimum of 4 days (DSM-IV-TR, 2000).

The word euthymia originates from Greek and combines the words 'eu' meaning 'well' and 'thymo' meaning 'soul, emotion'. It refers to the state in-between recurring mood episodes, so called free intervals. When an individual with BD do not meet criteria for a hypomanic, manic, mixed, or depressive episode, they are considered to be euthymic or well (Fava & Bech, 2016). Periods of euthymia is a prerequisite for an episodic illness.

Cyclothymic disorder present with chronic, fluctuating mood episodes involving subthreshold hypomanic, or hypomanic, and depressive symptoms for at least two years (DSM-IV-TR, 2000). The hypomanic and depressive symptoms are not sufficient to meet full criteria for mania or depression.

Moreover, *bipolar spectrum* concepts have been proposed (Akiskal et al., 2006; Angst, 2007), which are described more thoroughly in the personality section.

Patients included in the St. Göran bipolar project went through a systematic diagnostic examination according to Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition, Text Revision (DSM-IV-TR). For a more detailed description of the diagnostic evaluation, please see the method section.

Prevalence

The total lifetime prevalence has been estimated to 0.6% for bipolar I disorder, 0.8% for bipolar II disorder, and 1.4% for subthreshold bipolar disorder (Merikangas et al., 2007). This sums up to a total prevalence of 2.8% for bipolar spectrum diagnoses, which means that about 147 million people would be affected worldwide. However, the study by Merikangas and colleagues (2007) suggested that the prevalence varies across countries ranging from 0.1% (India) to 4.8 (USA). According to the DSM-IV, it is equally likely that men and women are affected by bipolar I disorder (DSM-IV-TR, 2000). On the other hand, the WHO's World Mental Health Survey Initiative from 2007 showed that lifetime rates of bipolar I disorder and subthreshold BD were larger in males than in females (Merikangas et al., 2007). Bipolar II disorder is considered more common in women than in men (DSM-IV-TR, 2000).

Illness course

The average age at onset for BD is 20 years for both men and women (DSM-IV-TR, 2000). However, individuals with first-degree relatives with mood disorders are more likely to have an earlier age at onset. More than 90% of all individuals that have one mood episode go on to have future episodes. About 60-70% of all manic episodes and hypomanic episodes occur immediately before or after a depressive one. According to the kindling hypothesis, relapses in mood episodes get gradually less influenced by life stressors with time spent ill, and the intervals between episodes tend to shrink as the individual ages (Grande et al., 2016). This not only warrants early detection of the disorder but also stresses the need for prophylactic treatment to prevent episodes.

Kessler et al. (2006) investigated a large sample of US workers and showed that approximately three quarters of individuals with BD had depressive episodes during a 12-month period, and 60% had manic-hypomanic episodes (Kessler et al., 2006). On average 98 (median 60) days were spent in a depressive episode during a year. These numbers differ substantially from the Swedish National Quality Register for Bipolar Disorder (Bipolär) where approximately 38% of individuals with BD had any depressive episode during a 12-month period (2018), and 28% had any manic-hypomanic episode. Of

note, the illness course of BD has changed with modern medical treatment (Angst & Sellaro, 2000). Data from the days before modern medical treatment suggest that the length of manic episodes had a median duration of 5–6 months. A common cause of relapses today is non-adherence to medication (Colom, Vieta, Tacchi, Sánchez-Moreno, & Scott, 2005). Co-occurring psychiatric diagnoses are also a risk factor (Bipolär Årsrapport, 2014). In any type of BD, the premenstrual period may be associated with worsening of a mood episode (DSM-IV-TR, 2000).

Models of the ‘staging hypothesis’ suggest that the illness course move along a progressive path with loss of psychosocial functioning in the prodromal phase, and with cognitive decline in the later stages of the illness (Berk, 2009; Berk et al., 2017; Grande et al., 2016; Kapczinski et al., 2014).

BD is a potentially deadly condition: completed suicides occurs in 10-15% of all individuals with bipolar I and II disorder (DSM-IV-TR, 2000). A Swedish population-based study from 2001 showed that the standardized mortality ratios for suicide in BD were 15.0 for males and 22.4 for females, while corresponding numbers for unipolar depression were 20.9 and 27 (Ösby, Brandt, Correia, Ekblom, & Sparén, 2001). The suicide mortality rate was most evident at younger ages and adjacent to receiving a diagnosis.

Familial pattern

Bipolar disorders tend to run in families and are highly heritable. In a Swedish population-based study, the heritability (the portion of illness accounted for by genetic factors) for BD was estimated to 59% (Lichtenstein et al., 2009). Childhood shared environmental effects was estimated to 3.4% and non-shared environmental effects to 38%. This study also showed that schizophrenia and BD partly shared genetic risks. Interestingly, ADHD and BD has also been shown to share genetic factors (Larsson et al., 2013). Other twin and family studies have arrived at slightly higher heritability estimates, where genetic influences explain 80-85% of the risk (Barnett & Smoller, 2009). Hence, even though genetic variation accounts for most of the population risk, the etiology of BD is complex and multifactorial.

Common co-occurring conditions

Several other psychiatric disorders present with fluctuations in mood and activity level and BD needs to be differentiated from, e.g., ADHD and borderline personality disorder. In addition, a majority of individuals with BD also meet life time criteria for other psychiatric disorders (Table 1). The high

number of comorbidities begs the question whether some of these comorbid conditions are actually distinct disorder or merely show that individuals with BD present a plethora of symptoms that fulfill criteria for several diagnoses. Thus, the high comorbidity is likely to not only reflect true comorbid conditions but also to be a diagnostic artefact from using a categorical diagnostic system (Wittchen, 1996).

The 12-month prevalence for attention-deficit/hyperactivity disorder (ADHD) among 8- to 15-year old US children is 9 percent (Merikangas et al., 2010). In Sweden, ADHD occurs in approximately every 20 children (Gillberg, Fernell, & Råstam, 2015). The criteria for adult ADHD are met for at least half of those who met diagnostic criteria in childhood. The prevalence rates of individuals suffering from both ADHD and BD varies across different studies (Table 1). One explanation could be that ADHD and BD present with some similar symptoms, which might complicate diagnoses. A possible consequence is that the comorbid condition BD+ADHD is under-diagnosed and under-treated (Klassen, Katzman, & Chokka, 2010). It is important to identify individuals with co-occurring BD+ADHD as they present with more severe illness course and lower every day functioning. Interestingly, an earlier study conducted on the SBP-cohort showed that individuals with BD who met the criteria for childhood ADHD, but did not fulfil criteria for adult ADHD, also showed worse illness course than individuals with BD without a history of ADHD (Rydén et al., 2009).

Table 1
Common life-time co-occurring developmental
and psychiatric conditions in BD subtypes

Condition	Life-time co-occurring developmental and psychiatric conditions		
	BD-I %	BD-II %	Comments
<i>Developmental:</i>			
ADHD	28	28	In the SBP-cohort 16 % of all patients with BD met the criteria for ADHD (Rydén et al., 2009).
<i>Psychiatric:</i>			
Any anxiety disorder	77	75	
Any substance use disorder	52	35	
Alcohol dependence	31	17	
Drug dependence	24	8	
Suicide attempts	26	21	
Self-mutilation	38	27	Interestingly, most commonly observed in subjects with bipolar I disorder (Joyce, Light, Rowe, Cloninger, & Kennedy, 2010)
Borderline personality disorder	10	20	(Zimmerman & Morgan, 2013)
PTSD	21	16	(Hernandez et al., 2013)

Prevalence rates from (Merikangas et al., 2011) unless specified in comments

Quality of life and functioning

Bipolar disorder is one of the most debilitating disorders in the developed world according to the World Health Organization (WHO, 2004). ‘Quality of life’ is rarely defined in the literature of BD (Morton, Michalak, & Murray, 2017). However, the most common definition was coined by the WHO: “an individual's perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (The WHOQOL Group, 1995). Impairment in psychosocial functioning, i.e., a person’s ability to perform activities of daily living and to engage in meaningful interpersonal relationships, is a significant feature of BD even during euthymia (Michalak & Murray, 2010). Occupational functioning is an important aspect of psychosocial functioning and reduced among individuals living with BD (Bonnín et al., 2014; Gilbert & Marwaha, 2013; Mur, Portella, Martinez-Aran, Pifarre, & Vieta, 2009; Ryan et al., 2013). Individuals living with BD are more often unemployed compared not only to the general population but also in comparison to people suffering from

unipolar depression. Moreover, people with BD who remain employed might gravitate toward less demanding work roles (Marwaha, Durrani, & Singh, 2013). However, there is a significant heterogeneity in functioning among individuals with BD ranging from high functioning individuals to people with large impairments in multiple domains (Solé et al., 2018). Factors that have been linked to the functional outcome in BD are co-occurring psychiatric conditions (Hajek et al., 2005; Zimmerman et al., 2010) and impaired cognitive functioning (O'Donnell et al., 2017)

Treatment

Common medications used to treat bipolar disorder include mood stabilizers, atypical antipsychotics, and antidepressants (Sachs, Printz, Kahn, Carpenter, & Docherty, 2000). Lithium has been used for decades and is the first-line treatment in BD as it effectively prevents manic and depressive mood episodes (Joas et al., 2017) as well as suicidal behavior (Song et al., 2017). In Swedish psychiatric care, virtually all individuals with BD are prescribed some medication (Persson et al., 2017). A significant majority of individuals in both type I and type II BD groups use mood stabilizing drugs. According to data from the Swedish national quality register Bipolär, two-thirds of the type I BD group received lithium treatment, and the second most common mood-stabilizing drug was lamotrigine. In type II BD, lamotrigine was the most commonly prescribed mood-stabilizing drug and lithium was the second most common. Lamotrigine was twice as common in type II as in type I. Nearly half of the subjects with bipolar I disorder and over one-third of bipolar II disorder subjects were treated with an antipsychotic drug. Over one-third of the subjects with bipolar I disorder and over half of bipolar II disorder subjects used an antidepressant. Medical treatment used for ADHD have increased dramatically during recent years and are twice as common in patients with bipolar II disorder compared with bipolar I disorder, whereas benzodiazepines or benzodiazepine-like drugs are more common among individuals with bipolar I disorder. Differences in medication were significant even after adjusting for age, sex, and co-occurring anxiety and substance use disorders. Sex differences in treatment have been demonstrated in routine clinical settings in Sweden; women were more frequently treated with antidepressants, lamotrigine, electroconvulsive therapy, benzodiazepines, and psychotherapy whereas men were more often treated with lithium (Karanti et al., 2015).

There is emerging evidence of the benefits of adding psychosocial interventions and psychotherapies to drug treatment in BD (Geddes & Miklowitz, 2013; Swartz & Swanson, 2014). The most common interventions

are summarized here. *Psychoeducation* aims to improve illness insight, to make patients better in understanding and detect early symptoms, and to develop coping strategies (Francesco Colom et al. (2003). Specific group psychoeducation programs have been shown to be effective in reducing the number of relapses and the number and length of hospitalizations, but also in increasing the length of euthymic intervals (Colom & Vieta, 2006). We recently found that psychoeducation reduces the risk of mood episodes and inpatient care also when implemented in routine clinical practice (Joas et al., 2019, in press). *Interpersonal and social rhythm therapy* assumes that individuals with BD have disturbances in both circadian rhythm and sleep–wake cycles (Frank, Swartz, & Kupfer, 2000). This specific therapy focuses on identification of life events (both negative and positive) that might cause irregular sleep–wake rhythms, which in turn lead to mood symptoms. *Cognitive Behavior Therapy* (CBT) approaches has also been developed (Scott et al., 2006), with a broad repertoire of interventions aiming at acceptance of the disorder, reducing irregularity in mood symptoms, and identifying psychosocial stressors and interpersonal problems that may increase the risk of mood episodes. But CBT also teach coping strategies and aims to change dysfunctional automatic thoughts. *Family focused therapy* contains an extensive program that involves family members and includes psychoeducation, communication enhancement training, and problem-solving skills (Miklowitz, George, Richards, Simoneau, & Suddath, 2003). Family focused therapy has been shown to increase the length of euthymic intervals.

Cognitive functioning

Cognitive function can be defined as a “general mental capability involving reasoning, problem solving, planning, abstract thinking, complex idea comprehension, and learning from experience” (Gottfredson, 1997). Different aspects of cognitive functioning can be measured with different cognitive tests. “Neuropsychological assessment is, in short, a means of measuring in a quantitative, standardized fashion the most complex of human behavior – attention, perception, memory, speech and language, building and drawing, reasoning, problem solving, judgment, planning, and emotional processing” (Lezak, 2012, p. 15).

