Exploring neurocognition across the psychosis continuum

Exploring Neurocognition *across* the Psychosis Continuum

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EXPLORING NEUROCOGNITION
ACROSS
THE PSYCHOSIS CONTINUUM

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Chapter 1
Introduction

INTRODUCTION

In the fifth edition of his textbook in 1896, Kraepelin classified what was previously considered to be a unitary concept of psychosis into two different diagnoses (Angst, 2002). He proposed a dichotomy between manic depressive insanity and dementia praecox based on the episodic and relatively benign course of the former compared to the latter. In today's classification systems, such as DSM IV (APA, 1994) and ICD-10 (WHO, 1999), bipolar disorder and schizophrenia are still separated.

Bipolar disorder – phenomenology and aetiology

Bipolar disorder represents a heterogeneous group of mood disorders that is defined by the presence of episodes of mania or hypomania, often alternating with episodes of depression. Mania and depression are the two poles of emotional extremes, depressive episodes representing periods of persistent depressed feelings or loss of interest, mania and hypomania representing periods of abnormally elevated, expansive or irritable mood. A bipolar disorder is diagnosed when at least one manic or hypomanic episode has occurred during life time. Bipolar disorders are divided into two major subgroups, bipolar I disorder and bipolar II disorder, that are differentiated by the presence of a manic episode in the former whereas in the latter depressive episodes with at least one period of hypomania must have occurred. The life time risk to develop bipolar I disorder is estimated around 1.3% (ten Have, Vollebergh, Bijl, & Nolen, 2002) whereas life time prevalence for a broader bipolar spectrum (including bipolar disorder NAO, cyclothymia, and hypomania induced by antidepressive medication) is estimated around 5.2% (Regeer et al., 2004). Bipolar disorder is a lifelong, chronic illness with an onset between the ages of 15 and 30 in the majority of cases. The disorder interferes considerably with patients' social and occupational functioning and has a large burden and cost for society (Oswald et al., 2007).

There is no single cause for bipolar disorder. Family studies have indicated a large heritability factor in bipolar disorder, and first-degree relatives of bipolar patients have an eight times increased risk to develop the disorder (Craddock & Jones, 2001). Most likely, genes interact with environmental factors in causing the disorder, with degree of influence of various factors differing between individuals.

Schizophrenia – phenomenology and aetiology

Schizophrenia is one of the most severe mental disorders. Among the main symptoms are delusions, hallucinations, thought disorders, catatonic and chaotic behav-

iour and negative symptoms (such as flat affect and emotion, poverty of speech and avolition). Negative symptoms tend to be chronic, while positive symptoms (such as delusions and hallucinations) are more transient and tend to react better to antipsychotic medication. A diagnosis of psychotic disorder is made when above mentioned symptoms interfere with social and occupational functioning (APA, 1994). Neurocognitive deficits are often present in psychotic disorders although they are not currently part of the criteria in diagnostic classification systems. The estimated life time prevalence of schizophrenia is about 1 % in the population (Jablensky et al., 1992). Age of onset has the largest peak between the ages of 20 and 28 for males and between 26 and 32 for females. Schizophrenia is a chronic disease and known to be a major cause of disability, having a profound impact on people's social and professional lives.

Schizophrenia is a very heterogeneous disease with multiple causes. In general, it is assumed that genes and environment interact in causing the illness. First-degree relatives have a tenfold risk to develop the disorder, suggesting a substantial genetic contribution. The inheritance pattern, however, appears to be complex, with multiple genes of small effect. Genetic factors alone are not sufficient to cause schizophrenia. Environmental factors such as living in an urban environment (Kirkbride et al., 2006; van Os, 2004), childhood abuse (Janssen et al., 2004), pre- and perinatal complications (Buka & Fan, 1999) and stress in daily life (Myin-Germeys, Delespaul, & van Os, 2005), play an important role in the aetiology of psychotic disorders as well.

The end of an era: Return of the unitary concept of psychosis?

The reader will have noticed that the characteristics of bipolar disorder and schizophrenia overlap to some extent in the above descriptions. Current findings of overlap between bipolar disorder and schizophrenia are increasingly challenging the validity of the Kraepelinian dichotomy. The existence of a diagnosis of 'schizoaffective disorder', which is used to categorize the great number of patients that do not fit properly into either diagnoses, is probably the best illustration of the lack of a strict distinction between these disorders. It was Kraepelin himself who admitted already in 1920 that, '...it is becoming increasingly clear that we cannot distinguish satisfactorily between these two illnesses...'. His proposed dichotomy, however, still stands.

Findings of overlap

Findings of overlap come from various areas. First of all, there is a great amount of overlap in phenomenological characteristics. Psychotic symptoms, the hallmark of schizophrenia, also occur in a large number of bipolar patients, and mood

symptoms such as depression and mania can also be present in schizophrenia. In addition to this, epidemiological characteristics of the two disorders, such as age of onset, lifetime risk (Torrey, 1999) and risk factors (Cannon & Dean, 2004; Torrey & Miller, 1997) tend to show overlap. Schizophrenia and bipolar disorder are both highly heritable and studies suggest familial co-aggregation between both disorders (Cardno, Rijsdijk, Sham, Murray, & McGuffin, 2002). Recent linkage and association studies have identified overlapping genetic loci for schizophrenia and bipolar disorder (Badner & Gershon, 2002; Craddock, O'Donovan, & Owen, 2005). In brain structure investigations, ventricular enlargement, volumetric reduction of prefrontal regions, and white matter pathology have been consistently identified in schizophrenia but appear to be also present, although to a lesser degree, in patients with bipolar disorder (McDonald et al., 2004). Another domain of overlap between bipolar disorder and schizophrenia concerns pharmacological treatment. Atypical antipsychotic medication used for treatment of schizophrenia may also be successful in treatment of bipolar disorder, and recent studies suggest that mood stabilizing drugs may be an effective adjuvant in schizophrenia (Casey et al., 2003).

Alternative models

Although the categorical distinction between bipolar disorder and schizophrenia may be of benefit in clinical practice, the findings of overlap between schizophrenia and bipolar disorder suggest that the artificial split between disorders does not represent the psychosis phenotype as it occurs in the population. From the 1980s a continuum view has gained support (Crow, 1990), implying a continuum from unipolar to bipolar disorder to schizoaffective psychosis and up to schizophrenia. According to this view psychotic symptoms are considered as non-specific to disease. Instead, a dimensional view describing phenomenology on individual dimensions is thought to provide a more valid representation of psychopathology.

Murray and colleagues (Murray et al., 2004) aimed to explain similarities and dissimilarities between bipolar disorder and schizophrenia by suggesting that bipolar disorder and schizophrenia share susceptibility genes that cause a predisposition to psychosis in general. When, in addition to this predisposition, a neurodevelopmental impairment is present, a schizophrenia-like phenotype will emerge. The neurodevelopmental impairment predisposition will contribute to the expression of negative and deficit symptoms and, in association with these symptom domains, to the cognitive deficits characteristic of schizophrenia. In the absence of these neurodevelopmental impairments, however, a more affective psychotic phenotype like bipolar disorder will emerge. The hypothesised distinction between good outcome

psychotic disorder without developmental impairment (characterised by positive and affective symptoms) and poor outcome psychotic disorder with developmental impairment (with negative and cognitive symptoms) in fact goes back to the publication by Robins and Guze (Robins & Guze, 1970) that hypothesised, albeit within the more narrow domain of schizophrenia alone, two broad dimensions separated along similar lines.

Neurocognitive functioning in severe mental illness

In the above mentioned model describing the similarities and differences between psychosis with and without developmental impairment, another important characteristic present in both schizophrenia and bipolar disorder is implicated. The disorders also overlap in the presence of neurocognitive impairment. This will be the focus of the present thesis.

Neurocognitive impairment as endophenotypic marker

The presence of neurocognitive impairment is a core feature of schizophrenia. Impairments are found among a broad range of cognitive domains with largest effect sizes of deficit reported for attention, (working) memory and executive functioning (Heinrichs & Zakzanis, 1998; Keefe, Eesley, & Poe, 2005). Cognitive impairments are independent of positive symptoms (Dominguez, Viechtbauer, Simons, van Os, & Krabbendam, 2008) and remain relatively stable throughout the course of the illness. Cognitive alterations in similar domains are also found, to a lesser degree, in first-degree relatives of schizophrenia (Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004; Snitz, Macdonald, & Carter, 2006) and in persons at psychometrically defined risk for the disorder (Voglmaier, Seidman, Salisbury, & McCarley, 1997). The findings that cognitive impairment is i) heritable, ii) associated with schizophrenia but not just the consequence of the disorder, and iii) present in relatives of patients and in those at psychometrical risk for the disorder, have led to the suggestion that neurocognitive impairments may represent the expression of the genetic vulnerability to schizophrenia and can be seen as a psychosis endophenotype (Gottesman & Gould, 2003).

Bipolar disorder is similarly accompanied by cognitive deficits and there are many studies showing decreased cognitive functioning during depressive episodes and mania (Martinez-Aran et al., 2004). Traditionally, it was assumed that cognitive functioning would return to normal in periods between episodes, but evidence is now accumulating that stable, euthymic bipolar patients continue to exhibit cognitive impairments (Robinson et al., 2006). Some researchers have suggested that cognitive impairment is a core symptom in bipolar disorder, similar to schizophrenia, and that it may likewise be a endophenotypic marker for bipolar disorder

(Glahn, Bearden, Niendam, & Escamilla, 2004). If this is true, cognitive alterations should be detectable in the first-degree relatives of bipolar patients. The number of studies performed on cognitive functioning in relatives of bipolar disorders, however, is limited, and results have been inconsistent.

Direct comparisons of cognitive performance in schizophrenia and bipolar patients suggest that the pattern of cognitive deficits is rather similar but that groups differ in the severity of impairment (Krabbendam, Arts, van Os, & Aleman, 2005). Comparisons of cognitive performance in relatives of patient groups are scarce and could provide more information regarding the role of neurocognition as endophenotype in bipolar disorder and schizophrenia. In short, investigation of similarities and differences in the neurocognitive domain could further our understanding of the true relationship between the two disorders.

Neurocognitive impairments as predictor of outcome

Cognitive impairment in severe mental illness is not only important given the possible role as a marker of genetic vulnerability, but also as a predictor of functional outcome. In schizophrenia it has been suggested that outcome is more strongly associated with stable illness characteristics such as cognitive impairment than with the more variable positive symptoms of psychosis (Green, 1996; Green, Kern, & Heaton, 2004). However, other studies suggested that it is not so much the severity of acute symptoms but rather the level of persisting symptoms that impact on outcome (Norman et al., 1999). One limitation of many published studies on cognition-outcome relationships is their cross-sectional design. To be able to investigate true predictive value of neurocognition on outcome, longitudinal studies investigating the impact of neurocognition on *changes* in functional outcome relative to baseline levels are required. A review of longitudinal studies concluded that there was considerable support for longitudinal associations between cognition and outcome (Green et al., 2004), but other studies suggested that longitudinally less variance in outcome is explained than cross-sectional associations suggest (Milev, Ho, Arndt, & Andreasen, 2005; Stirling et al., 2003).

In bipolar disorder, the relationship between neurocognitive functioning and outcome is less extensively investigated than in schizophrenia. This is not surprising as for a long time it was assumed that bipolar disorder patients would return to their normal level of psychosocial and cognitive functioning in-between episodes. With increasing knowledge of the persistence of cognitive impairment in at least a subgroup of bipolar patients, some studies have now been conducted on the functional significance of this impairment, suggesting that in bipolar disorder cognitive impairments likewise affect the functioning of patients in their daily lives (Green, 2006).

Aims and outline of the thesis

The overall goal of this thesis is to investigate the aetiological and predictive value of cognitive impairment in both bipolar disorder and schizophrenia and to discuss their similarities and differences in the context of a continuum view of severe mental illness.

Part 1: Neurocognition as endophenotype

In the first part of this thesis, the role of neurocognitive functioning as endophenotypic marker for bipolar disorder and schizophrenia will be explored. First, the evidence of neurocognitive functioning as endophenotypic marker in bipolar disorder is evaluated in a meta-analysis of studies investigating neurocognitive functioning in bipolar patients and in their first-degree relatives (chapter 2). The possible role of neurocognitive functioning as genetic vulnerability marker for both bipolar disorder and schizophrenia is further investigated in a direct comparison of neurocognitive functioning in patients with schizophrenia and bipolar disorder and their relatives, in order to examine shared and non-shared characteristics in the cognitive domain. Data for this study are drawn from two samples, the BIPOLCOG study, a study on cognitive functioning in 81 patients with bipolar disorder and their healthy first-degree relatives, and the Maastricht site of the national GROUP study, a large study investigating similar cognitive domains in 345 patients with non-affective psychotic disorder and their healthy first-degree relatives (chapter 3).

In schizophrenia, a distinction is made between psychosis with predominantly negative symptoms and developmental impairment and cognitive impairment on the one hand and psychosis with predominantly positive symptoms and without developmental impairment and cognitive impairment on the other. A consistent finding is the lack of any significant associations between neurocognitive dysfunction and the positive symptoms of psychosis. The extension of this model to the continuum spanning affective and non-affective psychosis, results in testable hypotheses regarding the cognitive profile of relatives of patients with bipolar disorder. In the BIPOLCOG study we investigated whether this model can be extended to bipolar disorder (chapter 4). Previous studies have reported associations between cognitive endophenotypes of non-affective psychoses and the catechol-O-methyltransferase (COMT) gene. Given the suggested overlap between schizophrenia and bipolar disorder, in this thesis the endophenotypic nature of neurocognitive dysfunction is further explored by examining the role of the COMT gene in patients with a diagnosis of bipolar disorder in the BIPOLCOG study (chapter 5).

Part 2: Cognition as predictor of outcome

In the second part of this thesis, the predictive value of cognitive impairment on outcome in both bipolar disorder and schizophrenia is evaluated. In patients with psychotic disorders and in subjects with different levels of risk for psychosis, it is investigated whether cognitive alterations associated with the liability to psychosis are more than neutral indicators of risk for psychosis by examining the predictive value of neurocognitive functioning on outcome. This is done in the 'Cognitive Functioning in Psychosis' (CoP) study, investigating cognitive functioning and outcome in 29 patients with non-affective psychotic disorders, 46 non-psychotic first-degree relatives and 41 subjects at psychometrically defined risk for psychosis (chapter 6). The relative contribution of cognition in the prediction of outcome over and above the predictive value of symptoms is explored in a combined group of patients with affective and non-affective psychosis, as is the question whether cognition has true long-term prognostic value in relation to changes in outcome, taking into account the baseline level of functioning. Data for this study are drawn from the baseline and year 2 assessments of the UK700 Case Management Trial, a 2-year randomised controlled trial comparing the efficacy of different intensities of case management in 708 psychotic patients (chapter 7). Finally, associations between symptomatology, cognitive functioning and psychosocial functioning are explored in both schizophrenia and in bipolar disorder, to be able to compare the relative influence of neurocognition on psychosocial functioning in both disorders. This was done with data from the GROUP and BIPOLCOG study (chapter 3).

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CHAPTER 2

META-ANALYSES OF COGNITIVE FUNCTIONING IN EUTHYMIC BIPOLAR PATIENTS AND THEIR FIRST-DEGREE RELATIVES

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Abstract

Background: Previous work suggests that in particular impairments in executive function and verbal memory may persist in euthymic bipolar patients and serve as an indicator of genetic risk (endophenotype). **Methods:** A systematic review of the literature was undertaken. Effects sizes were extracted from selected papers and pooled using meta-analytic techniques. **Results:** In bipolar patients, large effect sizes ($d>0.8$) were noted for executive function (working memory), mental speed and verbal memory. Medium effect sizes ($0.5<d<0.8$) were reported for aspects of executive function (fluency, concept shifting, executive control), visual memory, and sustained attention. Small effect sizes ($d<0.5$) were found for visuoperception. In first-degree relatives, effect sizes were small ($d<0.5$), and only significantly different from healthy controls for executive function. **Conclusion:** Executive function is a candidate bipolar endophenotypes given medium deficits in these domains in bipolar patients and small, but intermediate, cognitive impairments in first-degree relatives.

Key words: bipolar patients; cognition; meta-analysis; relatives

Introduction

Christensen and colleagues (2006) investigated cognitive function in healthy twins discordant for bipolar disorder and found evidence for an association between cognitive dysfunction and genetic liability. The authors concluded that cognitive dysfunction may be a candidate indicator of genetic risk or endophenotype (Gottesman and Gould 2003) for bipolar disorder. Thus, there is evidence that cognitive dysfunction persists in euthymic bipolar patients (Robinson *et al.* 2006; Savitz *et al.* 2005a) and also non-twin genetically sensitive studies suggest that aspects of cognition can possibly be regarded as endophenotype for bipolar disorder (Glahn *et al.* 2004; Hasler *et al.* 2006; Savitz *et al.* 2005b). Possible candidate neurocognitive endophenotypes in bipolar disorder are executive function (Glahn *et al.* 2004; Savitz *et al.* 2005b), attention (Burdick *et al.* 2006; Hasler *et al.* 2006), and verbal memory (Glahn *et al.* 2004; Hasler *et al.* 2006). A recent meta-analysis of cognitive deficits in euthymic bipolar patients (Robinson *et al.* 2006) provides further evidence for executive function and verbal learning as possible endophenotypes for bipolar disorder.

The aim of the present review was to estimate the meta-analytic effect size of cognitive functioning in euthymic bipolar patients and their first-degree relatives, thus updating a previous systematic review of patients (Robinson *et al.* 2006), and adding a new review for first degree relatives. The hypothesis was that first-degree relatives show cognitive deficits in the same areas as bipolar patients, albeit to a lesser degree.

Methods

Study selection

Articles were identified through a literature search in PUBMED / MEDLINE, PSYCHINFO, and EMBASE covering the period between January 1985 and September 2006, using the keywords "bipolar disorder" or "manic depress*" and "family"/ "familial" or "first-degree relative" with "cognit*" or "neuropsych*".

The following criteria were used for inclusion: i) the study evaluated cognitive performance using standardized and reliable neuropsychological testing procedures; ii) the study compared adult asymptomatic bipolar patients who were diagnosed using a recognised criterion-based diagnostic system and / or first-degree relatives with a healthy control group, matched for age, sex and education; iii) the study reported uncorrected mean test scores and standard deviations for both the patient and / or family and control group; iv) the study was published as an original article in a peer-reviewed English language journal; and v) the study with bipolar patients clearly defined euthymia or provided scores on mood rating scales

indicating that patients were euthymic (euthymia defined as a cut-off score of <8 on the Hamilton Depression Rating Scale and the Young Mania Rating Scale, and / or a score on mood rating scales below this cut-off point).
The references of retrieved articles were hand-searched for further relevant articles. A second study on the same patient group was only included if it reported different tests.

Data Analysis
Meta-analyses were performed using STATA (version 9.2), using a random effects model. For each test parameter an effect size was calculated, which was Cohen's *d*, the difference between the means of both groups (bipolar patients and / or first-degree relatives vs. controls) divided by the pooled standard deviation. Effect sizes were weighted for sample size, in order to correct for upwardly biased estimation of the effect in small samples. Effect sizes were expressed in such a way that positive effect sizes always indicated poorer performance by the patient or family group. The corresponding *z*-value and significance level provide an indication of the two-sided statistical significance of the association at 5% alpha. A homogeneity statistic was calculated in order to test to what degree the studies can be taken to share a common population effect size. A significant *Chi-square*-statistic indicated heterogeneity of the individual effect sizes.
Meta-regression is a technique for trying to work out whether particular characteristics of studies are related to the sizes of the treatment effect. Thus, in the case of significant heterogeneity, meta-regression, using STATA (version 9.2), was performed in order to examine whether any heterogeneity found could possibly be explained by study differences in age structure, sex ratio, and mean educational level.

Results

Bipolar patients
Twenty-eight studies were included in the meta-analysis (table 1, appendix). Four of these stratified their samples by a third variable (Ferrier *et al.* 1999; Nehra *et al.* 2006; Torrent *et al.* 2006; van Gorp *et al.* 1998). For reasons of homogeneity, in the case of stratification, only one study group was included, with bias to the less severe patients or those with a better established diagnosis. Thus, Ferrier *et al.* (1999) stratified by outcome, contrasting a good outcome versus a poor outcome group; for the purpose of the current meta-analysis only the good outcome group was included. The study by Nehra and colleagues (2006) used first and multiple episode patients, only established bipolar patients with multiple episodes were included in the current analysis. Van Gorp and colleagues (1998) included patients with and

without prior alcohol dependence, only the group without alcohol dependence was used in the analysis. Finally, Torrent and colleagues (2006) used BP-I and BP-II patients, only BP-I patients were included.

Neuropsychological domains

The neuropsychological tests used in these studies were divided into 11 categories measuring approximately the same cognitive construct (adapted from Krabbendam *et al.* 2005). A neuropsychological test was included by the *a priori* criterion of having been used in at least four different studies. *Immediate verbal memory* was assessed using word list learning (California Verbal Learning Test (CVLT) (Delis 1987); Rey Auditory Verbal Learning Test (RAVLT) (Rey 1964); Auditory Verbal Learning Test (AVLT) (Brand and Jolles 1985)). For the purposes of the analysis, results of these comparable tests were included together. *Delayed verbal memory* was assessed using the delayed recall version of the CVLT, RAVLT, and AVLT. *Delayed visual memory* was measured using the delayed recall version of the Rey Osterrieth Complex Figure (Rey 1941). *Working memory* was assessed using the Digit Span (Wechsler 1955). *Verbal fluency* was measured using either words from a certain category or beginning with a certain letter (FAS; (Benton 1978)). *Concept formation and shifting* was assessed with the Wisconsin Card Sorting Test (WCST; (Heaton 1981)); number of perseverative errors and categories achieved were separately analysed. *Executive control* was measured using the Stroop Color-Word interference (Stroop 1935) and Trailmaking Test part B (Reitan 1958). *Sustained attention* was assessed using a variant of the Continuous Performance Test (Kurtz 2001). The test parameter used was number and/or percentage correct response. *Mental Speed* was measured using the Digit Symbol Substitution Test (DSST; (Wechsler 1955)) and the Trailmaking Test part A (Reitan 1958). *Visuoperception* was assessed using the copy version of the Rey Osterrieth Complex Figure (Rey 1941). *Intelligence* was measured using the full scale NART (Grober 1991) or the WAIS-R vocabulary score (Wechsler 1981), both good estimates of premorbid intelligence.

Meta-analytic results patients

All effect sizes were in the same direction (table 2), suggesting worse performance in euthymic bipolar patients compared to healthy controls.

In all instances, with the exception of visuoconstruction (Rey copy) and intelligence, bipolar patients displayed significantly poorer performance compared to controls. The largest effect sizes were evident for working memory (Digit Span backward), delayed and immediate verbal recall (CVLT), and mental speed (DSST) (effect sizes > 0.8). Medium effect sizes ($0.5<d<0.8$) were observed for fluency (categories), executive control (Trail B, Stroop), concept shifting (WCST persever-

ative errors), delayed visual memory (Rey figure), sustained attention (CPT) and mental speed (Trail A). A small effect size (0.2<d<0.5) was noted for concept shifting (WCST categories), fluency (FAS) and working memory (Digit Span forward).

Table 2. Results of meta-analyses of cognitive test performances differences between bipolar patients versus normal controls

Test	k[1]	n bipolar	n control	d[2]	95% CI[3]	z[4]	p value	Chi-square[5]	p value
Digit backward	6	222	205	1.02	0.49 to 1.54	3.85	0.000	30.50	0.000
CVLT delayed recall	10	269	282	0.85	0.60 to 1.09	6.83	0.000	16.27	0.061
DSST	7	202	249	0.84	0.53 to 1.14	5.32	0.000	13.76	0.032
CVLT immediate rec.	12	369	382	0.82	0.65 to 0.99	9.25	0.000	13.96	0.235
Fluency categories	7	178	178	0.75	0.44 to 1.04	4.83	0.000	10.91	0.091
Trail B	10	319	306	0.75	0.42 to 1.10	4.47	0.000	33.93	0.000
Stroop time	6	116	124	0.73	0.32 to 1.13	3.49	0.000	11.00	0.051
WCST Pers. Err.	10	268	288	0.72	0.58 to 0.95	5.90	0.000	15.24	0.085
Stroop correct	8	258	268	0.65	0.47 to 0.83	7.17	0.000	2.37	0.937
Rey figure	4	98	89	0.62	0.32 to 0.92	4.04	0.000	2.01	0.570
CPT correct	4	74	85	0.58	0.09 to 1.08	2.31	0.021	6.52	0.089
Trail A	10	319	306	0.58	0.42 to 0.75	7.02	0.000	4.88	0.845
WCST Categories	10	268	288	0.49	0.22 to 0.76	3.59	0.000	19.76	0.019
FAS	12	369	382	0.47	0.30 to 0.65	5.14	0.000	15.54	0.159
Digit forward	6	222	205	0.37	0.15 to 0.59	3.33	0.001	6.19	0.288
Rey copy	4	103	94	0.22	-0.06 to 0.51	1.52	0.129	2.89	0.409
IQ	8	237	247	0.16	-0.11 to 0.44	1.15	0.250	15.36	0.032

[1] Number of studies included in the analysis; [2] mean, weighted effect size Cohen's d; [3] 95 % confidence interval; [4] test of significance of effect size (p); [5] test of within category heterogeneity between studies (p)

For five out of 17 analyses there was evidence for significant heterogeneity between the results of the different studies. The largest heterogeneity was found for working memory (Digit Span backward), executive control (Trail B) and concept shifting (WCST categories). Two studies were largely responsible for this heterogeneity, namely the study of Balanza-Martinez and colleagues (2005) and Goswami and colleagues (2006). Both showed larger effect sizes. In a sensitivity analysis of working memory (Digit Span backward) excluding the study of Goswami and colleagues (2006), the observed heterogeneity largely disappeared (before exclusion: χ^2=30.50, p=0.000; after exclusion: χ^2=5.70, p=0.223). The effect size reflecting bipolar-control differences remained significant (d=0.73; p=0.000). The study of Goswami and colleagues (2006) caused most of the heterogeneity in the analysis on executive control (Trail B). Leaving this study out resulted in non-significant heterogeneity (before exclusion: χ^2=33.93, p=0.000; after exclusion: χ^2=10.78, p=0.214). The effect size reflecting bipolar-control differences remained significant (d=0.58; p=0.000). In the case of concept shifting (WCST categories), heterogeneity was largely caused by the studies of Balanza-Martinez and colleagues (2005) (before exclusion: χ^2=19.76, p=0.019; after exclusion: χ^2=11.21, p= 0.190). The

effect size reflecting bipolar-control differences remained significant (d=0.39; p=0.000). The fact that the most significant heterogeneity was due to only two studies, suggests that certain characteristics of these studies may be responsible for this finding. The study by Balanza-Martinez and colleagues (2005) was relatively small and used a bipolar population with rather low educational level and no specification of characteristics of disease (duration, number of episodes etc.). One could speculate that they described a rather severely ill population. Goswami and colleagues (2006) used a rather young population with a relatively long duration of illness and early illness onset. This study too likely included a rather severely ill group of patients.

Meta-regression revealed a significant effect of sex ratio on the concept formation and shifting case-control difference (WCST) (p= 0.001; B= -2.63; 95 % CI –4.156 to –1.11). This finding indicates that studies with higher male / female ratios showed smaller effect sizes. Age had a significant effect on the case-control difference of concept formation (WCST) and working memory (Digit Span backward) (p= 0.000; B= -32.51; 95 % CI –43.6 to – 21.4, and p=0.029; B= -11.18; 95 % CI –21.2 to –1.18). Thus, studies with higher mean age showed smaller effect sizes. Finally, educational level had a significant effect on the working memory case-control difference (Digit Span backward), fluency (FAS) and concept formation (WCST) (p=0.03; B= -0.014; 95 % CI –0.027 to –0.001; p=0.007; B= 36.93; 95 % CI 8.38 to 52.24; p=0.014; B= 2.53; 95 % CI 0.52 to 4.55). This points in the direction of larger effect sizes in studies with higher educated participants. In conclusion, part of heterogeneity may be due to differences between the various studies in these independent variables.

Meta-analytic results first-degree relatives

A total of fourteen studies were included (table 3, appendix). Two of these studies used more than one family group (McIntosh *et al.* 2005; Sobczak *et al.* 2003). In the study by McIntosh *et al.* (2005), a group of unaffected relatives from bipolar families and a group from "mixed" families was used; only the group from bipolar families was included in the analyses. Sobczak *et al.* (2003) used a group of first-degree relatives of BP-I patients and a group of relatives of BP-II patients; only the group of family-members of BP-I patients was used in the meta-analysis.

The neuropsychological tests used in the studies were divided in the same categories as described earlier and included only if used in at least four different studies. This resulted in less cognitive domains analysed than in the bipolar studies. These domains were *immediate and delayed verbal memory, working memory, concept formation and shifting, verbal fluency, executive control, mental speed*, and *intelligence.* The Visual Verbal Learning Test used in the study by Sobczak and colleagues (2003), measuring im-

mediate and delayed verbal memory and resembling the CVLT and RAVLT (Lezak 1995), was added to the analysis.

Table 4. Results of meta-analyses of cognitive test performance differences between first-degree relatives versus normal controls

Test	k[1]	n relatives	n control	d[2]	95% CI[3]	z[4]	p value	Chi-square[5]	p value
Stroop	4	71	125	0.49	0.05 to 0.93	2.16	0.031	5.35	0.148
Trail B	7	143	234	0.37	0.15 to 0.60	3.27	0.001	4.98	0.546
FAS	4	68	102	0.27	-0.04 to 0.59	1.70	0.090	3.01	0.391
CVLT immediate	4	73	94	0.22	-0.09 to 0.53	1.38	0.167	0.08	0.994
CVLT delayed recall	4	75	191	0.21	-0.07 to 0.50	1.45	0.146	2.11	0.550
IQ	5	119	191	0.19	-0.27 to 0.65	0.82	0.414	12.77	0.012
Digit span backward	5	79	266	0.18	-0.33 to 0.69	0.69	0.490	13.29	0.010
WCST Pers. Err.	6	140	192	0.17	-0.09 to 0.43	1.26	0.207	6.26	0.282
DSST	4	74	225	0.14	-0.16 to 0.45	0.91	0.361	3.66	0.300
Trail A	7	143	234	0.13	-0.09 to 0.35	1.14	0.256	5.28	0.508
Digit span forward	4	60	152	0.04	-0.72 to 0.81	0.11	0.911	15.23	0.002
WCST Categories	4	82	127	0.04	-0.36 to 0.43	0.18	0.861	5.35	0.148

[1] Number of studies included in the analysis; [2] mean, weighted effect size Cohen's d; [3] 95 % confidence interval; [4] test of significance of effect size (p); [5] test of within category heterogeneity between studies (p)

Meta-analysis of the neuropsychological domains indicated that all meta-analytic effect sizes were in the direction of worse performance in the first-degree relatives compared to the healthy controls (Table 4). Effect sizes, however, were much smaller than in the bipolar-control comparisons (< 0.5), and only significantly different for executive control (Stroop and Trail B).

There was evidence of significant heterogeneity for three out of twelve analyses, namely for the domains of intelligence and working memory (Digit Span). Heterogeneity may be due to the small number of studies with small, heterogeneous groups of first-degree relatives with different family histories and genetic load. The study by Gourovitch and colleagues (1999), for example, using monozygotic twins, showed relatively large but differential effect sizes for working memory and verbal memory, contributing to heterogeneity. Meta-regression revealed no significant effects of the independent variables examined.

Discussion

Patients

This meta-analysis of cognitive functioning in euthymic bipolar patients provides evidence of cognitive impairments in these patients, particularly in the realm of executive functioning and verbal memory. Large effect sizes were found for working memory, executive control, concept shifting, fluency, verbal recall, and mental speed.

The finding of both executive and memory impairments has been described in the quantitative meta-analysis by Robinson and colleagues (2006), despite the fact that we used somewhat stricter inclusion criteria for euthymia and included more recent studies.

There was substantial heterogeneity between the results of the different studies, the largest heterogeneity being noted for working memory, concept shifting, executive control, and fluency. Two studies (Balanza-Martinez 2005; Goswami *et al.* 2006) largely caused this heterogeneity, possibly because of inclusion of relatively severely ill patients with a higher number of (psychotic) episodes. Thus, greater number of episodes, greater length of illness and higher number of hospitalizations has been associated with greater level of neuropsychological dysfunction in bipolar patients (Robinson and Ferrier 2006). Heterogeneity may also be caused by the differential effects of age, sex, and education on the cognitive domains mentioned above, as revealed by meta-regression.