Individual differences in intelligence

Differences in intelligence are partly heritable (Deary, 2013). The proportion of differences in intelligence explained by genetic factors is approximately 20% – 30% in childhood and increases to as high as 70% – 80% in midlife (Deary,

Johnson, & Houlihan, 2009). Polygenic scores derived from genome-wide association studies (GWAS) of intelligence can currently predict 4% of the variance in intelligence (Plomin & von Stumm, 2018). Individual differences in intelligence profoundly impact people's lives as it predicts success in major life areas, e.g., work, education, social life, and everyday functioning (Gottfredson, 1997).

The g-factor

Healthy people who perform well on one cognitive test tend to perform well on a wide range of other tests. In other words, different tests of cognitive function are positively correlated (Deary et al., 2009). This pattern is seen when a large group of people are tested with several different cognitive tests. This phenomenon is known as general intelligence, general mental ability, or general cognitive ability, *g* for short. Spearman showed already in 1904 that a person's *g* accounts for about half of the inter-individual differences in cognitive ability. Some individual tests correlate more closely to each other and therefore represent different domains, e.g., processing speed and perceptual functioning. However, these domains are also highly correlated (Deary, Penke, & Johnson, 2010). Actually, independently from *g*, the main types of mental abilities in which people differ are those that are specific for individual tasks (Carroll, 1993). In summary, as long as a satisfactory number of tests are given to a group of people, any group will produce a *g*-score that is not unique for the tests given. Hence, the resulting *g*-score would be the same with almost any choice of tests. Nevertheless, certain single tests, e.g., the Raven test, appear to be particularly reliable in indicating general intelligence (Deary & Batty, 2007).

Different psychometric models of human intelligence have been suggested (Johnson & Bouchard Jr, 2005). Notably, it has been suggested that executive functioning is not related to *g*. Individuals with frontal lobe damages with poor results on tests measuring executive functioning show unaffected results on intelligence tests such as WAIS-III (Friedman et al., 2006). Executive functioning is not a uniformly defined construct but is usually separated into three categories: shifting, updating, and inhibiting (Friedman et al., 2006). Friedman et al., (2006) demonstrated that both inhibiting and shifting are weakly coupled to general intelligence whereas updating was more closely related. The working memory construct reflects the storage component and the central executive or attention component. Working memory is believed to be related to *g*. Engle et al. showed that working memory – but not short-term

memory – was strongly associated with fluid intelligence (Engle, Laughlin, Tuholski, & Conway, 1999).

Life course

Intelligence shows substantial stability across the life course in healthy persons (Deary et al., 2009). According to Deary (2009), aging breeds an essential difference between two types of intelligence, fluid and the crystallized intelligence. Fluid intelligence concerns comprehending and figuring out problems there and then. Crystallized intelligence concerns retrieval of well-established knowledge such as vocabulary or general knowledge. Fluid intelligence show age-related cognitive decline while crystallized intelligence shows little age-related decline. The mechanism of cognitive decline is well characterized even though it might be difficult to separate non-pathological from pathological cognitive decline (Deary et al., 2009). Age affect the variance shared by all tests but in particular processing speed and memory (Deary 2013). Therefore, tests that capture vocabulary knowledge is often used to estimate premorbid functioning, for example the National Adult Reading Test (NART) (Blair & Spreen, 1989).

Ecological validity of cognitive tests

Historically, cognitive tests were developed to identify brain damage (Chaytor & Schmitter-Edgecombe, 2003). With time, the type of questions asked by clinicians have shifted focus from brain damages to assess real-world functioning in school or at the work place. Chaytor (2003) defined ecological validity as follows: “the degree to which results obtained in controlled experimental conditions are related to those obtained in naturalistic environments” (from Tupper and Cicerone, 1990). The extent to which a cognitive test reflects an individual’s real-world functioning is hence called ecological validity. The construction of tests has changed since the aim of assessment no longer is to discriminate brain-injured from normal individuals. A recurring problem is the lack of consensus concerning what a test actually measures. Two clinicians may have different aims with administering the same test. With respect to measuring the loosely defined construct of executive functioning, it has been shown that self-reports in fact predict impaired real-world functioning better than tests aimed at assessing executive functioning (Barkley & Fischer, 2011).

Cognitive impairment

Cognitive impairment is difficult to define. There is no established threshold that define impairment in clinical practice. It depends on contextual factors such as premorbid ability, but also on what one can expect the progress to be (Cullen et al., 2016; Roux et al., 2019). The presumed cause of impairment also matters. The term ‘mild cognitive impairment’ (MCI) is for example seldom used in the bipolar disorder field. There are various subtypes of MCI with different etiologies, yet the concept is tightly coupled to the thought of progression (Petersen et al., 2009).

In study I of this thesis, the clinical significance of cognitive impairments in bipolar disorder is investigated.

Cognitive impairments in bipolar disorder

One of the first studies on cognitive impairment in bipolar disorder was carried out more than 20 years ago in Sweden. Anne Tham and colleagues (1997) investigated neuropsychological performance in euthymic patients with recurring mood disorders. They showed overall lowered test results and suggested a subgroup of patients defined by more relapses and episodes of hospitalization showing cognitive dysfunction even when euthymic. Ever since, several numbers of studies have shown that cognitive impairment persist during euthymia. The last fifteen years has seen meta-analyses conducted on cross-sectional studies in the field (Arts, Jabben, Krabbendam, & Van Os, 2008; Bora, Yucel, & Pantelis, 2009; Krabbendam, Arts, van Os, & Aleman, 2005; Robinson et al., 2006; Torres, Boudreau, & Yatham, 2007). By and large, these analyses find group level differences in global measures across broad cognitive domains such as processing speed, attention, different memory tests, and executive functioning.

In response to the lack of consensus in the field and discrepancies across studies, a reanalysis was made in 2013 comprising data from 31 studies on cognitive functioning in BD. This time the analysis controlled for important baseline factors such as age, IQ, and sex (Bourne et al., 2013). Authors found that cognitive deficits remained significant after adjusting for these factors. They showed that individuals with BD had small to moderate effect sizes on established differences in performance on all 11 outcome measures from 4 selected neuropsychological tests (verbal learning, Trail Making Test, Digit span, and Wisconsin Card Sorting Test). They also found that lingering minor

depressive symptoms and the effects of some drug treatments may contribute to differences compared with controls, but could not fully explain them.

Taken together, group-level mean differences between individuals with BD and healthy controls (HC) have been reported. Large effect sizes tell us there are large differences between groups. Nevertheless, it does reveal the proportion of adults with BD with clinically relevant cognitive impairment. It is possible that group mean differences harbor a significant within-group variation, ranging from normal performance to severe impairment in BD. It is also possible that some individuals suffer from specific impairments and some suffer from multi-domain impairments. If the overall group differences are being driven by a subgroup of patients with marked levels of impairment, this would obscure the true picture of cognitive impairment in the BD population, which may be severe for some and absent for others. Heterogeneity in cognitive function in BD has been investigated with regard to clinical subphenotypes, as well as heterogeneity in cognitive functioning in the BD population. (Iverson, Brooks, Langenecker, & Young, 2011; Martino et al., 2008).

In *study I and III*, we investigated clinical subgroups with respect to cognition and in *study II* we investigated the possibility of cognitive subgroups in BD.

It is also possible that mean group differences are a result of case-mix differences or demographic differences. To exemplify this, we compared individuals with BD with another group of individuals with BD, all of them included in the St. Göran Bipolar Project, but in two different Swedish cities. Patients underwent the same systematic diagnostic examination procedure and followed the same study protocol. We found that the bipolar disorder groups differed significantly in Full scale IQ (FSIQ) between the cities. Individuals with BD in Stockholm performed significantly better ($M = 106, SD = 14$) than individuals with BD in Gothenburg [$M = 98, SD = 13, t(270) = -5.023, p < .001$, partial $\eta^2 = 0.086$]. Individuals with BD in Stockholm also had significantly higher education level than individuals with BD in Gothenburg ($p < 0.001$).

The majority of studies in this field conduct mean group analysis to investigate differences in cognitive impairments. Using the same approach, we could assert that BD patients in Gothenburg are cognitively impaired compared with the same patient group in Stockholm. Needless to say, this might be explained by case mix differences.

Based on the fact that individual cognitive low-level cognitive abilities, i.e., the performance on individual tests as opposed to domain level, are positively correlated in a typical pattern, we argue that multivariate projection techniques are a better way to detect cognitive impairments across groups. Such techniques make it possible to identify individuals that deviate from expected/in comparison with healthy controls.

In *study II* of this thesis, we examined whether the correlation structure between various cognitive abilities differs between individuals with bipolar disorder and healthy controls.

Long term trajectory of cognitive functioning in bipolar disorder

The construct of staging in bipolar disorder rests on the hypothesis that psychopathology moves along a progressive path, where a decline in cognitive impairment is seen in the later course of the disorder (Berk et al 2017). The paradigm of accelerated aging suggests that patients with BD experience accelerated cognitive decline in older days compared with a healthy population (Rizzo et al., 2014). Decreased levels of Brain-Derived Neurotrophic Factor, Oxidative stress, and vascular burden are some factors that have been suggested to be associated with cognitive impairments in elderly individuals with BD (Andreazza et al., 2015; Gildengers et al., 2010; Soares et al., 2016). A recent review show that history of BD significantly increases the risk of dementia in older adults (Diniz et al., 2017), a risk that increases with the number of episodes in depressive and bipolar affective disorders (Kessing et al., 2004).

An important limitation of our knowledge and understanding of this episodic and potentially progressive disorder is that most research is based on cross-sectional studies. Considering the limited numbers of long-term studies, it is as yet undecided whether BD has a progressively deteriorating course of cognitive functions or not.

In *study IV* of this thesis, we investigated the trajectory of cognitive function in bipolar disorder over 6 years.

How can cognitive impairments be explained?

Genetic factors do not fully explain cognitive impairments seen in psychiatric disorders (Millan et al., 2012). To understand the etiology, developmental and environmental factors must also be considered. For example, uncontrolled

stress and hypothalamic–pituitary–adrenal axis overactivity can prompt cognitive impairments across the lifespan.

Efforts have been made to compile potential causes of cognitive impairments in the field of bipolar disorder. Savitz and colleagues (2005) pointed out the following potential causes: (i) iatrogenic, (ii) acute functional changes associated with depression or mania, (iii) permanent structural lesions of a neurodegenerative origin, (iv) permanent structural lesions that are neurodevelopmental in origin, and (v) permanent functional changes that are most likely genetic in origin. I will outline evidence for each of these potential causes below:

(i) Roux and colleagues (2019) found in accordance with Bourne (2013) an association between antipsychotic medication and cognitive impairment. Moreover, our research group found a negative effect of antipsychotic medication after controlling for the effect of psychotic episodes (Pålsson et al., 2013). Long-term use of benzodiazepines has also been associated with cognitive impairment (Barker, Greenwood, Jackson, & Crowe, 2004). Interestingly, it has been showed that tapering benzodiazepine use among long-term users can significantly improve cognitive performance without any substantial negative effects on subjective well-being or psychosocial functioning (Baandrup, Fagerlund, & Glenthøj, 2017). A meta-analysis showed that lithium carbonate had mild negative effects on some aspects of memory and creativity, and moderate effects on psychomotor performance in patients with euthymic affective disorders (Wingo, Wingo, Harvey, & Baldessarini, 2009). However, there were no differences in cognitive performance between healthy volunteers who received lithium and those who received a placebo, which imply that the association in patients might have been confounded by indication. The impact of anticonvulsants on cognition in individuals with BD have not been determined. Cognitive side effects has been shown to be less prominent in patients receiving lamotrigine compared with patients on valproate or carbamazepine (Daban et al., 2006). To complicate matters further, the majority of individuals with BD are on combinations of drug treatments.

(ii) Cognitive functioning may be state-dependent as cognitive impairments are more pronounced during affective episodes of the illness course than when patients are euthymic (Martínez-Arán et al., 2004). Bourne (2013) showed that residual mood symptoms were associated with lower performance on some

cognitive tests, but the effect sizes were low. No association was detected between mania scores and a dozen of cognitive tests.