Heterogeneity may additionally be caused by residual mood symptoms, because of the variation in the criteria used to define euthymia. It was not possible to include measures of mood as a variable for the meta-regression, however, as the studies included did not use, or did not report, uniformly measured items of mood. Another confound is medication, the use and reporting of which varied between studies. The effects of different types of medication on cognitive function in bipolar patients are not systematically studied, but the effects of lithium may be rather modest, given the small effect size (d=0.3) in the study by Goswami and colleagues (2002). Furthermore, cognitive deficits are still evident in medication-free patients (Goswami 2002; Strakowski *et al.* 2004). Another source of heterogeneity may be the type of bipolar disorder under investigation. Although most studies used bipolar I patients, not all studies specified the type of patients included. Bipolar I patients may show greater, and or different, deficits in cognitive function than bipolar II patients (Harkavy-Friedman *et al.* 2006; Torrent *et al.* 2006). Matching on education versus IQ may be a confound too, given the study by Glahn and colleagues (2006), who describe less educational attainment despite comparable IQ levels in bipolar patients versus normal controls. Matching on educational attainment could thus give rise to underestimation of the difference in cognitive function between bipolar patients and normal controls. Finally, differences in somatic comorbidity (and comedication) between bipolar patients and normal controls, could contribute to differences in cognitive performance (Newcomer 2006).

First degree relatives

The meta-analysis in first-degree relatives showed worse performance in all cognitive domains studied, compared to controls. Effect sizes, however, were small and

significant only in the domain of executive functioning. This suggests that executive functioning may be a trait marker for the genetic liability for bipolar disorder. Heterogeneity between the results of the different studies may be due to the small number of studies with relatively small, heterogeneous groups of first-degree relatives with different family histories and genetic load. Contrary to the patient meta-analysis, meta-regression revealed no effects of sex, education and age on the meta-analytic effect size, suggesting more robust results and fewer sources for underlying heterogeneity.

The possible influence of family history as a source of heterogeneity is illustrated by the study by Schubert and McNeil (2005), who described greater cognitive impairment in offspring of mothers with schizophrenia-spectrum psychosis versus offspring of mothers with affective-spectrum psychosis. Furthermore, Sobczak and colleagues (2003) found more pronounced cognitive impairments in first-degree relatives of bipolar I patients compared to relatives of bipolar II patients. Another possible source of heterogeneity is the fact that only a small number of studies controlled for subclinical mood symptoms in first-degree relatives and controls. Finally, only a small number of studies directly compared cognitive function between bipolar patients, first-degree relatives and healthy controls (Ferrier *et al.* 2004; Frangou *et al.* 2005b; McIntosh *et al.* 2005).

Our meta-analysis on cognitive function in first-degree relatives of bipolar patients is, to the best of our knowledge, the first in the literature. Comparison with other meta-analytic reviews is therefore only possible with first-degree relatives of other patient groups, for example patients with schizophrenia. Such a comparison is topical, given the fact that bipolar and schizophrenia phenotypes likely share genetic risk factors (Craddock *et al.* 2006). Various meta-analyses of cognitive function in first-degree relatives of patients with a diagnosis of schizophrenia (Sitskoorn *et al.* 2004; Snitz *et al.* 2006; Szoke *et al.* 2005) describe the largest effect sizes (d= 0.5 to 0.6) for executive functioning and verbal memory, with somewhat different effect sizes for different executive tests used and greater effect sizes in multiplex families (Heydebrand 2006). This qualitative pattern of effects sizes and tests are rather similar to those presented here for the relatives of patients with bipolar disorder. In the review by Snitz and colleagues (2006), the type of biological relative, parent, sibling, or offspring did not impact on effect sizes of cognitive deficits in unaffected first-degree relatives of patients with a diagnosis of schizophrenia. Asymmetric psychiatric exclusion criteria and screening controls more stringently than relatives did influence the effect sizes in the review by Snitz and colleagues (2006). Therefore, this source could also contribute to the heterogeneity observed in the current meta-analysis.

Heydebrand (2006), reviewing meta-analyses on cognitive function in relatives of patients with a diagnosis of schizophrenia, concludes that the most consistent deficit shown by relatives is impaired performance on 'maintenance plus' frontal-lobe tasks, requiring increased effort and higher central executive processing. This cognitive phenotype therefore may be a likely candidate endophenotype for both schizophrenia and bipolar disorder. In this respect it may be important that memory performance is affected by executive dysfunction, as shown by shared variance of 50-60% (Duff *et al.* 2005). A quantitative review of cognitive functioning in patients with schizophrenia and bipolar disorder yielded largest (differences in) effect sizes on executive function and verbal memory; bipolar patients generally better performing than patients with schizophrenia (Krabbendam *et al.* 2005). Important in this respect is the fact that there were only quantitative, and not qualitative, differences between bipolar patients and patients with a diagnosis of schizophrenia, which fits in with current models of the relationship between both disorders. Murray and colleagues (2004) hypothesize that certain shared susceptibility genes may predispose individuals to psychosis in general. A candidate gene may be neuregulin 1, which influences susceptibility to bipolar disorder and schizophrenia, especially in bipolar patients with mood-incongruent psychotic features and patients with a diagnosis of schizophrenia with mania (Green *et al.* 2005). Polymorphisms of neuregulin, influencing, amongst others, synaptic signalling by glutamate receptors, play possibly a role in cognition (Harrison and Law 2006; Schillo *et al.* 2005; Scolnick *et al.* 2006). Other candidate genes in this respect are Disc 1 (Cannon *et al.* 2005; Porteous *et al.* 2006; Ross *et al.* 2006) and BDNF (Bath and Lee 2006), both related to susceptibility to schizophrenia as well as bipolar disorder on the one hand, and cognitive dysfunction (executive function and memory) on the other. Finally, COMT-polymorphisms may play a role as well, in particular the COMT Val^{158}Met polymorphism and other polymorphisms on the same gene, that have been associated with prefrontal cognitive functioning in schizophrenia and bipolar patients and their first-degree relatives (Bertolino *et al.* 2006; Goldberg *et al.* 2003; Mata *et al.* 2006; Minzenberg *et al.* 2006; Rosa *et al.* 2004). Interestingly, the COMT Val^{158}Met polymorphism influences the improvement of cognitive functioning in patients with a diagnosis of schizophrenia treated with clozapine (Woodward *et al.* 2006), and differential effects are described of these polymorphisms on the results of different tests of executive function (Tunbridge *et al.* 2006). Furthermore, the COMT Met^{158}Met genotype is associated with heightened reactivity and connectivity in corticolimbic circuits, leading to inflexible processing of affective stimuli contributing to emotional dysregulation (Drabant *et al.* 2006). Tunbridge and colleagues (2006), reviewing the literature on COMT polymorphisms, conclude that the Met allele is associated with improved executive func-

tion compared with the Val allele, but also with impaired emotional processing. Bilder and colleagues (2004) hypothesize that the COMT Met allele, associated with low enzyme activity, results in increased levels of tonic dopamine (DA) and reciprocal reductions in phasic DA in subcortical regions and increased D1 transmission cortically, leading to increased stability but decreased flexibility of neural networks. This model fits in with results from, amongst others, f-MRI-studies pointing in the direction of dysregulation of prefrontal area influence on subcortical neural regions, explaining cognitive dysfunction and mood symptoms (Brooks *et al.* 2006; Strakowski *et al.* 2005; Yurgelun-Todd 2006).

To summarize, executive function may be a candidate endophenotypes for the genetic liability for bipolar disorder, as suggested by the current meta-analyses on bipolar patients and their first-degree relatives.

Guidelines for future research on cognitive deficits in schizophrenia and bipolar patients and their relatives (adapted from (Heydebrand 2006)) are: i) sufficient sample size to allow the examination of specific cognitive deficits as well as for genetic testing; ii) use of cognitive measures that are sufficiently specific and sensitive, and have ecological validity; iii) longitudinal studies; iv) recruitment of heterogeneous control samples; v) control for psychopathology; and vi) investigation of heterogeneity of cognitive function in patients and relatives, in relation to neurobiological findings.

Appendix

Table 1. Studies with bipolar patients included in the meta-analysis

Author, year	N		Definition of euthymia	Neuropsychological test parameters	d[1]
	Patients	Controls			
Altshuler, 2004	40	22	HDRS[2]<6	CVLT[11] immediate recall	0.75
			YMRS[3]<7	CVLT delayed recall	0.78
			prospectively for 3 months	Rey Figure delayed	0.57
				FAS[12]	0.16
				WCST[13] pers. err.	0.77
				WCST cat.	0.89
				Stroop time	0.41
				Trail A	0.38
				Trail B	0.40
				IQ	0.20
				Rey Figure copy	0.30
Balanza-Martinez, 2005	15	26	HDRS<8	FAS	1.28
			HDRS: 3.4 (2.9)	Fluency cat.	1.79
			CARS[4]<8	WCST pers. err.	1.67
			CARS: 1.3 (1.8)	WCST cat.	1.48
			2 months euthymia	Stroop time	1.62
				Trail A	0.68
				Trail B	0.89
				DSST[14]	1.05
Blumberg, 2003	15	20	HDRS<8	Stroop time	0.74
			HDRS: 7.3 (7.1)		
			CARS<8		
			CARS: 4.1 (5.0)		
Bozikas, 2005	19	30	MADRS[5]<9	CPT[15]	0.10
			MADRS: 1.53 (2.61)		
			YMRS<9		
			YMRS: 3.16 (2.48)		
Cavanagh, 2002	20	20	HDRS<8	CVLT delayed recall	0.96
			1.0 (2.9)	FAS	0.29
			MMS[6]<3	Stroop correct	0.61
			MMS: 0.5 (1.5)		
Clark, 2002	30	30	HDRS<9	CVLT immediate recall	0.48
			HDRS: 2.07 (2.26)	CVLT delayed recall	0.95
			YMRS<9	CPT	0.96
			YMRS:1.67 (2.22)		
Clark, 2005	15	15	HDRS<9	CPT	1.00
			HDRS: 3.2 (2.5)		
			YMRS<9		
			YMRS: 1.9 (2.5)		
Deckersbach, 2004	30	30	HDRS: 3.4 (2.6)	CVLT immediate recall	1.40
			YMRS: 1.0 (1.6)	CVLT delayed recall	1.67
Deckersbach, 2004a	25	25	HDRS: 3.3 (2.5)	Rey Figure delayed	0.70
			YMRS: 1.2 (1.5)	Rey Figure copy	0.06
Dixon, 2004	15	30	BDI[7]: 6.5 (4.3)	FAS	0.17
			YMRS: 2.7 (2.2)	Fluency cat.	0.30
				Stroop correct	0.82
				IQ	-0.32
Ferrier, 1999	20	20	HDRS: 2.7 (2.1)	RAVLT[16] immediate recall	0.93
			MSS[8]: 4.1 (1.9)	Rey Figure delayed	0.92
				Digit Span Backward	1.11
				FAS	0.40
				Trail A	0.81
				Trail B	0.92
				DSST	0.81

				Digit Span forward	0.28
				Rey Figure copy	0.64
Fleck, 2003	14	40	HDRS<10	CVLT immediate recall	1.01
			HDRS: 3.7 (2.8)	CVLT delayed recall	0.77
			YMRS<10		
Frangou, 2005a	10	43	HDRS<6	WCST pers. err.	0.55
			HDRS: 3.0 (1.2)	WCST cat.	0.04
			YMRS<6		
			YMRS: 1.1 (0.5)		
			at least 1 month		
Frangou, 2005b	44	44	HDRS<10	FAS	0.88
			HDRS: 7	WCST pers. err.	0.38
			MRS[9]<10	WCST cat.	0.25
			MRS: 0	Stroop correct	0.57
				IQ	0.31
Goswami, 2006	37	37	euthymia >1 month	RAVLT immediate recall	0.69
			HDRS: 2.35 (1.48)	Digit Span backward	2.28
			MSRS[10]: 7.91 (4.88)	Trail A	0.54
				Trail B	1.99
				DSST	0.19
				Digit Span forward	0.50
Krabbendam, 2000	21	22	HDRS: 3.4 (3.0)	AVLT[17] immediate recall	0.94
			YMRS: 0.77 (1.5)	AVLT delayed recall	0.93
				Fluency cat.	0.54
				Stroop time	0.67
				DSST	1.12
Larsson, 2005	18	18	HDRS: 3 (3)	IQ	0.12
			YMRS: 2 (3)		
			follow-up for 4 to 8 weeks		
Malhi, 2005	12	12	HDRS<7	Stroop time	1.02
			HDRS: 4.3 (1.1)		
			YMRS<7		
			YMRS: 0.9 (0.5)		
Martinez-Aran, 2004	44	30	HDRS<9	CVLT immediate recall	0.84
			HDRS: 3.6 (2.6)	CVLT delayed recall	0.96
			YMRS<7	Digit Span backward	0.86
			YMRS: 1.4 (1.8)	FAS	0.56
			6 months remission	Fluency cat.	0.83
				WCST pers. err.	0.62
				WCST cat.	0.38
				Stroop correct	0.59
				Trail A	0.90
				Trail B	0.57
				Digit Span forward	0.56
				IQ	0.75
McIntosh, 2005	27	50	HDRS: 5	FAS	0.71
			YMRS: 2	DSST	1.34
				IQ	-0.07
Nehra, 2006	30	20	HDRS<8	FAS	0.45
			HDRS: 2.67 (0.92)	Fluency cat.	0.46
			YMRS<8	WCST pers. err.	0.37
			YMRS: 1.47 (1.25)	WCST cat.	0.07
				Trail A	0.41
				Trail B	0.69
Strakowski, 2004	10	10	HDRS<8	CPT	0.21
			HDRS: 3.1 (2.5)		
			YMRS<6		
			YMRS: 1.6 (1.8)		
Thompson, 2005	63	63	HDRS<8	RAVLT immediate recall	0.59
			HDRS: 2.1 (1.7)	Digit Span backward	0.37
			YMRS<8	FAS	0.36
			YMRS: 1.4 (2.0)	Stroop correct	0.58
			Prosp. verified for 1 month	Trail A	0.47
				Trail B	0.23

				DSST	0.91
				Digit Span forward	0.05
Thompson, 2006	20	20	HDRS<8	Digit Span backward	0.75
			HDRS: 1.90 (2.38)	Digit Span forward	0.25
			YMRS<8		
			YMRS: 1.40 (2.08)		
Torrent, 2006	38	35	HDRS<9	CVLT immediate recall	0.58
			HDRS: 4.29 (2.51)	CVLT delayed recall	0.80
			YMRS<7	Digit Span backward	0.86
			YMRS: 0.79 (1.19)	FAS	0.41
				Fluency cat.	0.76
				WCST pers. err.	0.56
				WCST cat.	0.23
				Stroop correct	0.58
				Trail A	0.80
				Trail B	0.57
				Digit Span forward	0.70
Van Gorp, 1998	13	22	HDRS<7	CVLT immediate recall	0.70
			YMRS<6	CVLT delayed recall	0.52
				Rey Figure delayed	0.25
				FAS	-0.11
				WCST pers. err.	0.95
				WCST cat.	1.00
				Stroop time	0.08
				Trail A	0.32
				Trail B	0.24
				Rey figure copy	-0.09
Varga, 2006	19	31	MADRS: 2.26 (3.69)	AVLT immediate recall	1.52
			MRS: 2.32 (4.10)	AVLT delayed recall	1.04
				WCST pers. err.	0.55
				WCST cat.	0.15
				Stroop correct	0.80
				Trail A	0.53
				Trail B	1.24
				DSST	0.54
				IQ	0.57
Zubieta, 2001	15	15	HDRS<6	Fluency cat.	0.77
			HDRS: 3.4 (2.1)	WCST pers. err.	1.52
			YMRS<4	WCST cat.	0.84
			YMRS: 0.4 (0.6)	Stroop correct	1.12
			at least 6 months euthymia		

[1] Effect size, positive values indicate better performance in controls; [2] Hamilton depression Rating Scale; [3] Young Mania Rating Scale; [4] Clinician Administered Rating Scale for Mania; [5] Montgomery-Asberg Depressive Rating Scale; [6] Modified Manic Scale; [7] Beck Depression Inventory; [8] Manic State Scale; [9] Manic Rating Scale; [10] Manic State Rating Scale; [11] California Verbal Learning Test; [12] Verbal fluency test; [13] Wisconsin Card Sorting Test; [14] Digit Symbol Substitution Test; [15] Continuous Performance Test; [16] Rey Auditory Verbal Learning Test; [17] Auditory Verbal Learning Test

Table 3. Studies with first-degree family members included in the meta-analysis

Author, year	N		Sample characteristics	Neuropsychological test parameters	d[1]
	Relatives	Controls			
Christensen, 2006a	7	36	MZ twins discordant for bipolar disorder	Stroop	0.37
				Trail A	0.20
				Trail B	0.63
Christensen, 2006b	14	52	DZ twins discordant for bipolar	Stroop	0.45
			disorder	Trail A	-0.10
				Trail B	0.25
Clark, 2005	27	47	10 parents; 12 siblings; 5 children	CVLT[6] immediate recall	0.20
			HDRS[2]: 1.2 (1.9)	CVLT delayed recall	0.12
			YMRS[3]: 0.4 (1.1)		
Ferrier, 2004	17	17	first-degree relatives	RAVLT[7] immediate recall	0.18
			HDRS: 0.82 (1.01)	Digit Span backward	0.99
			YMRS: 0.47 (1.28)	FAS[8]	-0.12
			controls	Stroop	0.00
			HDRS: 0.35 (0.86)	Trail A	-0.07
			YMRS: 0.18 (0.53)	Trail B	0.37
				DSST[9]	0.24
				Digit Span forward	0.39
Frangou, 2005	15	43	unaffected offspring of bipolar probands	WCST[10] pers. err.	-0.42
				WCST cat.	-0.53
				WAIS-R IQ	-0.09
Gourovitch, 1999	7	15	MZ twins	CVLT immediate recall	0.33
				CVLT delayed recall	0.80
				Digit Span backward	0.97
				FAS	0.28
				WCST pers. err.	0.52
				Trail A	-0.10
				Trail B	0.01
				Digit Span forward	1.16
				WAIS-R IQ	0.40
Keri, 2001	20	20	unaffected siblings	Digit Span backward	-0.18
			BP-I probands	FAS	0.12
				WCST pers. err.	0.10
				WCST cat.	0.11
				Digit Span forward	-0.33
Kieseppa, 2005	19	114	twins discordant for BP-I	CVLT delayed recall	0.08
				Digit Span backward	-0.18
				DSST	-0.12
Kremen, 1998	14	44	relatives of psychotic bipolar pro-bands	WCST pers. err.	0.09
				WCST cat.	0.45
				Trail A	-0.28
				Trail B	-0.11
				DSST	-0.05
				WAIS-R IQ	-0.58
McIntosh, 2005	24	50	unaffected relatives with > 1 first-or second degree BP-proband	FAS	0.58
				DSST	0.50
			HDRS: 1.5 (median)		
			YMRS: 0		
			controls		
			HDRS: 0		
			YMRS: 0		
Pirkola, 2005	16	100	unaffected co-twins	Digit Span backward	-0.30
			3 MZ 13 DZ	Digit Span forward	-0.78
Sobczak, 2003	22	15	first-degree relatives BP-I	VVLT immediate recall	0.25
				VVLT delayed recall	0.34
Szoke, 2006	51	50	first-degree relatives	WCST pers. err.	0.22

			of BP-I patients	Trail A	0.41
				Trail B	0.54
Toulopoulou, 2006	50	69	17 parents, 23 siblings	WAIS-R IQ	0.42
			10 children		
Zalla, 2004	33	20	11 parents, 22 siblings	WCST pers. err.	0.57
			MADRS[4] < 16	WCST cat.	0.12
			MAS[5] < 7	Stroop	1.03
				Trail A	0.31
				Trail B	0.60
				WAIS-R IQ	0.79

[1] effect size, positive values indicate better performance in controls; [2] Hamilton Depression Rating Scale; [3] Young Mania Rating Scale; [4] Montgomery-Asberg Depressive Rating Scale; [5] MAS Beck and Rafaelsen Mania Scale; [6] California Verbal Learning Test; [7] Rey Auditory verbal Learning Test; [8] Verbal fluency; [9] Digit Symbol Substitution Test; [10] Wisconsin Card Sorting Test

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CHAPTER 3

NEUROCOGNITIVE FUNCTIONING AS INTERMEDIARY PHENOTYPE AND PREDICTOR OF FUNCTIONING ACROSS THE PSYCHOSIS CONTINUUM: STUDIES IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Abstract

Objective: Neurocognitive functioning may represent an indicator of genetic risk and poor outcome in both schizophrenia and bipolar disorder. In this study, shared and non-shared characteristics in the cognitive domain in both disorders were analysed in order to determine to what degree neurocognitive functioning may represent a predictor of the familial vulnerability and poor functioning that both disorders share. **Method:** Neurocognition, psychopathology and psychosocial functioning were assessed in samples of patients with DSM-IV diagnosis of schizophrenia spectrum disorder (n=345) and bipolar disorder (n=76), first-degree relatives of both patient groups (n=331 and n=37, respectively) and healthy controls (n=260 and n=61, respectively). Multiple regression models were used to investigate the effect of group status on neurocognition and to explore associations between cognition, symptoms and psychosocial functioning in the two groups. **Results:** Cognitive deficits were more severe and more generalized in schizophrenia spectrum patients compared to bipolar disorder patients; cognitive alterations were present in relatives of patients with schizophrenia spectrum disorders but not in relatives of bipolar patients. The association between neurocognitive dysfunction and psychosocial functioning was more generalized in schizophrenia spectrum disorders than in bipolar disorder; for both disorders, associations were only partly mediated by symptoms. **Conclusion:** The evidence for cognitive dysfunction as a marker of familial vulnerability is stronger for schizophrenia than for bipolar disorder. Although the presence of multiple cognitive deficits is shared by the two groups, the severity of cognitive deficits and its consequences appear to partly differ between schizophrenia and bipolar disorder, which is in line with a model that implies the specific presence of a neurodevelopmental impairment in the former but not in the latter.

Key words: neurocognition, vulnerability marker, schizophrenia, bipolar disorder, outcome

Introduction

The question whether schizophrenia and bipolar disorder are truly distinct diseases is becoming increasingly important now that diagnostic boundaries are being re-evaluated during the development of the DSM-V. Investigating similarities and differences between both illnesses may help to elucidate this issue. One area of interest is neurocognitive functioning, given its putative roles as an intermediary phenotype and functional outcome predictor in both disorders.

Both schizophrenia and bipolar disorder are characterized by the presence of neurocognitive impairment. In schizophrenia, cognitive impairment is considered a core and stable feature of the illness that is present across a broad range of neuropsychological domains, but most consistently reported in the domains of memory, executive functioning and attention (Dollfus et al., 2002; Heinrichs & Zakzanis, 1998). Evidence that the cognitive performance of first-degree relatives is intermediate to the performance of schizophrenia patients and controls suggests that neurocognitive impairment may represent a marker of the genetic vulnerability to the disease (Faraone et al., 2000; Keefe et al., 1994; Krabbendam, Marcelis, Delespaul, Jolles, & van Os, 2001). In bipolar disorder, it has long been assumed that cognitive impairments are transient and limited to periods of affective disturbance. This has been contradicted by recent studies indicating that cognitive deficits, particularly in the domains of verbal memory and executive functioning, may persist in euthymic, stable bipolar patients (Arts, Jabben, Krabbendam, & Van Os, 2008; Robinson et al., 2006). Some studies have reported cognitive alterations in first-degree bipolar relatives (Antila et al., 2007; Clark, Sarna, & Goodwin, 2005; Ferrier, Chowdhury, Thompson, Watson, & Young, 2004), suggesting that in bipolar disorder neurocognitive impairment may similarly be a trait marker of genetic vulnerability to the disease (Glahn, Bearden, Niendam, & Escamilla, 2004).

Although cognitive impairments overlap in schizophrenia and bipolar disorder and may be a marker of genetic vulnerability for both disorders, only a few studies have compared neurocognitive performance in bipolar and schizophrenia patients and their relatives. McIntosh and colleagues showed that whereas alterations in memory functioning were related to an increased liability to psychosis in general, abnormalities in intellectual functioning were related to liability to schizophrenia more specifically (McIntosh, Harrison, Forrester, Lawrie, & Johnstone, 2005). In a study that examined executive functioning in bipolar and schizophrenia families, there were no deficits specifically related to one of both disorders (Zalla et al., 2004). Therefore, the first goal of this study was to extend this literature by investigating the role of neurocognitive functioning as a potential genetic vulnerability

marker for both disorders in two large samples of subjects, and to investigate shared and non-shared characteristics in the cognitive domain.

A second key reason for studying neurocognition in schizophrenia and bipolar disorder is its putative role in functional outcome. In schizophrenia, cognitive deficits are consistently related to functional outcome (Green, Kern, & Heaton, 2004), and it has been suggested that cognition predicts social and occupational functioning equally well as negative symptoms do (Dickinson & Coursey, 2002; Milev, Ho, Arndt, & Andreasen, 2005; Norman et al., 1999), and even better than positive symptoms (Bryson & Bell, 2003; Green, 1996). Predictors of functional recovery in bipolar disorder are less investigated because of the long-held assumption that bipolar disorder is an episodic illness with full recovery between episodes. In line with growing insight that symptom recovery does not necessarily imply functional recovery, recent studies have suggested that cognitive functioning may contribute substantially to psychosocial functioning in bipolar disorder (Atre-Vaidya et al., 1998; Dickerson et al., 2004; Martinez-Aran, Vieta, Colom et al., 2004). Therefore, the second aim of this study was to explore the relative contribution of symptoms and cognitive functioning to psychosocial functioning in schizophrenia and in bipolar disorder.

Methods

Subjects

The subjects in this study were recruited in the context of two related projects.

Schizophrenia spectrum study

The study sample consisted of patients with a schizophrenia spectrum disorder (SZ), their first-degree relatives and controls from the general population; the sample was recruited between September 2004 and January 2008, during the course of the baseline measurement of the Maastricht site Genetic Risk and Outcome of Psychosis (GROUP) project. Inclusion criteria for the Maastricht GROUP project were: fluent in Dutch, aged 16 to 55 years (with the exception of patients' parents) and, for patients, a diagnosis of schizophrenia spectrum psychosis according to DSM-IV. For a patient to participate, at least one of his or her siblings had to take part in the study. Siblings had to be free of any lifetime non-affective psychotic disorder and have at least one brother or sister with a diagnosis of schizophrenia spectrum psychosis participating in the study. For the control subjects, the occurrence of any psychotic disorder in either the subject or a first-degree family member constituted an exclusion criterion.

Patients were recruited through community mental health centres and psychiatric hospitals in the catchment area, namely South Limburg (Netherlands) and Flanders (Belgium). All first-degree relatives were sampled through participating patients. For the purpose of the current analyses, only siblings were included in the relatives group. Control subjects were recruited through newspaper advertisements and random mailings in nearby municipalities. The Comprehensive Assessment of Symptoms and History (CASH) (Andreasen, 1987) sections on affective and psychotic disorders were used to confirm the presence of a diagnosis of schizophrenia spectrum psychosis in patients, the absence of such a diagnosis in siblings, and the absence of a lifetime diagnosis of any psychotic disorder or any current affective disorder in the healthy controls. Healthy controls were additionally interviewed using the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992) in order to confirm the absence of family histories of psychotic or bipolar disorders in their first-degree relatives.
The initial sample consisted of 353 patients, 342 siblings and 263 control subjects. As data on neuropsychological performance and/or diagnosis were missing for some subjects, the risk set comprised 345 patients, 331 siblings and 260 controls. In the patient group, 266 had a diagnosis of schizophrenia, 38 had a diagnosis of schizo-affective disorder, 5 had a diagnosis of delusional disorder, 8 had a diagnosis of brief psychotic disorder and 28 had a diagnosis of psychotic disorder NOS. Of the 331 siblings, 43 had a diagnosis of a single episode of major depressive disorder (of whom 38 were in full and 5 were in partial remission), 13 had a diagnosis of recurrent major depressive disorder (of whom 6 were in partial and 7 were in full remission) and 275 received no diagnosis. Of the controls, 29 had a diagnosis of a single episode of major depressive disorder (in full remission), 8 had a diagnosis of recurrent major depressive disorder (in full remission) and 223 received no diagnosis. Written informed consent conforming to the local ethics committee guidelines was obtained from all subjects.

Bipolar study
This study sample consisted of patients with bipolar disorder (BD), healthy first-degree relatives of patients with BD and controls from the general population. The sample was recruited between June 2004 and July 2007, during the baseline measurement of the BIPOLCOG study (Jabben, Arts, Krabbendam, & Van Os, 2009), which focused on cognitive functioning in bipolar disorder.
Inclusion criteria for the BIPOLCOG study were: fluent in Dutch, aged 18 to 60 years and, for patients, a diagnosis of bipolar disorder according to DSM-IV (APA, 1994). Relatives had to be free of any lifetime bipolar or psychotic disorder and have at least one first-degree relative with a diagnosis of bipolar disorder. For the

control subjects, the occurrence of any psychotic or bipolar disorder in either the subject or a first-degree family member constituted an exclusion criterion.
Patients were recruited through in-patient and out-patient mental health service facilities in South Limburg, and through the local association of bipolar patients and their families. First-degree relatives were sampled through participating patients. Control subjects were recruited from the general population through a random mailing in the local area from a listing of all eligible individuals in the general population.
The computer program OPCRIT was used to derive and confirm DSM-IV diagnoses on the basis of current and lifetime recorded symptomatology listed in the Operational Criteria Checklist for Psychotic Illness (OCCPI) (Mc Guffin, Farmer, & Harvey, 1991). First-degree relatives and controls were clinically and diagnostically interviewed using the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen, Flaum, & Arndt, 1992) and OPCRIT criteria to exclude individuals with a diagnosis of BD or psychotic disorder. Healthy controls were additionally interviewed using the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992) in order to confirm the absence of family histories of psychotic or bipolar disorders in their first-degree relatives.
The initial sample consisted of 81 patients, 39 first-degree relatives and 61 healthy control subjects. Due to missing data on diagnosis or neuropsychological performance, the final risk set comprised 76 patients with bipolar disorder, 37 relatives and 61 controls. In the patient group, 57 had a diagnosis of bipolar I disorder, 17 received a diagnosis of bipolar II disorder and 2 were diagnosed with schizoaffective disorder bipolar type. In the group of relatives, four had a diagnosis of major depression disorder (in full remission). The other relatives had no history of psychiatric disorder. One control subject had a history of major depression disorder but was in full remission at the time of the study. Written informed consent conforming to the local ethics committee guidelines was obtained from all subjects.

Psychiatric assessment
In both study samples the presence of psychiatric symptoms at the time of testing was assessed using the extended Brief Psychiatric Rating Scale (BPRS-E: (Lukoff, Nuechterlein, & Ventura, 1986)). This scale assesses a wide range of current psychopathology, including symptoms of depression, mania, psychosis, anxiety and withdrawal in the previous two weeks.
In the schizophrenia spectrum study, patients' current symptoms were quantified using the Positive and Negative Syndrome Scale (PANSS). A five-factor model was used, generating scores on positive, negative, disorganization, excitement and emo-

tional distress symptom dimensions (van der Gaag et al., 2006). In the bipolar study, participants' current depressive and manic symptomatology was assessed using the 21-item Hamilton Rating Scale for Depression (Hamilton, 1967) and the Young Mania Rating Scale (Young, Biggs, Ziegler, & Meyer, 1978), respectively.
Psychosocial functioning in both patient groups was assessed using the Global Assessment of Functioning (APA, 1994). In the original instructions, the GAF rating encompasses functioning as well as symptom ratings, but in the current study the version of the GAF in which functioning can be rated as a separate score was used.

Neurocognitive assessment
In the schizophrenia spectrum study, intellectual functioning was estimated using the four-subtest version (Information, Block design, Digit symbol coding, Arithmetic) of the Dutch version of the Wechsler Adult Intelligence Scale - III (Blyler, Gold, Iannone, & Buchanan, 2000; Wechsler, 2000). Overall intellectual functioning in the bipolar study was estimated using three Groningen Intelligence Test (GIT-2) subtests (Mental rotation, Word analogies, Mental arithmetic) (Luteijn & Barelds, 2004), yielding results that are comparable to those of the Wechsler Adult Intelligence Scale - III.

The following neurocognitive tests were administered in both study samples:
The Dutch version of the Visual Verbal Learning Test (Rey, 1964) was administered as a measure of verbal memory. In three consecutive trials, 15 monosyllabic non-related words had to be memorized and reproduced. The total number of words recalled over the three trials was used as a measure of immediate recall. Delayed recall was measured after a 20-minute delay.
Sustained attention was measured with the CPT-HQ – a version of the continuous performance test that is also known in the literature as CPT-3-7 or CPT-AX and in which the participant should respond to the letter Q only if it was preceded by the letter H. In the CPT-HQ, 300 stimuli (i.e. letters) were presented in a randomized sequence, at a rate of one per second. Each letter was presented for 150 ms, after which an empty screen was presented for 850 ms. The participant responded to a target by pressing the space bar of the PC keyboard. Presentation of an H-Q target pair had a probability of .18 (n=28) among the 150 sequential letter-pairs. In a similar number of sequential letter-pairs, the letter Q was presented following a letter other than H (I, L, J or T). In another 28 pairs, the letter H was presented followed by a letter other than Q (I, L, J or T). For further information, see Smid and colleagues (Smid, De Witte, Homminga, & van den Bosch, 2004) the present CPT-HQ is the non-choice version mentioned in the Discussion). Outcome meas-

ures were expressed as the proportion of correct detections and the reaction time of correct detections (Nestor, Faux, McCarley, Shenton, & Sands, 1990).
The Flanker CPT (Cogtest plc, London) (Eriksen & Schultz, 1979; Posner, Inhoff, Friedrich, & Cohen, 1987) is a measure of selective visual control of attention. Subjects are instructed to respond by pressing the right or left mouse button depending on whether the middle element in a display of five lines has an arrowhead pointing to the right or the left. There are three trial types: i) neutral trials, in which the flankers are horizontal lines without arrowheads, ii) congruent trials, in which all flankers have an arrowhead pointing in the same direction as the target, and iii) incongruent trials, in which the flankers point in the direction opposite that of the target. The incongruent condition involves more cognitive effort, because the flankers are associated with a response that needs to be suppressed. Half of the stimuli are presented above the fixation cross and the other half are presented below it in order to prevent the subjects from keeping their gaze fixed in one position. The test consists of 144 trials of neutral, congruent and incongruent flankers, which are presented randomly. Outcome measures are the mean reaction time for correct responses (RT) and the sum of correct trials in each condition.

Statistical Analyses

Statistical analyses were performed using STATA 10.0 (Statacorp, 2007). For convenience of interpretation of the data, cognitive reaction time variables were recoded so that in the analyses a higher score on all neurocognitive variables indicated a better performance. In both study samples, a dummy variable indicating disorder vulnerability was constructed with value 1 for controls, 2 for relatives and 3 for patients (hereafter: 'group').

1. Neurocognitive functioning of schizophrenia spectrum and bipolar patients and their first-degree relatives

First, to investigate the presence of cognitive dysfunctions in patients and their relatives, multiple regression models with group entered as dummy variable were used to investigate the effect of group status on neurocognitive performance. The non-independence of observations within families was addressed by the use of the 'robust' command in STATA – a procedure that calculates robust estimates of variance that are suitable for clustered data. Analyses were performed separately in the bipolar and schizophrenia study and *a priori* adjusted for age, sex and education by entering these variables into the equation. In bipolar disorder, these analyses were repeated excluding BD patients without strictly defined euthymia (euthymia: HDRS score <8 and YMRS score <8).

Then, in both groups associations between neurocognition and current symptomatology were examined by means of Pearson correlation coefficients. In SZ patients, current symptomatology was measured by the five dimensions obtained in a previous factor analysis on the PANSS (van der Gaag et al., 2006). In BD patients, current depressive and manic/hypomanic symptomatology was measured using total HDRS and YMRS scores, respectively.
To examine the specificity of cognitive impairment across diagnostic category, standardized neurocognitive scores were generated by calculating individual z-scores for each variable using the respective control groups as the reference. This allows for direct comparisons of neurocognitive functioning of groups that differ in demographic and illness characteristics. Again, multiple regression models adjusted for clustering within family were used to investigate the effect of group status on the standardized cognitive test scores, focusing on the relevant contrasts between (i) SZ and BD patients and (ii) SZ and BD relatives.

2. Association between cognition and psychosocial functioning in schizophrenia spectrum and bipolar disorder
In order to investigate associations between neurocognition and psychosocial functioning, multiple regression analyses, a priori adjusted for age, sex and education, were applied. Associations were investigated in SZ and BD patients separately. A single neurocognitive variable was entered as predictor of GAF score; in the case of a significant association, symptomatology measures were additionally entered into the equation to investigate the impact of neurocognition on functioning in addition to current symptoms. In SZ patients, current symptomatology was controlled for using PANSS symptom dimensions (van der Gaag et al., 2006) whereas in the BD sample total HDRS and YMRS scores were entered into the equation.

Analyses were then re-computed excluding those patients who did not have a narrow diagnosis of schizophrenia in the schizophrenia spectrum study (n=79) or bipolar disorder in the bipolar study (n=2), and controls in the schizophrenia spectrum study who were using antidepressants (n=6).

Results

Neurocognitive functioning in SZ
Demographic characteristics, symptom scores and neurocognitive test scores of the sample in the schizophrenia study are presented in table 1.

Table 1. Demographics, symptom scores and neurocognitive test results of the schizophrenia study sample

	Controls (n=260)		SZ relatives (n=331)		SZ patients (n=345)	
	mean	SD	mean	SD	mean	*SD*
Demographics[a]						
Gender M/F	87 / 173		154 / 177		245 / 100	
Age range	16 - 55		16 - 55		16 - 55	
Age (years)	32.0	11.9	29.2	9.5	29.5	9.4
Educational level	5.3	1.8	5.0	2.1	4.3	2.0
IQ	110.3	16.6	104.9	17.0	95.2	16.9
Medication (cases)						
antipsychotics atypical	0		1		236	
antipsychotics typical	0		0		73	
antidepressants	6		9		76	
BPRS	-		-		35.9	13.6
PANSS	-		-			
Positive					13.3	6.8
Negative					12.5	6.2
Disorganization					14.3	6.2
Excitement					10.6	3.9
Emotional distress					14.5	6.3
GAF	-		-		57.4	16.2
Word List Learning						
immediate recall	28.6	5.6	27.1	5.5	23.0	6.6
delayed recall	9.9	2.7	9.4	2.6	7.6	3.0
CPT-HQ						
% correct detections	0.99	0.04	0.98	0.07	0.93	0.12
RT correct detections	411.5	76.5	421.7	78.6	440.8	84.8
Flanker CPT						
correct-neutral	46.0	2.5	45.8	2.7	43.3	5.9
correct-congruent	46.1	2.6	46.0	3.0	43.0	6.4
correct-incongruent	42.7	4.6	42.4	4.9	38.2	7.8
RT-neutral	511.1	63.2	521.7	68.9	553.0	94.0
RT-congruent	513.8	65.0	523.1	71.4	559.3	98.1
RT-incongruent	569.4	62.7	579.8	71.4	611.0	101.2

[a]Between-group differences for demographic characteristics; gender: χ^2=89.73, p=0.00, age: F=6.34, p=0.00, educational level: F=22.69, p=0.00 and IQ: F=62.06, p=0.00.

Multiple regression analyses showed that SZ patient status was associated with a significantly worse neurocognitive performance on all the administered tests compared to controls (table 2).

SZ relatives performed significantly worse than controls on tests of Word List Learning, accuracy and RT of the CPT-HQ and the RT measures on all three conditions of the Flanker CPT. For all tests, the degree of cognitive impairment was related to degree of psychosis vulnerability, with SZ relatives scoring intermediate to patients and controls (table 2).

Table 2. Associations between neurocognitive performance and group status in the schizophrenia study (controls were used as reference category)

	SZ relatives		SZ patients	
	β	p	β	*P*
Word List Learning				
immediate recall	-0.10	0.01	-0.33	0.00
delayed recall	-0.07	0.04	-0.28	0.00
CPT-HQ				
% correct detections	-0.06	0.04	-0.24	0.00
RT correct detections	-0.12	0.00	-0.25	0.00
Flanker CPT				
correct-neutral	-0.01	0.69	-0.26	0.00
correct-congruent	-0.01	0.62	-0.29	0.00
correct-incongruent	-0.02	0.63	-0.29	0.00
RT-neutral	-0.13	0.00	-0.34	0.00
RT-congruent	-0.12	0.00	-0.35	0.00
RT-incongruent	-0.12	0.00	-0.33	0.00

All analyses adjusted for age, sex and education
For all cognitive variables: higher values indicate better performance

Pearson correlation coefficients indicated that correlations between positive symptoms and neurocognitive test scores were between -0.02 and -0.13 and significant only for CPT-HQ RT (r=-0.13, p=0.03) and Flanker CPT congruent condition RT (r=-0.12, p=0.05) performance. For negative symptoms, Pearson coefficients were significant for all tests (r between -0.11 and -0.27, p <0.05). Disorganization symptoms were also significantly correlated with most neurocognitive tests (r between -0.13 and -0.22, p <0.05), with the exception of CPT-HQ RT (r=-0.04, p=0.48). Symptoms of excitement only correlated significantly with CPT-HQ accuracy (r=-0.12, p =0.03, other coefficients between 0.01 and -0.09). Emotional distress symptoms correlated significantly with none of the neurocognitive variables idem (r between -0.00 and -0.08). For all significant associations a higher symptom score was associated with worse cognitive performance.

Neurocognitive functioning in BD

Demographic characteristics, symptom scores and neurocognitive test scores of the bipolar study sample are presented in table 3.

Multiple regression analyses showed that BD patient status was associated with a significantly worse neurocognitive performance on the majority of administered tests (table 4). Patients did not differ significantly from controls on CPT-HQ RT and Flanker RT neutral and incongruent conditions only. However, neurocognitive performance in BD relatives was comparable to that of controls. Effect sizes were in the expected direction but very small, with the exception of the Word List Learning Test, on which relatives performed slightly better than controls.

Table 3. Demographics, symptom scores and neurocognitive test results of the bipolar study sample

	Controls (n=61)		BD relatives (n=37)		BD patients (n=76)	
	mean	SD	mean	SD	mean	SD
Demographics[a]						
Gender M/F	23 / 38		20 / 17		35 / 41	
Age range	25 - 56		18 - 58		27 - 60	
Age (years)	45.3	8.7	40.0	12.1	44.4	7.9
Educational level	5.8	1.7	6.5	1.7	5.6	2.1
IQ	103.4	13.5	107.8	15.7	97.9	14.6
Medications (cases)						
antipsychotics	0		0		23	
anticonvulsants	0		0		43	
lithium	0		0		37	
antidepressants	0		2		14	
BPRS	25.0	1.7	26.8	3.2	33.4	6.4
HDRS	0.23	0.9	0.41	1.0	4.03	4.3
YMRS	0.07	0.3	0.30	0.9	1.61	2.5
GAF	89.7	3.3	84.7	5.5	67.2	10.7
% previous psychotic					50.7 %	
Word List Learning						
immediate recall	25.7	4.9	26.9	6.2	23.2	5.2
delayed recall	8.6	2.5	9.3	2.8	7.2	2.9
CPT-HQ						
% correct detections	0.99	0.02	0.99	0.02	0.95	0.07
RT correct detections	473.1	78.0	487.4	88.0	476.3	86.6
Flanker CPT						
correct-neutral	44.9	4.0	45.8	2.3	43.1	6.2
correct-congruent	45.7	3.3	45.7	2.7	43.3	6.4
correct-incongruent	42.1	5.1	43.2	3.4	38.9	8.9
RT-neutral	647.2	65.1	636.6	65.6	669.1	86.9
RT-congruent	644.2	55.8	640.7	60.8	669.7	85.3
RT-incongruent	706.3	64.6	704.0	75.5	721.7	82.7

[a]Between-group differences for demographic characteristics; gender: χ^2=2.57, p=0.28, age: F=4.09, p=0.02, educational level: F=3.14, p=0.05 and IQ: F=6.23, p=0.00.

To investigate whether cognitive dysfunction is a true trait characteristic in bipolar disorder, *post hoc* analyses were performed excluding BD patients without strictly defined euthymia (euthymia: HDRS score <8 and YMRS score <8). Twelve bipolar patients were excluded and investigation of cognitive dysfunctions in this new sample yielded similar results, the only exception being that for the number of correct responses on the Flanker CPT in the neutral condition, the association slightly reduced and was no longer significant (β=-0.18, p=0.07).

Pearson coefficients for the correlation between HDRS depression score and neurocognitive performance ranged between 0.00 and -0.26 but were significant only for the delayed recall condition of Word List Learning (r= -0.26, p=0.03, other coefficients between 0.00 and -0.23). A higher depression score was associated

with a worse verbal memory performance. Hypomanic symptoms were not significantly correlated with any of the neurocognitive tests (coefficients between 0.14 and -0.20).

Table 4. Associations between neurocognition and group status in the bipolar study (controls were used as reference category)

	BD relatives		BD patients	
	β	P	β	p
Word List Learning				
immediate recall	0.03	0.70	-0.20	0.01
delayed recall	0.07	0.43	-0.23	0.01
CPT-HQ				
% correct detections	-0.02	0.60	-0.37	0.00
RT correct detections	-0.09	0.31	-0.03	0.76
Flanker CPT				
correct-neutral	-0.04	0.53	-0.20	0.03
correct-congruent	-0.10	0.13	-0.26	0.01
correct-incongruent	-0.04	0.43	-0.24	0.01
RT-neutral	-0.03	0.66	-0.16	0.07
RT-congruent	-0.06	0.39	-0.20	0.03
RT-incongruent	-0.05	0.48	-0.12	0.19

All analyses adjusted for age, sex and education
For all cognitive variables: higher values indicate better performance

Comparing cognitive performance in SZ and BD

The mean z-scores for neurocognitive variables in both patient and relative groups and the results of regression analyses are presented in table 5. Multiple regression analyses showed that SZ patients performed significantly worse than BD patients on all administered tests, with the exception of CPT-HQ accuracy. SZ relatives performed significantly worse than BD relatives on both conditions of Word List Learning and Flanker CPT RT neutral condition. Trends towards significance were found for RT in the other Flanker CPT conditions (see table 5).

Associations between cognitive functioning and psychosocial functioning

In SZ patients, neurocognitive test performance on all cognitive tests was significantly associated with GAF score. Associations were consistently in the direction of a better cognitive performance being predictive of a higher GAF score (table 6). After additional adjustment for current symptomatology, associations of immediate and delayed recall conditions of Word List Learning with GAF remained significant (immediate recall: β=0.16, p=0.00; delayed recall: β=0.20, p=0.00). Accuracy on the CPT-HQ was no longer significantly predictive of GAF (β=0.06,

p=0.18), whereas the association with the RT was reduced but still significant (β=0.13, p=0.01). The previously significant associations of Flanker CPT with GAF disappeared (all betas between 0.03 and 0.07, and p values > 0.15).

Table 5. Mean Z-scores of neurocognitive performance in the research groups and schizophrenia-bipolar comparisons

	BD relatives (n=37)		SZ relatives (n=329)		BD relatives vs SZ relatives		BD patients (n=76)		SZ patients (n=345)		BD patients vs SZ patients	
	M	SD	M	SD	β	p	M	SD	M	SD	β	p
Word List Learning												
immediate recall	0.23	1.3	-0.25	1.0	-0.23	0.00	-0.52	1.1	-0.98	1.2	-0.32	0.00
delayed recall	0.28	1.1	-0.19	0.9	-0.28	0.00	-0.57	1.2	-0.85	1.1	-0.18	0.01
CPT-HQ												
% correct	0.06	0.9	-0.23	1.8	-0.06	0.34	-1.59	2.9	-1.34	3.2	-0.04	0.61
RT correct	-0.18	1.1	-0.13	1.0	-0.01	0.94	-0.04	1.1	-0.38	1.1	-0.21	0.01
Flanker CPT												
correct-neutral	0.20	0.6	-0.06	1.1	0.02	0.75	-0.46	1.6	-1.07	2.3	-0.18	0.00
correct-congruent	-0.01	0.8	-0.04	1.2	0.08	0.14	-0.74	1.9	-1.22	2.5	-0.14	0.02
correct-incongruent	0.22	0.7	-0.06	1.1	-0.00	0.94	-0.61	1.7	-0.99	1.7	-0.15	0.02
RT-neutral	0.16	1.0	-0.17	1.1	-0.17	0.02	-0.34	1.3	-0.66	1.5	-0.33	0.00
RT-congruent	0.06	1.1	-0.14	1.1	-0.14	0.08	-0.46	1.5	-0.70	1.5	-0.28	0.00
RT-incongruent	0.04	1.2	-0.17	1.1	-0.14	0.08	-0.24	1.3	-0.66	1.6	-0.33	0.00

All analyses adjusted for age, sex and education
For all cognitive variables: higher values indicate better performance
For BD relatives versus SZ relatives, the former were used as the reference category; for BD patients versus SZ patients, the former were used as the reference category

PANSS negative (betas between -0.23 and -0.29, p values <0.00), disorganization (betas between -0.14 and -0.21, p values <0.02) and emotional distress (betas between -0.16 and -0.18, p values <0.02) symptom scores, were significantly associated with outcome in the above-mentioned models in the direction that higher symptom scores predicted lower GAF scores.

In BD patients, significant associations were found between neurocognitive performance and GAF score for RT in the neutral and congruent conditions of the Flanker CPT (neutral: β=0.27, p=0.03, congruent: β= 0.23, p=0.05), whereas trends towards significance were reported for RT in the incongruent condition (β=0.23, p=0.06) and for CPT-HQ RT (β=0.20, p=0.09). A better cognitive performance was associated with a higher GAF score.

Table 6. Associations between neurocognitive performance and psychosocial functioning measured by GAF in the two patient groups

GAF	SZ patients		BD patients	
	β	p	β	p
Word List Learning				
immediate recall	0.21	0.00	0.10	0.45
delayed recall	0.22	0.00	0.16	0.27
CPT-HQ				
% correct detections	0.19	0.01	0.13	0.23
RT correct detections	0.20	0.00	0.20	0.09
Flanker CPT				
correct-neutral	0.13	0.02	0.05	0.63
correct-congruent	0.12	0.02	0.05	0.71
correct-incongruent	0.14	0.02	0.09	0.47
RT-neutral	0.19	0.00	0.27	0.03
RT-congruent	0.23	0.00	0.23	0.05
RT-incongruent	0.20	0.00	0.23	0.06

All analyses adjusted for age, sex and education
For all associations: higher values indicate better performance

Associations were reduced but did not disappear after additionally entering symptom measures into the equation (CPT-HQ RT: β=0.17, p=0.10; Flanker RT neutral: β=0.27, p=0.03; Flanker RT congruent β=0.20, p=0.07; Flanker RT incongruent β=0.22, p=0.10). Higher HDRS depression ratings were consistently associated with lower GAF scores (betas between -0.42 and -0.46, p values <0.01), whereas YMRS mania/hypomania symptoms were not significantly predictive of GAF score (betas between -0.05 and -0.17, p values >0.12).

Repeating the analyses excluding patients who did not have a narrow diagnosis of schizophrenia or bipolar disorder and controls who were using antidepressants, yielded comparable results for the analyses on neurocognitive performance in both disorders (data not shown). Regarding neurocognition-outcome relationships, in schizophrenia patients the associations between neurocognition and GAF were only significant for tests of verbal memory and RT on the CPT-HQ, mirroring the results obtained in previous analyses after additional adjustment for symptoms. In the bipolar study, associations did not change.

Discussion

Summary of findings

Schizophrenia spectrum patients showed a generalized impairment across the cognitive domains that were studied. Their relatives performed intermediately and significantly different from controls on tasks of verbal memory, sustained attention and reaction time components of selective attention. Bipolar patients similarly

showed impairment in all three domains, although not consistently on all the task parameters. The cognitive performance of their first-degree relatives was comparable to that of controls. Comparison of schizophrenia spectrum and bipolar study samples indicated that patients were impaired in overlapping cognitive domains but that the impairments were more severe in patients with schizophrenia spectrum diagnoses. Relatives of schizophrenia spectrum patients were cognitively more impaired than bipolar relatives on tasks of verbal memory and reaction time components of selective attention

In schizophrenia spectrum patients, performance on most neurocognitive tests was associated with psychosocial functioning, whereas in bipolar patients this was true for reaction time components of selective attention only. For both groups, associations between neurocognition and psychosocial functioning were partly mediated by symptoms. In the schizophrenia spectrum sample, negative, disorganization and emotional distress symptoms were associated with psychosocial functioning to a similar degree as neurocognition, whereas in the bipolar sample depressive symptoms were strongly associated with psychosocial functioning.

Neurocognition as vulnerability marker in SZ and BD

The finding of cognitive deficits in multiple domains in schizophrenia spectrum patients is consistent with many previous studies that showed moderate to large effect sizes of deficits in verbal memory, sustained attention and selective attention (Aleman, Hijman, de Haan, & Kahn, 1999; Bilder et al., 2000; Heinrichs & Zakzanis, 1998), and confirms the idea of cognitive impairment as a core feature of the disorder (Altshuler et al., 2004; Keefe, 1995). The finding that first-degree relatives of schizophrenia spectrum patients performed intermediate to patients and controls on most cognitive tests and differed significantly from controls on tasks of verbal memory, sustained attention and reaction time components of selective attention is in accordance with previous studies (Heydebrand, 2006; Kremen & Hoff, 2004; Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004), and adds further evidence to the suggestion that neurocognitive impairments are putative markers of the genetic vulnerability to schizophrenia (Gur et al., 2007; Snitz, Macdonald, & Carter, 2006).

Bipolar disorder patients differed significantly from controls on most cognitive tests, as previously reported in studies showing cognitive impairment in stable bipolar patients in verbal memory and attentional domains (Balanza-Martinez et al., 2005; Clark, Iversen, & Goodwin, 2002; Martinez-Aran, Vieta, Colom et al., 2004; Quraishi & Frangou, 2002). Although cognitive alterations in verbal memory and attention in relatives of bipolar patients have been found in some studies (An-

tila et al., 2007; Ferrier et al., 2004), in the current study cognitive performance of bipolar relatives was comparable to that of controls. This is in contradiction to the conclusion of a recent literature review (Glahn et al., 2004) that neurocognitive impairments represent candidate intermediary phenotypes for bipolar disorder. However, the more recent systematic review of Balanza-Martinez showed that the evidence in support of neurocognitive deficits in bipolar relatives is sparse (Balanza-Martinez et al., 2008), and a recent quantitative meta-analysis showed that differences between relatives and controls were generally small and significant only for the domain of executive control (Arts et al., 2008).

Comparison of schizophrenia spectrum and bipolar patients indicated that although both groups performed worse than controls in the domains of verbal memory and selective attention, schizophrenia spectrum patients were significantly more impaired than bipolar patients. Patients were equally impaired in the accuracy measure of sustained attention, but differed in their reaction times on this task as only schizophrenia spectrum patients were slower than controls on this task component.
Previous studies comparing neurocognitive functioning in schizophrenia and bipolar disorder have yielded variable results (Altshuler et al., 2004; Dickerson, Sommerville, Origoni, Ringel, & Parente, 2001; Hawkins et al., 1997; Rossi et al., 2000; Tabares-Seisdedos et al., 2003) but the broad conclusion that cognitive impairment in schizophrenia and bipolar disorder are qualitatively similar but quantitatively more marked in schizophrenia (Krabbendam, Arts, van Os, & Aleman, 2005; Schretlen et al., 2007) seems justified.

Relatives of schizophrenia spectrum patients in this study had a poorer cognitive performance than bipolar relatives, and differences reached significance for tests of verbal memory and reaction time components of selective attention. These findings are in line with the results of the few studies that have compared the cognitive performance of schizophrenia and bipolar relatives, namely that in general there is a more severe and generalized pattern of cognitive impairment in schizophrenia relatives (Keri, Kelemen, Benedek, & Janka, 2001; Kremen, Faraone, Seidman, Pepple, & Tsuang, 1998; Pirkola et al., 2005; Zalla et al., 2004).
This study showed that, contrary to widespread assumptions, associations between symptoms and cognition were equally present in both groups. Although the magnitude of the associations was larger in the bipolar sample, it lacked statistical precision possibly due to the smaller sample size in the latter study. Cognitive performance in the schizophrenia spectrum sample was related to both negative and disorganized symptoms but not to positive symptoms, as was shown in previous studies

(Dominguez, Viechtbauer, Simons, van Os, & Krabbendam, 2008; Harvey, Koren, Reichenberg, & Bowie, 2006; O'Leary et al., 2000). In line with previous suggestions (Kravariti, Dixon, Frith, Murray, & McGuire, 2005), our data indicate that cognition shows qualitatively differential relationships with symptom dimensions, whereas differences between diagnostic categories are only quantitative.

Predictors of psychosocial functioning in schizophrenia and bipolar disorder

In schizophrenia spectrum patients, a better cognitive performance was predictive of higher psychosocial functioning as measured by GAF, a finding that is consistent with previous reviews on cognition-outcome associations in schizophrenia (Green, 1996; Green et al., 2004). The predictive value of a better performance in learning and verbal memory, and reaction times of sustained attention, was independent of the severity of current symptoms (Milev et al., 2005; Prouteau et al., 2005; Toulopoulouand & Murray, 2004). However, negative, disorganization and emotional distress symptoms were also significantly associated with psychosocial functioning, and effect sizes for negative symptoms were comparable to those of the cognitive measures. Thus, specific symptom dimensions equal cognition in terms of their relevance in the prediction of functional outcome in schizophrenia (Milev et al., 2005; Norman et al., 1999).

In the bipolar sample, faster reaction time on a selective attention task was significantly associated with better psychosocial functioning. Other neurocognitive variables, however, were unrelated to outcome in this study. Controlling for residual symptoms showed that the associations with attentional reaction time variables remained significant, but that depressive symptomatology was a stronger predictor of psychosocial functioning than neurocognition in the bipolar sample. Only a few studies have investigated cognition-outcome associations in bipolar disorder; some showed positive associations between cognitive functioning on memory and executive functioning tests and GAF score in bipolar patients (Martinez-Aran, Vieta, Colom et al., 2004; Martinez-Aran, Vieta, Reinares et al., 2004; Torrent et al., 2006). On the basis of current and previous findings, it can be concluded that clinical state is a crucial variable in predicting outcome in bipolar disorder. Not only may clinical variables, including subsyndromal depression (Marangell, 2004), be more predictive of psychosocial outcome than cognition (Martinez-Aran et al., 2002), but cognition may also be more strongly related to functional outcome during depression or mania/hypomania than in the euthymic state (Malhi et al., 2007).

Cognition-outcome associations seem stronger in schizophrenia than in bipolar disorder (Laes & Sponheim, 2006; Martinez-Aran et al., 2002), and are possibly restricted to more selective cognitive deficits in bipolar disorder (Jaeger & Vieta,

2007). In contrast, residual symptomatology appears to make a larger contribution to functioning in bipolar disorder than in schizophrenia.

Explaining similarities and differences

In sum, although the presence of multiple cognitive deficits is shared by the two groups, schizophrenia spectrum disorders are associated with more severe and more generalized deficits, which seems to reflect the genetic vulnerability as well as the impact on daily life to a greater extent than in bipolar disorder.

The current findings support a model that explains similarities and differences between schizophrenia and bipolar disorder by suggesting that the disorders have partly shared susceptibility genes predisposing to psychosis in general but are differentiated by the presence of a neurodevelopmental impairment in the former but not in the latter (Murray et al., 2004). According to this model, the neurocognitive dysfunctions in schizophrenia and bipolar disorder have partly different origins. It is hypothesized that in schizophrenia dysfunctions are a consequence of problems in early brain development, whereas in bipolar disorder dysfunctions are more likely to be a consequence of the disease process itself. The presence of premorbid cognitive impairments in pre-schizophrenia children but not in pre-bipolar subjects (Cannon et al., 2002), findings of lower premorbid IQ estimation in schizophrenia as compared to bipolar disorder (Gilvarry et al., 2000), and other developmental delays as well as pregnancy and birth complications in schizophrenia (Verdoux et al., 1997) but not in bipolar disorder (Scott, McNeill, Cavanagh, Cannon, & Murray, 2006), are in line with this suggestion. The finding that in bipolar disorder cognitive deficits are associated with severity and progression of the illness (Robinson & Ferrier, 2006), and studies showing that the presence of cognitive alterations is more marked in schizophrenia relatives than in bipolar relatives, add further credence to this idea. A recent review on the causes of neurocognitive dysfunction in bipolar disorder suggested that the evidence was more in favour of a neurodegenerative model rather than a neurodevelopmental one (Goodwin, Martinez-Aran, Glahn, & Vieta, 2008).

On the other hand, the qualitatively similar pattern of neurocognitive dysfunctions in both disorders may also suggest partial aetiological overlap. Previous studies have shown a large degree of cognitive heterogeneity within the group of bipolar patients. There appears to be a subgroup of bipolar patients who are cognitively more severely impaired, even to a similar degree as in schizophrenia patients, and whose relatives also show significant cognitive alterations (Balanza-Martinez et al., 2005; Sobczak, Honig, Schmitt, & Riedel, 2003). In the context of a continuum model spanning affective and non-affective psychosis, it can be suggested that this subgroup of bipolar subjects may be more towards the non-affective, neurodevel-

opmental side of the continuum, and that for this subset of bipolar patients cognitive impairments may reflect a genetic vulnerability that is also observable in their first-degree relatives.

It is currently being argued that cognitive impairment should be included in the diagnostic criteria for schizophrenia (e.g.(Keefe, 2008)). Given the importance of neurocognition in terms of biology, function and treatment of severe mental illnesses, it can be suggested that any dimensional representation of psychopathology should include variation in neurocognitive functioning in addition to other symptom dimensions. The present findings show that there is quantitative rather than qualitative variation in neurocognitive functioning across diagnostic boundaries, providing no specificity in diagnostic terms. However, current and previous findings suggest that there are valid developmental neurocognitive contrasts between schizophrenia and bipolar disorder that should be used for DSM-V / ICD11 (van Os, 2008). Future studies should focus on methods of proper assessment of developmental cognitive deficits.

Methodological considerations

The current results should be interpreted in the context of several methodological issues.

First, the cognitive assessment was limited and the broad domain of executive functioning could not be completely covered by the test battery. However, the study focused on domains that have been robustly associated with schizophrenia and bipolar disorder. Second, the sample sizes in the two studies were not balanced, which may have caused effect sizes in the larger sample of schizophrenia patients to be more statistically precise than in the sample of bipolar patients. Third, it cannot be excluded that the study had a bias towards inclusion of subjects who were functioning relatively well, yielding samples that are not representative of the entire population. Fourth, most patients were medicated, which may have confounded the results. However, studies investigating adverse cognitive side effects of psychotropic medication show that if negative effects are present, effect sizes are small (Goldberg, 2008), and some atypical antipsychotic drugs even seem to improve cognitive functioning (Keefe, Silva, Perkins, & Lieberman, 1999). Finally, psychosocial functioning in this study was assessed by a global measure of psychosocial function (the GAF score), which may have caused results to be different from studies in which more explicit outcome measures were used.

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CHAPTER 4

INVESTIGATING THE ASSOCIATION BETWEEN NEUROCOGNITION AND PSYCHOSIS IN BIPOLAR DISORDER: FURTHER EVIDENCE FOR THE OVERLAP WITH SCHIZOPHRENIA

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Abstract

Objective: In schizophrenia a distinction is made between psychosis with developmental impairment and cognitive impairment on the one hand and psychosis without developmental impairment and positive symptoms on the other. In this study it was investigated whether this model can be extended to bipolar disorder by testing the hypothesis that neurocognitive functioning is inversely related to positive psychotic symptoms in bipolar disorder. **Method:** Neurocognitive functioning and psychopathology were assessed in i) 76 patients with bipolar disorder, ii) 39 of their healthy first-degree relatives, and iii) 61 healthy controls. Cognitive performance of bipolar patients and that of their first-degree relatives was investigated taking into account the possible moderating effect of the level of expression of psychosis in patients and relatives. **Results:** Bipolar patients showed impaired cognitive performance on multiple cognitive domains, whereas performance of their relatives was comparable to that of controls. A history of psychotic symptoms in patients was suggestive of less likelihood of cognitive alterations in relatives, and the presence of subclinical psychotic symptoms within the group of relatives predicted better cognitive performance. **Conclusions:** The finding of similar psychosis-cognition associations in bipolar disorder as implied by the two pathways leading to non-affective psychotic disorders, suggests that this model might be extended to the continuum spanning affective and non-affective psychosis. This is in line with the idea of a partially overlapping vulnerability to bipolar disorder and schizophrenia and provides an explanation for the apparent differences in cognitive alterations in those at risk for the two disorders.

Key words: bipolar disorder; schizophrenia; psychosis; neurocognition; vulnerability markers

Introduction

In the search for causal mechanisms of affective and non-affective psychosis, a productive focus may be the study of underlying markers of vulnerability. Intermediary phenotypes associated with genetic risk may be closer to underlying mechanisms than illness symptoms that are the consequence of complex and varying gene-environment interactions (Kendler, 2001).

Genetic and epidemiological studies suggest that there is substantial overlap in genetic risk for bipolar and non-affective psychotic disorders (Berrettini, 2003; Cardno, Rijsdijk, Sham, Murray, & McGuffin, 2002; Potash, 2006) and cognitive impairment is one of the most frequently investigated intermediary phenotypes. The presence of neurocognitive dysfunctions in patients with bipolar disorder is well established. Although deficits are generally worse during periods of affective disturbance, two recent meta-analyses (Arts, Jabben, Krabbendam, & Van Os, 2008; Robinson et al., 2006) provide evidence for trait-like cognitive dysfunctions in euthymic bipolar patients, in particular in the domains of executive functioning and declarative memory. If neurocognitive deficits truly represent markers of genetic risk for bipolar disorder (Glahn, Bearden, Niendam, & Escamilla, 2004), cognitive alterations should be detectable in subjects with a genetic vulnerability to bipolar disorder, such as first-degree relatives of patients. In a recent systematic review and meta-analysis of 14 studies of relatives of bipolar patients, Arts and colleagues (Arts et al., 2008) concluded that individuals at risk differed on some cognitive measures from controls, but that effect sizes were rather small and present only for the domains of executive control and immediate verbal memory. The evidence for cognitive alterations as intermediary phenotype associated with genetic risk is much stronger for non-affective psychotic disorders such as schizophrenia. Not only are cognitive deficits in bipolar disorder less severe than those found in schizophrenia (Krabbendam, Arts, van Os, & Aleman, 2005), relatives of patients with bipolar disorder appear to have, if present at all, milder cognitive alterations (Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004) compared to relatives of schizophrenia. These findings are in line with studies showing that in children destined to develop schizophrenia or bipolar disorder, developmental cognitive impairment is present in the former but not the latter group (Cannon et al., 1997; Reichenberg et al., 2002).