(iii) In line with the construct of staging in BD, a decline in cognitive impairment has been demonstrated late in the course of the disorder (Berk, 2009; Berk et al., 2017). And in line with the paradigm of accelerated aging, individuals with BD experience accelerated cognitive decline in old age compared with a healthy population (Rizzo et al., 2014). Cognitive impairment has also been associated with illness severity indices (Bora, 2018; Sanchez-Morla et al., 2018) such as prior psychotic manifestations (Savitz, van der Merwe, Stein, Solms, & Ramesar, 2009), and the number of affective episodes, particularly manic episodes (Mann-Wrobel, Carreno, & Dickinson, 2011).

(iv) ADHD and BD co-occur and there is a genetic overlap between the two diagnoses (Larsson et al., 2013; van Hulzen et al., 2017). Individuals with co-occurring conditions are under-diagnosed as well as under-treated (Klassen et al., 2010). Comorbid ADHD is seldom controlled for in analyzes of cognition in BD, c.f., Bourne (2013) and Roux (2019).

(v) First-degree relatives to individuals with BD present with cognitive impairments. In fact, executive functioning and verbal memory have been suggested as candidate endophenotypes for the genetic liability for BD (Arts, Jabben, Krabbendam, & van Os, 2011; Bora, Yucel, & Pantelis, 2009).

Consequences of impaired cognitive functioning

Cognitive dysfunction negatively impacts educational, occupational, and domestic functioning (Bonnín et al., 2014; Depp et al., 2012; Gilbert & Marwaha, 2013; Mur et al., 2009; Ryan et al., 2013). Executive dysfunction in particular has been linked to poor occupational functioning (Bonnín et al., 2014; Gilbert & Marwaha, 2013; Mur et al., 2009; O'Donnell et al., 2017; Ryan et al., 2013).

Therapeutic approaches for cognitive impairments

A number of pharmacological interventions have been tested to treat cognitive impairments without conclusive results. There is currently no drugs approved to treat cognitive impairments in bipolar disorder (Sanches, Bauer, Galvez, Zunta-Soares, & Soares, 2015). Nonpharmacological interventions on the other hand, for instance functional remediation that not only target cognitive impairments but also poor functioning, have showed some promising results (Martínez-Arán et al., 2011; Vieta, Torrent, & Martínez-Arán, 2014).

Personality

Rooted in Hippocrates theories of four humours: chole (yellow bile), melanchole (black bile), sanguis (blood) and flegma (phlegm), the Greek physician Galen explained differences in individuals in temperamental terms (Stelmack & Stalikas, 1991). It was thought that imbalance in different humours, temperaments, or psychological dispositions lead to mental problems. In modern times, a variety of theories have been developed to understand how personality constitutes are linked to psychic suffering, e.g., psychoanalytic, humanistic, and cognitive theories (Freud, 1983; Rogers, 1956; Watson, 1913). Thus, the concept of personality is multifaceted and based on various theoretical basic assumptions.

Fundamental states

Kraepelin (1921) postulated that there are “certain temperaments” which may be regarded as “rudiments of manic depressive insanity”. “They may throughout the whole of life exist as peculiar forms of psychic personality without further development; but they may also become the point of departure for morbid process which develops under peculiar conditions and runs its course in isolated attacks” (Kraepelin, 1921, p. 118). The “depressive temperament” is characterized by a “permanent gloomy emotional stress in all experiences of life” (p.118). In this patient group, mood is predominantly depressed and accompanied by a weak feeling of guilt, anxiety, and a lack of self-confidence. Kraepelin describes these individuals as experiencing interrupted series of “periodic melancholia”, suddenly interrupted by periodic mania. The “manic temperament” is regarded as the antithesis of the depressive temperament. In these individuals, mood is exalted and they tend to act carelessly and with great confidence. In addition, they are restless, charming, and live in constant feud. The slightly hypomanic states might develop into pronounced hypomania with rare attacks of pure depression. The “irritable temperament” is best explained as a “mixture of fundamental states” (Kraepelin, 1921, p. 130). These individuals are easily offended; the mood is subject to frequent change and they are impulsive. Additionally, they come too easily to delusional interpretations of life events. Lastly, the “cyclothymic temperament” is characterized by “frequent, more or less regular fluctuations of the psychic state to the manic or to the depressive state” (Kraepelin, 1921, p. 131). These individuals can be sparkling and full of joy, and after some time they become blue, ill-humored, and again after few months they are full of energy again. In the beginning of their illness course they have short-lived passing attacks that with time tend to turn more frequent and long lasting.

The trait concept

Words to describe people in general constitutes the foundation for conceptualizing modern personality traits (Cattell, 1943). In the ambitious work of Cattell, four to five thousand words were categorized into about 160 categories. This semantic reduction was made with correlation statistics and yielded clusters of related words. The work took place entirely within the framework of normal psychology. Since the 1940s, the personality field has attempted to determine the optimal number of categories – traits – necessary to account for the variation in a person's styles of behavior in different cultures. “Traits refer to stability of behavior and beliefs about enduring dispositions” (Matthews, Deary, & Whiteman, 2009, p. 85). Assessment of traits is often conducted with self-rating questionnaires.

Temperaments are constructs partly separated from traits and can be described as biologically rooted, observable, behavior tendencies that emerge early in life and are stable to a certain degree while undergoing a socialization process (Matthews et al., 2009).

Stable traits and transient states are also separate constructs, and measured separately. States “refer to any reliably measurable characteristics, but typically, state variables refer to conscious, verbally reportable qualities such as moods” (Matthews et al., 2009, p. 85). Unlike trait tests, state tests should not show high retest reliability.

Eysenck (1984) proposed a tridimensional model with biological roots: Extraversion-Introversion, Neuroticism, and Psychoticism. Costa and McCrae (1992), on the other hand, organized personality into five factors: Neuroticism (N), Extraversion (E), Openness to Experience (O), Agreeableness (A), and Conscientiousness (C). This five-factor model is measured with the revised NEO Personality Inventory (NEO PI-R). The theoretical formulation of personality traits has an hierarchical structure with broad descriptions of phenotypes that can be divided in different ways and on different levels in the hierarchy (Bouchard Jr & Loehlin, 2001). There are a substantial overlap between the three- and five dimensional models as well as others concepts in the field of personality (Bouchard Jr & Loehlin, 2001; Zuckerman & Cloninger, 1996).

Whatever trait-model used, it is built on the assumption that one can predict how a person will act or react in a number of different situations. In order to say that a trait is valid, it must be stable over time. Personality is substantially

heritable. Behavior genetic studies suggest that 40 – 49% of individual differences in personality traits are due to genetics (Van Den Berg et al., 2014; Vukasović & Bratko, 2015). Several studies have shown that personality is relatively stable (Edmonds, Goldberg, Hampson, & Barckley, 2013; Hampson & Goldberg, 2006), but it has also been suggested that personality changes gradually throughout life (Harris, Brett, Johnson, & Deary, 2016).

The Swedish universities Scales of Personality (SSP) (Gustavsson et al., 2000) is a revised version of the Karolinska Scales of Personality (KSP) inventory (Schalling, 1970). The inventory was originally developed to explore the associations between personality traits and biological markers and as such predictive for health behavior and psychiatric illness. It is explicitly stated that the SSP does not intend to cover the full range of personality traits. The SSP was evaluated on a large sample of the Swedish population, which resulted in a three-dimensional model: Neuroticism, Aggressiveness, and Extraversion. The SSP traits have been shown to correlate with those measured with the NEO-PI-R, in particular the Neuroticism scales (Aluoja et al., 2009). The importance of evaluating the scales in various clinical samples was emphasized in the development of the SSP. Personality traits as measured with SSP has been studied in relation to different conditions such as schizophrenia, depressive and/or anxiety disorders, individuals undergoing in vitro fertilization, and post-partum depression (Fagerberg, Söderman, Gustavsson, Agartz, & Jönsson, 2016; Iliadis et al., 2015; Volgsten, Ekselius, Poromaa, & Svanberg, 2010). However, to our knowledge, personality traits has not been evaluated with SSP in BD. Personality traits measured with NEO Five-Factor Inventory during euthymic phases of BD have been suggested to be predictive of future mood course, suggesting that personality traits might be prognostic markers of the illness process (Barnett et al., 2011).

In *study V*, we examined personality traits measured with SSP in individuals with bipolar disorder in comparison with healthy controls, and investigated the association between personality traits and illness course.

The latest versions of Diagnostic and Statistical Manual for mental disorders (DSM) use a categorical approach of ten specific personality disorders to assess personality. Nevertheless, it has been shown that there is no clear boundary between normal and pathological personality. An alternative pathological personality trait model was suggested in Personality and Personality Disorder Assessment and Diagnoses for DSM-5 (Skodol et al.,

2011). Six broad, higher order personality traits were suggested: negative emotionality, detachment, antagonism, compulsivity and schizotypy. This re-conceptualization also intended to identify personality-related problems and patient-specific personality trait profiles in addition to specific personality disorders. However, no change came about.

Gray's conceptual framework

Gray took his point of departure from Eysenck's postulated differences between introverted and extraverted neurotics (Gray, 1986). He suggested that personality traits have a strong biological foundation and postulates two different systems; the Behavioural Activation System (BAS) and a Behavioural Inhibition System (BIS). BIS regulates avoidance behaviors and is activated to avoid punishment (punishment system). BAS on the other hand regulates approach behaviors and is activated to reach a goal, and is involved in the generation of anticipatory of positive affect (reward system). BAS and Extraversion have nearly the same psychometric construct. Extraversion is related to mood maintenance, which is different from mood repair predicted by Neuroticism, and may be a way for extraverts to extend arousal (Robinson, Watkins, & Harmon-Jones, 2013). For example, individuals with BD show rumination on positive affect. According to the BAS Hypersensitive Model of Bipolar Spectrum Disorder, individuals with higher sensitivity are at risk for BD and hypomanic/manic episodes by virtue of a hypomanic personality that interact with positive and negative life events, so called BAS-events (Urošević, Abramson, Harmon-Jones, & Alloy, 2008). Conversely, individuals high in BIS are at greater risk for episodes of depression (Alloy et al., 2008).

Bipolar spectrum

A bipolar spectrum concept has been proposed with a continuous distribution of depressive and hypomanic/manic symptoms and disorders from normal to pathological (Angst, 2007). Akiskal et al. (2006) propose a state-trait continuum and that it is possible to grade bipolar types and unipolar depression in terms of *emotionality*. Atypical depressive presentations and mood temperaments are part of that continuum (Ghaemi, 2013). Akiskal et al. (2006) showed that the most salient differences between bipolar I and II disorder are the levels of Neuroticism. Individuals with BD II and recovered unipolar depressed patients showed abnormally elevated scores in Neuroticism, whereas individuals with BD I scored near normal. However, in BD II, fluctuations between subsyndromal depressive and hypomanic symptoms accounted for high scores in Neuroticism, while dysthymic symptoms predicted outcome in unipolar patients. These differences between BD I and

BD II might explain why bipolar type II patients more often are diagnosed with personality disorder, even though Neuroticism might actually be characteristic for the BD II subtype.

In *study V* of this thesis, we investigated differences between bipolar I and II in terms of personality traits.

Neuroticism

It is well known that high levels of Neuroticism is strongly associated with common mental disorders, e.g., anxiety, mood, and substance use disorders (Ormel et al., 2013). Neuroticism actually predicts a wide variety of outcomes such as mental and general health service use and quality of life (Lahey, 2009). Trait features associated with Neuroticism are for instance anxiety, anger hostility, depression, self-consciousness, impulsiveness, and vulnerability (Costa Jr & McCrae, 1992). Significant genetic associations have been found between Neuroticism and depressive symptoms, major depressive disorder, subjective well-being, and BD (Luciano et al., 2018). Personality factors may influence the kind of life-events individuals experience: Neuroticism influences stress vulnerability (Matthews et al., 2009), in particular when exposed to threat appraisals (Schneider, 2004). Individuals high in Neuroticism tend to use less problem-focused, and more emotion-focused and avoidance strategies.

The *p*-factor

Caspi et al. (2014) showed that one General Psychopathology Factor – the *p* factor – underlies core psychopathological processes, represented by an Internalizing (including anxious and depressive symptoms) and an Externalizing dimension (including aggressive, delinquent, and hyperactive-impulsive symptoms). *p* is characterized by high Neuroticism and low Agreeableness and Conscientiousness. A general factor in psychopathology can be described analogously to *g* – the general cognitive ability. *p* summarizes an individuals' tendency to develop any type of psychopathology. Consequently, higher scores on *p* are related to impairments in real-world-functioning, worse developmental histories, and reduced cognitive functioning.