Any theory explaining the apparent genetic overlap between bipolar disorder and schizophrenia should be able to explain these rather different cognitive profiles in individuals at genetic and developmental risk for the two disorders. Thus, one way to explain the weaker presence of cognitive impairments in relatives of patients with bipolar disorder is to assume that most of the cognitive impairments seen in patients is related to the ongoing illness process and its treatment, but that some is

also due to genetic effects that are shared to a small degree with schizophrenia and measurable in the relatives of patients. In an attempt to explain the similarities and dissimilarities between bipolar disorder and schizophrenia, Murray and colleagues (Murray et al., 2004) suggested that bipolar disorder and schizophrenia share some susceptibility genes that can cause a predisposition to psychosis in general. When, in addition to this predisposition, neurodevelopmental impairment is present, a schizophrenia-like phenotype will emerge. The neurodevelopmental impairment predisposition will contribute to the expression of negative and deficit symptoms and, in association with these symptom domains (Dominguez, Viechtbauer, Simons, van Os, & Krabbendam, 2008) to the cognitive deficits characteristic of schizophrenia. In the absence of these neurodevelopmental impairments, however, a more affective psychotic phenotype like bipolar disorder will emerge. The hypothesised distinction between good outcome psychotic disorder without developmental impairment (characterised by positive and affective symptoms) and poor outcome psychotic disorder with developmental impairment (with negative and cognitive symptoms) in fact goes back to the seminal publication by Robins and Guze (Robins & Guze, 1970) that hypothesised, albeit within the more narrow domain of schizophrenia alone, two broad dimensions separated along similar lines. The extension of this model to the continuum spanning affective and non-affective psychosis, results in testable hypotheses regarding the cognitive profile of relatives of patients with bipolar disorder. Thus, if the distinction between psychosis with developmental impairment and cognitive impairment on the one hand and psychosis without developmental impairment and positive symptoms on the other is also valid in bipolar disorder, than bipolar patient-relative dyads with more expression of cognitive impairment should have less expression of positive psychotic symptoms.

To this end, three hypotheses were investigated: (i) the presence of a history of positive psychotic symptoms in patients with bipolar disorder will be associated with less likelihood of altered cognitive functioning in the proband relative, and, similarly, (ii) within the group of relatives of bipolar patients, presence of subclinical positive psychotic symptoms will be associated with less likelihood of cognitive alterations. Further, if cognitive impairment in patients with bipolar disorder is mainly illness-related while in relatives, if present at all, it may be the genetic expression of developmental impairment that is weakly shared with schizophrenia, iii) neurocognition in patients and relatives should be at best weakly correlated.
These hypotheses were investigated by comparing cognitive performance of bipolar patients and that of their first-degree relatives with that of a group of healthy

controls, taking into account the possible moderating effect of the level of expression of positive psychotic symptoms in patients and relatives.

Methods

Subjects

The individuals in this study were participants in the BIPOLCOG study, a study on cognitive functioning in bipolar disorder (BD) in which three groups were investigated i) patients with bipolar disorder, ii) healthy first-degree relatives of patients with bipolar disorder, and iii) healthy control participants. All subjects were between the ages of 18 and 60 years, fluent in Dutch, had an IQ>70 and were without a history of neurological disorders such as epilepsy and concussion with loss of consciousness.

Patients were recruited through in-patient and out-patient mental health service facilities in South-Limburg, the Netherlands and through the local association of bipolar patients and their families. Initial inclusion criteria for patients were the lifetime prevalence of bipolar disorder according to the RDC (Research Diagnostic Criteria) (Spitzer, Endicott, & Robins, 1978). The computer program OPCRIT was used to derive and confirm diagnoses on the basis of current and lifetime recorded symptomatology listed in the Operational Criteria Checklist for Psychotic Illness (OCCPI) (Mc Guffin, Farmer, & Harvey, 1991).

First-degree relatives, free from a lifetime history of BD or psychosis, were sampled through participating patients and had at least one first-degree relative with a diagnosis of BD. Control subjects were recruited from the general population through a random mailing. First-degree relatives and controls were clinically and diagnostically interviewed with The Comprehensive Assessment of Symptoms and History (CASH: (Andreasen, Flaum, & Arndt, 1992)) and OPCRIT criteria to exclude those presenting a diagnosis of BD or psychotic disorder. Healthy controls were additionally interviewed with the FIGS (Maxwell, 1992) in order to confirm the absence of family histories of psychotic or bipolar disorders.

The initial sample consisted of 81 patients, 39 first-degree relatives and 61 healthy control subjects. Three patients were excluded because data on diagnosis were missing. Data on neuropsychological performance were missing for two patients. As a consequence, the risk set for the current study consisted of 76 patients with BD, 39 relatives and 61 controls.

There were 45 patients with an RDC diagnosis of bipolar I disorder, 17 patients with an RDC diagnosis of schizoaffective disorder bipolar or manic type, 13 patients with an RDC diagnosis of bipolar II disorder and one patient with an RDC diagnosis of mania. In the group of relatives, 8 had an RDC diagnosis of major

depression in the past and one of hypomania. The other relatives were free from a history of psychiatric disorder. Three controls had a history of major depression.
Forty-five patients were included without a participating first-degree relative. The remaining patients and relatives originated from 26 families, of which 16 families contributed one patient and one relative, six families contributed one patient and at least two relatives, two families contributed two patients, one family contributed two patients and five relatives and one family contributed two relatives. The 39 participating relatives were 31 siblings, 5 sons and 3 daughters.

Procedure

Participants were examined during two sessions with an interval of approximately two months. The double session served to enhance statistical power. During both sessions, neuropsychological testing and psychiatric interviewing took place and questionnaires were filled out. In the first session, basic demographic information was collected from all subjects, and in the BD group information on illness characteristics was obtained. Written informed consent, conforming to the local ethics committee guidelines, was obtained from all subjects. Neuropsychological tests and psychiatric interviews were conducted by trained psychologists, and each session took approximately two hours to complete.

Psychopathology

In each session, current depressive and manic psychopathology of all subjects was assessed using the 21-item Hamilton Rating Scale for Depression (Hamilton, 1960) and the Young Mania Rating Scale (Young, Biggs, Ziegler, & Meyer, 1978) respectively. To further asses the presence of psychiatric symptoms at the time of testing, the extended Brief Psychiatric Rating Scale (BPRS-E: (Lukoff, Nuechterlein, & Ventura, 1986)) was administered. This scale assesses a wider range of current psychopathology, including symptoms of depression, mania, psychosis, anxiety, and withdrawal in the past two weeks.
The Community Assessment of Psychic Experiences (CAPE), a 42-item self-report instrument, was used to assess dimensions of the subclinical psychosis and depressive phenotype. In this questionnaire, 20 items measure positive psychotic experiences, 14 items rate negative experiences and 8 cognitive depressive experiences. The frequency of the experience was rated on a four-point scale of "never", "sometimes", "often" and "nearly always". For a detailed description of the CAPE, see http://www.cape42.homestead.com (M. Hanssen, Krabbendam, Vollema, Delespaul, & Van Os, 2006; Stefanis et al., 2002; Verdoux & van Os, 2002). The scale has been validated against clinical interview measures of schizotypy and psychosis-proneness (Konings, Bak, Hanssen, van Os, & Krabbendam, 2006) and

discriminatory validity was shown contrasting different patient groups (M. S. Hanssen, Bijl, Vollebergh, & van Os, 2003). OPCRIT criteria were used to derive the presence of a history of positive psychotic symptoms in patients on the basis of current and lifetime recorded symptomatology listed in the OCCPI (Mc Guffin et al., 1991). Information was obtained from patients' reports and medical files.

Neurocognitive assessment

Neurocognitive tests were administered by computer, using E-prime for Windows on a 15-inch monitor Toshiba Tecra laptop. The neurocognitive test battery included tasks measuring various neurocognitive domains, guided by previous evidence of impaired performance among these domains in BD patients and their relatives (Antila et al., 2007; Arts et al., 2007; Ferrier & Thompson, 2002; Murphy & Sahakian, 2001; Robinson et al., 2006).

Overall intellectual functioning was estimated using three Groningen Intelligence Test (GIT) subtests (Mental Rotation, Word Analogies and Mental Arithmetic) (Luteijn & van der Ploeg, 1983), yielding results that are comparable to those of the Wechsler Adult Intelligence Scale (Wechsler, 1981). Verbal learning and memory was assessed with the standardized Dutch version of the Visual Verbal Learning Test (Rey, 1964). In three consecutive trials, 15 monosyllabic non-related words had to be memorized and reproduced. The total number of words recalled over the three trials was used as a measure of immediate recall. Delayed recall and recognition memory were measured after a 20 minute delay.

Digit Span Forward and Digit Span Backward of the Wechsler intelligence Scale III (Wechsler, 2000) were used as measures of attention - working memory, respectively. Sustained attention was measured with a continuous performance test, the CPT-HQ version, a variant of the CPT-AX. Subjects were instructed to respond as quickly as possible by pressing the spacebar whenever target stimulus 'Q' was preceded by an 'H' on the screen. Outcome measures were expressed as the proportion correct detections, the reaction time of correct detections, and the proportion false alarms (Nestor, Faux, McCarley, Shenton, & Sands, 1990).

The Tapping Speed test (Cogtest plc, London) is a finger tapping test alternating between the right and left hand, that was used as a simple measure of motor speed and manual dexterity. The Cogtest version is similar to the Finger Tapping Test or the Finger Oscillation Test of the Halstead Reitan Neuropsychological Battery (Reitan & Wolfson, 1985). Subjects were asked to tap a key on the keyboard with their index finger as fast as they could for 8 seconds in five trials for each hand. Outcome measures were the total number of taps with the index finger of each hand and the latency to each and every response, thereby generating an index of the variance in tapping speed.

The Flanker CPT (Cogtest plc, London) (Eriksen & Schultz, 1979; Posner, Inhoff, Friedrich, & Cohen, 1987) is a measure of selective visual control of attention. Subjects are instructed to respond by pressing the right or left mouse button depending on whether the middle element in a display of five lines has an arrowhead pointing to the right or left. There are three trial types: i) neutral trials in which the flankers are just horizontal lines without arrowheads, ii) congruent trials in which all flankers have an arrowhead pointing in the same direction as the target, and iii) incongruent trials, in which flankers are pointing in opposite direction from the target. The test consists of 144 trials of neutral, congruent and incongruent flankers, which are presented randomly. Outcome measures were the mean reaction time for correct responses (RT) and the sum of correct trials in each condition.
The Strategic Target Detection Task (STDT: Cogtest plc, London) (Weintraub & Mesulam, 1987) is a task similar to the paper and pen 'cancellation'-tests or the 'cross-out' subtest of the WAIS III, where subjects are required to cross-out target stimuli embedded among distracters. In this computerized version, subjects are not told in advance which of the various stimuli is the target but have to learn by given feedback and thereby modifying their future responses. This is an aspect of the SDTD similar to the Wisconsin Card Sorting Test. Performance was scored by the mean reaction time for correct responses and the total number of correct and incorrect responses and perseverative errors
In the Set Shifting Test (SST: Cogtest plc, London) (Bilder, Turkel, Lipschutz-Broch, & Lieberman, 1992), subjects are asked to respond as fast as possible to the direction in which a square appears on the computer screen by pressing the corresponding key on the keyboard. In the first phase, the square appears randomly on either the left or the right side of the screen, in order to establish baseline reaction time. Subsequently, the participant learns the first 'response set', which is a simple right-right-left sequence. After some experience with this rule, reaction time usually decreases from the baseline reaction time as subjects learn to anticipate the next stimulus in the sequence. This provides a measure of set acquisition, or implicit learning. Then, without prior warning, the response set is reversed (to left-left-right). This shift in response set is usually associated with an increase in reaction time, slower than the baseline reaction time. This is called the set shifting effect. The subject goes through 3 reversals altogether to obtain reliable measures. Outcome measures are reaction times and errors in the imitation and reversal conditions.

Statistical Analyses

Before analyses, cognitive variables were inspected for outliers. Since observations in which a mechanical failure took place were already registered as missing, it was

decided to replace values with deviation more than three standard deviations from the mean with the closest value within the same group (Tabachnick & Fidell, 1996). Statistical analyses were performed using STATA 10.0 (Statacorp, 2007).

In order to reduce the number of dependent neuropsychological variables in the analyses (Krabbendam, Marcelis, Delespaul, Jolles, & van Os, 2001) a principal component analysis (PCA) followed by varimax rotation was performed on the neuropsychological variables and interpreted on the basis of scree plot and eigenvalues. Based on the component loadings, a summary measure for each component was calculated, composed of the relative loading of each variable that loaded on this particular component. These scores were transformed to z-scores which were subsequently used as neurocognitive variables in the regression analyses.

A dummy variable indicating bipolar vulnerability was constructed with value 1 for controls, value 2 for first-degree relatives and value 3 for patients, reflecting increasing risk for BD (hereafter: group).

Observations of subjects were clustered at the level of session and at the level of family. In order to take these different levels of clustering into account, the main effect of group on cognition was assessed with multilevel random regression analyses, controlling for session and including a family random effect in the model, using the XTREG routine in STATA, with cognitive test values as dependent variables and bipolar liability as the independent variable. Analyses were repeated entering residual depressive and manic symptom scores in the equation, examining the mediating effect of residual affective symptoms. All analyses were *a priori* adjusted for the possible confounding effects of age and sex by entering these variables into the equation.

In order to investigate the first hypothesis, pairwise comparisons of all available patient-relative pairs within the same family were used to examine, using multilevel regression analyses, the relationship between a history of psychosis in the patients and neurocognition in the relatives. A history of psychosis was coded as a dichotomous ('yes' or 'no') variable defined by the life time presence of at least one positive psychotic symptom in OPCRIT (Mc Guffin et al., 1991).

Subsequently, to investigate the second hypothesis, multilevel random regression analyses with Group X CAPE trait psychosis interactions were fitted to examine a possible moderating effect of subclinical positive psychotic symptoms on neurocognitive performance within the group of relatives. Analyses were additionally adjusted for the possible confounding effect of education. For significant interactions, the STATA LINCOM routine was used to calculate stratified effect sizes according to the appropriate linear combinations. Stratified effect sizes were calculated for CAPE trait psychosis scores of one and two standard deviations below and above average in relatives compared to controls.

The third hypothesis was investigated, similar to the first hypothesis, by examining pairwise associations between patients' and relatives' neurocognitive functioning.

Results

Demographic characteristics, psychiatric measures and neuropsychological test scores are presented in table 1. Five controls, one relative and six patients did not participate during the second session, as a result of which neurocognitive data on the second session were missing for these subjects.

Principal Component Analyses

Based on scree plot and eigenvalues of components after PCA, eight components were retained accounting for 70% of the variance. Components and component loadings are presented in table 2. The first component was interpreted to represent *fine motor speed*, the second *set shifting – reaction time*, the third *attention - accuracy*, the fourth *attention - reaction time*, the fifth *verbal memory*, the sixth *set shifting - accuracy*, the seventh *mental flexibility*, and the eighth *attention - working memory*.

Group differences

Being a patient predicted neurocognitive performance on all but two cognitive factors (table 3). First-degree relatives, however, only differed significantly from controls on *set shifting - accuracy* and *set shifting - reaction time*, though in opposite directions, as for accuracy relative status predicted a better performance whereas for reaction time being a relative was related to worse performance.

After adjustment for residual mood symptoms, the effect size for the association between patient status and *fine motor speed* reduced significantly. A slight reduction in effect size was found for the association between patient status and cognitive performance in the domains of *verbal memory* and *attention - working memory*. In other cognitive domains, effect sizes did not change after adjustment for residual mood symptoms (table 3).

Table I. Demographics, clinical characteristics and results of neurocognitive assessment

	Control subjects (n=61)		First-degree relatives (n=39)		BD patients (n=76)	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Gender M / F	23 / 38		20 / 19		37 / 39	
Age range	25 - 56		18 - 58		27 - 60	
Age (years)	45.3	8.7	40.7	12.2	44.7	7.9
Educational level	5.8	1.7	6.3	2.0	5.5	2.2
GIT IQ	119.5	9.6	117.6	14.0	113.2	11.7
BPRS total score (24 - 57)	25.2	2.3	27.4	4.3	33.1	6.3
HDRS total score (0 - 25)	0.34	1.44	1.03	2.32	4.05	4.45
YMRS total score (0 - 9)	0.06	0.30	0.32	0.87	1.37	2.17
CAPE psychosis	0.18	0.19	0.23	0.16	0.35	0.25
Clinical characteristics:						
age at onset					27.4	8.9
duration of illness					6.1	5.1
total number of episodes					8.4	6.2
number of hospitalizations					1.6	2.2
% previous psychotic					50,7%	
Verbal learning and memory						
Word List Learning						
total immediate recall	26.0	5.5	26.7	6.5	22.6	6.9
delayed recall	8.5	2.6	9.2	3.3	6.8	3.1
recognition	13.9	1.1	13.9	1.3	13.0	2.2
Attention and concentration						
Digit Span forward	9.0	1.7	9.2	2.0	8.5	1.8
Digit Span backward	6.9	2.0	7.6	2.5	5.9	1.9
Flanker correct-neutral	45.7	3.0	46.3	1.9	43.9	5.3
Flanker correct-congruent	46.4	2.1	46.4	1.7	44.0	5.6
Flanker correct-incongruent	43.2	4.1	44.1	3.2	39.9	8.0
Flanker RT-neutral	634.2	53.0	623.4	58.5	679.6	86.5
Flanker RT-congruent	632.6	49.2	629.3	60.7	679.6	84.7
Flanker RT-incongruent	691.5	53.4	688.0	68.6	730.1	81.6
CPT-HQ RT correct detections	471.9	76.7	489.8	93.4	479.2	94.1
CPT-HQ % correct detections	98.9	2.5	97.1	9.0	95.4	6.7
Executive functioning						
STDT number correct	85.0	6.6	85.3	7.0	83.6	5.7
STDT number incorrect	24.3	11.0	22.1	6.4	24.8	10.3
STDT perseverative errors	4.1	3.3	4.7	2.5	4.6	2.9
STDT RT correct	701.9	199.2	656.0	225.8	732.9	256.7
SST basal RT	362.5	40.1	376.9	55.1	417.5	85.0
SST start imitation RT	378.9	47.9	406.0	57.1	429.8	65.8
SST end imitation RT	344.4	61.6	349.6	72.7	386.5	81.4
SST start reversal RT	385.1	48.9	419.1	50.3	442.6	72.8
SST end reversal RT	340.4	56.6	348.3	72.9	382.7	93.2
SST imitation errors	0.82	1.1	0.83	0.94	1.4	1.5
SST reversal errors	0.93	1.1	0.98	1.2	1.6	1.9
Fine motor speed						
Finger tap rate right	180.2	22.6	178.1	22.2	184.4	26.1
Finger tap rate left	192.7	23.7	190.9	27.9	204.1	29.5
Finger tap total hits right	279.4	35.3	282.0	32.9	272.5	39.5
Finger tap total hits left	260.3	31.1	264.3	36.5	246.2	34.5

All neurocognitive tests and psychiatric interviews were administered during both sessions, with the exception of STDT, SST and the CAPE, that were administered only in the second session.
CPT, Continuous Performance Test; STDT, Strategic Target Detection Test; SST, Set Shifting Test.

Table 2. Component composition and loadings after PCA with varimax rotation

Component:	1	2	3	4	5	6	7	8
WLT immed. recall	-0.0184	0.0435	-0.0378	-0.0116	0.5718	0.0560	0.0066	0.0909
WLT delayed recall	-0.0200	0.0246	-0.0338	-0.0434	0.6165	0.0463	-0.0225	-0.0470
WLT recog	0.0057	-0.1346	0.2839	0.0300	0.3886	-0.1480	0.0889	-0.2527
CPT HQ - % corr	0.0803	-0.0501	0.3037	0.0726	0.0621	-0.1324	0.0685	0.1004
CPT HQ - RT	0.0459	0.0027	-0.0596	0.1334	0.1197	-0.3263	-0.0328	0.1704
Flanker count neu	-0.0215	0.0286	0.4869	-0.0072	-0.0620	0.0373	-0.0122	0.0765
Flanker count con	0.0266	-0.0164	0.4969	0.0372	-0.0097	0.0317	-0.0034	0.0236
Flanker count inc	0.0215	-0.0125	0.4879	-0.0266	-0.0144	0.0839	-0.0367	0.0274
Flanker RT neu	-0.0176	0.0011	0.0433	0.5437	-0.0145	0.0269	0.0016	-0.0251
Flanker RT con	0.0014	-0.0074	0.0181	0.5399	0.0016	0.0245	0.0080	-0.0467
Flanker RT inc	-0.0429	-0.0210	-0.0355	0.5552	-0.0525	-0.0162	-0.0185	0.0335
STDT corr	0.1009	-0.0588	-0.0690	0.0361	0.1302	-0.0884	-0.4218	0.2241
STDT incor	0.0232	-0.0238	-0.0891	0.0558	0.0207	0.0041	0.6260	0.0635
STDT persv err	0.0010	0.0360	0.0613	-0.0553	0.0227	-0.0358	0.6049	0.0579
STDT RT corr	-0.1293	0.2185	0.1986	-0.0341	0.0746	-0.0494	-0.1448	-0.0617
SST basal RT	0.0505	0.3195	0.0491	0.1275	-0.0848	0.0454	-0.0606	-0.0207
SST start im RT	0.0238	0.4982	-0.0586	0.0151	-0.0049	0.1370	0.0304	-0.0197
SST end im RT	-0.0180	0.4911	-0.0163	-0.0170	0.0126	-0.0465	0.0252	-0.0018
SST start rev RT	0.1005	0.3511	-0.0008	0.0127	0.0916	-0.0481	-0.0314	0.0204
SST end rev RT	-0.0429	0.4280	0.0424	-0.0194	0.0498	-0.1443	0.0505	0.0255
SST im errors	0.0186	0.0050	0.0341	0.0327	0.0457	0.6016	0.0571	-0.0222
SST rev errors	-0.0060	-0.0091	0.0109	0.0102	0.0311	0.6251	-0.0557	0.0517
TST tap rate right	0.4888	-0.0459	-0.0225	-0.0073	0.0529	0.0423	-0.0267	0.0176
TST tap rate left	0.4553	0.0733	0.0500	-0.0399	-0.0910	-0.0408	0.0182	-0.0743
TST hits right	0.4768	-0.0473	0.0007	-0.0027	0.0359	0.0279	-0.0197	0.0419
TST hits left	0.4662	0.0665	0.0356	-0.0508	-0.1031	-0.0302	0.0162	-0.0584
DS forward	-0.0547	-0.0380	0.0977	-0.0162	-0.0895	-0.0735	0.0492	0.6747
DS backward	0.0481	0.0483	-0.0648	-0.0049	0.1183	0.1294	0.0128	0.5855

Eight components accounting for 70% of variance. Groupings for the different components are shaded.

Pairwise comparisons

Forty-two pairs of patient and sib within the same family were used to investigate pairwise associations. The presence of a history of positive psychotic symptoms in patients accounted for a significant proportion of the variance in neurocognitive functioning in the corresponding relatives in the domain of *fine motor speed* (ß=0.94, p=0.00). For *set shifting - reaction time* (ß=0.48, p=0.11), *attention - accuracy* (ß=0.21, p=0.12), *verbal memory* (ß=0.56, p=0.15) and *attention - working memory* (ß=0.74, p=0.10) the findings were suggestive of an association. Associations were consistently in the direction that relatives of patients with a history of positive psychotic symptoms showed a better cognitive performance. The presence of a history of psychotic symptoms in patients did not predict neurocognitive functioning in corresponding relatives in domains of *attention - reaction time* (ß=0.22, p=0.51), *set shifting - accuracy* (ß=-0.28, p=0.55), and *mental flexibility* (ß=-0.08, p=0.81).

Examination of pairwise associations between patients' and relatives' neurocognitive functioning showed that cognitive performance in patients did not account for variance in cognitive performance in corresponding relatives (all Beta's between 0.13 and 0.11, p>0.21).

Table 3. Association between neurocognitive functioning and the group variable reflecting risk for bipolar disorder (controls were used as reference category)

Outcome measure*	Group			+ Adjustment for HDRS and YMRS	
Fine motor speed					
	Relatives (1)	ß#= 0.12	p= 0.55	ß= 0.20	p= 0.32
	BD patients (2)	ß= -0.45	p= 0.01	ß= -0.13	p= 0.49
Set shifting - RT					
	Relatives (1)	ß= -0.49	p= 0.01	ß= -0.49	p= 0.01
	BD patients (2)	ß= -0.74	p= 0.00	ß= -0.73	p= 0.00
Attention - accuracy					
	Relatives (1)	ß= -0.05	p= 0.79	ß= -0.05	p= 0.75
	BD patients (2)	ß= -0.56	p= 0.00	ß= -0.46	p= 0.00
Attention - RT					
	Relatives (1)	ß= -0.32	p= 0.10	ß= -0.30	p= 0.13
	BD patients (2)	ß= -0.75	p= 0.00	ß= -0.72	p= 0.00
Verbal memory					
	Relatives (1)	ß= 0.16	p= 0.38	ß= 0.19	p= 0.29
	BD patients (2)	ß= -0.65	p= 0.00	ß= -0.53	p= 0.00
Set shifting - accuracy					
	Relatives (1)	ß= 0.44	p= 0.05	ß= 0.42	p= 0.06
	BD patients (2)	ß= -0.03	p= 0.88	ß= -0.13	p= 0.57
Mental flexibility					
	Relatives (1)	ß= -0.04	p= 0.86	ß= -0.06	p= 0.79
	BD patients (2)	ß= 0.02	p= 0.92	ß= 0.06	p= 0.80
Attentional span and working memory					
	Relatives (1)	ß= 0.15	p= 0.44	ß= -0.15	p= 0.44
	BD patients (2)	ß= -0.63	p= 0.00	ß= -0.54	p= 0.00

All analyses a priori adjusted for age, sex and session
*For all outcome measures: higher values indicate better performance
ß = All Betas are standardised regression coeffients indicating the change in outcome associated with the risk for bipolar disorder
HDRS, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale

Does subclinical psychosis affect relative-control differences?

There were significant two-way Group X CAPE trait interactions in the neurocognitive domains of *fine motor speed* (ß=0.44, p=0.05, 95% confidence interval (CI): 0.01, 0.87), *set shifting - reaction time* (ß=0.53, p=0.00, 95% CI: 0.23, 0.84), *attention - reaction time* (ß=0.39, p=0.04, 95% CI: 0.01, 0.76), and *verbal memory* (ß=0.46, p= 0.02, 95% CI: 0.08, 0.83), indicating that the association between group and cognition was moderated by subclinical psychotic symptoms in the relatives.

Stratified effect sizes (table 4) indicate that for relatives an above average subclinical psychosis score predicted better *fine motor speed* compared to controls. A similar

interaction pattern was found for *verbal memory*. In relatives, a lower subclinical psychosis score predicted more cognitive alterations in *attention - reaction time* compared to controls. For *set shifting - reaction time,* stratification showed that in relatives, an above average subclinical psychosis score predicted better cognitive performance than in controls, whereas a below average subclinical psychosis score was related to worse performance.

Table 4. Group X CAPE trait psychosis interactions (in relatives, controls as reference category)

Outcome measure	CAPE subclinical psychosis				
	- 2 SD*	-1 SD	mean	+1 SD	+2 SD
Fine motor speed	ß= -0.62, p=0.15 CI#: -1.49, 0.24	ß= -0.19, p=0.49 CI: -0.72, 0.35	ß= 0.25, p=0.26 CI: -0.18, 0.69	ß= 0.69, p=0.05 CI: 0.01, 1.37	ß= 1.13, p=0.04 CI: 0.08, 2.18
Set shifting - RT	ß= -1.00, p=0.00 CI: -1.67, -0.33	ß= -0.46, p=0.06 CI: -0.94, 0.02	ß= 0.07, p=0.76 CI: -0.37, 0.51	ß= 0.60, p=0.05 CI: 0.01, 1.19	ß= 1.14, p=0.01 CI: 0.31, 1.96
Attention - acc	ß= -0.20, p=0.38 CI: -0.65, 0.25	ß= -0.05, p=0.74 CI: -0.32, 0.23	ß= 0.11, p=0.38 CI: -0.13, 0.34	ß= 0.26, p=0.17 CI: -0.11, 0.63	ß= 0.41, p=0.15 CI: -0.16, 0.98
Attention - RT	ß= -0.78, p=0.03 CI: -1.51, -0.06	ß= -0.40, p=0.08 CI: -0.84, 0.04	ß= -0.01, p=0.95 CI: -0.38, 0.36	ß= 0.37, p=0.22 CI: -0.22, 0.97	ß= 0.76, p=0.11 CI: -0.16, 1.68
Verbal memory	ß= -0.56, p=0.09 CI: -1.43, 0.11	ß= -0.20, p=0.43 CI: -0.69, 0.29	ß= 0.26, p=0.23 CI: -0.16, 0.67	ß= 0.71, p=0.03 CI: 0.09, 1.33	ß= 1.17, 0=0.02 CI: 0.23, 2.11
Set shifting - acc	ß= 0.70, p=0.16 CI: -0.27, 1.66	ß= 0.53, p=0.09 CI: -0.08, 1.14	ß= 0.37, p=0.16 CI: -0.14, 0.88	ß= 0.20, p=0.61 CI: -0.57, 0.97	ß= 0.04, p=0.95 CI: -1.13, 1.20
Mental flexibility	ß= 0.05, p=0.91 CI: -0.83, 0.92	ß= -0.04, p=0.90 CI: -0.65, 0.57	ß= -0.12, p=0.65 CI: -0.67, 0.42	ß= -0.21, p=0.57 CI: -0.95, 0.53	ß= -0.30, p=0.58 CI: -1.35, 0.76
Attentional span - working memory	ß= 0.47, p=0.32 CI: -0.45, 1.38	ß= 0.26, p=0.36 CI: -0.30, 0.83	ß= 0.06, p=0.80 CI: -0.40, 0.52	ß= -0.14, p=0.69 CI: -0.86, 0.57	ß= -0.35, p=0.54 CI: -1.45, 0.75

All analyses adjusted for age, sex, session and education.
For *Attention - accuracy, Set Shifting - accuracy, Mental flexibility and Attention - Working memory,* Group X CAPE trait interactions were non significant (all Beta's between -0.12 and 0.37, and p>0.38).
*Effect sizes indicate the change in cognition scores associated with CAPE trait scores of -2 to +2 standard deviations below and above average in relatives compared to controls.
#CI = 95% confidence interval

Discussion

Summary of findings

The results of this study can be summarised as follows. Patients with bipolar disorder showed impaired performance on multiple cognitive domains, whereas cognitive performance of their first-degree relatives was comparable to that of controls on most cognitive tasks. The presence of a history of positive psychotic symptoms in patients was associated with less likelihood of cognitive alterations in relatives and the presence of subclinical psychotic symptoms within the group of relatives predicted less likelihood of cognitive alterations. Additionally it was found

that cognition in patients did not account for variance in cognitive functioning in corresponding relatives.

Neurocognitive functioning in bipolar patients and their relatives

The finding of cognitive dysfunctions in bipolar patients is consistent with previous studies reporting deficits in verbal memory (Altshuler et al., 2004; Fleck et al., 2003; Krabbendam et al., 2000; Martinez-Aran et al., 2004), attention (Bora, Vahip, & Akdeniz, 2006; Clark, Iversen, & Goodwin, 2002; Thompson et al., 2005) and executive functioning (Dixon, Kravariti, Frith, Murray, & McGuire, 2004; Frangou, Donaldson, Hadjulis, Landau, & Goldstein, 2005; Goswami et al., 2006; Zalla et al., 2004). Patients did not show impairment in all executive domains, as a deficit was found on *set shifting – reaction time*, but not on measures of *mental flexibility*. This is in line with a previous suggestion by Ferrier and colleagues (Ferrier, Stanton, Kelly, & Scott, 1999) who concluded that BD patients do not show a global dysexecutive syndrome but are more impaired on tasks requiring a stronger working memory component.

First-degree relatives in this study performed significantly worse than controls only on *set shifting – reaction time* measures. This finding is consistent with that of Clark and colleagues (Clark, Sarna, & Goodwin, 2005), who also found deficits in relatives on an attentional shift task but not in verbal memory. The absence of cognitive alterations on other cognitive functions is inconsistent with studies reporting cognitive alterations in relatives in verbal memory (Ferrier, Chowdhury, Thompson, Watson, & Young, 2004; Keri, Kelemen, Benedek, & Janka, 2001; McIntosh, Harrison, Forrester, Lawrie, & Johnstone, 2005), attention and psychomotor speed (Antila et al., 2007; Pierson, Jouvent, Quintin, Perez-Diaz, & Leboyer, 2000; Sobczak et al., 2002). In a recent review and meta-analysis of studies on cognition in relatives, individuals at risk for bipolar disorder differed from controls, but effect sizes were small and significant only for executive control (Arts et al., 2007).

Cognitive alterations and positive psychotic symptoms

In line with our first hypothesis, the presence of a history of positive psychotic symptoms in patients with bipolar disorder co-occurred with less likelihood of altered cognitive functioning in the proband relative, albeit statistically significant for one domain only. Relatives of patients with a history of psychotic symptoms performed significantly better than relatives of patients without such history on a measure of *fine motor speed*, whereas for *set shifting - reaction time*, *attention – accuracy, verbal memory* and *attention - working memory* findings were suggestive of an association in the same direction.

The second hypothesis was also confirmed. Cognitive alterations, in partially overlapping domains of *fine motor speed*, *set shifting - reaction time*, *attention -reaction time*, and *verbal memory,* were more likely to occur in relatives with lower subclinical psychosis scores, whereas relatives with a higher degree of subclinical psychosis showed better cognitive functioning compared to controls.
This is, to our best knowledge, the first study investigating the association between positive psychotic symptoms in patients with bipolar disorder and cognitive functioning in their proband relatives, and between subclinical psychotic symptoms and cognitive alterations within relatives. Several studies, however, have investigated the relationship between a history of psychosis and cognitive functioning in patients with bipolar disorder, but results are inconsistent (Albus et al., 1996; Glahn et al., 2007; Martinez-Aran et al., 2004; Selva et al., 2007). Some studies found that a history of psychosis was associated with impaired verbal memory (Martinez-Aran et al., 2004) and executive control functioning (Glahn et al., 2007), whereas other studies failed to find an association with neurocognition (Goldberg et al., 1993; Selva et al., 2007).
It can be suggested that in patients, cognitive dysfunctions reflect the neuropsychological consequences of the disorder and possible history of psychosis, which can lead to disrupted brain processing and resulting functioning. Studies in individuals at risk for bipolar disorder are entirely different, as they are not confounded by the influence of disease and treatment variables, and therefore represent a valuable strategy for studying the role of cognitive alterations as genetic vulnerability makers. Support for the third hypothesis, that cognition in patients and relatives are unrelated, is in line with the idea that cognitive impairment in patients is mainly illness-related and in relatives, if at all present, the genetic expression of developmental impairment.

Based on the current study, the evidence for cognitive alterations as intermediary phenotype associated with genetic risk for bipolar disorder is not strong, at least not for the broad range of phenotypical expressions of bipolar disorder. It was found, however, that bipolar patient-relative dyads with more expression of cognitive impairment had less expression of positive psychotic symptoms. Given the suggested genetic overlap between bipolar disorder and schizophrenia (Berrettini, 2003; Cardno et al., 2002; Potash, 2006), these findings suggest that the hypothesised distinction in schizophrenia between good outcome psychosis without developmental impairment (characterised by positive and affective symptoms) and poor outcome psychosis with developmental impairment (with negative and cognitive symptoms), (Myin-Germeys, Krabbendam, Jolles, Delespaul, & van Os, 2002; Robins & Guze, 1970) might be extended to the continuum spanning affective and

non-affective psychosis (Murray et al., 2004). The finding of a similar psychosis-cognition association in bipolar disorder, as implied by the two pathways leading to non-affective psychotic disorders (Robins & Guze, 1970), is in line with the idea of a partially overlapping vulnerability to bipolar disorder and schizophrenia, and provides an explanation for the apparent differences in cognitive alterations in those at risk for the two disorders. Some of the cognitive variation in bipolar disorder appears to be due to genetic effects that is shared to a small degree with schizophrenia and is measurable in relatives of patients. Dissimilarities in cognitive alterations can be explained by additional developmental impairment in schizophrenia, resulting in negative and deficit symptoms and the cognitive deficits characteristic of schizophrenia (Murray et al., 2004). In the absence of these neurodevelopmental impairments, a more affective psychotic phenotype may emerge.

Methodological issues

The present results must be regarded within the context of some methodological issues. First, a broad range of cognitive domains was investigated with recently developed tasks, what can make direct comparison of cognitive effect sizes between studies more difficult. However, the use of these different, recently developed tasks also has benefits, as replication of previous findings in similar cognitive domains with different tasks increases the strengths of the findings. Second, although sample sizes were sufficiently large for group comparisons, the fact that not each patient had a participating sib may have caused a lack of power in the pairwise sib-patient analyses. This may have caused some associations to be only suggestive whereas with a larger relatives group, effects might have been more precise but similar in pattern. Finally, all patients were taking medication. However, patients were relatively stable when tested and studies on the cognitive effects of lithium (Engelsmann, Katz, Ghadirian, & Schachter, 1988; Honig, Arts, Ponds, & Riedel, 1999) and valproate (Devinsky, 1995; Senturk et al., 2007) are not consistent. In addition, in the current paper the focus was on relatives who did not use medication.

Conclusion

Given the suggested genetic overlap bipolar disorder and schizophrenia, the current findings suggest that the hypothesised distinction in schizophrenia between good outcome psychosis without developmental impairment (characterised by positive and affective symptoms) and poor outcome psychosis with developmental impairment (with negative and cognitive symptoms) might be extended to the continuum spanning affective and non-affective psychosis. This is in line with the idea of a partially overlapping vulnerability to bipolar disorder and schizophrenia

and provides an explanation for the apparent differences in cognitive alterations in those at risk for the two disorders.

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CHAPTER 5

COMT SINGLE MARKER AND HAPLOTYPE ASSOCIATIONS WITH BIPOLAR DISORDER AND NEUROCOGNITIVE FUNCTIONING

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Abstract

Objective: Previous studies have reported associations between cognitive endophenotypes of non-affective psychoses and the COMT gene, but only few studies examined the effects of COMT on cognitive performance in bipolar disorder. In this study it was investigated whether single markers in the COMT gene and their haplotypes were associated with bipolar liability and cognitive functioning. **Method:** Patients with bipolar disorder (n=68) and healthy controls (n=61) completed a neurocognitive test battery. Saliva swabs were used to obtain DNA from all participants. **Results:** The G allele of rs165599 was associated with bipolar liability (OR=1.70, p=0.07) and the risk alleles of rs165599 (β= -1.62, p=0.04) and rs737865 (β= -0.99, p=0.04) were associated with cognitive performance, independent of bipolar diagnosis. Haplotypes were not associated with bipolar risk, and rs165599 appeared to be a stronger predictor of bipolar disorder status than haplotypes. **Conclusion:** The finding that the minor allele of rs165599 is overrepresented in bipolar disorder and is associated with reduced verbal memory performance suggests that this SNP at the downstream position of the COMT gene might be involved in COMT regulation, leading to increased bipolar disorder susceptibility and the cognitive impairments associated with this disorder. Larger studies are required to investigate possible superallelic effects of COMT on cognitive functioning.

Introduction

Bipolar disorder is a complex psychiatric disorder that is highly heritable (Cardno et al., 1999). Although several genes have been implicated in the disorder, few consistent results have emerged. A common underlying genetic susceptibility for bipolar disorder and schizophrenia has been suggested, and there is evidence for overlap between both disorders on several domains (Murray et al., 2004). One area of overlap is the presence of cognitive dysfunction, as deficits in verbal declarative memory and executive functioning are not only present in schizophrenia (Heinrichs & Zakzanis, 1998) but also in euthymic, stable bipolar patients (Arts, Jabben, Krabbendam, & Van Os, 2008; Robinson et al., 2006). These cognitive impairments may reflect the underlying genetic vulnerability for the schizophrenia and bipolar disorder (Gottesman & Gould, 2003; Hasler, Drevets, Gould, Gottesman, & Manji, 2006).

Recent linkage evidence has pointed to several candidate susceptibility genes implicated in both bipolar disorder and schizophrenia (Berrettini, 2003; Craddock, O'Donovan, & Owen, 2005). One candidate gene is located on 22q11 and codes for the enzyme catechol-*O*-methyltransferase (COMT). COMT has an important function in dopamine transmission in the brain, in particular in the prefrontal cortex (Weinberger et al., 2001). Findings of impaired frontal executive functions in schizophrenia and in bipolar disorder, together with studies showing that variation in the COMT genotype is associated with cognitive functioning, suggest that COMT might be a putative susceptibility gene for both schizophrenia and bipolar disorder (Badner & Gershon, 2002).

The COMT gene, particularly the Val158Met polymorphism (rs4680), has been extensively tested for an association with schizophrenia. Although some studies showed a positive association between the *Val* allele and schizophrenia (Chen et al., 2004; Egan et al., 2001; Shifman et al., 2002), two recent meta-analyses suggest that the evidence for the involvement of COMT in schizophrenia is limited (Fan et al., 2005; Munafo, Bowes, Clark, & Flint, 2005). The COMT rs4680 *Met* allele has been associated with a better cognitive performance on executive prefrontal tasks in schizophrenia patients in some studies (Bilder et al., 2002; Egan et al., 2001; Malhotra et al., 2002; Mata et al., 2006; McIntosh, Harrison, Forrester, Lawrie, & Johnstone, 2005). Results are, however, highly inconsistent, both in terms of finding associations and the type of cognitive task and allele involved.

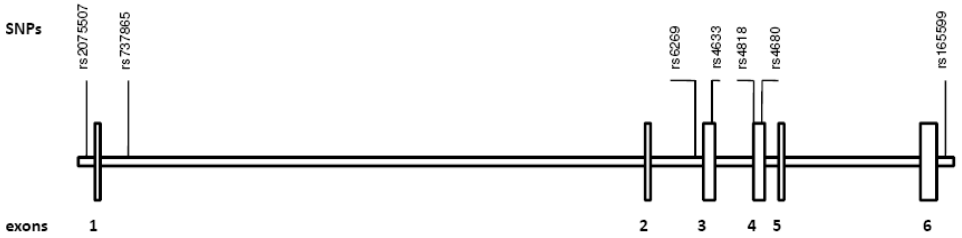
COMT is less investigated in bipolar disorder but there is some evidence that it may be related to vulnerability for the disorder. Although several studies investigat-

ing the association between bipolar disorder vulnerability and COMT provided negative results (Gutierrez et al., 1997; Kunugi et al., 1997; Prata et al., 2006; Serretti, Rotondo, Lorenzi, Smeraldi, & Cassano, 2006), in other studies the low activity *Met* allele has been associated with the rapid cycling variant of bipolar disorder (Kirov et al., 1998; Papolos et al., 1996) and a greater number of positive symptoms (Goghari & Sponheim, 2008). Significant associations have been found between COMT SNP rs165599 and risk for bipolar disorder (Burdick et al., 2007; Funke et al., 2005; Shifman et al., 2004), whereas an association with Val158Met (rs4680) was found in the study of Funke and colleagues (Funke et al., 2005) but not other studies (Burdick et al., 2007; Dickerson et al., 2006; Shifman et al., 2004).

While most studies have investigated the effect of single nucleotide polymorphisms (SNPs) on functioning, it has been shown that the combination of SNPs in the gene may modulate the activity of the gene (Nackley et al., 2006). Investigation of haplotypes combining functional SNPs within the gene may provide a more effective research strategy in studying the genetics of human brain function (Meyer-Lindenberg et al., 2006).
A three-SNP (G-G-G) haplotype (rs737865, rs4680, rs165599) has been found to confer risk to bipolar disorder and schizophrenia (Shifman et al., 2004), a finding consistent with results from the study of Funke and colleagues (Funke et al., 2005), revealing a potentially protective haplotype for psychotic and affective disorders containing the opposite alleles: G-A-A-A (-287A/G, rs737865, rs4680, rs165599).

Only very few studies have investigated COMT in relation to cognitive functioning in bipolar disorder. The *Val/Val* genotype of COMT Val158Met was associated with a larger cognitive impairment in bipolar patients in the study of Dickerson and colleagues (Dickerson et al., 2006), whereas this SNP was not associated with cognitive functioning in other studies (Burdick et al., 2007; Szoke et al., 2006). Genetic variation at COMT SNP rs165599 has been found to be associated with prefrontal aspects of a verbal learning test (Burdick et al., 2007).
In the current study the role of COMT in bipolar disorder was further investigated. We aimed at coding the SNPs at either ends of the COMT gene that are part of the previously identified risk haplotype (Shifman et al., 2004), and its intermediate markers (see figure 1). Thus, we investigated a whole section of the COMT gene allowing us to investigate haplotypes that may have stronger associations with a phenotype and possible super allelic effects. Seven markers were genotyped (the P2 promoter region SNP rs2075507, rs737865, rs6269, rs4818, rs4633, Val158Met (rs4680), and rs165599) and it was examined whether single SNPs and their haplotypes were associated with bipolar liability and cognitive functioning.

Figure 1: The COMT gene, locations of genotyped markers are indicated



Methods

Subjects

The individuals in this study were participants in the BIPOLCOG study (Jabben, Arts, Krabbendam, & Van Os, 2009) a study on cognitive functioning in bipolar disorder (BD) in which three groups were investigated i) patients with an RDC diagnosis of BD (Research Diagnostic Criteria) (Spitzer, Endicott, & Robins, 1978), ii) healthy first-degree relatives of patients with BD, and iii) healthy control participants without a family history of psychotic or bipolar disorders. For the purpose of the current study, only patients and controls were used in the analyses. All subjects were between the ages of 18 and 60 years, fluent in Dutch, had an IQ>70 and were without a history of neurological disorders such as epilepsy and concussion with loss of consciousness. The initial sample consisted of 81 patients and 61 healthy control subjects. Four patients were excluded because data on diagnosis or neuropsychological performance were missing. Nine patients did not give consent for the collection of DNA material. As a consequence, the risk set for the current study consisted of 68 patients with bipolar disorder and 61 controls. All subjects were Caucasian white.

Of the 68 patients RDC diagnoses were: bipolar I disorder (n=41), schizoaffective disorder bipolar or manic type (n=17), bipolar II disorder (n=9), and mania (n=1). Three controls had a history of major depression, now in full remission.

Procedure

In a cross-sectional study design, basic demographic information and DNA samples were collected from the subjects. Neuropsychological testing and psychiatric interviewing was done by trained psychologists. Current depressive and manic psychopathology of all subjects was assessed using the 21-item Hamilton Rating Scale for Depression (Hamilton, 1960) and the Young Mania Rating Scale (Young,

Biggs, Ziegler, & Meyer, 1978) respectively. In the BD group additional information on illness characteristics was collected. Written informed consent, conforming to the local ethics committee guidelines, was obtained from all subjects.

Neurocognitive assessment

Neurocognitive tests were administered by computer, using E-prime for Windows on a 15-inch monitor Toshiba Tecra laptop. The neurocognitive test battery included tasks measuring various neurocognitive domains, guided by previous evidence of impaired performance among these domains in BD patients (Antila et al., 2007; Arts, Jabben, Krabbendam, & Van Os, 2007; Ferrier & Thompson, 2002; Murphy & Sahakian, 2001; Robinson et al., 2006)

Overall intellectual functioning was estimated using three Groningen Intelligence Test (GIT-2) subtests (Mental Rotation, Word Analogies and Mental Arithmetic) (Luteijn & Barelds, 2004), yielding results that are comparable to those of the Wechsler Adult Intelligence Scale III (Wechsler, 2000a).

The standardized Dutch version of the Visual Verbal Learning Test (Rey, 1964) was administered as measure of verbal memory. In three consecutive trials, 15 monosyllabic non-related words had to be memorized and reproduced. The total number of words recalled over the three trials was used as a measure of immediate recall. Delayed recall was measured after a 20 minute delay.

Digit Span Forward and Digit Span Backward of the Wechsler intelligence Scale III (Wechsler, 2000b) were used as measures of attention and working memory, respectively.

The Flanker CPT (Cogtest plc, London (Eriksen & Schultz, 1979; Posner, Inhoff, Friedrich, & Cohen, 1987) is a measure of selective visual control of attention. Subjects are instructed to respond by pressing the right or left mouse button depending on whether the middle element in a display of five lines has an arrowhead pointing to the right or left. There are three trial types: i) neutral trials in which the flankers are just horizontal lines without arrowheads, ii) congruent trials in which all flankers have an arrowhead pointing in the same direction as the target, and iii) incongruent trials, in which flankers are pointing in opposite direction from the target. In this study the outcome measure was the sum of correct trials in the incongruent condition.

Sustained attention was measured with a continuous performance test, the CPT-HQ version, a variant of the CPT-AX (Nestor, Faux, McCarley, Shenton, & Sands, 1990). The outcome measure was the proportion of correct detections.

The Strategic Target Detection Task (STDT: Cogtest plc, London (Weintraub & Mesulam, 1987) is a task similar to the paper and pen 'cancellation'-tests or the 'cross-out' subtest of the WAIS III, where subjects are required to cross-out target

stimuli embedded among distracters. In this computerized version, subjects are not told in advance which of the various stimuli is the target but have to learn by trial-and-error on the basis of feedback. The target stimulus changes without prior notice and subjects have to find out which target is the new correct one, an aspect of the STDT similar to the Wisconsin Card Sorting Test. The total number of correct responses was used as the outcome measure.
The Tapping Speed test (Cogtest plc, London) is a finger tapping test alternating between the right and left hand, which was used as a simple measure of motor speed. The Cogtest version is similar to the Finger Tapping Test or the Finger Oscillation Test of the Halstead Reitan Neuropsychological Battery (Reitan & Wolfson, 1985). Subjects were asked to tap a key on the keyboard with their index finger as fast as they could for 8 seconds in five trials for each hand. Outcome measure was the mean tap-rate for the subject's dominant hand.

COMT-genotyping

Buccal cell samples were collected with sterile swabs (Omniswab, Whatman®). DNA was extracted using QIAamp DNA Mini Kits (Qiagen). In total, seven SNPs within the COMT gene were determined. Six SNPs were genotyped using TaqMan® SNP Genotyping assays (Applied Biosystems): rs4680 (assay ID C__25746809_50), rs4633 (assay ID C___2538747_20), rs4818 (assay ID C___2538750_10), rs6269 (assay ID C___2538746_1_), rs165599 (assay ID C___2255335_10) and rs737865 (assay ID C___2255420_10). SNP rs2075507 (formerly designated as rs2097603) was genotyped using a Custom TaqMan® SNP Genotyping assay designed with File Builder Software version 3.1 (Applied Biosystems). All assays were run on a 7900HT Fast Real-Time PCR System (Applied Biosystems).

Statistical analyses

Single SNP effects:

The association between bipolar status and neurocognitive performance was estimated using multiple linear regression models with bipolar status entered as an independent indicator variable adjusted for age and sex, regressed on to each neurocognitive test, in turn, using STATA 10.0 (Statacorp, 2007).
Single SNP associations were next examined a) comparing allele frequencies between cases and controls and b) regressing them on to the quantitative cognitive tests, comparing parameters using asymptomatic, likelihood ratio test.
To examine the effect measure modification of bipolar status on the single SNP effects we entered an interaction term in the model SNP-bipolar status.

Haplotype Associations:
Multimarker haplotypes were imputed using the standard EM (expectation maximization) algorithm using the 7 SNPs haplotypes, the linkage disequilibrium measures and haplotype architecture were validated using Haploview 4.1 (Barrett et al, 2005). The conditional associations of the haplotypes with the dependant variables; bipolar status and each cognitive test were performed (with standard errors assessed by permutation methods). In order to determine whether one haplotype panel had a stronger effect on cognition than other imputed panels haplotype specific comparisons were carried out.

Results

Demographic characteristics of the study sample are presented in table 1. Allelic/genotype frequencies are presented in table 2. All SNPs were in Hardy Weinberg equilibrium (data not shown).

Single SNP effects
Patients performed significantly worse than controls on most cognitive tests (Betas between -0.18 and -0.35 and p-values <0.04). For STDT (β= -0.09, p=0.35) and TST (β= -0.14, p=0.11) the performance of patients and controls did not differ significantly but effect sizes were in the expected direction (Jabben et al., 2008).
Investigation of the association between the single SNPs and disorder status showed no significant allelic or genotypic associations with bipolar disorder status (see table 2). However, a trend towards an overrepresentation of the G allele of rs165599 in the bipolar group was found: χ^2=3.27, p=0.07, OR=1.70. After bonferroni adjustment this association was no longer significant: p=0.49. Repeating the analyses restricted to patients with a diagnosis of bipolar I disorder did not change the results.

Associations between SNPs and cognitive performance are presented in table 3.
The minor allele of rs165599 was significantly associated with a worse Word List Learning Test - immediate recall performance. This significance reduced after Bonferroni adjustment: p=0.29. The minor allele of rs737865 was associated with a worse Word List Learning - delayed recall performance and with a worse Flanker CPT performance. These associations reduced after Bonferroni adjustment (WRT p=0.31; Flanker CPT p=0.15). For Digit Span, trends were found towards an association of the minor allele of rs2075507 with a better cognitive performance, but these trends disappeared after Bonferroni adjustment (DS forward: p=0.73; DS backward: p=0.79).

Table 1. Demographics, symptom and neurocognition scores per group

	Controls (n=61)	BD patients (n=68)
Gender M/F	23 / 38	33 / 35
Age (SD)	45.3 (8.7)	45.1 (7.8)
Educational level (SD)	5.8 (1.7)	5.5 (2.2)
GIT IQ (SD)	119.5 (9.6)	113.0 (12.1)
SYMPTOMS	**Mean (SD)**	**Mean (SD)**
BPRS	25.0 (1.7)	33.5 (6.3)
HDRS	0.2 (0.8)	3.8 (4.0)
YMRS	0.1 (0.3)	1.6 (2.4)
NEUROCOGNITION		
Verbal learning and memory		
Word List Learning		
total immediate recall	25.7 (4.9)	22.9 (5.4)
delayed recall	8.6 (2.5)	7.2 (3.0)
Attention and concentration		
Digit Span		
forward	9.0 (1.9)	8.3 (1.9)
backward	6.6 (1.9)	5.5 (1.9)
Flanker CPT	42.1 (5.1)	38.5 (9.0)
CPT-HQ %correct	98.8 (2.4)	95.1 (6.5)
Executive functioning		
Strategic Target Detection	84.4 (10.7)	83.0 (6.1)
Fine motor speed		
Finger Tapping Test	180.8 (22.2)	188.1 (36.1)

Table 2. Genotype and allele frequencies of COMT polymorphisms

	Patients					Controls					P-value	
SNP	n	genotype			MAF	n	Genotype			MAF	genotype	allele
		1/1	1/2	2/2			1/1	1/2	2/2			
rs2075507	67	7	37	23	0.381	61	12	28	21	0.426	0.30	0.48
rs737865	68	8	28	32	0.324	60	7	23	30	0.308	0.94	0.79
rs6269	68	11	36	21	0.427	61	13	23	25	0.402	0.22	0.69
rs4633	68	12	38	18	0.456	61	15	25	21	0.451	0.24	0.94
rs4818	68	11	35	22	0.419	61	13	24	24	0.410	0.38	0.88
rs4680	67	12	37	18	0.455	59	15	24	20	0.458	0.26	0.97
rs165599	68	5	30	33	0.294	61	2	20	39	0.197	NA	0.07

SNP, Single nucleotide polymorphism; MAF, minor allele frequency. Minor and major alleles are denoted by 1 and 2, respectively: rs2075507, 1 = G, 2 = A; rs737865, 1 = C, 2 = T; rs6269, 1 = G, 2 = A; rs4633, 1 = C, 2 = T; rs4818, 1 = G, 2 = C; rs4680, 1 = G, 2 = A; rs165599, 1 = G, 2 = A.

Investigation of SNP/status interactions showed a near significant rs2075507/status interaction for Flanker CPT performance (β patients = 7.05, β controls = -0.41 Z-score GxE= -1.81, p=0.07), the minor allele being associated with a better performance in the patient group. Although not significant, notably large SNP/status interactions were found for rs737865 (β patients = -1.57, β controls = -0.27, Z-score GxE= 1.43, p=0.15) and rs165599 (β patients = -0.93, β controls= 0.21 Z-score GxE= 1.10, p=0.27) on the delayed recall condition of the

Word List Learning Test, the minor allele of both SNPs being associated with a worse cognitive performance in the patient group.

Table 3. Cognitive performance – minor allele associations

SNP	WLT		WRT		CPT - HQ		DS_forward		DS_backward		Flanker - CPT		STDT		TST	
	β	p	β	p	β	p	β	p	β	p	β	p	β	p	β	p
rs2075507	0.90	0.21	0.71	0.15	0.12	0.47	0.70	0.10	0.62	0.11	3.33	0.11	0.75	0.87	1.17	0.81
rs737865	-0.53	0.45	-0.99	0.04	-0.13	0.42	-0.46	0.28	-0.28	0.47	-4.75	0.02	4.97	0.29	4.39	0.38
rs6269	0.04	0.95	0.21	0.65	-0.05	0.74	-0.16	0.70	0.08	0.82	-1.26	0.52	-0.26	0.95	2.63	0.58
rs4633	-0.21	0.75	-0.04	0.93	-0.03	0.85	-0.15	0.71	-0.02	0.95	-0.49	0.80	0.25	0.96	4.37	0.36
rs4818	-0.00	1.00	0.21	0.65	-0.05	0.75	-0.08	0.84	0.11	0.76	-1.16	0.56	-0.32	0.94	3.00	0.53
rs4680	-0.26	0.71	-0.05	0.92	-0.03	0.86	-0.16	0.71	-0.01	0.98	-0.67	0.74	0.16	0.97	4.14	0.40
rs165599	-1.62	0.04	-0.74	0.18	-0.00	0.98	-0.49	0.31	0.08	0.85	-2.49	0.29	3.90	0.46	0.14	0.98

For all variables a higher score indicates a better neurocognitive performance.
WLT, word list learning – immediate recall; WRT, word list learning – delayed recall; CPT, Continuous Performance Test; DS, Digit Span; STDT, Strategic Target Detection Test; TST, Tapping Speed Test

Haplotype effects

Linkage disequilibrium (LD) between the seven SNPs is presented in table 4. All SNPs were in LD and one haplotype block was inferred, consisting of all seven markers. Haplotype frequencies in the total sample and in patients and controls are presented in table 5.

No significant differences were found in the haplotype frequencies between patients and controls (see table 5). Permuted p values were calculated to compare haplotypes and single markers regarding their association with disorder status. Rs165599 was most strongly associated with status (χ^2=3.27, p=0.39), over haplotypes: ATGCGGG (χ^2=1.93, p=0.70), GTGCGGA (χ^2=1.68, p=0.78), GTGCGGG (χ^2=1.07, p=0.97) and GTATCAA (χ^2=1.06, p=0.97).

Table 4. Linkage Disequilibrium D' and D' confidence interval

	rs2075507	rs737865	rs6269	rs4633	rs4818	rs4680
rs737865	0.96 (0.81-0.99)	-				
rs6269	0.36 (0.15-0.53)	0.60 (0.45-0.72)	-			
rs4633	0.37 (0.16-0.53)	0.58 (0.41-0.72)	0.98 (0.92-1)	-		
rs4818	0.36 (0.15-0.53)	0.58 (0.42-0.70)	0.97 (0.94-1)	1 (0.95-1)	-	
rs4680	0.38 (0.17-0.54)	0.63 (0.45-0.75)	0.98 (0.94-1)	0.98 (0.94-1)	0.98 (0.92-1)	-
rs165599	0.22 (0.02-0.52)	0.25 (0.07-0.42)	0.36 (0.14-0.54)	0.57 (0.35-0.73)	0.36 (0.14-0.54)	0.61 (0.39-0.76)

Overall omnibus haplotype testing, investigating whether a haplotype structure model is a better predictor of cognitive functioning than a random model (no haplotypes having different effects), showed no significant associations for the various cognitive tests (WLT: F=1.45, p=0.17; WRT: F=1.38, p=0.20; CPT: F=0.21, p=0.99, DS forward: F=0.51, p=0.88; DS backward: F=0.96, p=0.48; Flanker CPT: F=1.34, p=0.22; STDT: F=0.81, p=0.62; TST: F=0.53, p=0.87).

Table 5. Haplotype estimated frequencies

	Total sample	Patients	Controls	Chi square	P value
Block 1					
G-T-A-T-C-A-A	0.241	0.215	0.270	1.062	0.30
A-T-A-T-C-A-A	0.190	0.190	0.189	0.000	0.99
A-C-G-C-G-G-A	0.127	0.108	0.149	0.951	0.33
A-C-G-C-G-G-G	0.110	0.124	0.095	0.529	0.47
G-T-G-C-G-G-A	0.083	0.062	0.107	1.676	0.20
A-C-A-T-C-A-A	0.063	0.067	0.058	0.097	0.76
G-T-A-T-C-A-G	0.042	0.052	0.031	0.687	0.41
A-T-G-C-G-G-A	0.039	0.048	0.030	0.573	0.45
A-T-A-C-C-G-G	0.030	0.028	0.032	0.041	0.84
G-T-G-C-G-G-G	0.029	0.039	0.017	1.065	0.30
A-T-G-C-G-G-G	0.013	0.023	0.003	1.928	0.17

However, haplotype specific comparisons indicated that there were (near) significant differences in effects of some haplotypes on cognitive performance: For DS backward: GTGCGGG (used as the reference haplotype) p=0.06; for WLT: ATACCGG β= -5.16, p=0.06; for WRT: GTGCGGA β= 3.86, p=0.01 and ACATCAA β= -0.10, p=0.07; for Flanker CPT: GTATCAG β= -13.90, p=0.04, GTATCAA β= 0.45, p=0.08 and ACGCGGA β= -7.65, p=0.09; and for TST: ATATCAA β= -8.23, p=0.06.

Discussion

In this study several SNPs and haplotypes along the COMT gene were investigated for an association with bipolar disorder and cognitive functioning. Marker rs165599 was found to be associated with bipolar risk and variation in rs165599 and rs737865 was associated with cognitive performance, independent of bipolar diagnosis. The common functional variant Val158Met was not associated with diagnosis nor with cognitive functioning. Haplotypes were not associated with bipolar risk, and rs165599 appeared to be a stronger predictor of bipolar disorder status than haplotypes.

Rs165599

The results of this study suggest a specific marker effect of rs165599 on disorder status, the G allele being overrepresented in subjects diagnosed with bipolar disorder. This is in line with previous studies reporting a significant association between the risk allele of SNP rs165599 and bipolar status (Burdick et al., 2007; Funke et al., 2005). Also in the study of Shifman and colleagues (Shifman et al., 2004) SNP rs165599 was found to be associated with both schizophrenia and bipolar disorder status in an Israeli sample, over rs4680 and rs737865.

The risk allele of rs165599 was associated with a worse verbal memory performance in the current study, but this effect was not specific for bipolar patients. This finding is in accordance with previous studies in bipolar (Burdick et al., 2007) and schizophrenia patients (Chan et al., 2005) showing a significant effect of rs165599 on verbal memory performance.

Rs737865 and Rs2075507

Distribution of alleles of rs737865 and rs2075507 did not differ between bipolar patients and controls, suggesting that these markers are not associated with risk for bipolar disorder. COMT rs737865, however, was associated with delayed verbal memory performance and performance on a selective attention task (Flanker CPT), independent of diagnosis. This marker was similarly associated with worse performance on an n-back task in a previous study (Diaz-Asper et al., 2008), but not with any of the cognitive measures in the study of Burdick and colleagues (Burdick et al., 2007).

For rs2075507 a trend towards an association with performance on the test for attention/working memory could be reported, the risk allele being associated with a better cognitive performance. In addition to this, a near significant COMT/status interaction on the Flanker CPT was found with patients carrying the risk (G) allele having a better cognitive performance. This is in line with findings from a previous study in schizophrenia patients (Diaz-Asper et al., 2008), in which a significant COMT/diagnosis interaction in the opposite direction was found, with A-A patients performing worse on a CPT.

Val158Met (rs4680)

In most studies, the impact of COMT on disorder and executive functioning has been explained through variations in the functional Val158Met polymorphism that is involved in dopaminergic prefrontal activity. Val158Met has been associated with schizophrenia risk (Egan et al., 2001; Li et al., 1996) and with prefrontal cognitive functioning irrespective of psychiatric diagnoses (Egan et al., 2001; Goldberg et al., 2003; Malhotra et al., 2002). In the current study, Val158Met was not associated with bipolar disorder status nor with cognitive functioning. This is in line with two previous studies (Burdick et al., 2007; Szoke et al., 2006) investigating cognitive performance in bipolar patients. Dickerson and colleagues, however, did find that theVal158Met polymorphism affects verbal memory performance in patients with bipolar disorder (Dickerson et al., 2006). It has been suggested that discrepancies in finding associations with Val158Met, both regarding diagnosis and association with cognition, can be explained by the influence of haplotypic variation,

thus, by complex interactions between alleles at various loci within the COMT gene that may modulate the effect of Val/Met.

COMT haplotypes

One haplotype block consisting of all 7 markers was inferred in this study. These haplotypes (see table 5) contain the three haplotypes ACCG, ATCA and GCGG (rs6269-rs4633-rs4818-rs4680) in the central locus of the COMT gene previously found in the study of Nackley and colleagues (Nackley et al., 2006).

None of the haplotypes was associated with bipolar disorder status. Interestingly, when contributions to disorder status were compared between haplotypes and single markers, SNP rs165599 was the strongest predictor of group status, above several haplotypes.