The relationship between cognitive functioning and personality

The degree to which personality and cognitive ability are linked are as yet undecided (Rammstedt, Danner, & Martin, 2016). Personality may alter styles

of cognition and learning (Matthews et al., 2009). There are some evidence that personality and intelligence are related throughout life (Harris et al., 2016). However, the cross-sectional correlations between intelligence tests and major personality traits is rather weak (Matthews et al., 2009; Schaie, Willis, & Caskie, 2004). A positive correlation have been reported between Openness to experience and intelligence (Bartels et al., 2012; Chamorro-Premuzic & Furnham, 2008), whereas both Neuroticism and Conscientiousness have been found to be negatively correlated (Furnham, Dissou, Sloan, & Chamorro-Premuzic, 2007; Rammstedt et al., 2016). Eysenck proposed that persons high and low in trait anxiety show differences in cognitive functioning when processing threathening stimuli (Eysenck, MacLeod, & Mathews, 1987). In line with this, Neuroticism has been found to be associated with deficits in some aspects of attentional processing, perceptual ability, and working memory capacity (Eysenck et al., 1987; Modi, Kumar, Kumar, & Khushu, 2015). Older people who score high in Neuroticism perform poorer on tests measuring cognitive function, and also show more rapid decline in cognitive function, largely independent of depressive disorders (Chapman et al., 2012). Besides, they are at greater risk for dementia. Other traits might also have prognostic value: higher Extraversion and lower Openness have been associated with worse cognitive functioning over time. On the other hand, people with high Conscientiousness had a less pronounced cognitive decline.

In *study VI* of this thesis, we investigated the potential overlap between cognitive functioning and personality.

Aims

The overarching aim of this thesis was to use traditional statistical methods along with multivariate projection methods to explore cognitive function and personality in bipolar disorder.

The specific aims in each paper included in this thesis were:

- I. a) to identify those neuropsychological tests that most reliably tell euthymic bipolar patients and healthy controls apart; b) to clarify the extent to which these cognitive impairments are clinically significant in a neuropsychological sense as opposed to merely statistically different from a healthy control group; c) to elucidate if individuals with bipolar disorder I and II are cognitively dissimilar; d) to elucidate if the degree of cognitive impairment is associated with psychosocial and clinical variables.
- II. to investigate whether the correlation structure between various cognitive abilities differs between individuals with bipolar disorder and healthy controls.
- III. to compare the neuropsychological profiles of adult BD patients with and without comorbid ADHD.
- IV. a) to elucidate if long-term changes in cognitive functioning in individuals with bipolar disorder differ from normal human cognitive aging, and b) to investigate if subsets of patients feature different cognitive trajectories.
- V. a) to study personality traits in individuals with bipolar disorder type I and II in comparison with healthy controls; and b) to investigate the association between personality traits and illness course.
- VI. a) to explore whether the cognition/personality interface is altered in bipolar disorder; and b) to investigate if combining cognitive predictors with personality measures increase the prognostic power.

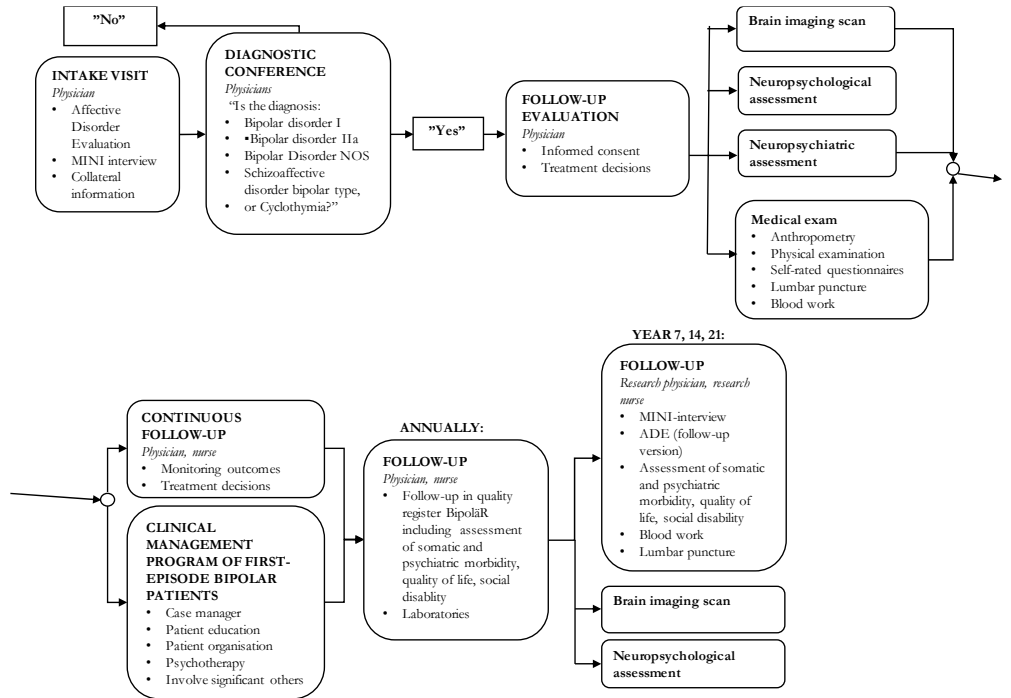
Methods

The St. Göran bipolar project (SBP) is an interdisciplinary, prospective, naturalistic study of bipolar disorder. The aims of this project are to study the course and outcome of treatment in standard psychiatric health care, and to investigate the pathophysiology of bipolar disorder. Yet, the overarching goal is to reduce time spent ill and suffering for individuals with BD, and to improve everyday functioning and quality of life. To these ends, the ambition is to follow most study subjects for the length of their lifetime. Patients have been recruited and followed-up at two specialized out-patient clinics in Stockholm and Gothenburg. The papers included in this thesis are based on data collected in Stockholm.

Recruitment process

New and ongoing patients that met the inclusion criteria was offered the opportunity to be included in the study. The objectives, procedures, and a clear explanation of the risks and benefits of the study was presented orally and in writing prior to study inclusion. Healthy controls were contacted by mail with written information and informed orally over telephone and at the examination. The voluntary nature of research participation was clearly explained to patients and controls, as was their right to withdraw consent or to leave the study at any time. Patients were informed that the decision to accept or decline participation in the study would not affect their regular health care. All participants provided written consent. Copies of the signed consent form were given to all participants. Without this consent, no data was entered into the study database.

Figure 1
The SBP flowchart below outlines key study events



Clinical assessments and diagnostic procedures at baseline

Psychiatric interview

Bipolar disorder diagnoses were established using the Swedish version of the Affective Disorder Evaluation (ADE), which is a semi-structured interview developed for the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (Sachs et al., 2003). The ADE is a systematic assessment of the patient's current mental state, psychiatric history, and affective diagnosis according to DSM-IV criteria as per the Structured Clinical Interview for DSM-IV (SCID). Moreover, The M.I.N.I. International Neuropsychiatric Interview (M.I.N.I.) was used to screen for other psychiatric diagnoses than mood disorders (Sheehan et al., 1998). Clinical best estimate diagnoses were set based on all information available at admission by a consensus panel of experienced board with certified psychiatrists specialized in BD.

The evaluation of ADHD was conducted independent from the baseline assessment by two board-certified psychiatrists. The examination was conducted when patients were clinically stable and rating-scales were if possible supplemented with parental interview (or other next to kin).

Rating scales and questionnaires

Rating scales and questionnaires were administered to obtain information about patients' and healthy controls' psychiatric symptoms, but also to describe past and present behavior, e.g., creativity, personality, sense of coherence, different areas of functioning. The following scales and questionnaires were included in *study I-VI* (Table 2).

Table 2
Scales from SBP used in paper I-VI

Scale	Rating scales and questionnaires and specific focus
	Focus
Adult ADHD Self-Report Scale (ASRS)*	Screens for adult ADHD
Brown Attention-Deficit Disorder Scales (Brown-ADD)*	Screens for executive cognitive functioning associated with ADHD in adults
Ritvo Autism Asperger's Diagnostic Scale (RAADS)	Screens for symptom in Autistic Disorder and Asperger's Disorder
The Autism- Tics, AD/HD and other comorbidities inventory (A-TAC)*	Screens for autism spectrum disorders, ADHD, tic disorders, developmental coordination disorders, learning disorders, and associated childhood mental disorders
Sheehan Disability Scale (SDS)	Assesses functional impairment in work/school, social life, and family life
Autism Spectrum Quotient (AQ)	Screen for high functioning autism spectrum disorders
Alcohol Use Disorders Identification Test (AUDIT)	Screens for alcohol-related problems
Drug Use Disorders Identification Test (DUDIT)	Screens for drug-related problems
Young Mania Rating Scale (YMRS)	Assesses manic symptoms
Montgomery-Åsberg Depression Rating Scale (MADRS)	Assesses depressive symptoms
Clinical <i>Global Impressions – Severity and Improvement Scales</i> (CGI)	Assesses severity of illness, improvement and treatment response
Global Assessment of Functioning (GAF)	Assesses how well a person function with respect to activities of daily life
Sheehan Disability Scale (SDS)	Assesses patients' subjective experiences of functional impairment
Psychological general wellbeing (PGWB)	Assesses anxiety, depressed mood, positive well-being, self-control, general health

Note. * used to establish childhood or adult ADHD in the SBP-cohort in Stockholm

Swedish universities Scales of Personality (SSP)

This scale measure 91 items consisting of a statement with a four-point response format. All items are grouped into 13 scales (Table 3) that form different dimensions of personality such as Neuroticism, Aggressiveness, and Extraversion (disinhibition). The scale can be found in the Appendix.

Table 3

The SSP with corresponding personality traits and description of subjects with high scores of the constituent scales

SSP and corresponding trait	SSP and characteristics of subjects with high scores
Neuroticism:	
Lack of assertiveness	Lacks ability to communicate effectively and to be self-assertive in different social situations
Mistrust	No trust or confidence in others
Somatic trait anxiety	Autonomic disturbances and feels restless and tense
Psychic trait anxiety	Worrying and has low self-confidence
Stress susceptibility	Stress vulnerable
Embitterment	Unsatisfied and becomes easily jealous
Aggressiveness:	
Social desirability	Adjusts easily socially to different situations and among others
Physical trait aggression	Starts fights and hits back
Verbal trait aggression	Engage in verbal arguments in an aggressive way
Trait irritability	Irritable and impatient
Extraversion (disinhibition):	
Detachment	Lack of emotional connections with others
Adventure seeking	Desire for activities involving sensations and risk
Impulsiveness	Impulsive, thoughtless, and indiscreet

Neuropsychological assessment

The SBP cognitive battery has been set out as a fundamental part in reaching overall study aims. The tests were originally selected by psychologist Björn Hultman together with Mikael Landén with valued guidance from psychologist Håkan Nyman to secure an extensive and rigorous investigation of cognitive functioning in both patients and healthy controls. A licensed psychologist tested patients' cognitive functioning over two sessions. The healthy controls were assessed by trained research associates, supervised by a licensed psychologist, at a single session. For patients, the cognitive testing session occasionally lag behind the clinical assessment at study entry due to limited number of psychologists carrying out cognitive testing. Table 4 shows test included in the SBP cognitive battery.

Table 4
 Tests included in the SBP cognitive battery

Key tests of the SBP cognitive battery		
Test	Assessment activity	Measures
Wechsler Adult Intelligence Scale Third Edition (WAIS-III):	Includes verbal and non-verbal performance tests	Measure of adult's intellectual ability
Block Design	The subject has to use blocks to construct replicas of patterns presented	Visuospatial organization
Matrix reasoning	Visual pattern completion and analogy problems	Fluid intelligence
Comprehension	Open-ended questions	Common sense and judgment
Information	Open-ended questions	General knowledge
Similarities	The subject has to explain what each pair of concepts has in common	Verbal concept formation
Vocabulary	Definitions of words	Vocabulary
Arithmetic	Solve arithmetic problems	Working memory
Digit span	Comprises digit span forward- and backward. The subject has to repeat sequence digits, first exactly as given and then backward.	Immediate verbal recall (attention). And working memory
Symbol Search	Series of symbols, each consisting of a target and a search group, from which the subject has to choose the appropriate box pending on the presence of target.	Attention and processing speed

Test	Assessment activity	Measures
Digit Symbol-Coding	The subject is asked to fill in blank spaces according to a key with paired number and symbols.	Attention and processing speed.
Picture arrangement	Drawing of cartoon pictures that have to be arranged in stories.	Social cognition and sequential thinking. The ability to see relationships between events.
Letter-Number Sequencing	The subject listens to a sequence of randomized numbers and letters (alternating) and is asked to repeat them in numerical and alphabetical order.	Attention and working memory.
Picture completion	The subject has to identify important parts which are missing in incomplete pictures.	Visual perception and organization and attention.
Conners' Continuous Performance Test II (CPT II)	The subject is asked to execute a computerized test, in which stimuli (target letters and non-targets) are presented rapidly during 14 minutes. The subject has to respond in accordance to stipulated rules.	Vigilance, inattentiveness, and impulsivity.
Claeson-Dahl Verbal Learning and Retention Test	A 10-word list task, which the subject is asked to learn through listening. The retention dimension involves remembering as many words as possible from the original list, and to present them in the right order. Eventually, the subject is asked to recognize the words from the original list among similar distractors.	Verbal learning, episodic memory, and immediate and delayed recall.
Rey Complex Figure Test and Recognition Trial (RCFT)	A test of visuospatial constructional ability and visual memory. The subject is asked to copy a complex figure. Thereafter to draw the figure from memory after 3 and 30 min. The subject is also asked to recognize the components from the original illustration among similar distractors.	Visuospatial constructional ability, and visual memory (immediate and delayed recall, and recognition).