Previously a risk GGG (rs737865, rs4680, rs165599) and a protective GAAA haplotype (-287, rs737865, rs4680, rs165599) have been described for bipolar disorder (Funke et al., 2005; Shifman et al., 2004). We could not replicate these findings in the current study, but in both previous studies, singular SNP rs165599 was associated with bipolar risk.

In exploratory analyses we examined associations between COMT haplotypes and cognitive test performance. Although omnibus models, comparing the predictive value of haplotype structure models with a non-haplotype model on cognitive performance showed no overall significant differences, (trends towards) significant associations between specific COMT haplotypes and cognitive functioning were found in this study. This indicates that some haplotype panels had a stronger effect on cognition than other panels, suggesting that COMT is relevant for cognitive functioning.

Limitations

The main limitation of the current study is its small sample size. This may have caused the study to be underpowered and makes results difficult to interpret. It can be suggested that some near significant associations may not reach significance due to a lack of power. In addition to this, most associations did not survive the stringent correction for multiple corrections. However, the finding that rs165599 is associated with risk for bipolar disorder and with verbal memory performance is a replication of previous findings, and the exploratory results from our haplotype analyses suggest that this part of the COMT gene is involved in cognitive performance. These results may contribute to hypotheses on possible super allelic effects that have to be tested in larger studies.

Conclusions

The current findings suggests that rs165599 at the down stream position of the COMT gene might be involved in COMT regulation, leading to increased bipolar disorder susceptibility and cognitive impairments associated with this disorder. Exploratory results from the haplotype analyses suggest that this part of the COMT gene is involved in neurocognitive functioning but larger studies are needed to discover possible super allelic effects.

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CHAPTER 6

COGNITIVE ALTERATIONS IN GROUPS AT RISK FOR PSYCHOSIS: NEUTRAL MARKERS OR INDICATORS OF SOCIAL DISABILITY?

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Abstract

Objective: To investigate whether cognitive alterations associated with vulnerability to psychosis, are associated with expression of psychopathology and functional outcome in groups at different levels of risk for psychotic illness. **Method:** Neurocognition, psychopathology and functional outcome were measured in subjects with variable risk for psychosis: i) 29 patients with psychotic disorder, ii) 46 subjects at familial risk, iii) 41 subjects at psychometric risk, and iv) 54 control subjects. **Results:** Dose-response relationships between cognitive dysfunction and increasing risk for psychosis were found. Cognitive alterations were predicted by negative symptoms in patients and by positive psychotic experiences in the familial risk group. In both at risk groups, cognitive speed was associated with functional outcome. **Conclusion:** Some cognitive impairments serve as neutral endophenotypic marker across the psychosis continuum. However, other cognitive alterations associated with transmission of psychosis may have a direct impact on the pathway from risk to psychopathology and alterations in functioning.

Key words: psychosis; high-risk; endophenotypes; neurocognition; outcome

Introduction

Cognitive dysfunction is a core symptom of schizophrenia, as alterations in the domains of attention, executive functioning and memory (Dollfus et al., 2002; Heinrichs & Zakzanis, 1998; Zalla et al., 2004) have been reported consistently in patient-control comparisons. Cognitive dysfunctions represent a stable trait as deficits persist during clinical remission (Hughes et al., 2003). Subtle cognitive alterations in similar domains are also measurable in persons at genetically (Faraone et al., 1995; Faraone et al., 1999; Keefe et al., 1994; Krabbendam, Marcelis, Delespaul, Jolles, & van Os, 2001) and psychometrically (Dinn, Harris, Aycicegi, Greene, & Andover, 2002; Voglmaier, Seidman, Salisbury, & McCarley, 1997) defined risk for the disorder, with apparently larger effect sizes in the former compared to the latter. This suggests that cognitive impairments in schizophrenia may represent the expression of vulnerability to psychotic disorder and can be construed as a psychosis endophenotype (Gottesman & Gould, 2003).

Research in patients shows that cognitive impairment is weakly associated with symptoms and more strongly with functional outcome. In schizophrenia, symptoms may be grouped into several symptom dimensions in order to reduce phenomenological heterogeneity. Research on the association between cognition and symptom dimensions demonstrates that cognitive deficits are associated with negative symptoms, and to a lesser extent with symptoms pertaining to the disorganization domain (Baxter & Liddle, 1998; Bilder et al., 2000; Lucas et al., 2004). In addition, it has been suggested that different symptoms profiles may be associated with different patterns of cognitive alterations (Liddle & Morris, 1991; O'Leary et al., 2000). With regard to the positive symptoms of psychosis, most studies report little evidence of an association with cognitive dysfunction, although this is likely due in part to ceiling effects in samples with uniformly high levels of positive symptoms or failure to distinguish between persistent and transitory positive symptoms (Brazo et al., 2002; Malla, Norman, Manchanda, & Townsend, 2002; O'Leary et al., 2000; Penades, Gasto, Boget, Catalan, & Salamero, 2001). Cognitive impairment has often been associated with poorer functional outcome in schizophrenia. In reviews of the literature on this topic, Green (Green, 1996; Green, Kern, & Heaton, 2004) concluded that functional outcome was relatively independent of symptom improvement and more associated with stable characteristics such as cognitive functioning. Thus, verbal memory, card sorting/executive functioning and verbal fluency impacted on various measures of functional outcome (Green, 1996; Green et al., 2004). In recent studies, however, in particular processing speed (Lysaker, Bryson, Davis, & Bell, 2005; Milev, Ho, Arndt, & Andreasen, 2005) and attention (Dickinson & Coursey, 2002; Milev et al., 2005) were associated with functional outcome in patients, depending on which outcome measure was used.

Previous research suggests that the psychosis phenotype may be expressed as a continuous distribution of experiences (Johns & van Os, 2001; van Os, Hanssen, Bijl, & Ravelli, 2000) taking on the form of psychometric psychosis proneness which is transmitted at relatively stable levels in families in the general population (Hanssen, Krabbendam, Vollema, Delespaul, & Van Os, 2006). Previous work has demonstrated that measures of psychometrically defined psychosis proneness in the general population are weakly associated with cognition (Krabbendam, Myin-Germeys, Hanssen, & van Os, 2005; Tien, Costa, & Eaton, 1992), suggesting the link with alterations in cognition is also continuously distributed and present outside the realm of clinical disorder.

Given the fact that cognitive alterations in patients with psychotic disorder have been associated with both illness (symptoms) and disability (functional outcome), the question rises if and to what degree a similar impact on illness-related and disability-related measures may exist in at-risk groups with similar, though attenuated levels of cognitive alterations. If associations between cognition and symptoms and disability are limited to patient groups, a causally contributing mechanism of cognitive impairment to the pathway from at-risk state to clinical disorder is unlikely. However, if the association between cognitive alterations and expression of symptomatology and disability can be demonstrated in at-risk groups, cognitive alterations may represent more than neutral indicators of genetic risk and also contribute to social disability outside the realm of clinical disorder.

Aims of the study

To investigate whether cognitive alterations, associated with psychosis liability, are more than neutral indicators of genetic risk for psychosis, by examining whether associations exist with expression of psychopathology and functional outcome in groups with different levels of risk for psychosis.

Material and methods

Subjects

The individuals in this study were participants in a larger study, the 'Cognitive Functioning in Psychosis' (CoP) study in which four groups were investigated i) patients with history of non-affective psychoses, ii) first-degree relatives of patients with non-affective psychosis (familial risk group) iii) subjects scoring high (>75th pct.) on the positive dimension of psychosis-proneness measured by the Community Assessment of Psychic Experiences (CAPE) (Stefanis et al., 2002) (psychometrically defined risk group), and iv) subjects with an average score (40th – 60th percentile) on the CAPE (control group). All subjects were between the ages of 18 and 55 years, fluent in Dutch, and without a history of neurological disorders such

as epilepsy and concussion with loss of consciousness. Written informed consent, conforming to the local ethics committee guidelines, was obtained from all subjects. Patients were recruited from catchment areas of the Community Mental Health Centre and Psychiatric Hospital in an area in the South of the Netherlands. Initial inclusion criteria for patients were the lifetime prevalence of a period of psychosis (at least two weeks) in clear consciousness, according to the RDC (Research Diagnostic Criteria) (Spitzer, Endicott, & Robins, 1978).

Relatives (free from a lifetime history of psychosis) were sampled through participating patients or through associations for relatives of patients with psychotic symptoms. Subjects at psychometrically defined risk and healthy control subjects were recruited from an earlier longitudinal study conducted in the city of Sittard (Continuum of Mental Disorders study, COMED) (Hanssen et al., 2003). The original CoP study included 45 patients, 47 non-psychotic first degree relatives, 41 subjects at psychometrically defined risk for psychosis and 54 healthy controls with an average level of psychotic experiences.

Three patients were excluded because data on diagnosis or symptomatology were missing. Data on neuropsychological performance were missing for 10 patients and 1 relative because of withdrawal of consent. The computer program OPCRIT was used to confirm diagnoses, on the basis of current and lifetime recorded symptomatology listed in the OCCPI (Mc Guffin, Farmer, & Harvey, 1991). Three patients were excluded because they did not meet criteria for a psychotic disorder using RDC criteria. As a consequence, the research sample of the current paper consisted of 29 patients with psychosis, 46 non-psychotic first degree relatives, 41 subjects at psychometric risk for psychosis and 54 control subjects with an average level of psychotic experiences. According to RDC criteria there were 22 patients (76%) with a diagnosis of narrow schizophrenia, 5 patients (17%) with a diagnosis of unspecified functional psychosis, and 2 patients (7%) with a diagnosis of schizoaffective disorder.

Patients and first-degree relatives originated from 38 families, of which 14 families contributed one case or one relative, 12 families contributed one case and one relative, four families contributed more than one relative, 7 families contributed one case and at least two relatives and one family contributed two patients and two relatives.

Neuropsychological assessment

The Stroop Colour Word Test (SCWT) and the Trail Making Task (TMT) were used to measure speed of information processing, selective attention and cognitive set shifting. The shortened version of the SCWT was used, which involves three cards displaying forty stimuli each: colour names, coloured patches and colour

names printed in inconsistent ink colours (cards I, II and III respectively). A modified version of the TMT (Vink & Jolles, 1985) was used in this study and consisted of three parts. In part A, subjects had to draw lines to connect consecutively numbered circles. In part B, the same had to be done for lettered circles. In part C, subjects connected the same number of consecutively numbered and lettered circles by alternating between the two sequences.
The word naming and colour naming tasks of the SCWT and the number tracking and letter tracking tasks of the TMT were used as measures of processing speed. The interference task of the SCWT (card III) can be considered as a measure of selective attention and inhibition, the number/letter shifting task of the TMT a measure of set shifting. Both can be considered functions of executive control. Semantic fluency was used to evaluate psychomotor speed although it can also be considered as a measure of strategy-driven retrieval from semantic memory. The subjects were required to name as many animals as possible in 1 minute.

To obtain a global level of general intellectual functioning two subtests of the Groningen Intelligence Test (GIT) were employed, a widely used Dutch intelligence test (Luteijn & van der Ploeg, 1983). This test yields results that are comparable to those of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981). The standardized scores of two subtests for visuo-spatial reasoning and verbal logical reasoning were used as measures of global intellectual functioning.

Psychiatric assessment

CAPE. The Community Assessment of Psychic Experiences (CAPE), a 42-item self-report instrument, was used to assess dimensions of the subclinical psychosis phenotype. In this questionnaire, 20 items measure positive psychotic experiences, 14 items rate negative experiences and 8 cognitive depressive experiences. The frequency of the experience was rated on a four-point scale of "never", "sometimes", "often" and "nearly always". For a detailed description of the CAPE, see (Hanssen et al., 2006; Stefanis et al., 2002; Verdoux & van Os, 2002) (http://www.cape42.homestead.com). The CAPE was used to select the psychometrically defined risk group and the control subjects.
SAPS and SANS. Presence of positive and negative symptoms in subjects were quantified using the Scale for Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1983). The organization of the SAPS/SANS scale reflects the traditional concept in which the phenomenological heterogeneity of schizophrenia is reduced in two broad dimensions: positive and negative symptoms. However, numerous studies have indicated that the symptomatology of schizophrenia is better described by a three dimensional model, with at least three dimensions describing the

phenomenology of the disease. Liddle and colleagues (Liddle, 1987) calculated three different clusters of symptoms that are derived from these scales through factor and principal component analyses in previous research: *psychosis* (delusions, hallucinations), *negative* (affective flattening and blunting, alogia, avolition, anhedonia) and *disorganization* (positive formal thought disorder, inappropriate affect, bizarre behaviour) (Andreasen, Arndt, Miller, Flaum, & Nopoulos, 1995).

Functional outcome. Functional outcome of subjects was measured using the WHO Life Chart Schedule (WHO, 1992). This is a semi-structured instrument, designed to assess the long-term course of schizophrenia in the domains of psychopathology, treatment, residence and work. For the purpose of investigating functional outcome in this study, the number of months of independent community living and occupational functioning in the past two years were used as dependent variables.

All ratings were conducted by trained interviewers on the basis of a standard clinical interview, observed behaviour during the interview and review of all available clinical material.

Analyses

Before analysis the cognitive variables were checked for outliers. Values with deviation more than three standard deviations from the mean were replaced with the closest value within the same group (Tabachnick & Fidell, 1996).

Statistical analyses were performed using STATA 9.0. (Statacorp, 2005). A four-level group variable was constructed to reflect increasing risk for psychosis, according to strength of association with cognitive variables in the literature as discussed above (0=controls, 1=psychometrically defined risk group, 2=familial risk group, 3=patients); control subjects were used as the reference category. Regression models of neuropsychological dependent variables were examined to assess the effect of group membership on cognitive performance. The group variable was entered as a dummy variable to investigate possible dose-response relationships between cognitive variables and the four-level variable reflecting psychosis risk. The non-independence of observations within families was addressed by adjusting variance estimates in all analyses by use of the command 'robust' in STATA. By this procedure robust estimates of variance are computed, producing estimators for clustered data, whereby observations that are not independent across groups (i.e., families) are allowed. For those analyses that showed a dose-response relationship between group and cognitive test, the overall association was reported as well.

In order to reduce the number of dependent neuropsychological variables in our analyses, Principal Component Analysis was performed on the neuropsychological

variables. Factors with eigenvalues greater than unity were retained, and the resulting factor structure was examined using the scree test and clinical interpretation. The relationship between symptomatology and cognitive functioning was investigated using multiple regression models. Symptomatology was measured using the three dimensions of schizophrenia symptomatology derived from the SAPS and SANS scales. For each dimension, a four-level variable, hereafter referred to as "dimensional load", reflecting tertiles of values greater than 0 was constructed. Associations between the dimensional load variables and cognition were investigated in each group. Multiple linear regression, adjusted for symptomatology, was also used to investigate the association between cognitive functioning and functional outcome. Analyses were adjusted *a priori* for the effects of age, sex and educational level and repeated with additional adjustment for intellectual functioning. Effect sizes were expressed as standardized regression coefficients.

Power analysis

A power analysis revealed that the power to detect a large effect size in the comparison of cognitive functioning between patients and controls in the current study was 94%. The power to detect a moderate effect size between subjects at psychometric risk and controls was 66% and between relatives and controls 70%.

Results

Subject characteristics are presented in Table 1. In Table 2, the mean scores per group on the neuropsychological tests, measures of psychopathology, and outcome variables are summarized.

Table 1. Demographic characteristics of the subjects

	Controls (0) n=54	Psychometric risk group (1) n=41	Familial risk group (2) n=46	Patients (3) n=29
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Gender M/F	21/33	16/25	17/29	23/6
Age (years)	47.2 (7.6)	44.3 (9.8)	40.5 (11.7)	32.9 (10.2)
Education (years)	13.5 (3.3)	12.9 (3.5)	13.1 (3.6)	12.3 (2.8)
GIT visuo-spatial - standardized score	7.2 (1.8)	6.9 (1.8)	7.3 (2.2)	6.0 (2.3)
GIT verbal logical - standardized score	7.5 (1.8)	6.7 (2.0)	6.9 (2.2)	6.3 (1.9)

Cognitive functioning and increasing risk for psychosis

Multiple regression analyses showed a dose-response relationship between cognitive functioning and psychosis risk for TMT A, TMT B, TMT C and Fluency,

cognitive performance decreasing with increasing psychosis vulnerability (see Table 3). For these task a summary linear trend could be reported (TMT A: ß=0.25, p=0.03, TMT B: ß=0.34, p=0.00, TMT C: ß=0.24, p=0.01, and Fluency: ß=-0.23, p=0.00). Additional adjustment for intellectual functioning did not substantially change the results, except for the SCWT III, where a dose-response relationship was found only after additional adjustment (psychometrically defined risk group: ß=0.09, p=0.11, familial risk group 2: ß=0.11, p=0.07, patients: ß=0.41, p=0.01).

Table 2. Summary of performance on neuropsychological tasks and symptom scores per group

	Controls (0)		Psychometrically defined risk group (1)		Familial risk group (2)		Patients (3)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Neurocognition								
SCWT (sec)[a]								
Card I	54	17.1 (3.6)	41	19.1 (4.9)	46	16.8 (3.2)	28	17.2 (3.1)
Card II	54	22.2 (4.4)	41	23.2 (4.4)	46	22.6 (5.5)	28	25.7 (6.5)
Card III	54	36.4 (7.6)	41	39.3 (9.4)	46	37.5 (8.3)	28	50.2 (28.1)
TMT (sec)[a]								
Trial a	54	32.7 (9.6)	41	33.9 (10.8)	46	33.4 (10.6)	29	39.0 (19.7)
Trail b	54	30.9 (9.1)	40	32.4 (11.7)	46	36.6 (20.1)	29	45.6 (32.1)
Trial c	54	56.2 (29.9)	41	58.3 (34.0)	46	65.6 (37.6)	28	75.2 (58.8)
Fluency[b]	54	26.9 (6.8)	40	25.7 (6.8)	46	25.1 (5.6)	29	21.4 (5.6)
Psychopathology								
SAPS total	54	1.1 (2.2)	41	2.9 (4.5)	46	2.5 (4.9)	29	27.8 (17.3)
SANS total	54	1.5 (2.4)	41	1.9 (2.8)	46	2.0 (4.0)	29	10.7 (11.2)
Dimensional loading								
-positive	54	0	41	0.2 (0.5)	46	0.2 (0.6)	29	2.0 (1.1)
-negative	54	0.7 (0.9)	41	0.8 (1.0)	46	0.7 (0.9)	29	2.1 (1.1)
-disorganization	54	0.6 (0.9)	41	1.1 (1.1)	46	0.9 (1.1)	29	2.3 (1.0)
Functional status								
Work - months (24 = max)	53	22.9 (4.2)	41	21.7 (5.7)	44	21.4 (6.8)	28	8.3 (9.8)
Independent living (24 = max)	54	23.9 (0.5)	41	23.9 (0.5)	46	24.0 (0.0)	28	16.9 (8.1)

[a] Higher scores indicating poorer performance
[b] Higher scores indicating better performance

Being a patient predicted performance on all neuropsychological tests, patients performing significantly worse than controls on all of the tests, with the exception of SCWT card I. On this task, the psychometrically defined risk group performed significantly worse (ß=0.23, p=0.02), whereas no differences were found for the familial risk group and patients compared to the controls. On TMT B and TMT C, not only the patient group, but also the familial risk group differed significantly from the group of control subjects (see Table 3). On SCWT card III, the psychometrically defined risk group also differed from the controls in addition to the patients (ß=0.11, p=0.04). After adjustment for intellectual functioning, a trend towards a difference between the familial risk group and the group of controls was apparent for TMT A (ß=0.14, p=0.06), SCWT III (ß=0.11, p=0.07) and Fluency

(ß=-0.14, p=0.07). After adjustment for intellectual functioning, the psychometrically defined risk group no longer differed significantly from the controls on SCWT III.

Table 3. Associations between cognitive functioning and the group variable reflecting risk for psychosis (Controls were used as reference category)

	Psychometrically defined risk group (1)			Familial Risk group (2)			Patients (3)		
	β	t	p-value	β	t	p-value	β	t	p-value
TMT a	0.07	0.93	0.36	0.10	1.29	0.20	0.34	2.22	0.03
TMT b	0.05	1.11	0.27	0.20	2.20	0.03	0.40	2.72	0.01
TMT c	0.03	0.44	0.66	0.17	1.99	0.05	0.26	2.24	0.03
SCWT I	0.23	2.43	0.02	0.00	0.01	0.99	0.06	0.67	0.50
SCWT II	0.08	1.04	0.30	0.05	0.59	0.55	0.24	2.34	0.02
SCWT III	0.11	2.03	0.04	0.11	1.85	0.07	0.46	2.94	0.00
Fluency	-0.06	-0.73	0.47	-0.13	-1.60	0.11	-0.28	-3.29	0.00

Note: all analyses adjusted for age, sex and years of education

On TMT B and TMT C, not only the patient group, but also the familial risk group differed significantly from the group of control subjects (see Table 3). On SCWT card III, the psychometrically defined risk group also differed from the controls in addition to the patients (ß=0.11, p=0.04). After adjustment for intellectual functioning, a trend towards a difference between the familial risk group and the group of controls was apparent for TMT A (ß=0.14, p=0.06), SCWT III (ß=0.11, p=0.07) and Fluency (ß=-0.14, p=0.07). After adjustment for intellectual functioning, the psychometrically defined risk group no longer differed significantly from the controls on SCWT III.

Risk for psychosis and summary measure of cognitive impairment: cognitive speed

Principal component analysis of the neuropsychological variables resulted in a one-factor solution accounting for 54 % of the total variance. All the neuropsychological variables loaded on this factor (factor loadings from 0.33 to 0.42) which was termed "cognitive speed", as performance on all used tests was highly dependent on speed of information processing. Higher scores on the factor indicate poorer performance. Group was significantly associated with this factor (ß=0.29, p=0.00) and a monotonic dose-response relationship between cognitive speed and risk for psychosis was found after adjustment for intellectual functioning (psychometrically defined risk group: ß=0.10, p=0.14, familial risk group: ß=0.16, p=0.02, patients: ß=0.33, p=0.00), performance decreasing with increasing psychosis risk.

Cognitive functioning and psychopathology

Examination of the association between the dimensional loading variables and the summary measure of cognitive speed indicated that in the psychometrically defined risk group, a trend towards a significant association in the expected direction was only found between negative symptoms and cognitive speed (ß=0.25, p=0.09) (see Table 4). No significant associations were found for dimensional loading of positive symptoms and disorganization. In the familial risk group, positive, but not negative dimensional loading was associated with cognitive speed (ß=0.30, p=0.03). In the group of patients, a strong and significant positive association between symptomatology and cognitive speed was found for negative dimensional loading only (ß=0.48, p=0.00) (Table 4).

Table 4. Associations between psychopathology and cognitive speed

Cognitive speed	Psychometrically defined risk group (1)			Familial risk group (2)			Patients (3)		
	β	t	p-value	β	t	p-value	β	t	p-value
Positive	0.13	0.89	0.38	0.30	2.27	0.03	0.17	0.95	0.35
Negative	0.25	1.77	0.09	-0.02	-0.15	0.88	0.48	3.18	0.00
Disorganization	0.03	0.23	0.82	0.23	1.62	0.11	0.15	0.87	0.39

Note: All analyses adjusted for age, sex and years of education

Cognitive functioning and functional outcome

In the psychometrically defined risk group, there was a trend towards a negative association (ß=-0.34, p=0.1) between cognitive speed and number of months at work. This trend towards significance became stronger after entering dimensional loading measures in the equation (ß=-0.38, p=0.09). The various psychopathology dimensional loading variables were not significantly associated with occupational functioning in this group.

A strong and significant negative association was found between number of months at work and cognitive speed in the familial risk group (ß=-0.45, p=0.01), indicating that a reduction of cognitive speed was associated with reduced occupational functioning. Entering the dimensional loading variables in the equation did not change this association, but negative dimensional loading was also independently associated with occupational functioning (ß=-0.42, p=0.01). In the patient group, the association between occupational functioning and cognitive speed was neither large nor significant (ß=0.10, p=0.64), and also psychopathology dimensional loading measures were not associated with occupational functioning. In none of the groups was cognitive speed associated with independent community living (all Beta's between –0,27 and 0.17, p>0.20).

Discussion

Findings

The results of this study can be summarized as follows. Cognitive performance was associated with the degree of genetic liability to psychosis. There was a dose-response relationship between cognitive dysfunction and increasing risk for psychosis for speed of information processing, selective attention, and set shifting (executive control), in which the degree of cognitive impairment (order: patients - familial risk - psychometric risk - controls) paralleled the degree of risk for psychosis. Negative symptoms were associated with cognitive functioning only at the disorder end of psychosis risk, whereas in the familial risk group, cognitive alterations were associated with positive symptoms. In the familial and psychometrically defined risk groups, but not in patients, there was an association between cognitive performance and occupational functioning.

Cognitive vulnerability markers across a continuum of risk

The finding that cognitive functioning was associated with the level of risk for psychosis is in accordance with previous studies indicating impaired cognitive performance in relatives (Krabbendam et al., 2001; Kremen & Hoff, 2004) and, to a lesser degree, in psychometrically defined at-risk subjects (Dinn et al., 2002; Krabbendam et al., 2005; Siever & Davis, 2004; Tien et al., 1992). In a review on cognitive performance in relatives of schizophrenia patients (Kremen & Hoff, 2004) impairments were found on measures of perceptual motor speed, sustained attention, concept formation, declarative memory and verbal fluency which is overlapping with frequently reported cognitive deficits in schizophrenia patients (Heinrichs & Zakzanis, 1998). In a study by Hoff and colleagues (Hoff et al., 2005) non-psychotic relatives were particularly impaired on measures of psychomotor speed, verbal fluency and cognitive inhibition. In a quantitative meta analysis (Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004) in relatives, the largest effect sizes were found for verbal recall and visuomotor speed (TMT B) and smallest on the SCWT which parallels the current data in that the strongest associations were found on the TMT and no clear associations existed with SCWT. Psychometrically defined vulnerable subjects showed impairment relative to controls on domains of executive function, working memory, verbal learning and attention (Siever & Davis, 2004). Verbal fluency was associated with psychometric psychosis proneness in a previous study (Krabbendam et al., 2005), where it was shown that in a general population sample, higher levels of psychometrically defined risk were associated with worse verbal fluency. The present findings add credence to the suggestion that cognitive deficits in schizophrenia might be putative endophenotypes for the disorder (Faraone et al., 1999). By including four groups with increasing levels of

risk for psychosis and using group as a linear variable of continuous schizophrenia liability, it was assumed that the differences between groups are equal, and this may not be the case. However, testing linear hypotheses of schizophrenia risk using at-risk groups has been proven a useful and statistically powerful way to identify markers of familial risk (Faraone et al., 1999; Sharma et al., 1997). Assuming that the groups in this study reflect the expression of a graded genetic predisposition to the disorder, the present study demonstrates that cognition can be usefully construed as a vulnerability marker across a continuum of psychosis risk (Johns & van Os, 2001; van Os et al., 1999).

Cognitive performance and psychopathology

The finding of an association between negative symptoms and cognitive speed in patients are in accordance with previous research showing that severity of negative symptoms is associated with several neuropsychological deficits, especially in the domains of verbal memory, verbal fluency, psychomotor speed and executive function (Bilder et al., 2000; Heydebrand et al., 2004; Keefe et al., 2006). The current results indicate that in subjects at familial risk for psychosis, cognitive alterations are also associated with psychopathology, as in the familial risk group the positive symptom dimension was associated with cognitive speed. The contrast between the patient and the familial risk group is interesting, and confirms that in non-patients, the subtle low-grade expression of experiences resembling the positive symptoms of psychosis are a reliable indicator of risk for psychotic disorder, both in terms of genetic transmission (Hanssen et al., 2006; Kendler et al., 1993) and of future transition to disorder (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Hanssen, Bak, Bijl, Vollebergh, & van Os, 2005; Poulton et al., 2000), whereas once the illness becomes established, negative symptoms appear to be a more reliable indicator of vulnerability.

In addition to negative symptoms, disorganization was associated with cognitive functioning in patients in previous studies (Brazo et al., 2002; O'Leary et al., 2000; Van der Does, Dingemans, Linszen, Nugter, & Scholte, 1996). However, there is evidence that different symptom dimensions may be associated with different patterns of neuropsychological functioning (Bilder et al., 2000; O'Leary et al., 2000), and information processing speed was mainly associated with negative symptoms in previous research (Van der Does et al., 1996). It has been suggested that the negative symptom dimension is associated with more widespread cognitive impairment and disorganization more with higher order processing (O'Leary et al., 2000). Post-hoc analyses suggested that the lack of association with disorganization was not caused by the use of a summary cognitive factor of cognitive speed, as

disorganization was similarly not associated with performance on TMT C, SCWT card III and Fluency, tasks that are considered measures of higher control.

Cognitive performance and outcome

Previous research has consistently reported an association between cognitive functioning and outcome in patients (Green, 1996; Green et al., 2004). The current findings in patients did not support this as cognitive speed was not associated with the outcome measures used. However, the absence of an association was due to a lack of variation in the outcome measures used, as in the Netherlands only very few patients are in competitive employment given the fact that there is a powerful financial disincentive for patients to seek employment. Similar findings were reported from France, where a similar disincentive exists (Verdoux, Liraud, Assens, Abalan, & van Os, 2002).

An important finding in the current study was that alterations in cognitive speed in the familial and the psychometrically defined at-risk group were associated with variation in occupational functioning. Post-hoc analyses showed that this association was not present in controls, suggesting that the decrease in occupational functioning was not simply the consequence of poorer cognitive functioning but is associated with social disability in the context of vulnerability to psychosis. Processing speed has been identified as a critical factor in mediating employment outcome in previous research (Lysaker et al., 2005; Milev et al., 2005) and the present results underline the importance of cognitive speed in vocational outcome not only in clinical samples but also in those at-risk for the disorder.

Neutral indicators of genetic risk or markers of early disability?

In addition to previous findings that cognitive dysfunctions in patients with psychotic disorder have been associated with both illness (symptoms) and disability (functional outcome) the present findings show that cognitive alterations, as indicators of psychosis vulnerability, also impact on the expression of psychopathology and functional outcome in at-risk groups. The presence of these associations in at-risk groups suggests that cognitive endophenotypes in psychosis are not always neutral indicators of genetic risk and that its transmission can be associated with clinical risk, expressed in psychopathology and social disability across all levels of risk.

Limitations

The results of the present study should be viewed in the light of several methodological issues. First, the cognitive assessment was limited to a few measures that all

reflected cognitive speed. Therefore the findings have been confined to the selected tests, and future research will be necessary to investigate whether the results can be generalized to other cognitive domains.

Second, although investigating subclinical phenotypes, psychometric instruments developed for clinical use were applied to asses presence and severity of symptoms (SAPS and SANS). This may have caused an underestimation of the association between symptoms and cognition in the at-risk groups. Furthermore, the subclinical psychosis group was defined on the basis of positive psychotic experiences and it can be argued that this may have caused little variation in subclinical negative symptoms. This seems unlikely however, as positive and negative symptoms are highly associated (Stefanis et al., 2002), in particular in non-clinical groups.

Some researchers have suggested that a three-dimension model of schizophrenia psychopathology is too limited, and in addition to these three symptom dimensions a depression dimension has been reported in schizophrenia (Holthausen, Wiersma, Knegtering, & Van den Bosch, 1999). Although its relationship with cognitive functioning has not been studied extensively yet, depression has consistently been found to affect cognitive functioning, and two studies on cognitive functioning in schizophrenia that included depressive symptoms reported that these symptoms were associated with a reduced performance on cognitive measures (Holthausen et al., 1999; Rocca et al., 2005). Thus part of the reported psychopathological associations may be reducible in part to the effect of depression. Depressive symptomatology may also explain part of the observed association between cognitive functioning and outcome in the at risk groups.

Fourth, the outcome assessment in this study was limited to a few outcome measures and the used measures were not very detailed. Number of months at work and of independent living were used as the dependent variable and it can be argued that a more sensitive measure of outcome might have produced more powerful results with respect to the association between cognition and outcome. This might have caused the outcome variables to show a ceiling effect, but the use of such objective indices of outcome has some clear advantages. The fact that only patients were interviewed about their functioning may also pose a weakness, given that schizophrenia may be associated with reduced insight (Amador & David, 2004). However, the use of objective indices of outcome in the current study probably minimized the influence of any impairment of insight.

Finally, some families only contributed one patient or one relative; it would have been better to include only pairs of patients and their relatives from the same family, as this would increase power and control for within-family confounders.

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CHAPTER 7

IS PROCESSING SPEED PREDICTIVE OF FUNCTIONAL OUTCOME IN PSYCHOSIS?

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Abstract

Objective: To investigate the contribution of processing speed in the prediction of various domains of outcome in psychosis. **Method:** Data were drawn from the UK700 Case Management Trial of 708 patients with chronic psychotic illness. Regression analyses were applied to investigate cross-sectional and longitudinal associations between processing speed at baseline and measures of service use, social outcome and subjective outcome, taking into account current psychopathology and adjusting for baseline values of the outcome measure. **Results:** Cross-sectionally, processing speed was associated with all three domains of outcome, although only associations in the social and subjective outcome domain remained significant after controlling for psychopathology and the effects differed between and within domains of outcome. Prospectively, only the subjective outcome measure of number of met and unmet needs (CAN) was weakly associated with baseline neurocognitive performance after adjustment for baseline needs. Other associations disappeared after adjustment for the baseline measure of outcome and/or baseline psychopathology. **Conclusion:** The finding of weak cross-sectional associations in the absence of specific and unconfounded longitudinal associations suggests that processing speed is an independent dimension of disease severity rather than a causal factor impacting on social outcome. Nevertheless, longitudinal change in patient reported needs may be weakly sensitive to baseline cognitive impairment.

Key Words: functional outcome; psychosis; processing speed; symptoms

Introduction

Given the substantial heterogeneity in course among individuals with a diagnosis of schizophrenia, identifying course predictors remains crucially important. In the search for predictors of outcome, the roles of various clinical and demographic characteristics have been investigated (Breier, Schreiber, Dyer, & Pickar, 1992; Lieberman et al., 1996; R. M. G. Norman et al., 2005; Robinson, Woerner, McMeniman, Mendelowitz, & Bilder, 2004), and there is now an impressive quantity of literature showing the importance of neurocognitive deficits in functional outcome in schizophrenia in terms of statistical associations (Green, 1996; Green, Kern, Braff, & Mintz, 2000). In particular neurocognitive functioning in domains of verbal memory, vigilance and executive functioning has been emphasized to be important predictor of functional outcome (Green et al., 2000), although other studies also demonstrated the importance of processing speed in the prediction of everyday functioning (Dickinson, Iannone, Wilk, & Gold, 2004; Milev, Ho, Arndt, & Andreasen, 2005).

It has been suggested that outcome in psychosis is more strongly associated with stable characteristics, such as cognitive functioning, than to the much more variable positive symptoms of psychosis (Bryson & Bell, 2003; Green, 1996). However, there is evidence that the symptoms of psychosis do impact on various measures of outcome (van Os et al., 1999) and studies comparing neurocognitive and symptom measures in their relative associations with subsequent outcome do not entirely support the conclusion that cognition is a better predictor than symptomatology (Addington, Saeedi, & Addington, 2005; Dickinson & Coursey, 2002; Milev et al., 2005; R. M. Norman et al., 1999). Some researchers proposed that it is not so much the absolute level of symptoms at the time of an acute episode, that at baseline typically are uniformly high and therefore not discriminative, but rather the level of subsequent persistence of symptoms that predict outcome (R. M. Norman et al., 1999). Therefore, it is important to investigate symptoms and neurocognition in the same group of patients in a stable phase of the illness so the prognostic value of both indices can be compared.

A large proportion of studies investigating the relationship between cognition and outcome use a cross-sectional design, while reports on longitudinal relationships between predictors and baseline-adjusted outcome are essential to evaluate their true long-term prognostic value (A. Malla & Payne, 2005). In a review of longitudinal studies (Green, Kern, & Heaton, 2004), it was concluded that there was considerable support for longitudinal associations between neurocognition and community outcome. Other longitudinal studies, however, found that neurocognition at onset was only weakly associated with outcome at follow-up compared to the much stronger cross-sectional associations, indicating that neurocognition explains

less of the variance in outcome than cross-sectional studies would suggest (A. K. Malla, Norman, Manchanda, & Townsend, 2002; Milev et al., 2005; Stirling et al., 2003). Moreover, only few studies examined neurocognition in relation to *changes* in functional outcome, by taking into account baseline level of functioning. If baseline levels of the outcome measure are not taken into account, "predictive" associations with follow-up measures may merely reflect associations that were already apparent at baseline, and serve as passive indicators of disease severity (van Os, Wright, & Murray, 1997).

The inconsistency of findings may also partly be due to the fact that outcome is not a unitary concept, and different domains of outcome may differ in their cognitive and symptom correlates. For example, one study suggested that the used cognitive measures were only prognostic of the subjective outcome domain of quality of life, whereas the objective outcome measure of rehospitalisation was better predicted by demographic and clinical variables (Sota & Heinrichs, 2004). Also, different symptoms differentially influence outcome. A previous analysis of the current data (van Os et al., 1999) revealed that reductions in psychopathology were associated longitudinally with improvement in outcome, but the size of associations was different for the various dimensions of symptoms and functioning.

The aim of the current study was to clarify the role of processing speed as a prospective predictor of various domains of outcome in a large sample of stable patients with chronic psychotic illness. Extending a previous analysis of the same data (van Os et al., 1999), in which the impact of psychopathology dimensions on outcome was assessed, this study investigated the relative importance of processing speed in the prediction of functional outcome. First, the cross-sectional relationship between processing speed and various measures of outcome was investigated, in order to evaluate whether processing speed was associated with baseline measures of the outcomes examined over and above measures of symptomatology. Secondly, the prognostic value of processing speed on functional outcome was examined by investigating longitudinally whether processing speed at baseline was, over and above symptomatology, associated with baseline-adjusted outcome measures at follow-up.

Methods

Sample

Data were drawn from the baseline and year 2 assessments of the UK700 Case Management Trial, a 2-year randomised controlled trial comparing the efficacy of different intensities of case management in psychotic patients (Burns et al., 1999; Metcalfe et al., 2005). The rationale and detailed methodology of the UK700 study

have been reported elsewhere (UK700Group, 1999a, 1999b). The 708 patients in the UK700 study were recruited at the point of discharge from the hospital or in the community. Criteria for inclusion were: 1) presence of a psychotic illness according to the Research Diagnostic Criteria (Spitzer, Endicott, & Robins, 1978), 2) aged between 16 and 65 years, 3) hospitalized for psychotic symptoms at least twice, the most recent admission within the past 2 years, 4) absence of obvious organic brain damage or a primary diagnosis of substance abuse.
Subjects were interviewed at baseline and at one and two year follow-up. Baseline assessments took place prior to randomisation and involved the collection of socio-demographic data and a clinical and neuropsychological assessment. Clinical assessments were also carried out one year and two years after randomisation. For the present study data were drawn from the baseline and year 2 follow up assessment.

Neuropsychological assessment
A short neuropsychological assessment took place at baseline and consisted of the Trail Making Test (TMT) parts A and B (Reitan, 1958) and the National Adult Reading Test (NART) (Nelson & Willison, 1991). The TMT is primarily a test of visual conceptual and visuomotor tracking and can be considered a measure of processing speed (Lezak, 1995). In part A, subjects had to draw lines to connect consecutively numbered circles. In part B, subjects connected the same number of consecutively numbered and lettered circles by alternating between the two sequences. It therefore, reflects more complex information processing than part A. The score is the time to complete each part of the test.
Additionally, level of premorbid intelligence was estimated using the NART. This reading test makes minimal demands on current cognitive capacity and is relatively resistant to neurological and psychiatric disorder. Therefore, it can be considered a useful measure of premorbid intellectual functioning in the group of patients with a psychotic illness.

Psychopathology assessment
At baseline, the Operational Criteria Checklist for Psychotic Illness (OCCPI) (Mc Guffin, Farmer, & Harvey, 1991) was completed for all patients and the computer program OPCRIT was used to derive diagnoses. For the present study, the RDC diagnostic system was used (Spitzer et al., 1978).
At baseline and at follow up, current psychopathology was measured using the Comprehensive Psychopathology Rating Scale (Jacobsson et al., 1978). For the purpose of this research the symptom dimensions derived from previous factor analysis were used (van Os et al., 1999). Four psychopathology dimensions were

retained, reflecting depressive, manic, negative and positive symptoms. Standardised factor scores were calculated and had a mean of zero and a standard deviation of 1.

Functional outcome assessment

Functional outcome was assessed at baseline and at two year follow-up. Service use was assessed by the number of hospital admissions and by the number of days spent in hospital over the past two years, measured using a slightly modified version of the Life Chart Schedule (WHO, 1992).

Social outcome was assessed using measures of employment, independent living and social disability. The number of months in employment and independent living over the past two years were measured using the Life Chart Schedule (WHO, 1992). Employment was composed of fulltime and part-time jobs, sheltered jobs, retirement or being a student. Independent community living was defined as the total number of months in independent community living over the past two years. Social disability was assessed using the WHO Disability Assessment Schedule (DAS) (Jablensky, Schwartz, & Tomov, 1980; WHO, 1992). The two 'overall behaviour' items and the nine 'social roles' items were used to rate the level of social disability, higher scores indicating higher rates of disability.

Subjective outcome was measured by reported quality of life and needs for care. Quality of Life (QoL) was rated using a structured self-report interview (Lancashire Quality of Life Profile (Oliver, Huxley, Priebe, & Kaiser, 1997) based on the Lehman Quality of Life Interview (Lehman, Ward, & Linn, 1982). It consists of 100 items assessing QoL and life satisfaction in nine areas (subscales). The mean of the subscales was used as the dependent variable, higher scores reflecting better QoL. The Camberwell Assessment of Need (CAN) (Phelan et al., 1995) assesses 22 areas of need, each area including four sections. In the current study only the first section was used; this establishes whether there is a need, by asking about difficulties in that area. Responses are rated on a three point scale (0 = no serious need; 1 = no/moderate problem because of continuing intervention (met need); 2 = current serious problem (unmet need)). The number of met and the number of unmet needs were used as dependent variables. Needs were scored as viewed by the patient, thus constituting a subjective outcome.

Statistical analyses

For convenience of interpretation of the data, TMT variables were recoded so that a higher score on neurocognitive variables indicated a better performance. First, to investigate the extent of the relationship between the processing speed variables and symptomatology partial correlations were calculated, adjusting the symptom dimen-

sions for each other. For the investigation of cross-sectional associations between cognitive variables and outcome, multiple linear regressions, *a priori* adjusted for the basic confounders age, sex, educational qualifications, ethnicity, and centre, were applied. Separate models were used for each of the three neurocognitive variables. Functional outcome at baseline was used as dependent variable, and the neurocognitive measure and the basic confounders as independent variables. In case of significant or near significant associations (p-values ≤ 0.10), psychopathology dimensions were additionally entered into the equation simultaneously in order to investigate whether the cognitive variable had prognostic value in addition to current symptoms.

Likewise, for the investigation of longitudinal associations between cognition at baseline and outcome at follow-up, multiple linear regression analyses, *a priori* adjusted for age, sex, educational qualifications, ethnicity, centre and case management intervention, were applied. First, a single neurocognitive variable was entered as predictor of functional outcome at follow up. In case of significant or near significant associations (p-values ≤ 0.10), analyses were repeated, adjusted for the equivalent of the outcome variable at baseline, in order to examine the true association with change in the functional outcome variable over time. If a (near) significant association remained, psychopathology dimensions at baseline were additionally entered into the equation in order to examine whether the neurocognitive variable had longitudinal prognostic value in addition to symptoms. Finally, a sensitivity analysis was done, in which the cross-sectional and longitudinal analyses were repeated excluding patients with an RDC diagnosis of affective or unspecified psychosis in order to examine whether correlations were confounded by the inclusion of individuals with a diagnosis other than schizophrenia spectrum disorders. Effect sizes were expressed as standardised regression coefficients (ß).

Results

Demographic characteristics

Seven-hundred and eight patients entered the study. Mean age of participants at study entry was 38.3 years (SD 11.6); there were more men (57%) than women (43%). Just over half (52%) of the patients was white, 28% was African-Caribbean and 20 % pertained to other ethnic groups. Forty-five percent of the participant had no educational qualifications, 32% was classified as CSE/GCSE/O level and 23% had an A level or degree. The most common RDC diagnosis at study entry was schizophrenia (49%) followed by schizoaffective disorder (38%). Other patients were diagnosed as suffering from affective or non-specified psychosis.

Of the seven-hundred and eight patients who entered the study, 15% did not complete TMT A, 38% did not complete TMT B, and 38% of the participants did

not complete the NART. Characteristics of the patients with missing data are described in detail elsewhere (Gilvarry, Barber, van Os, & Murray, 2001). Briefly, patients who did not complete TMT were more likely to have negative symptoms, positive symptoms, to have less education and to be older. Those with missing TMT B scores were additionally more likely to be from lower socioeconomic groups. Patients not completing the NART were less likely to be white, more likely to be older, less educated and to show more negative, and more positive symptoms (Gilvarry et al., 2001). Summary scores of neurocognitive and functional outcome variables are presented in table 1.

Regarding the extent of the relationship between predictor variables of processing speed and symptom dimensions, partial correlation analyses revealed that TMT A was significantly associated with positive symptoms (r=0.12, p=0.05) and there was a trend towards an association with negative symptoms (r=0.07, p=0.09). No significant correlations were found for the other symptom dimensions (depression: r=0.02 and mania: r=0.05). TMT B was significantly associated with negative (r=0.20, p=0.00) and positive (r=0.14, p=0.01) symptoms, but not with mania (r=-0.03) and depression (r=0.01).

Table 1. Neurocognitive and functional outcome measures: summary

	Baseline		Follow up		Change scores	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Neuropsychological tasks						
TMT A	599	60.8 (39.5)				
TMT B	437	119.20 (62.2)				
Nart	586	106.40 (10.5)				
Service use (range)						
Number of hospital admissions (0-13)	707	1.9 (1.2)	703	1.1 (1.5)	703	-0.8 (1.7)
Time in hospital (0-730)	707	108.9 (112.6)	703	81.3 (125.4)	703	-28.0 (141.4)
Social outcome (range)						
Employment, months (0-24)	705	3.1 (6.6)	685	2.6 (6.5)	683	-0.3 (6.5)
Independent living, months (0-24)	707	16.8 (7.6)	698	15.7 (9.3)	698	-1.0 (7.0)
DAS total score (0-4.8)	696	1.2 (0.9)	596	1.1 (0.8)	587	-0.1 (0.9)
Subjective outcome (range)						
QoL (1.2-6.8)	689	4.3 (0.7)	526	4.6 (0.7)	513	0.3 (0.8)
CAN number of needs (0-14)	699	6.0 (3.0)	585	6.5 (3.1)	579	0.4 (3.5)
CAN number of unmet needs (0-14)	699	2.6 (2.3)	585	2.0 (2.4)	579	-0.7 (2.9)

Cross-sectional associations between cognition and outcome

In the outcome domain of service use, multiple regression analysis showed a trend towards a significant association between number of hospital admissions and performance on TMT B (ß=-0.10, p=0.07) (Table 2), a better test performance predicting fewer hospital admissions. Entering psychopathology dimensions into the

equation reduced the strength of this association (ß=-0.08, p=0.17). For time in the hospital a weak trend towards an association was found with TMT A (ß=-0.08, p=0.07) that was reduced only marginally after correcting for current psychopathology (ß=-0.08, p=0.09).

Regarding social outcome, a significant cross-sectional association was found between performance on TMT B and employment; a better cognitive performance was associated with a longer duration of employment (ß=0.12, p=0.02). Entering dimensions of psychopathology in the equation reduced the association (ß=0.08, p=0.13). TMT A was significantly associated with months in independent living (ß =0.11, p=0.01) and this association remained significant after entering psychopathology dimensions in the equation (ß =0.10, p=0.02). The trend towards an association between TMT B and independent living was reduced after entering psychopathology (ß =0.04, p=0.50). The outcome measure of social disability, measured with the DAS, was associated with TMT A and NART (see table 2). After adjustment for psychopathology, however, only the association with NART remained equally large and significant (TMT A: ß=-0.03, p=0.45, TMT B: ß=-0.01, p=0.90, NART: ß =-0.12, p=0.01).
In the subjective outcome domain, QoL score was significantly associated with NART performance (ß=-0.10, p=0.04); better NART performance was associated with a lower QoL score. This association was reduced but not nullified after adjustment for current psychopathology (ß=-0.08, p=0.08). For TMT performance no association with QoL was found. Number of met needs (CAN) was associated with none of the neurocognitive measures. The number of unmet needs (CAN) showed a significant association with TMT B (see table 2), worse cognitive performance being associated with an increased number of unmet needs. Adjustment for psychopathology dimensions only marginally reduced the strength of this association (ß=-0.12, p=0.02).

Longitudinal associations between cognition and outcome
Longitudinally, no significant associations were found for service use measures: number of hospital admissions and time in the hospital at follow up were not associated with TMT or NART performance at baseline (see table 2).
As to the social outcome domain, no longitudinal association was found between neurocognitive predictors and months of employment. The trend towards a significant positive association between independent living at follow-up and TMT A performance at baseline (ß=0.08, p=0.09) was reduced after adjustment for independent living at baseline (ß=0.01, p=0.73). Social disability (DAS) at follow-up was associated with TMT performance at baseline (see table 2). However, after

adjustment for social disability at baseline these associations were much reduced (TMT A: ß=-0.03, p=0.50, TMT B: ß=-0.07, p=0.17).
Regarding subjective outcome, no association was found between the neurocognitive variables at baseline and QoL at follow-up (see table 2). Number of met needs (CAN) however, showed a significant negative association with TMT A and B, impaired neurocognitive performance at baseline being associated with an increased number of needs at follow-up. Adjustment for the number of met needs at baseline did not reduce these associations (TMT A: ß=-0.08, p=0.09, TMT B: ß=-0.16, p=0.00) nor did additional adjustment for psychopathology (TMT A: ß=-0.07, p=0.10, TMT B: ß=-0.17, p=0.00). A similar pattern was found for the number of unmet needs at follow-up.

Table 2. Associations between neurocognitive variables and outcome measures

		Estimates cross-sectional		Estimates longitudinal	
		ß	p-value	ß	p-value
Service use					
Hospital admissions	TMT A	0.02	0.69	0.06	0.15
	TMT B	-0.10	0.07	0.03	0.60
	Nart	-0.04	0.40	0.08	0.13
Time in hospital	TMT A	-0.08	0.07	0.04	0.33
	TMT B	-0.00	0.95	0.04	0.50
	Nart	0.01	0.83	0.02	0.77
Social outcome					
Employment	TMT A	0.04	0.32	-0.03	0.52
	TMT B	0.12	0.02	0.05	0.35
	Nart	0.03	0.60	0.08	0.14
Independent living	TMT A	0.11	0.01	0.08	0.09
	TMT B	0.09	0.10	0.08	0.16
	Nart	0.01	0.92	0.03	0.56
Social disability	TMT A	-0.09	0.03	-0.08	0.09
	TMT B	-0.09	0.08	-0.11	0.05
	Nart	-0.11	0.02	-0.06	0.31
Subjective outcome					
QoL	TMT A	0.02	0.67	0.02	0.67
	TMT B	-0.07	0.21	-0.04	0.50
	Nart	-0.10	0.04	0.07	0.28
CAN Needs	TMT A	-0.04	0.40	-0.09	0.05
	TMT B	-0.08	0.11	-0.19	0.00
	Nart	-0.05	0.37	-0.10	0.08
CAN unmet Needs	TMT A	0.01	0.90	-0.11	0.02
	TMT B	-0.14	0.01	-0.21	0.00
	Nart	-0.08	0.10	-0.03	0.56

Note: all analyses adjusted for age, sex, educational qualifications, ethnicity and centre

Repeating cross-sectional and longitudinal analyses, excluding patients with an RDC diagnosis of affective or unspecified psychosis, did not change the pattern of results.

Discussion

The findings can be summarised as follows. Cross-sectionally, processing speed was associated with all three domains of outcome, although only the associations in the social and subjective outcome domain remained significant after controlling for psychopathology. Generally, processing speed but not premorbid intellectual performance was associated with objective outcome measures of hospital admissions, independent living and employment, whereas both the measures of premorbid intellectual functioning and processing speed were associated with subjective appraisal of outcomes, although not consistently so. The present results suggest that processing speed is associated with social and subjective outcomes over and above psychopathology, but not to services use.

The prospective prognostic value of processing speed and premorbid intelligence on functional outcome was less evident. Only the subjective outcome measure of number of met and unmet needs (CAN) was weakly associated with baseline processing speed performance after adjustment for the baseline level of needs.

The finding of weak cross-sectional associations in the absence of specific and unconfounded longitudinal associations suggests that processing speed is an independent dimension of disease severity rather than a causal factor impacting on aspects of social outcome.

Associations with service use

In the current study no clear cross-sectional or longitudinal association between processing speed and hospitalization was found. In a previous study (Fujii & Wylie, 2002) TMT B performance was prognostic of total duration of hospital inpatient status. Other prospective studies, however, did also not find an association between cognitive measures and hospitalization during the follow up period (Sota & Heinrichs, 2004; Stirling et al., 2003). Previous analyses on the current data set showed that reduction of positive and manic symptoms was strongly associated with a reduction in the number of hospital admissions (van Os et al., 1999), which is in accordance with the suggestion of Green (Green, 1996) that psychotic symptoms may be a better predictor of clinical outcome measures of psychosis.

Associations with social outcome

Cross-sectionally, cognitive speed was weakly associated in the expected direction with all three measures of social outcome. However, only the association with independent living remained significant after adjustment for current symptoms. The absence of an association between processing speed and months at work is in contradiction with other studies that did find a significant association between neurocognition and work performance in schizophrenia (Addington, McCleary, &

Munroe-Blum, 1998; Lysaker, Bryson, Davis, & Bell, 2005; Milev et al., 2005). Social disability was associated with premorbid intellectual functioning, also after controlling for psychopathology, suggesting that premorbid intellectual functioning explained variance in social outcome in addition to the four psychopathology dimensions that were previously reported to be strongly and independently associated with social disability (van Os et al., 1999).

The lack of longitudinal associations between processing speed, premorbid intellectual functioning and changes in the measures of social outcome is in accordance with a previous study (Verdoux, Liraud, Assens, Abalan, & van Os, 2002) in which no associations between cognitive variables and social outcome measured by employment and independent living were found. Other studies, however, did report an association between neurocognitive functioning and vocational functioning (Bryson & Bell, 2003; Gold, Goldberg, McNary, Dixon, & Lehman, 2002; McGurk & Meltzer, 2000). Previous analyses of this dataset showed that symptomatology was associated with social outcome since a reduction in positive and negative symptoms was associated with more time living independently and a reduction in all four psychopathology dimensions was associated with improvement in social disability (van Os et al., 1999).

Associations with subjective outcome

In cross-sectional analyses, premorbid intellectual functioning, measured by NART, was weakly though significantly associated with Quality of Life, in the direction that a better premorbid intelligence was associated with a lower appraisal of QoL. This is consistent with the results of Prouteau et al. (Prouteau et al., 2005) who reported a similar relationship between neurocognitive functioning and self-rated quality of life. Although, this appears to be a paradoxical finding as, generally, a better cognitive performance is associated with better outcome, it has been hypothesized that people with worse neuropsychological functioning have a lesser capacity for complex self-referencing. They therefore can directly translate improvements in their objective psychosocial status into enhanced subjective experience without being hindered by external or premorbid self-referencing (Brekke, Kohrt, & Green, 2001). Longitudinally, subjective QoL was not predicted by neurocognitive measures at baseline, which is in accordance with a previous study in which positive and negative symptoms were more important predictors of QoL than neurocognitive functioning in the long run (Addington et al., 2005). Previous research also taking into account depressive symptomatology, indicated that measures of subjective outcome were strongly associated with depression and to a lesser extent with negative symptoms (Smith et al., 1999; van Os et al., 1999).

Number of unmet needs (CAN) showed a weak association in the hypothesised direction with TMT B performance when measured at the same point in time, independent from psychopathology. Longitudinally the number of met and unmet needs on the CAN was strongly predicted by TMT performance at baseline, even after controlling for baseline levels of the outcome variable and for baseline psychopathology. This in accordance with a previous study that also found that need for care was predicted by speed of processing (Holthausen et al., 2007).

Methodological considerations

The results of the present study should be viewed in the light of several methodological issues. First, the current study only considered processing speed, while previous research has demonstrated the importance of other cognitive domains, for example verbal memory and executive functioning, in the prediction of functional outcome. Also, as different domains of outcome may differ in their cognitive correlates, a more extensive cognitive assessment will be required to investigate whether the same results will apply for other cognitive domains. However, previous research indicated that the attention/speed domain is one of the cognitive domains most relevant to functional outcome in schizophrenia (Lysaker et al., 2005; Milev et al., 2005) and that cognitive abnormalities in schizophrenia are mediated through a single common cognitive factor (Dickinson et al., 2004). Second, as mentioned in the results section, a proportion of the subjects did not complete the neuropsychological testing. There is reason to assume that these missing data are not random, as patients who did not complete the testing were most adversely affected by their illness. This may have biased the research population to be less impaired than the original sample thereby causing less variation in outcome and its predictors. Third, in the current study a relatively chronic population was studied. This may have caused less variation in outcome than when first episode patients would have been investigated, and the results may not generalise to first episode patients. However, much of the work suggesting true predictive power of baseline cognition, summarised by Green (Green, 1996), was on chronic patients. Fourth, the current sample consisted of patients with a diagnosis of psychosis in general, and did not focus on one diagnostic category. A categorical approach does not capture the broad heterogeneity of psychosis and schizophrenia and therefore it was suggested that outcome may be best investigated using a dimensional approach to psychopathology of psychosis (Carlsson, Nyman, Ganse, & Cullberg, 2006; Rosenman, Korten, Medway, & Evans, 2003). The previously reported absence of any pattern of interaction with diagnostic category in the current sample (van Os et al., 1999) and the stability of findings when repeated in schizophrenia and schizoaffective diagnoses only, appears to justify this approach. Finally, al-

though the current results did not show a consistent relationship between processing speed, premorbid intellectual functioning and outcome, previous results in the UK700 study, examining the effect of different intervention types on outcome, showed a significant interaction effect between type of case management and borderline-intelligence status (Tyrer, Hassiotis, Ukoumunne, Piachaud, & Harvey, 1999). Patients with borderline intellectual functioning treated with intensive case management had a mean of only 47 days in hospital compared with 105 days for those treated with standard care. No differential effects of intervention type were found for the group with normal intelligence (Tyrer et al., 1999). Similar gains for borderline IQ patients, treated with intensive case management were shown in satisfaction with services, total costs and needs (Hassiotis et al., 2001). Therefore, neurocognition, at least at the level of basic intelligence, is a relevant factor in the selection of appropriate treatment and this finding should not be obscured by the lack of any important associations between neurocognition and outcome in the current study.

Conclusion

The current findings suggest that, cross-sectionally, processing speed is associated with measures of social and subjective outcome, but not consistently so, as the effects of the predictors differ between and within domains of outcome. Prospectively, the evidence for an association between change in outcome and neurocognition is highly inconsistent; after adjustment for the baseline levels only the number of met and unmet needs measured by the CAN were weakly sensitive to baseline neurocognitive performance. This is in contradiction with studies supporting longitudinal associations between cognition and community outcome (Carlsson et al., 2006; Green et al., 2004), but in accordance with other studies reporting a relationship between cognition and outcome when measured concurrently, but not prospectively (Addington et al., 2005). The present results are in accordance with previous findings that neurocognition is longitudinally more associated with subjective measures of outcome (Sota & Heinrichs, 2004). Altogether, the associations between processing speed and outcome, cross-sectionally and longitudinally, are not substantially stronger than the associations with psychopathology.

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Chapter 8
Epilogue

EPILOGUE

The sharp categorical distinction between schizophrenia and bipolar disorder as represented in psychiatric diagnostic manuals does not fit the clinical reality in which symptoms often overlap. In addition to overlapping symptomatology, several other findings challenge the traditional Kraepelinian dichotomy: schizophrenia and bipolar disorder show overlap in epidemiological features and possibly even share part of their genetic background.
An important domain which may yield further insight into the nature of the similarities between the disorders is the presence of cognitive dysfunctions. The studies described in this thesis have focused on the aetiological and predictive value of cognitive functioning in bipolar disorder and schizophrenia. The results are discussed within a continuum view of severe mental illness.

In the first part of this thesis, the overlap and differences in the role of cognition as marker of the genetic vulnerability for schizophrenia and bipolar disorder was studied. First, the evidence of neurocognitive functioning as endophenotypic marker in bipolar disorder was evaluated using meta-analytic techniques. Second, in order to investigate shared and non-shared characteristics in the cognitive domain, neurocognitive functioning in patients with schizophrenia was compared directly to that of bipolar disorder. This study also compared neurocognitive performance between the relatives of both patient groups. The subjects in this comparison came from the Maastricht site of the GROUP study and the BIPOLCOG study.
Third, a consistent finding in schizophrenia is the lack of any significant associations between neurocognitive dysfunction and the positive symptoms of psychosis. This thesis investigated whether a similar pattern of associations is present in bipolar disorder, since this could provide further evidence regarding the suggested overlap between both disorders. This was done in the BIPOLCOG study. Finally, in the same study, the endophenotypic nature of neurocognitive dysfunction was further explored by examining the role of the COMT gene, both in relation to disorder vulnerability and cognitive functioning.

In the second part of this thesis the role of neurocognition as predictor of social and community functioning was evaluated. First, the relative predictive value of cognition and symptoms on functional outcome was explored in a combined group of patients with affective and non-affective psychosis in the UK700 study. In this sample it was further investigated whether cognition has true long-term prognostic value in relation to *changes* in outcome. Second, in a different sample

recruited in the context of the CoP study, we examined whether neurocognitive alterations associated with the liability have predictive value for functional outcome in groups at different levels of psychosis-risk in. Finally, the relative influence of neurocognition on psychosocial functioning was compared between the schizophrenia sample from the GROUP study and bipolar disorder patients in the BIPOLCOG study.

Neurocognition as intermediary phenotype in severe mental illness

Both bipolar disorder and schizophrenia are complex disorders in which genes and environment interact in causing the illness. Due to the genetic complexity of these disorders and the imprecision of psychiatric diagnoses as phenotype for understanding its genetic bases, genetic research in psychiatry so far has failed to be successful. In the last decade, the endophenotype approach has gained interest. An endophenotype, or genetic vulnerability marker or intermediary phenotype, is an indicator of genetic risk, mediating between genotype and phenotype (disorder). An endophenotype is assumed to be more directly linked to susceptibility genes, and is generally less complex and easier to measure than the disease phenotype (Gottesman & Gould, 2003) and may therefore help to elucidate the genetic aetiology of psychiatric disorders. For an endophenotype to be useful it must be (Hasler, Drevets, Gould, Gottesman, & Manji, 2006): 1) associated with illness, 2) heritable, 3) state independent, 4) co-segregated with the illness within families, 5) also present in unaffected relatives at a higher rate than in the general population. In the broad domain of severe mental illness, cognitive impairment may be one of the most promising candidate endophenotypes.

Neurocognitive impairment is a core deficit of schizophrenia (Heinrichs & Zakzanis, 1998) and there is convincing evidence that neurocognitive functioning, in particular in domains of verbal memory, attention and executive functioning, can be regarded an endophenotype for this disorder (Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004; Snitz, Macdonald, & Carter, 2006). Studies investigating cognitive functioning in bipolar patients and their relatives have provided no decisive answer to the question whether this is also the case for bipolar disorder.

Is neurocognition a marker of the genetic vulnerability for bipolar disorder?

It has long been assumed that cognitive deficits in bipolar disorder are limited to episodes of affective disturbance and that functioning would return to normal when patients are in remission. However, evidence is accumulating that neurocognitive alterations persist in euthymic bipolar patients. In this thesis, this was further examined by means of a quantitative meta-analysis of 28 studies investigating cognition in euthymic bipolar patients. The results showed that euthymic bipolar pa-

tients were impaired with large effect sizes in the domains of executive function (working memory), mental speed and verbal memory (chapter 2), suggesting that cognitive impairment is a core deficit in bipolar disorder, similar to schizophrenia. However, for cognitive functioning to be a marker of the genetic liability for bipolar disorder, cognitive alterations should also be detectable in healthy first-degree relatives of bipolar patients. A Meta-analysis of 14 studies on this topic indicated that the evidence for this was weak: effect sizes were small and bipolar relatives only differed significantly from controls in the domain of executive functioning (chapter 2). In a recent systematic review of the literature Balanza-Martinez and colleagues drew a similar conclusion by stating that 'the evidence in support of the presence of cognitive deficits in first-degree relative of bipolar patients is quite sparse' (Balanza-Martinez et al., 2008). However, the current finding of large deficits in executive functioning in bipolar patients, and small, but intermediate cognitive alterations in bipolar relatives, suggests that this cognitive domain may be a trait marker for the genetic liability for bipolar disorder.

Different cognitive profiles in bipolar disorder and schizophrenia?

Whereas cognitive dysfunction is a core deficit in bipolar disorder, similar to schizophrenia, the evidence for neurocognition as endophenotype in bipolar disorder is only weak. Given the suggested overlap between the two disorders, investigating shared and non-shared characteristics in the cognitive domain in schizophrenia and bipolar disorder could provide further evidence regarding their mutual relationship and the differences in cognitive functioning as genetic vulnerability marker for these disorders.

A previous review of studies comparing cognitive functioning in schizophrenia and bipolar disorder patients showed that deficits were qualitatively similar, but quantitatively more marked in schizophrenia patients compared to those diagnosed with bipolar disorder (Krabbendam, Arts, van Os, & Aleman, 2005). In this thesis, cognitive performance of schizophrenia patients and their healthy siblings from the GROUP study was compared to that of bipolar patients and their relatives from the BIPOLCOG study. Results showed that the two patient groups had a similar pattern of deficits but that dysfunctions were more severe in schizophrenia compared to bipolar disorder, and that schizophrenia relatives performed worse than bipolar relatives on several domains (chapter 3). This indicates that not only are cognitive deficits in bipolar disorder less severe than those found in schizophrenia, the relatives of patients with bipolar disorder appear to have, if present at all, milder cognitive alterations compared to relatives of schizophrenia patients.