Test	Assessment activity	Measures
Delis-Kaplan Executive Function System (D-KEFS):		Key aspects of executive functions including mental flexibility, concept formation, problem solving, and inhibition.
Color-Word Interference Test (CWIT)	The subject has to read names of colors (e.g., red, blue, green) printed in dissonant colors. Thereafter, the subject is asked to switch between reading words and naming the colors of the words.	The ability to inhibit automatic verbal responses, and cognitive flexibility.
Trail Making Test (TMT)	The subject has to connect a sequence of 25 sequential numbers and/or letters as fast as possible. Thereafter the subject has to alternate between connecting numbers and letters in numerical and alphabetical order.	The ability to inhibit automatic responses, and cognitive flexibility
Design Fluency Test (DFT)	The subject has to draw as many different designs as possible in 60 seconds by connecting a set of printed dots.	The capacity of initiating problem-solving behavior, cognitive flexibility, and inhibition of automatic responses.
Verbal Fluency Test (VFT)	The subject is asked to say as many words as possible from a given category (phonemic and semantic) in 60 seconds. Thereafter, to alternate between words from two semantic categories.	Language skills and verbal processing ability, as well as problem solving and inhibition.
Tower Test	The subject has to move discs from a starting position to a target position, in accordance to stipulated rules.	Planning and aspects of problem solving, e.g., the ability to inhibit perseverative and impulsive responses.

Note. Freely after Lezak (2012) and the manual for Claeson-Dahl Verbal Learning and Retention Test Claeson & Nyman (1998).

Other assessments

The SBP investigations also included a magnetic resonance imaging brain scan at baseline and follow-up. Cerebrospinal fluid was also collected through lumbar puncture to shed light on the pathophysiology of BD. None of these measures are, however, used in this thesis.

Other variables

A wealth of information was collected at study entry on, e.g., heritability, somatic diagnoses, years of completed education, occupational status, age at onset, number of affective episodes, medication status, and lifetime history of psychosis et cetera.

Inclusion and exclusion criteria

Inclusion criteria for patients:

- i) Current age \geq 16 years of age;
- ii) Meets DSM-IV Criteria for Bipolar I disorder, Bipolar II disorder, Bipolar NOS, Cyclothymia, or Schizoaffective Manic/Bipolar type;
- iii) Completed baseline evaluation with the ADE (the complete set of investigations varies across study subjects as not everybody volunteered for all examinations);
- iv) Oral and written informed consent to participate in the study.

Exclusion criteria for patients:

- i) Unwilling or unable to comply with study requirements, e.g., complete forms, or attend planned evaluations;
- ii) Not competent to give informed consent in the opinion of the examiner.

Of note, specific inclusion criteria were established for patients in paper I-VI depending on study objectives. However, in all papers, only bipolar I and II disorder patients were included. Euthymia, when used as an inclusion criterion, was defined as stable mood according to treating physician together with scores below 14 on the MADRS and YMRS rating scales.

Inclusion criteria for healthy controls:

- i) signed informed consent
- ii) completed questionnaires, psychiatric interview, blood tests and screening neuropsychological tests

Exclusion criteria for healthy controls:

- i) any current psychiatric disorder or current treatment with any

- psychotropic drug
- ii) a history of conduct disorder or ADHD, bipolar disorder, schizophrenia, or other psychiatric disorders other than past minor depressive episodes, previous isolated episodes of panic disorder or eating disorders, which had remitted spontaneously or with short term psychotherapy.
 - iii) a first degree relative with bipolar disorder or schizophrenia
 - iv) overconsumption of alcohol as revealed by carbohydrate deficient transferrin (CDT) in blood test or AUDIT responses indicating large consumption (>8 standard drinks per time more than 2 times per week), and/or amnesia and/or loss of control more than once per month
 - v) any illicit drug use
 - vi) pregnancy, untreated endocrine disorders, other medical illness, dementia or neurological disorder other than mild migraines
 - vii) subjects presenting conditions that precluded magnetic resonance imaging of the brain (e.g., metal implants, shrapnel, and certain heart operations). This exclusion criterion was due to a planned brain magnetic resonance imaging for another part of the St. Görän bipolar project.

Sample

Table 5

The study sample included in *study I-VI* from the Stockholm SBP-cohort

Study sample from the SBP Stockholm cohort								
Subjects	N	Age at	Age at	Women	Total no. of	WAIS-III	WAIS-III	At least
		onset	inclusion		mood	FSIQ	Vocabulary	
		<i>M</i>	<i>M</i>	(%)	<i>M</i>	<i>M</i>	<i>M</i>	of tertiary
								education
BD I	161	19	36	58	15	105	11	50
BD II	99	19	39	65	32	109	12	66
Other	33	20	38	60	9	105	11	58
HC	115		38	55		114	11	62

Note. Other = meets DSM-IV Criteria for Bipolar NOS, Cyclothymia, or Schizoaffective Manic/Bipolar type, FSIQ = Full Scale Intelligence Quotient

Statistical analyses

In *study I, II, and VI*, we used multivariate projection methods to examine similarities *and* differences between individuals with BD and healthy controls. Principal component analysis (PCA) forms the basis of multivariate data analysis. A PCA reduces data dimensions and summarizes systematic variation in a model by aggregating variables in ‘components’ or ‘latent variables’ that describe the correlations structure (Eriksson, Byrne, Johansson, Trygg, & Vikström, 2013). A PCA-model shows both how observations are related and how variables are related. By creating a PCA-model, it is possible to detect variables that contribute similar information to the model, as well as variables that contribute with unique information to an observation.

To understand how PCA works, “consider a matrix (X) with N observations and K variables. For this matrix we construct a variable space with as many dimensions as there are variables. Each variable represents one co-ordinate axis” (Eriksson et al., 2013, p. 37)“. The first principal component (PC1) represents the maximum variance direction in the data (X). The PC1 is a line to which observations can be projected. Thus, each observation (each study subject in our case) acquires a score on PC1. The second principal component (PC2) reflects the second largest source of variation in data, and is orthogonal to the PC1. When two principal components have been derived they form a two-dimensional plane that can be visualized in a coordinate system, which can be seen as a window into a multidimensional space. The principal component loadings give information on variables of importance. The PCA model can be evaluated by the goodness of fit parameters R^2X (the explained variation) and Q^2X (the predicted variation). The difference between these two parameters should not exceed 0.2-0.3. The actual values of R^2X and Q^2X are highly application dependent, and the model can be useful even if Q^2X is less than 0.5 as it separates useful information (PC) from noise.

The Projection to Latent Structures by means of partial least squares (PLS) is a regression extension of a PCA that is commonly used for prediction. In a PLS, the variables are divided into two blocks called X (predictor variables) and Y (response variables) A PLS connects the information from these two blocks to develop a relationship between them. PLS does not give information about how much of the variability in X is predictive.

To draw conclusions about similarities and differences among observations, a Coomans' plot can be constructed. Model-membership of an observation can be decided by plotting observations' model distances (DModXs') against each

other in a scatter plot. If a Coomans' plot shows a large overlap between two groups, the conclusion is that the groups are similar.

Orthogonal partial least squares discriminant analyses (OPLS-DA) operates by dividing the systematic variation in a dataset into two parts: one that is predictive of class membership, and one that is uncorrelated, orthogonal, to the class membership. Hence, whereas the PCA is an *unsupervised analysis* that maximizes the variance of each component regardless of class membership (i.e., the model is not given any a priori information on phenotype), the OPLS-DA is a *supervised analysis* that aims to separate groups and is built to maximize the relationship between each component and the class membership (e.g., patients and controls).

For these multivariate analyses, we used the SIMCA software: SIMCA-P 13.0, SIMCA 14.0, and SIMCA 15.0 (Eriksson et al., 2013).

The following additional statistical methods were applied in *study III, IV, and V*: In *study III*, differences in cognitive functioning between individuals with BD with and without comorbid ADHD were tested with t-tests. In *study IV*, the main analysis tested if the change in cognitive function over time differed between patients and controls. To this end, we conducted repeated measures Analysis of variance (ANOVA) with group (patients vs. healthy controls) as a Between-Subject Factor. Binary logistic regression analyses were used to estimate strength of associations which were expressed as odds ratios. In *study V*, we conducted multivariate analysis of variance with a covariate (MANCOVA) to investigate overall group differences in SSP personality traits. Binary logistic regression analyses were used to estimate strength of associations, which are expressed as odds ratios with 95% confidence intervals. Statistical significance was set at a two-sided P-value of < 0.05, when not corrected for multiple testing (*study VI*). For the above analyses, we used IBM SPSS Statistics.

Approvals from the ethics committee

All studies in this thesis were approved by the Ethics committee of the Karolinska Institutet, Stockholm, Sweden (Dnr: 2005/554-31/3, 2009/1221-32)

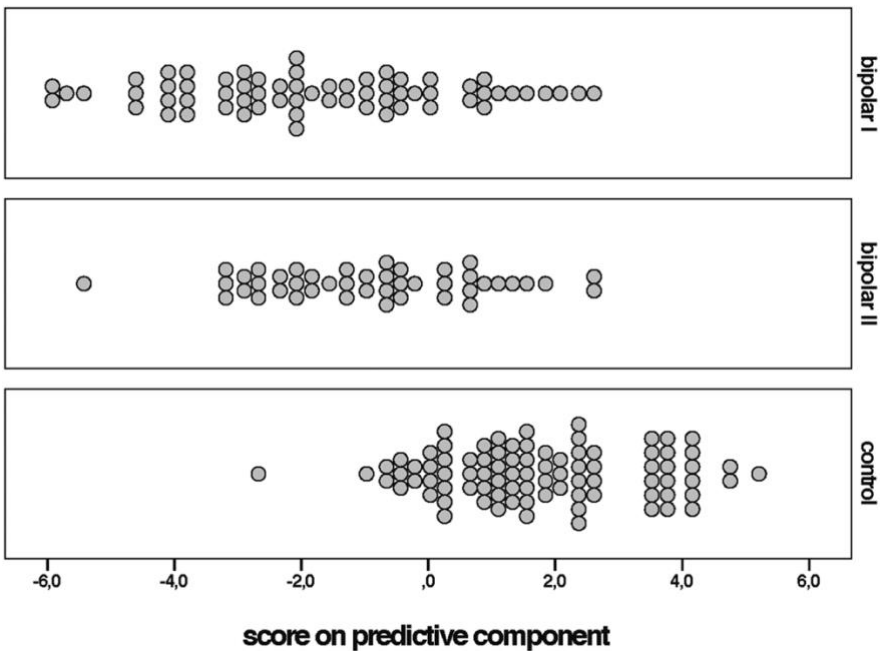
Results

Results of study I

This study examined the clinical relevance of cognitive impairments in BD. We also examined if cognitive abilities differ between BD subtypes and HC. Results showed that individuals with BD I and II, and HC were partially separated based on their performance on a comprehensive battery of cognitive tests (Figure 2).

Figure 2

The OPLS-DA score plot shows a partial separation between patients with bipolar I disorder (top panel), bipolar II disorder (middle panel), and healthy controls (lower panel). Each participant's score is represented by a circle. The scores corresponds to $t[1]$ values on the component predictive of diagnostic group.



Both BD type I and type II were associated with cognitive impairment that for a sizeable minority is significant in a clinical neuropsychological sense. At the 11th percentile threshold, the prevalence for clinically significant impairment ranged from 11 to 48% across different cognitive tests, e.g., >40

% on TMT 4 and block design. (Results in *Study I* show no impairment prevalence rates if no group differences between patients and healthy controls were found.)

The combination of cognitive tests that most reliably detected cognitive impairment in BD were tests from D-kefs (TMT, VF, CWIT) and Symbol Search from WAIS-III. We found no associations between cognitive functioning and clinical and psychosocial outcomes.

Note. Figure and results from Sparding et al., 2015. *PLoS One*, 10(1).

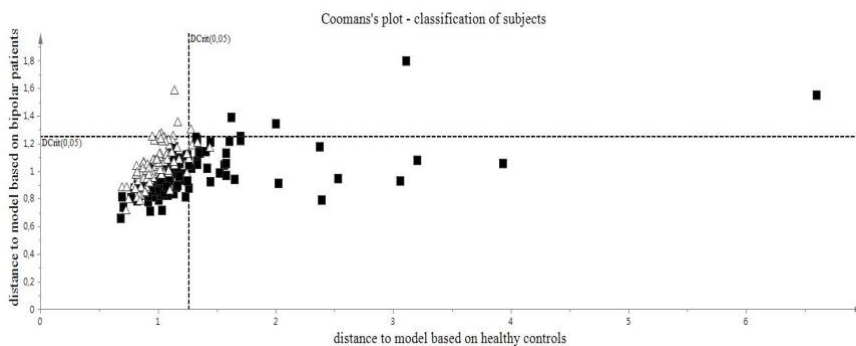
Results of study II

This study investigated whether the correlation structure between cognitive abilities differs between individuals with bipolar disorder and healthy controls. Given the dissimilarities of the PCA models of cognition in BD and HC, we constructed a Coomans' plot (Figure 3), in which the model distances (DModX's) for BD and HC were plotted against each other. The figure shows that approximately 30% of BD patients do not fit to the cognitive model built for healthy controls. We call this group the 'cognitive subgroup' of BD patients. The correlation structure of the constituent neuropsychological variables thus differed between this cognitive subgroup of BD and the majority of BD individuals, where the main difference concerned learning and memory aspects of Digit Symbol Coding, Claeson-Dahl, and the Rey Complex Figure Test. Moreover, there was also an increase in the number of rule violations in the Tower test in the cognitive subtype group.

The cognitive subtype group was similar to the rest of the individuals with BD with regard to demographic and clinical variables. For example, the two groups had similar scores on the MADRS and YMRS inventories, and did not differ by sub-diagnosis (type I/type II).

Figure 3

The Coomans' plot of cognitive performance in patients with bipolar disorder and healthy controls.



Note. The co-ordinates are the model distances (DModX values) to the models built for patients (y-axis) and healthy controls (x-axis). Patients are represented by black boxes and healthy controls by white triangles. Subjects that fit both models are found in the lower-left hand region of the plot. The cognitive subgroup of bipolar disorder patients (~30%) that did not conform to the model for healthy controls is found in the in the upper and lower right-hand quadrants. Figure and results from Sparding et al., 2017. Cognitive Neuropsychiatry, 22(5), 407-421.

Results of study III

This study compared the neuropsychological profiles of adult BD patients with and without comorbid ADHD. The groups did not differ significantly in their performance on nine out of ten cognitive tests (Table 6). Moreover, the groups did not differ with respect to sex, age, type of BD, or global IQ (as measured by WAIS-III).

However, the BD+ADHD group was significantly younger at age of first psychiatric symptom, as well as at age of first affective episode. The number of mixed episodes was significantly higher for the BD+ADHD group, whereas no group differences were found regarding number of manic, hypomanic, or depressive episodes. Lithium treatment was significantly more common in BD patients without ADHD, while other mood stabilizers were more common in the BD+ADHD group. No differences were found regarding level of education, employment status, or number of sick-leave days the previous year.

Table 6

Comparison of neuropsychological test performance of the pure bipolar disorder group and the bipolar disorder + ADHD group.

Cognitive test	Comparison of test profiles of individuals with and without comorbid ADHD				
	Pure BD	BD + ADHD	<i>t</i>	<i>p</i>	Cohen's <i>d</i>
	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)			
WAIS-III: Verbal Comprehension Index	109.8(13)	112.5(10.6)	-.98	.33	-.23
WAIS-III: Perceptual Organization Index	109.4(16.5)	106.1(14.4)	.91	.37	.21
WAIS-III: Working Memory Index	102.2(14.9)	95.4(11)	2.15	.03	.52
WAIS-III: Processing Speed Index	99.1(15.8)	95.9(10.4)	1.12	.27	.24
CPT2 Omission errors**	53.5 (15.8)	53.9(16.7)	-.10	.92	-.02
CPT2 Commission errors**	54.2(9.9)	54.4(10.1)	-.05	.96	-.02
ColorWord 4 (Inh/Swi)	9.9(3)	9.5(3.1)	.66	.51	.13
Tower Test Total	11.4(3.3)	10.4(3.7)	1.17	.25	.29
RCFT: Immediate recall	43.9 (14)	41.6(16)	.70	.49	.15
Claeson Dahl verbal learning	46(12.9)	48.8(9.3)	-1.15	.25	-.25

Note. Data were missing for some patients and therefore the N varies. Pure BD: n=56-64, BD + ADHD: n=23-31. ** Higher score indicates better performance on all tests except CPT, where lower score indicates better performance.

Results of study IV

This study examined if long-term changes in cognitive functioning in individuals with BD differ from normal aging. By and large, the change in cognitive functioning between baseline and six-year follow-up did not differ significantly between cases and healthy controls (Table 7). Moreover, the diagnostic subgroups BD I and BD II did not differ regarding change in cognition over the study period. The cognitive subgroup of individuals with BD identified in *study II* remained stable and did not change more or less than BD patients with normal performance at baseline, except for one test: the WAIS-III subtest 'block design', where the BD cognitive subtype slightly worsened while the rest of the individuals with BD slightly improved ($p=0.045$). Finally, patients who had at least one manic or mixed episode did not show greater cognitive decline than those with no manic or mixed episode.

Table 7

Individuals with bipolar disorder (BD) in comparison with healthy controls with respect to the change in performance on cognitive tests between baseline (T1) and follow-up (T2). Results are presented as mean raw scores with standard deviation (SD) and statistics for the group x time interaction.

Long-term trajectory of cognition in bipolar disorder and healthy controls										
Cognitive test	Bipolar disorder			Healthy controls			Group x time		Group x time ^a	
	T1 <i>M(SD)</i>	T2 <i>M(SD)</i>	N	T1 <i>M(SD)</i>	T2 <i>M(SD)</i>	N	F	<i>p</i>	η^2	<i>p</i>
CWIT 3: Inhibition	53(13)	57(25)	61	47(9)	47(9)	57	3.63	0.059	0.030	0.045
CWIT 4: Inhibition/Switching	61(15)	62(21)	61	55(12)	55(17)	56	0.13	0.91	0.00	0.81
VFT: CF	49(13)	50(11)	66	54(9)	55(11)	55	0.34	0.56	0.003	0.83
VFT: Switching	15(3)	16(4)	65	17(3)	16(2)	55	4.64	0.033	0.038	0.08
TMT 4: Switching	78(29)	78(35)	56	62(17)	65(27)	55	0.37	0.56	0.003	0.69
RCFT: time to copy	198(103)	190(97)	66	152(59)	156(71)	55	0.63	0.43	0.005	0.40
RCFT: IR	19(7)	18(8)	67	22(6)	22(6)	57	1.43	0.23	0.012	0.17
WAIS-III: Similarities	23(6)	25(6)	70	27(4)	27(5)	58	7.35	0.008	0.055	0.02
WAIS-III:	46(10)	47(14)	71	51(10)	52(10)	59	0.91	0.84	0.000	0.99
Block design										
WAIS-III: DSST	73(18)	68(19)	71	78(16)	73(17)	58	0.004	0.95	0.000	0.97
WAIS-III: SS	33(9)	33(10)	71	36(8)	38(8)	59	2.27	0.13	0.002	0.15
WAIS-III - DSC IL: Pairing	13(5)	12(5)	54	15(4)	14(5)	41	0.57	0.45	0.006	0.62
CD VL	87(71)	77(62)	34	64(56)	49(48)	50	0.91	0.66	0.002	0.66
CPT-II: Omissions	5(15)	5(9)	45	2(3)	2(3)	42	0.025	0.88	0.000	0.79

Note. ^a adjusted for age at baseline, η^2 =partial eta squared=effect size, abbreviations cognitive tests: CWIT=Color Word Interference Test, VFT=Verbal Fluency Test, CF=Category Fluency, TMT=Trail Making Test, RCFT=Rey Complex Figure test, IR=Immediate Recall, WAIS-III=Wechsler Adult Intelligence Scale III, DSST=Digit symbol substitution test, SS=Symbol Search, DSC IL=Digit-Symbol-Coding-Incidental Learning, CD VL=Clason-Dahl Verbal Learning (and Retention) Test, CPT-II: Omissions= Conners' Continuous Performance Test II Omissions.

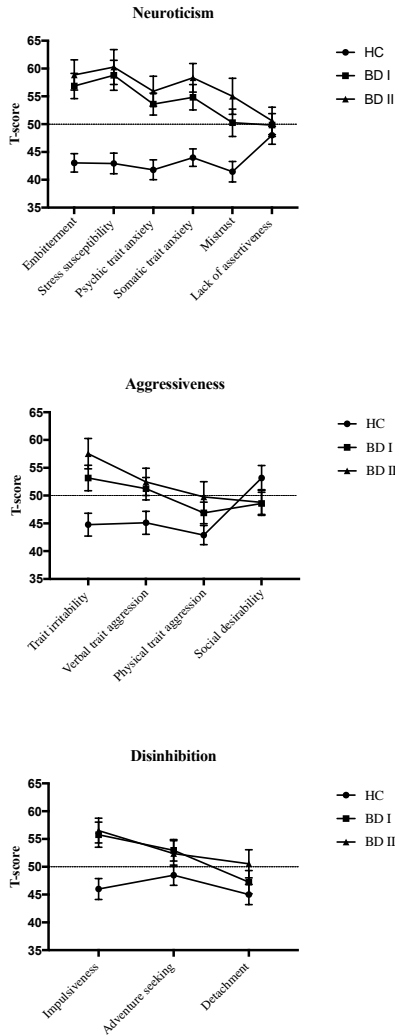
Results of study V

In this study, we examined if personality traits differ between individuals with BD and healthy controls. We also tested the association between personality traits and illness course. Individuals with BD I and II were similar with regard to their personality profile. Both groups featured high scores on all personality traits (except social desirability) as measured with the SSP: Neuroticism, Aggressiveness, and Extraversion (disinhibition). Both types of BD showed significantly higher scores than HC (Figure 4).

Yet, the personality scores did not have any prognostic value on illness course after controlling for concurrent depressive symptoms.

Figure 4

Mean T-scores with 95% CI on SSP-derived Neuroticism-, Aggressiveness-, and Disinhibition related subscales in patients with bipolar disorder (BD) I and II, and in healthy controls (HC). The ticked line shows the normative mean for a large Swedish sample (T-score = 50).



Note: Figure and results from Sparding et al. (2017). *BMC Psychiatry*, 17(1), 159

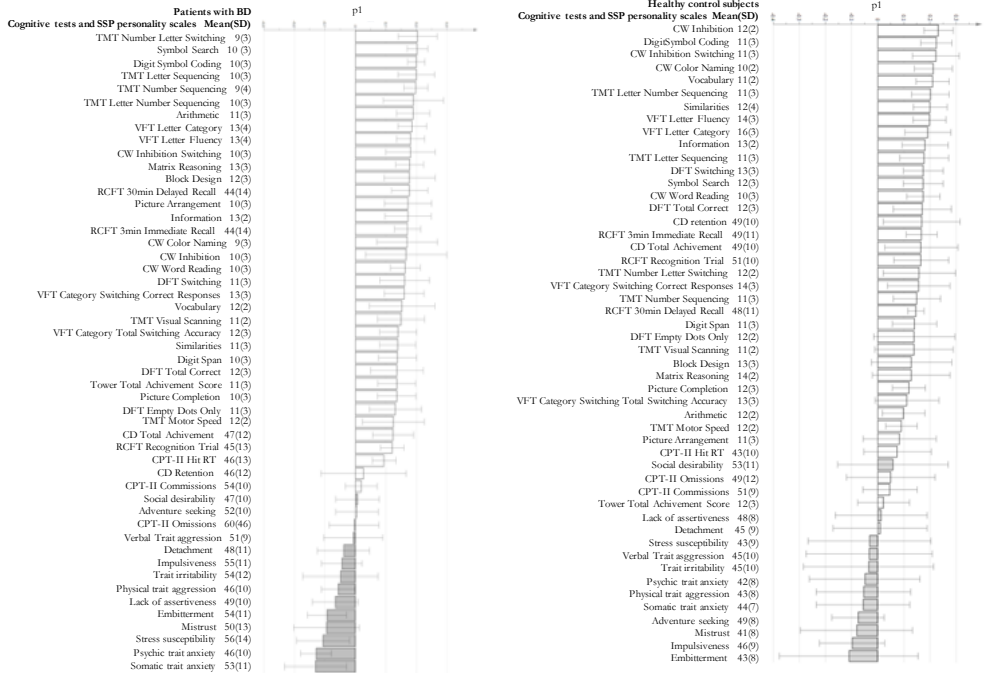
Results of study VI

In this study, we examined if the cognition/personality interface is altered in BD and if so, whether such difference would increase the understanding of the illness course. The correlational structure did indeed differ between HC and BD in that the performance on a wide range of cognitive tests and personality scales measured with SSP was not as tightly coupled or dominated by a single personality trait in HC as it was in BD (Figure 5). Neuroticism was more closely related to cognitive performance in individuals with BD than in HC. Somatic trait anxiety, Psychic trait anxiety, Stress susceptibility had the strongest bearing on cognitive tests measuring processing speed, inhibition, and cognitive flexibility.

Combining cognition and personality had limited predictive power on functional outcomes over a 6-year period. Yet, PCA-models for personality, cognition, and the combination of cognition and personality did predict family / home functioning at the six-year follow-up.

Figure 5

The column plot shows how cognitive tests and personality scales vary in relation to each other, which ones provide similar information, which ones are negatively correlated, or not related to each other, and which ones are not well explained by the model (p_1 close to 0). Mean and standard deviation (SD) are displayed as scale score, and T-score.



Note. Loadings (i.e., weighted averages of the variables) express the dominating correlation structure in the model. Hence, p_1 show how the X-variables correlate, i.e., relate to each other in PC1. And the statistical significance of each variable is indicated with 95% confidence interval.

Discussion

It has been well established that cognitive functioning is impaired in individuals with BD relative to HC (Arts et al., 2008; Bora et al., 2009; Mann-Wrobel, Carreno, & Dickinson, 2011; Robinson et al., 2006). However, there is no conclusive cognitive profile characterizing BD. The best way to describe the current state of knowledge is cognitive heterogeneity.

The overwhelming majority of studies has focused on the *magnitude* of mean group differences on different cognitive tests. It is, however, possible to establish differences with large effect sizes between groups despite that the groups are more similar than different, with leads to exaggerated differences (Hanel, Maio, & Manstead, 2018). We exemplified this in the Introduction by comparing the BD groups from Stockholm and Gothenburg. Even though both groups were examined with the same study protocol from SBP, we obtained group mean differences with moderate effect sizes. With the approach used in a majority of studies in this field, one might allege that BD patients in Gothenburg are cognitively impaired in comparison with BD patients in Stockholm, even though this is likely to be explained by case-mix differences.

Prevalence of cognitive impairments

The majority of studies do not report the prevalence of cognitive impairments in BD, which hampers comparisons across studies. *Study I* was included in a review by Cullen and colleagues (2016), which were first to systematically review the prevalence of cognitive impairment in euthymic BD. In *study I*, we defined impairment threshold as <1.25 S.D. below the healthy control mean. This 11th percentile impairment threshold revealed prevalence ranges between 11-48% across different cognitive tests. Surprisingly, the review by Cullen et al., demonstrated a wide variation in cognitive functioning in BD. At the 5th percentile impairment threshold, prevalence ranges were 5-58% for executive function, 10-52% for attention/working memory, 23-44% for speed/reaction time, 8-42% for verbal memory, and 12-33% for visual memory.

There is no consensus on the impairment threshold. A recent study by Roux et al. (2019) was the first to validate criteria in BD that previously had been used to assess cognitive impairments in severe and persistent mental disorders.

The following five criteria were validated:

- i) Individual Profile Rating (IPR): at least two domains impaired (domain impairment definition: mean domain score < 2 S.D. below the normative mean or < 2 S.D. below any other cognitive domain), or one domain < 3 S.D. below the normative mean.
- ii) Clinically Significant Cognitive Impairment (CSCI): at least two domains ≤ 1 S.D. below the normative mean.
- iii) Global Deficit Score (GDS): a mean deficit score ≥ 0.5 (the deficit score was computed from the mean of the T scores of all variables).
- iv) Martino et al., Soft Criteria (MSC): at least one measure of one cognitive domain < 1.5 S.D. below the normative mean.
- v) Martino et al., Hard Criteria (MHC): at least two measures of two different cognitive domains < 2 S.D. below the normative mean.

Three out of five criteria listed above use *average* scores for specific domains. We argue that performance variance seen in low-level cognitive abilities are not considered when calculating averages and that some valuable information is lost when doing so. Reporting domains can also make comparisons difficult because how domains are defined may differ among studies. The results are extremely criteria-dependent, e.g., the prevalence of cognitive impairment was 4% with IPR, 17.4% with CSCI, 12.4% with GDS, 66.8% with MSC, and 16.4% with MHC. Roux et al. (2019) concluded that only CSCI had satisfactory psychometric properties. Thus, only 12.4% of participants with euthymic BD had a clinically relevant cognitive impairment. They argue that previous studies in the field may have overestimated the prevalence of cognitive impairments in bipolar disorder. In the case of *study I*, the impairment threshold can be considered liberal compared with the validated criteria by Roux (2019).

It is important to emphasize that if performance on cognitive test in individuals with BD would have been evaluated against norms, results would not have been significant: Patients perform in line with expected average results on the majority of test measures. The group differences between individuals with BD and HC found in *study I* occur largely because HC perform above or much above average on the majority of cognitive tests. Of note, in Sweden approximately 40 per cent of the adult population have at least two years of tertiary education (Statistics Sweden, www.scb.se). Among patients from the SBP Stockholm cohort, 50-64 percent had the corresponding

education. It has been suggested that many studies have sampling bias favouring cognitively impaired patients (Roux et al., 2019), which thus does not seem to be the case in *study I-VI*. Most patients at the out-patient clinic in Stockholm that were invited to SBP volunteered to participate and we had few exclusion criteria meaning that patients with co-occurring conditions are included in the SBP-cohort and thus in *study I-VI*.

In the end, one cannot ignore the fact that there are a number of contextual factors, e.g., premorbid cognitive functioning and subjective decline that determine whether a patient can be considered suffering from cognitive impairments or not.

Subgroups

As was outlined above, it is possible that overall group differences in cognition are driven by one or more subgroups. Unlike the classical approaches in the field, we examined in *study I and II* whether the correlation structure between various cognitive abilities differs between individuals with bipolar disorder and healthy controls. To be able to handle about 50 different measures of cognitive functioning one can use multivariate data analysis. This makes it possible i) to examine measures that are highly correlated, ii) to look at all the measures together without losing any test specific information, iii) to discover underlying trends, so called “latent variables”, iv) to discriminate between groups, v) to avoid problems with mass significance, and vi) to identify similarities between groups. We argue that this statistical approach better reflects network alterations in brain regions underlying general cognitive performance demonstrated in psychiatric disorders (Sha, Wager, Mechelli, & He, 2019). We found that the majority of patients (70%) has the same correlation pattern among low-level cognitive abilities as healthy controls. Patients that deviated from the correlation structure seen in healthy controls formed a distinct subtype as their cognitive profile differed from the rest of the individuals with BD. The cognitive subtype group was additionally impaired in tests measuring different aspect of verbal and visual memory. This is interesting as we in *study I* showed that the *combination* of tests that most reliably detected cognitive impairment in bipolar disorder were measures of executive functioning/cognitive flexibility, shifting, inhibiting, and processing speed.

We and others (Burdick et al., 2014; Lee et al., 2017) have identified one or more cognitive subgroups among bipolar disorder patients. Given that the nature of cognitive impairments in this subgroup is as yet not fully understood,

we suggest broad cognitive screening in BD rather than focusing on a specific cognitive domain.

Despite the heterogeneity in cognitive profiles and presentations, it is known that cognitive impairment affects patients across the BD spectrum. However, few studies have investigated cognitive impairments in individuals with BD II compared with BD I (Solé et al., 2011). In the reanalysis carried out by Bourne (2013) on 31 data sets investigating cognitive performance in individuals with BD, only 12 percent out of 1276 patients had a bipolar II diagnosis. In *study I*, we suggested that there is a considerable overlap in cognitive performance in individuals with bipolar I and II disorders. This result is in line with a previous study from our research group that compared a part of the cognitive test battery in the same cohort of patients (Pålsson et al., 2013). By contrast, however, a recent meta-analysis that examined cognitive performance among subtypes of bipolar disorder suggested that individuals with BD I have more prominent impairments. Nevertheless, they concluded that different subtypes of the disorder do not explain the cognitive heterogeneity seen in the field (Bora, 2018). At present, we cannot exclude that individuals with BD II are as cognitively impaired as individuals with BD I.

ADHD

Determining the characteristics of cognitive impairments in a certain disorder is complicated by the possible co-occurrence with other psychiatric conditions. For example, the majority of studies (Bourne et al., 2013; Paul Roux et al., 2019) do not screen for ADHD despite that it frequently co-occurs with bipolar disorder (Rydén et al., 2009). In *study III*, we hypothesized that the prevalence of ADHD among individuals with BD might explain some of the cognitive impairments associated with BD. But our main finding was that the pure BD group did not differ from the BD + ADHD group. A study published in parallel with our work draws the same conclusion; it reported that individuals with BD and ADHD showed the same cognitive performance as those seen in individuals with BD alone (Torres et al., 2017). This is particularly interesting since executive dysfunction is thought to be a cardinal symptom of ADHD. Thus, ADHD is seen as a disorder accompanied by pronounced cognitive impairments that by definition are related to impaired everyday functioning. However, executive dysfunction is not a universal finding in ADHD but might occur only in a subgroup (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). Bipolar disorder on the other hand has been suggested to qualify as a dysexecutive syndrome (Thompson et al., 2009), but it is not considered a hallmark of the disorder.

A clinical problem that has been identified by researchers is that tests of executive functioning lack ecological validity when judged against ratings of executive functions in daily life, or direct observation in natural settings (Barkley & Murphy, 2010). It is therefore possible that individuals with BD suffer from executive dysfunction that affect everyday life to a greater extent than what can be detected with cognitive testing. This highlights the importance of supplementing cognitive testing with rating scales and questionnaires to capture executive dysfunction, preferably with self-ratings together with evaluations of next of kin.

Cognitive functioning, everyday life, and illness course

The research field of psychometric cognitive testing of individuals with BD rests on the assumption that it provides meaningful information not only pertaining to everyday life, social relations and work, but also to future illness course.

Processing speed performance has been shown to be the sole predictor of social and global functioning (Burdick, Goldberg, & Harrow, 2010). Also, verbal learning and memory have been shown to be more strongly related to scores on GAF than clinical symptoms. Cognitive performance has also been linked to poor occupational functioning (Bonnín et al., 2014; Gilbert & Marwaha, 2013; Mur et al., 2009; Ryan et al., 2013). In our research group, we have found that executive functioning is a more powerful predictor of occupational status in BD than IQ and clinical factors, e.g., illness severity (Drakopoulos, manuscript in preparation). However, in *study VI*, baseline cognitive performance only predicted functioning in family life and home responsibilities among the functional and illness course outcomes at the six-year follow-up.

Impaired cognitive functioning in bipolar disorder is most likely multifactorial. More severe or longstanding illness has been associated with greater cognitive impairment (Cullen et al., 2016). Moreover, Bourne et al., 2013 suggested that some of the cognitive heterogeneity may be influenced by drug effects (Bourne et al., 2013). Several studies have investigated the association between cognitive functioning and drugs with mixed findings (Cullen et al., 2016). To date, the strongest evidence of association has been found with antipsychotic medication and impaired cognitive functioning (Bourne et al., 2013; Cullen et al., 2016; Paul Roux et al., 2019). We, however, did not detect any association between clinical and functional outcomes and cognitive functioning in *study I*. Neither did we find any significant differences between the cognitive subgroup

and the majority of BD patients in *study II* with regard to clinical or functional variables.

However, our findings of an absence of an association between cognitive functioning and clinical variables and functional outcomes should be treated with caution. First, some of the prospective longitudinal data that are collected at baseline (e.g., prior affective episodes, age at first symptom) are difficult to obtain accurately and can be confounded by recall errors. Second, the impact of the illness may not be simply cumulative. Third, it should be noted that approximately 60 -70% of our BD patients were studying or working more than half of the time, which is high compared with previous reports (MacQueen, Young, & Joffe, 2001). As mentioned above, our BD-cohort is actually more well-educated than the general Swedish population. Fourth, the association between different clinical and functional outcomes and cognitive performance within the normal range can be different from that at the high and low end of test scores. Fifth, the degree to which results obtained during cognitive testing are related to difficulties in naturalistic environments are also affected by the ecological validity of each test.

Trajectory of cognitive functioning in bipolar disorder

Cross-sectional studies (*study I and II*) cannot decide the causes of cognitive impairments as the directionality of the association between different outcomes cannot be discerned. Although some longitudinal studies exist, most are short-term, lack control group, include elderly patients, or used limited cognitive test batteries (Bora & Özerdem, 2017). Contrary to the assumption that cognitive impairments may be progressive (Berk, 2009), several studies have shown that changes in cognitive functioning over time do not differ between patients with BD and HC (Bora & Özerdem, 2017). Six studies have followed individuals with BD and HC for 5 or more years (Hinrichs et al., 2017; Jiménez-López et al., 2019; Mora, Portella, Forcada, Vieta, & Mur, 2013; Ryan et al., 2016; Sanchez-Morla et al., 2018; Santos et al., 2014). By and large, these studies find that cognitive deficits in BD are stable over time. This is in line with our findings in *study IV*. Hinrichs and colleagues (2017) suggested that more stable cognitive function was associated with higher baseline intellectual ability, and that lower verbal IQ and education were related to increased cognitive decline in specific domains in BD. We did not specifically study that possibility in *study IV*.

It is likely that different bipolar subgroups present with different cognitive trajectories. We investigated if BD subtypes, patients with manic and mixed

episodes during follow-up, as well as the cognitive subgroup identified in *study II* differed in their respective cognitive trajectory. We found no evidence for differences among these subgroups. On the contrary, we found that the cognitive functioning was surprisingly stable over a period of six years. For instance, the results on tests that characterized the cognitive subtype group in *study II*, e.g., memory aspects of Digit Symbol Coding, Claeson-Dahl, and the Rey Complex Figure Test were strikingly similar at follow-up compared with baseline six years earlier. And the difference relative the rest of the BD group remained. This result strengthens the notion that there is a cognitive subtype group in BD. When it comes to predicting the prospective illness course in *study VI*, we could not use baseline cognition to predict illness course over a period of six years. However, we cannot exclude that cognitive impairments are a risk factor for relapse with longer follow-up.

If progressive cognitive impairment is not a general rule in BD, it remains to clarify at which point during the illness course cognitive impairments occur. One possibility is that cognitive impairment is a premorbid trait. Indeed, healthy first-degree relatives to patients with BD have been found to show similar but less pronounced cognitive impairments (Bora et al., 2009).

A possible explanation to the lack of decline in cognitive functioning over time is that the follow-up period (six years) was too short to identify substantial changes. Therefore, we just started a 14-year follow up of our cohort. Another possible objection is that the group is too young and that the decline occurs in older age, above 60 years. Speaking against this notion, however, several studies have been carried out in an elderly population without showing a faster progressive decline in cognitive functioning in BD compared to HC (Gildengers et al., 2013; Schouws, Comijs, Dols, Beekman, & Stek, 2016; Schouws, Stek, Comijs, Dols, & Beekman, 2012).

In summary, the majority of studies point in the direction of stable cognitive functioning over time in individuals with BD. However, in light of the limited number of longitudinal studies in the field, one cannot dismiss the possibility that subgroups of individuals with BD have a progressively deteriorating course of cognitive functions. The topic is worthy of future studies considering that BD has been associated with higher risk of dementia (Diniz et al., 2017; Kessing & Andersen, 2004).

Personality traits in bipolar disorder

The current view of BD as a categorical and episodic disorder could to some extent explain why the importance of personality traits for clinical and functional outcomes has been far less studied than cognitive functioning. It is, however, known that high levels of Neuroticism is strongly associated with common mental disorders (Ormel et al., 2013). In *study V*, we showed that BD I and II are associated with a personality profile comprising high scores on all traits of personality measured with SSP such as Neuroticism, Aggressiveness, and Extraversion (disinhibition). In line with Barnett (2011), we found high levels of Neuroticism in BD I. This conflicts with the proposed state-trait continuum model in which BD I is suggested to present with near average scores on Neuroticism (Akiskal et al., 2006). We also identified individuals with extreme values on two or more traits. This begs the question what personality styles such combinations give rise to. According to the BAS Hypersensitive Model of Bipolar Spectrum Disorder, a highly responsive BAS in BD II predicts future hypomanic episodes. Yet, in *study V* the personality scores could not predict illness course over a two year follow up. Another study with similar objectives as *study V* also found that both subtypes of BD were similar with regard to personality as measured with the revised NEO-FFI (Barnett et al., 2011). But they found that whereas BD was associated with high Neuroticism and Openness, Extraversion, Conscientiousness, and Agreeableness were low. Additionally, they fairly successfully predicted future illness course. It has been suggested that personality traits may reflect biologically based differences that cause diverse illness outcomes. But the same biological base could also underlie illness outcomes without the two being related (Matthews et al., 2009). A direct comparison across Barnett and *study V* is limited by the use of different personality inventories. In contrast to NEO-FFI, SSP only covers those specific personality traits that impart vulnerability to psychiatric disorder. Therefore, the overall high personality scores are not surprising. Nevertheless, all studies within the field struggle with the methodological concerns of separating stable traits and transient states, which is a challenge in the case of BD as residual mood symptoms may exist in clinically stable patients.

The cognition/personality interface

Personality and general cognitive ability are usually considered separate constructs (Maltby et al., 2007). In *study VI*, we investigated if modeling personality and cognition together could add insights and new knowledge about cognitive functioning in BD. We found that in individuals with BD, Neuroticism was more tightly coupled to the performance of cognitive tests

than for HC. Yet, combining baseline cognition and personality measures had limited predictive power on prospective illness course and functional outcomes at six-year follow-up.

The association between high Neuroticism and performance on cognitive test was not valid for HC. However, other studies have shown that anxiety symptoms among healthy elderly individuals predict subjective memory complaints (Balash et al., 2013) and objective episodic memory decline (Wetherell, Reynolds, Gatz, & Pedersen, 2002).

We focused on trait anxiety embedded in the broad personality trait of Neuroticism and not state anxiety. Trait anxiety have been shown to be associated with attentional deficits when processing threatening stimuli (Eysenck et al., 1987). It has been established that highly neurotic never-depressed individuals present negative affective processing biases in the cognitive domains of perception, learning/memory, and reward/feedback, but not attention (Roiser, Elliott, & Sahakian, 2012). The negative affective processing biases in highly neurotic individuals are qualitatively similar to those present in depressed states.

High scores on Neuroticism also characterize p , the general psychopathology factor encapsulating the essential features of a person's tendency to develop psychopathology (Caspi et al., 2014). In other words, p influences the risk of psychiatric symptoms. p is further characterized by low Agreeableness and Conscientiousness. Consequently, individuals high in p experience difficulties in regulation/control when dealing with self and others. Individuals high in p also showed less brain integrity in childhood (impairments on different cognitive tests and neurologic soft signs).

Those high in Neuroticism also show problems regulating positive and negative affects. The capacity to regulate emotions is important for human adaptation. It “includes conscious and unconscious processes that increase or decrease the experience or expression of negative or positive emotions” (Gross & Thompson, 2007, p. 274) The function of emotion regulation in healthy individuals is to direct goal-oriented behavior and help individuals to recover from negative life effects. Individuals with larger working memory capacity have been shown to be better at regulating their automatic behavior as affective information burden working memory (Robinson, Watkins, & Harmon-Jones, 2013).

It has also been demonstrated that high Neuroticism has clear adaptive costs with respect to impaired performance on demanding tasks in stressful environments. People with high Neuroticism are more prone to cognitive failures when dealing with everyday stressors. The importance of personality in the context of cognitive functioning is most likely characterized by a complex inter-relationship.

General discussion

Cognitive impairment is a common feature of psychiatric disorder (Sha et al., 2019). The most salient impairments found across distinct disorders are found in different aspects of attention (Millan et al., 2012). Besides, impairments in executive function, working memory, and salience processing are usually present in psychiatric disorders (Sha et al., 2019). These impairments share altered functional connectivity within and between core neurocognitive networks.

We and others tend to believe that one should find something specific for the disorder being studied, in our case bipolar disorder. Alas, the idea of disorder-specific correlates in the field of psychiatry are difficult to maintain when almost all psychiatric disorders present with various degrees of cognitive impairments along with difficulties with self-regulation and anxiety. The concept of a general psychopathology factor - p – rather imply that it is almost impossible to identify etiological factors that are exclusively a risk for a particular psychiatric disorder (Caspi et al., 2014).

In the clinic setting, we tend to focus on the emotional aspects of BD and risk missing those patients with enduring cognitive problems. Despite the findings in this thesis, it is premature to rule out long-term trajectory of cognitive functioning in BD. If an individual gradually deteriorates in everyday functioning and in their ability to work, screening for impairments in multiple cognitive domains should be carried out. Cognitive function is also of relevance when monitoring the patient after starting a new drug, in particular antipsychotic drugs. It should be the psychiatrist's duty to ask for cognitive side effects.

Having said that, one cannot narrow-mindedly dwell on the importance of cognitive functioning measured with cognitive tests in order to understand the life of individuals with BD better. In everyday life, experience, wisdom, and creativity matters. Also, the ability to have close and deep relationship with significant others is of great importance.

Limitations and future work

There are several limitations to consider in this work. First, all studies are limited by the lack of psychiatric control groups with other diagnosis than bipolar disorder, which would be important when studying illness features which are very likely to be transnosological. Second, even though the number of study subjects can be considered large for this field, an even larger N would have made it possible to carry out more subgroup analyses. A larger N had presumably made the PCA-models more well-fitted and valid. Third, in addition to the cognitive testing, our study subjects completed several questionnaires measuring cognitive symptoms. Here, we focused on the cognitive test measures but we would probably had gained a more complete picture of cognitive functioning in bipolar disorder by adding those questionnaires to the analyses. For example, *study I to III* might have benefitted from adding data from the Brown ADD scale as it might correspond better to executive dysfunction and real-world functioning. Fourth, when cognitive assessment is carried out in a clinical setting, the psychologist takes into consideration various qualitative aspects of the test performance and the individual's subjective experience of cognitive impairments. This often leads to in-depth and targeted testing when uncertainties emerge. This dynamic process is absent when all study subjects are tested in a research setting that require that the same test battery is administered regardless of problems. Fifth, the psychometric approaches dominating both in the fields of personality and cognitive functioning could always be questioned based on the lack of validity of certain instruments used. It is furthermore challenging to use these instruments in individuals whose lives are characterized by changes in mood and activity level. It is not always straightforward to establish that someone is in their habitual state and that they are actually euthymic.

The presentation of research findings in this field typically focuses on group means and p-values. We used multivariate projection methods to explore cognitive function and personality in bipolar disorder. Other methods to make similarities between groups more apparent have been suggested by Hanel et al., 2018. Another interesting approach is the network approach that offers a theoretical framework for thinking about psychopathology (Borsboom, 2017). The network approach hypothesizes that psychiatric disorders arise from causal interactions between symptoms in a network. There is a great need to compare cognitive profiles across several psychiatric disorders longitudinally in order to understand if any impairments can be considered to be diagnose specific. Moreover, clinically useful proxy markers for p would be valuable to

enable early identification of individuals at risk for developing psychopathology.

Virtually all patients with bipolar disorder are prescribed some medication that might impact cognitive function. An interesting avenue for further research is therefore to examine whether it is possible to improve cognitive function by tapering some of these drugs or optimize the dose. In addition, there are promising functional and cognitive remediation programs that need to be further evaluated and implemented in the clinical treatment programs for BD along with psychosocial and psychological treatments.

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