Extending the aetiological model of schizophrenia to bipolar disorder

Within the domain of schizophrenia, a distinction is made between 'poor outcome' psychosis with developmental impairment and cognitive impairment on the one hand and 'good outcome' psychosis without developmental impairment and positive symptoms on the other (Robins & Guze, 1970). It has been hypothesised that different mechanisms are involved in the development of these heterogeneous psychopathological expressions of non-affective psychosis, and that they are associated with different endophenotypic pathways (Myin-Germeys, Krabbendam, Jolles, Delespaul, & van Os, 2002).

The negative syndrome, or poor outcome form of psychosis, is characterized mainly by negative symptoms, cognitive impairment, a chronic and deteriorating course, and poor response to neuroleptic medication. Due to the presence of a developmental impairment in this subtype structural brain abnormalities are more prevalent. Cognitive impairment is strongly associated with the negative symptoms of psychosis but not with the positive symptoms, and is often regarded an endophenotypic marker of the negative syndrome. The positive syndrome, or good outcome form of schizophrenia, is characterized mainly by positive symptoms, has a more episodic course and good response to neuroleptic treatment, and is more reactive to environmental risk factors (Andreasen, 1985). Altered emotional reactivity to stressors is hypothesized to be an endophenotypic marker of the good outcome subtype of psychosis (Myin-Germeys & van Os, 2007). The idea of two different pathways involved in the aetiology of non-affective psychosis is supported by evidence from studies showing no (or even reverse) associations between cognitive performance and stress-sensitivity (Morrens et al., 2007; Myin-Germeys et al., 2002).

Given the suggested overlap between schizophrenia and bipolar disorder, it was investigated in this thesis whether the above-mentioned two-pathway model is also valid in bipolar disorder. Thus, if the distinction between psychosis with developmental impairment and cognitive impairment on the one hand and psychosis without developmental impairment and positive symptoms on the other applies to bipolar disorder, than bipolar patient-relative dyads with more expression of cognitive impairment should have less expression of positive psychotic symptoms. The association between positive psychotic symptoms and cognitive performance in bipolar patient-relative pairs was examined in the BIPOLCOG study. The results showed that a history of psychotic symptoms in bipolar patients was suggestive of less likelihood of cognitive alterations in their relatives, and, that the presence of subclinical psychotic symptoms within the group of relatives predicted better cognitive performance (chapter 4). The finding of similar psychosis-cognition associations in bipolar disorder as in schizophrenia, suggests that the hypothesised dis-

tinction in schizophrenia between good outcome psychosis without developmental impairment (characterised by positive symptoms) and poor outcome psychosis with developmental impairment (characterised by cognitive symptoms) (Myin-Germeys et al., 2002; Robins & Guze, 1970), might be extended to the continuum spanning affective and non-affective psychosis (Murray et al., 2004). These findings provide further support for the idea of a partially overlapping vulnerability to bipolar disorder and schizophrenia.

Is COMT a susceptibility gene in bipolar disorder?

In an attempt to link endophenotypes to the underlying susceptibility genes, previous studies have reported associations between cognitive endophenotypes of non-affective psychoses and the catechol-O-methyltransferase (COMT) gene. COMT has an important function in dopamine transmission in the brain, in particular in the prefrontal cortex (Weinberger et al., 2001), and it has been suggested to be a putative susceptibility gene for both schizophrenia and bipolar disorder (Badner & Gershon, 2002). Although COMT has been frequently investigated in schizophrenia, less is known about its role in bipolar disorder. In this thesis we investigated COMT single markers and haplotypes for an association with bipolar risk and cognitive functioning. In the BIPOLCOG study, cognitive functioning was measured in patients with bipolar disorder and healthy controls. Participants' DNA was obtained using saliva swabs. COMT SNP rs165599 was associated with bipolar risk and with cognitive performance, independent of bipolar diagnosis and rs165599 appeared to be a stronger predictor of bipolar disorder status than haplotypes (chapter 5). Variation in rs165599 and rs737865 was associated with cognitive performance, independent of bipolar diagnosis. (chapter 5). These findings suggests that rs165599 at the down stream position of the COMT gene might be involved in COMT regulation, leading to increased bipolar disorder susceptibility and cognitive impairments associated with this disorder. Exploratory results from the haplotype analyses suggest that this part of the COMT gene is involved in neurocognitive functioning but larger studies are needed to discover possible super allelic effects.

Neurocognitive functioning as predictor of outcome

Neurocognition may not only represent an indicator of familial vulnerability in severe mental illness, it may also be a predictor of poor psychosocial functioning in patients. Cognitive impairment in schizophrenia has been shown to be associated with functional outcomes such as an inability to maintain employment, difficulty in social relationships and difficulty in independent living. In schizophrenia patients, neurocognitive deficits are a better predictor of functional outcomes than positive

symptoms are (Green, Kern, & Heaton, 2004), although the influence of negative symptoms may also be important (Milev, Ho, Arndt, & Andreasen, 2005).

Cross-sectional associations

There is rather consistent evidence for cross-sectional associations between neurocognitive functioning and functional outcome in schizophrenia (Green, 1996), and cognitive speed is one of the cognitive domains consistently associated with outcome (Ojeda, Pena, Sanchez, Elizagarate, & Ezcurra, 2008). In order to compare the relative influence of neurocognition and symptomatology on outcome, both measures should be assessed in the same group of patients. We investigated the influence of processing speed on different measures of outcome in a large sample of patients with chronic (both affective and non-affective) psychotic disorder in the UK700 study and showed that cognitive speed was associated with measures of social outcome and subjective outcome, but not with services use (chapter 7). Although these associations remained significant after adjustment for symptomatology scores, the associations between cognitive speed and outcome were not substantially stronger than with measures of symptomatology (chapter 7).

In general, the results from this thesis are in agreement with previous studies reporting associations between neurocognitive functioning and outcome in psychotic disorders, but the current findings indicate that persisting symptoms should not be ruled out as an important predictor of functioning (Milev et al., 2005; Norman et al., 1999).

Is there long term predictive value?

Whereas cross-sectional associations between cognition and outcome are often reported, to investigate whether cognition has true long-term prognostic value, longitudinal studies are warranted. In a review, Green and colleagues concluded that there is considerable support for longitudinal associations between cognition and outcome (Green, Kern et al., 2004), but other studies suggested that longitudinally less variance in outcome is explained than cross-sectional associations suggest (Milev et al., 2005; Stirling et al., 2003). Importantly, many longitudinal studies did not take into account the baseline level of functioning, which is necessary to examine whether cognition can predict a *change* in outcome.

In the large sample of patients with chronic (both affective and non-affective) psychotic disorder from the longitudinal UK700 study, we investigated whether processing speed predicted *changes* in outcome. Although processing speed and outcome measures were associated when measured concurrently, no consistent prospective associations were found between speed and outcome measures after

controlling for baseline functioning (chapter 7). This suggests that the true longitudinal predictive value of processing speed on outcome appears to be limited.

More than neutral indicators of risk?

If associations between cognition and disability are limited to patient groups, a causally contributing mechanism of cognitive impairment to the pathway from at-risk state to clinical disorder is unlikely. However, if the association between cognitive alterations and expression of disability can be demonstrated in at-risk groups, cognitive alterations may represent more than neutral indicators of genetic risk and also contribute to social disability outside the realm of clinical disorder. We therefore investigated associations between cognition and functional outcome in groups at risk for non-affective psychosis in the CoP study, and showed that alterations in cognitive speed were significantly associated with variation in occupational functioning in first-degree relatives of patients and in a psychometrically defined risk group (chapter 6). This suggests that the association with social disability exists in the context of a vulnerability to non-affective psychosis and that cognitive endophenotypes are more than just neutral indicators of genetic risk.

Differential associations in schizophrenia and bipolar disorder

Whereas the influence of neurocognitive functioning on outcome is frequently studied in non-affective psychotic disorders like schizophrenia, only a few studies have been conducted in bipolar disorder due to the long held assumption that bipolar patients will regain full syndromal and functional recovery in between mood episodes. We now know, however, that 60% of bipolar patients continue to exhibit problems in work or social functioning during remission (MacQueen, Hajek, & Alda, 2005). By exploring associations between symptomatology, cognitive functioning and psychosocial functioning in patients from both the GROUP and the BIPOLCOG study, we were able to investigate to what degree neurocognitive functioning represents a predictor of the poor functioning that is characteristic of both schizophrenia and bipolar disorder (chapter 3). It was found that in patients with schizophrenia, neurocognitive test performance on tests for verbal memory, sustained and divided attention were all significantly associated with a global measure of psychosocial functioning. After adjustment for current symptoms, associations with verbal memory and reaction time on a sustained attention test remained significant, but negative symptoms were equally strong associated with psychosocial outcome (chapter 3). In bipolar disorder patients, only reaction times on a selective attention test were associated with psychosocial functioning, and depressive symptoms were more strongly related to outcome (chapter 3).

This and preliminary evidence from other studies (Laes & Sponheim, 2006; Martinez-Aran et al., 2002) suggests that cognition-outcome associations may be stronger in schizophrenia than in bipolar disorder and emphasize the importance of residual subsyndromal depressive symptoms in relation to functioning in bipolar disorder.

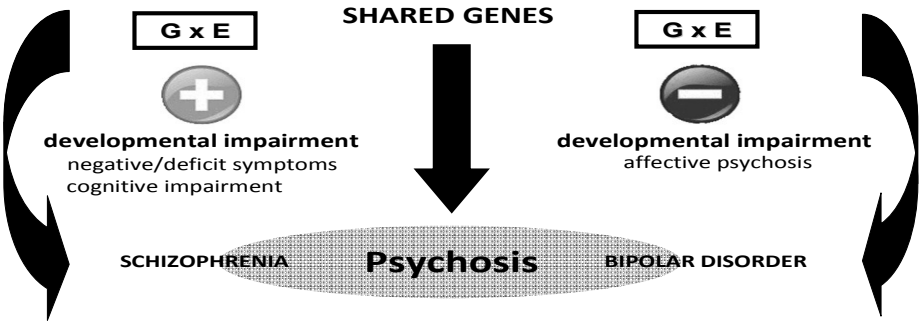
Explaining similarities and differences in neurocognitive performance

The findings from this thesis suggest that although the presence of multiple cognitive deficits is shared between schizophrenia and bipolar disorder, schizophrenia is associated with more severe and more generalized deficits, which seem to reflect the genetic vulnerability as well as impact on daily life to a greater extent than in bipolar disorder. Therefore, any theory explaining the overlap between schizophrenia and bipolar disorder should be able to deal with the finding of a) differences in severity of cognitive impairment between patients, b) different cognitive profiles in individuals at genetic risk for the two disorders, and c) differential influence of cognition on functional outcome.

In an attempt to explain similarities and differences between bipolar disorder and schizophrenia, Murray and colleagues (Murray et al., 2004) suggested that shared susceptibility genes predispose to psychosis in general. If due to the (inter)action between other genes and/or early environmental insults, additional neurodevelopmental impairment is present, schizophrenia will develop. In the absence of such developmental impairments an affective psychosis phenotype like bipolar disorder will emerge. According to this model bipolar disorder and schizophrenia are aetiologically distinct in the presence of a developmental impairment in the former but not in the latter (see picture 1).

This suggests that the cognitive dysfunctions in schizophrenia and bipolar disorder are partly due to different origins. The additional presence of neurodevelopmental impairment in schizophrenia might cause the more severe neuropsychological impairment observed in schizophrenia patients, that, due to its genetic liability, is also observable in their relatives.

Several findings are in line with the suggestion that a neurodevelopmental impairment is involved in the aetiology of schizophrenia but less clearly in bipolar disorder: The presence of premorbid cognitive impairments in pre-schizophrenia children but not in pre-bipolar subjects (Cannon et al., 2002), findings of lower premorbid IQ estimation in schizophrenia as compared to bipolar disorder (Gilvarry et al., 2000) and other developmental delays as well as pregnancy and birth complications that are found in schizophrenia (Verdoux et al., 1997) but not in bipolar disorder (Scott, McNeill, Cavanagh, Cannon, & Murray, 2006) are in support of this idea.



Picture I. Aetiological model for schizophrenia and bipolar disorder (adapted from Murray et al. 2004).

The cognitive deficits observed in bipolar disorder on the other hand, are more likely to be mainly the consequence of the disease process and its treatment. In bipolar patients a greater number of episodes, greater length of illness and higher number of hospitalizations, is associated with more severe neurocognitive dysfunction (Robinson & Ferrier, 2006) and cognitive deficits are more strongly associated with clinical symptoms and their fluctuations than they are in patients with schizophrenia (van Gorp, Altshuler, Theberge, Wilkins, & Dixon, 1998). Studies showing that the presence of neurocognitive alterations is more marked in schizophrenia relatives than in bipolar relatives add further credence to the idea that the cognitive dysfunctions may be partly due to different origins.
Recently, Goodwin and colleagues (Goodwin, Martinez-Aran, Glahn, & Vieta, 2008) reviewed the literature on the causes of cognitive impairment in bipolar disorder and concluded that the evidence was more in favor of a neurodegenerative model than of a neurodevelopmental model. Thus, cognitive deficits in bipolar patients very likely reflect the neuropsychological consequences of the disorder, leading to disrupted brain processing and resulting functioning.

Subgroups
Most of the cognitive impairment in bipolar patients appears to be due to the ongoing illness process and its treatment, but the finding of similar psychosis-cognition associations in bipolar disorder as in schizophrenia suggests that some

cognitive variation may also be due to genetic effects that are shared between both disorders and may be measurable in the relatives of patients with bipolar disorder.
There is evidence that the severity of cognitive impairment is heterogeneous in patients with bipolar disorder (Martino et al., 2008) and there may be subgroups within the bipolar population that are distinguished by their cognitive performance. It has been suggested that some bipolar patients show performance deficits similar to schizophrenia patients and have relatives who also show clear cognitive alterations (Balanza-Martinez et al., 2005). Altshuler and colleagues found a bimodal pattern of performance in bipolar patients on a test of executive functioning, the cognitive domain for which the strongest evidence as endophenotypic marker exists (Altshuler et al., 2004). Half of the bipolar patients performed similar to controls whereas the other half was comparable to schizophrenia patients, suggesting that the dysfunctions that are found in bipolar disorder patients might be due to a small group with more severe impairment.
What defines these subgroups in bipolar disorder remains to be elucidated, but in the context of a continuum model spanning affective and non-affective psychosis it can be hypothesized that bipolar patients with worse cognitive performance and affected relatives are more towards the non-affective side of the psychosis spectrum regarding symptomatology and aetiology. For this subgroup cognitive deficits may indeed be a marker of the genetic vulnerability for the disorder. Based on the findings in schizophrenia that social disability exists in the context of disorder vulnerability (chapter 6), it can further be hypothesized that in these patients cognitive deficits may be associated with functional outcome to a degree comparable to schizophrenia. Previous findings that bipolar patients with higher levels of cognitive impairment had lower psychosocial functioning and premorbid IQ, and a higher history of obstetric complications (Martino et al., 2008), are in line with this suggestion.

Implications for future classification systems

The validity of the Kraepelinian dichotomy is increasingly being challenged, as there appears to be only sparse evidence for a valid contrast between schizophrenia and bipolar disorder. Studies showing quantitative instead of qualitative differences in neurocognitive functioning in bipolar disorder and schizophrenia (chapter 3), similar psychosis-cognition associations in bipolar disorder as are found in schizophrenia (chapter 4), and findings of similar relationships between neurocognition and psychopathology across diagnostic categories (Smith, Barch, & Csernansky, 2008) suggest that there is variation in cognition across traditional diagnostic boundaries and support the idea that bipolar disorder may be on a continuum with schizophrenia. It has been proposed that currently, the most useful approach

to classification of severe mental illness is the combined use of categorical and dimensional representations of psychopathology (Allardyce, Gaebel, Zielasek, & van Os, 2007; van Os, 2008), in which individuals can be classified according to individual scores on psychopathology dimensions rating positive, negative, disorganization, cognitive, depressive and manic symptoms.

The findings from this thesis suggest that any dimensional representation of psychopathology should include variation in neurocognitive functioning in addition to other symptom dimensions, given the importance of neurocognition in terms of the biology, functioning and treatment of severe mental illness. It is currently being argued that cognitive impairment should be included in the diagnostic criteria for schizophrenia, since this would increase clinical awareness of cognitive impairment and could increase the 'point of rarity' with affective psychoses (Keefe, 2008). Investigation of the current level of neurocognitive functioning of patients, however, does not lead to significant diagnostic differences between bipolar and schizophrenia patients as there exists quantitative rather than qualitative variation in neurocognitive functioning, providing no specificity in diagnostic terms. However, current and previous findings suggest that there are valid developmental neurocognitive contrasts between both disorders than can be used in future classification systems (van Os, 2008). These qualitative differences may contribute to diagnostic specificity when methods to properly measure and discriminate premorbid and current level of cognitive functioning can be developed.

Clinical implications

The present findings have several clinical implications.

First, our results indicate that cognitive deficits are not only a core feature of schizophrenia but can also be present in euthymic bipolar patients. Informing patients about the nature of the cognitive impairment in bipolar disorder is necessary since patients often attribute their cognitive problems to medication use, which in turn may lead to medication non-adherence. However, relapses resulting from medication non-adherence appear to have a more adverse impact on cognitive functioning than the use of medication does (Goodwin et al., 2008).

Second, the finding that cognitive deficits are of functional significance in both schizophrenia and bipolar disorder implicates that this domain requires clinical attention. Cognitive enhancement strategies are likely to be beneficial in both disorders. In schizophrenia this has been recognized, given the development of the large initiative on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) (Green, Nuechterlein et al., 2004). Knowledge of cognitive enhancement strategies in bipolar disorder, on the other hand, is scarce due to assumption that cognitive functioning in bipolar disorder would return to

normal during remission. In schizophrenia, moderate improvements of neurocognitive functioning have been reported after treatment with second generation antipsychotic medication (Harvey & Keefe, 2001; Keefe et al., 2004) but the translation of its effects to real life functioning appears to be limited. Not much is known about the potential cognitive benefits of pharmacological treatment in bipolar disorder, but exploratory evidence shows advantageous effects of treatment with lamotrigine (Goldberg & Young, 2008).

Behavioral interventions, like cognitive remediation therapies for improving cognitive functioning and subsequent psychosocial functioning have been developed. In schizophrenia, moderate improvements in cognitive performance and a small but significant beneficial effect on psychosocial functioning were shown when remediation therapy was combined with psychiatric rehabilitation (McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007). In bipolar disorder, psychosocial interventions and/or cognitive remediation strategies have not yet been investigated, but it seems a reasonable assumption that these interventions may also contribute to cognitive improvement in bipolar disorder.

Third, this thesis showed that in both schizophrenia and bipolar disorder the presence of subsyndromal symptomatology is an important predictor of functional outcome and thus should not be neglected in treatment. Particularly in bipolar disorder, low-level depressive symptoms should be carefully monitored and treated, given their continuing influence on clinical course, impaired cognitive functioning, and difficulties in daily life functioning.

Directions for future research

The findings in this thesis suggest that in patients more towards the affective side of the psychosis continuum, cognitive impairment is more likely to be the consequence of the disease process and its treatment. What factors contribute to cognitive dysfunction in these patients remains to be investigated, but it is likely that it involves the combined action of iatrogenic and neurotoxic influences. Given that true euthymic periods may be more uncommon in bipolar disorder than was previously thought (Harvey, 2008), the influence of (minor) affective symptoms on cognitive performance should also be taken into account (Clark, Iversen, & Goodwin, 2002; Ferrier, Stanton, Kelly, & Scott, 1999). Longitudinal studies can provide a prospective framework in which the various determinants of cognitive performance in bipolar disorder can be further studied.

There is some evidence that, at least in subgroups of bipolar patients with more severe cognitive deficits, executive functioning is associated with the genetic vulnerability for bipolar disorder. It should be investigated what characterizes these subgroups, but it can be hypothesized that these bipolar patients are phenotypically

and aetiologically more towards the non-affective side of the psychosis spectrum; thus, have a larger degree of neurodevelopmental impairment that can be detected through the presence of more premorbid cognitive deviations and a stronger predictive role of neurocognitive functioning on functional outcome. Based on this, it seems more informative to investigate symptom dimensions instead of diagnostic constructs. In addition to this, future research is needed to separate cognitive dysfunctions that are related to the underlying vulnerability for severe mental illness from those that are more strongly linked to the disease processes.

Now there is evidence that cognitive deficits are present in at least part of the bipolar disorder patients, the predictive value of cognitive impairment on functional outcome in bipolar disorder should be more thoroughly investigated in longitudinal studies. In addition to this, effort should be undertaken to treat these cognitive deficits and the possible negative influence on functioning. Treatment intervention studies, aimed at investigating the influence of cognitive remediation in bipolar disorder and its outcome, may be a useful step in improving the negative consequences of cognitive dysfunction on disease outcome.
Future studies should aim at identifying (shared) endophenotypes for the symptom dimensions of schizophrenia and bipolar disorder, and attempt to link these markers to underlying susceptibility genes. The current findings suggest the involvement of the COMT gene in bipolar disorder, and exploratory results from haplotype analyses suggest that a whole part of the COMT gene is involved in cognitive performance. However, larger study samples are needed to investigate possible haplotypic effects. In addition to this, environmental influences should be taken into account to investigate interactions between genes and environment in the aetiology of affective and non-affective psychoses.

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SUMMARY
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SUMMARY

The presence of neurocognitive impairment is a core feature of schizophrenia, and it has been suggested that it may similarly be a trait characteristic in patients diagnosed with bipolar disorder. In schizophrenia, cognitive impairment is assumed to be a marker of the genetic vulnerability, or endophenotype, for the disorder, but it also appears to have predictive value regarding the functional outcome of schizophrenia patients. Given the suggested overlap between schizophrenia and bipolar disorder this thesis, *Exploring neurocognition across the psychosis continuum*, evaluates the aetiological and predictive value of cognitive impairment in both schizophrenia and bipolar disorder and discusses their similarities and differences in the context of a continuum view of severe mental illness.

Chapter 1 of this thesis discusses the phenomenology and aetiology of both bipolar disorder and schizophrenia. It gives an overview of diverse findings of overlap between the two illnesses and describes how these findings are increasingly challenging the traditional Kraepelinian dichotomy in which the two disorders are strictly separated. Neurocognitive impairment is presented as a core feature of both schizophrenia and bipolar disorder and the evidence for neurocognitive functioning as a marker of genetic vulnerability for both disorders is reviewed. It is argued that a direct comparison of both patient groups and their relatives is necessary to gain more information on the role of neurocognitive functioning as endophenotype in both disorders. Findings that cognitive impairments are a major predictor of functional outcome in schizophrenia are discussed, and it is suggested that to investigate true long term predictive value, longitudinal studies, controlling for baseline level of functioning, are necessary. It is further argued that studying similar cognition – outcome associations in bipolar disorder could give us more clues as to the nature of the overlap between bipolar disorder and schizophrenia

Chapter 2 evaluates the evidence for neurocognitive functioning as an endophenotypic marker in bipolar disorder in a meta-analysis of studies investigating neurocognitive functioning in euthymic bipolar disorder patients and their first-degree relatives. It was shown that bipolar patients have cognitive impairments, particularly in the domains of executive functioning, verbal memory and mental speed, for which large effect sizes were found. Relatives of bipolar disorder patients differed from controls on some cognitive measures but effect sizes were rather small and significant only in the domain of executive control. The finding of large deficits in executive functioning in bipolar patients, and small, but intermediate cogni-

tive alterations in bipolar relatives, suggests that this cognitive domain may be a trait marker for the genetic liability for bipolar disorder.

In **Chapter 3** the possible role of neurocognitive functioning as a marker of genetic vulnerability for both schizophrenia and bipolar disorder is investigated. In a direct comparison between both patient groups and between their relatives, the shared and non-shared cognitive characteristics were evaluated. Results showed that schizophrenia and bipolar patients were impaired in overlapping cognitive domains but that the impairments were more severe in patients with schizophrenia, and that schizophrenia relatives were cognitively more impaired than bipolar relatives on tasks of verbal memory and reaction time components of selective attention. In addition to this, associations between symptomatology, cognitive functioning and psychosocial outcome were explored in both schizophrenia and bipolar disorder patients. It was shown that in schizophrenia patients, performance on most neurocognitive tests was associated with psychosocial functioning, whereas in bipolar patients this was true for reaction time components of selective attention only. In schizophrenia, symptoms were associated with psychosocial functioning to a similar degree as neurocognition was, whereas in the bipolar sample depressive symptoms were more strongly associated with psychosocial functioning. The study showed that although the presence of multiple cognitive deficits is shared between the two groups, the severity of cognitive deficits and its consequences appear to partly differ between schizophrenia and bipolar disorder.

Chapter 4 describes a study investigating the association between psychotic symptoms and neurocognitive functioning in bipolar disorder. The study aimed at examining whether the distinction that is made in schizophrenia, between psychosis with developmental impairment and cognitive impairment on the one hand and psychosis without developmental impairment and positive symptoms on the other, can be extended to bipolar disorder. Neurocognitive functioning and psychopathology were assessed in patients with bipolar disorder, their first-degree relatives and healthy controls. Bipolar patients showed impaired cognitive performance on multiple cognitive domains, whereas performance of their first-degree relatives was comparable to that of controls on all but one domain, suggesting that the evidence for cognitive alterations as intermediary phenotype associated with genetic risk for bipolar disorder is not strong. The data did show, however, that a history of psychotic symptoms in bipolar patients was suggestive of less likelihood of cognitive alterations in their relatives, and that subclinical psychotic symptoms in relatives predicted a better cognitive performance. This finding of similar psychosis-cognition associations as implied by the two pathways to schizophrenia suggests

that this aetiological model can be extended to the continuum spanning affective and non-affective psychosis. This is in line with the idea of a partially overlapping vulnerability to bipolar disorder and schizophrenia.

Chapter 5 evaluates several single SNPs and haplotypes along the COMT gene for an association with bipolar disorder and cognitive functioning. Previous studies have reported associations between cognitive endophenotypes of non-affective psychoses and the catechol-O-methyltransferase (COMT) gene, but studies in bipolar disorder are scarce. Cognitive functioning was assessed in patients with bipolar disorder and healthy controls and from both groups DNA samples were obtained. Single marker rs165599 was associated with bipolar liability, whereas variation in rs165599 and rs737865 was associated with cognitive performance, independent of bipolar diagnosis. Haplotypes were not associated with bipolar risk, and rs165599 was a stronger predictor of bipolar disorder status than haplotypes. These findings suggests that variation in marker rs165599 at the down stream position of the COMT gene might lead to increased bipolar disorder susceptibility and cognitive impairments associated with this disorder.

Chapter 6 describes whether cognitive alterations associated with liability to psychosis are associated with expression of psychopathology and functional outcome in groups at different levels of risk for psychotic illness. Cognitive functioning, psychopathology and functional outcome were investigated in patients with non-affective psychotic disorders, a group of non-psychotic first-degree relatives and subjects at psychometrically defined risk for psychosis. Results showed that there was a dose-response relationship between level of cognitive impairment and increasing risk for psychosis, suggesting that cognition can be construed as a vulnerability marker across a continuum of risk. In both at risk groups, cognitive speed was associated with functional outcome, indicating that the association with social disability exists in the context of a vulnerability to psychosis and that cognitive endophenotypes are not just neutral indicators of risk. Thus, the study suggests that some cognitive alterations associated with transmission of psychosis may have a direct impact on the pathway from risk to psychopathology and alterations in functioning.

Chapter 7 evaluates the predictive value of cognitive processing speed over and above the contribution of symptoms in the prediction of social outcome in a combined group of patients with affective and non-affective psychosis. It explores whether cognition has true long-term prognostic value in relation to changes of outcome. Cross-sectionally, processing speed was weakly associated with outcome

but the effects differed depending on the outcome measures that were used. Longitudinal prognostic associations were weak or even absent after adjustment for the baseline level of outcome. Both cross-sectionally and longitudinally, the associations between speed and outcome were not substantially stronger than associations with psychopathology. The finding of weak cross-sectional associations in the absence of specific and unconfounded longitudinal associations suggests that processing speed is an independent dimension of disease severity rather than a causal factor impacting on social outcome in psychotic disorder.

Chapter 8 summarizes the results of the studies presented in this thesis. It attempts to explain the similarities and differences in aetiological and predictive value of cognitive functioning in schizophrenia and in bipolar disorder within a continuum view of severe mental illness. It is argued that the cognitive dysfunctions in schizophrenia and bipolar disorder stem from partly different origins. Finally, clinical implications and directions for further research are given.

SAMENVATTING

In de psychiatrisch diagnostische handboeken wordt een duidelijk categorisch onderscheid gemaakt tussen schizofrenie en de bipolaire stoornis. De twee stoornissen vertonen echter veel overeenkomsten in symptomatologie en in de praktijk blijken patiënten vaak niet eenvoudig in een van beide categorieën onder te brengen. Behalve in fenomenologie vertonen de bipolaire stoornis en schizofrenie duidelijke overeenkomsten in epidemiologische kenmerken, behandeling, en erfelijkheid. Ook cognitieve stoornissen lijken een belangrijke rol te spelen bij beide ziektebeelden.

Cognitieve stoornissen vormen een kernsymptoom van schizofrenie en er is steeds meer bewijs dat ook euthyme bipolaire patiënten cognitieve disfuncties vertonen. Cognitief functioneren wordt beschouwd als indicator van de genetische kwetsbaarheid voor schizofrenie en het blijkt het een goede voorspeller te zijn van het dagelijks functioneren van patiënten met deze stoornis. In dit proefschrift, *Exploring neurocognition across the psychosis continuum*, wordt in verschillende studies de rol van cognitie als endofenotype en voorspeller van functioneren bij schizofrenie en de bipolaire stoornis onderzocht en de bevindingen worden besproken binnen de continuüm opvatting van '*severe mental illness*'.

In **hoofdstuk 1** van dit proefschrift worden de fenomenologie en etiologie van de bipolaire stoornis en schizofrenie beschreven. Er wordt een overzicht gegeven van overeenkomsten tussen de twee ziektebeelden en besproken hoe deze bevindingen de dichotomie van twee strikt gescheiden ziektebeelden in twijfel trekken. Neurocognitieve stoornissen worden geïntroduceerd als symptoom van zowel schizofrenie als de bipolaire stoornis, en het bewijs dat neurocognitie kan worden beschouwd als indicator van de genetische kwetsbaarheid voor zowel schizofrenie als voor de bipolaire stoornis wordt besproken. Er wordt geopperd dat een directe vergelijking tussen de twee patiëntgroepen en hun familieleden nodig is om meer informatie te krijgen over de rol van neurocognitie als endofenotype bij beide stoornissen. Ook komt aan bod dat cognitieve stoornissen een belangrijke voorspeller zijn van het dagelijks functioneren van patiënten met schizofrenie, en er wordt beargumenteerd dat longitudinale studies nodig zijn om de voorspellende waarde van cognitie op de lange termijn te onderzoeken. Tevens wordt gesuggereerd dat het bestuderen van vergelijkbare cognitie-*outcome* associaties bij de bipolaire stoornis ons meer duidelijkheid kan geven over de mogelijke overlap tussen de bipolaire stoornis en schizofrenie.

In **hoofdstuk 2** wordt het bewijs voor neurocognitie als endofenotypische marker voor de bipolaire stoornis onderzocht. Een meta-analyse van studies naar cognitief functioneren bij euthyme bipolaire patiënten en hun eerstegraads familieleden toont dat patiënten met een bipolaire stoornis cognitieve disfuncties vertonen in executief functioneren, verbaal geheugen en informatieverwerkingssnelheid. Eerstegraads familieleden presteerden slechter dan controle proefpersonen op sommige cognitieve domeinen, maar de effectgrootten waren klein en bovendien alleen significant voor een maat van executieve controle. Deze meta-analyse laat zien dat patiënten met een bipolaire stoornis cognitieve afwijkingen vertonen in executief functioneren en dat eerstegraads familieleden van patiënten kleine maar tussenliggende afwijkingen vertonen in ditzelfde domein. Dit suggereert dat sommige maten van executief functioneren een indicator kunnen zijn van de genetische kwetsbaarheid voor de bipolaire stoornis.

Hoofdstuk 3 onderzoekt de rol van neurocognitie als indicator van de genetische kwetsbaarheid voor zowel schizofrenie als de bipolaire stoornis. In een directe vergelijking tussen de twee patiëntgroepen en hun eerstegraads familieleden werden de gedeelde en unieke cognitieve kenmerken van de twee stoornissen onderzocht. Tevens werd in beide patiëntgroepen de samenhang tussen symptomatologie, cognitief functioneren en psychosociaal functioneren bekeken. De resultaten toonden aan dat patiënten met een bipolaire stoornis en patiënten met schizofrenie cognitieve stoornissen vertonen in overeenkomstige cognitieve domeinen, maar dat deze stoornissen ernstiger zijn bij patiënten met schizofrenie. Tevens werd aangetoond dat familieleden van patiënten met schizofrenie duidelijkere cognitieve afwijkingen vertonen dan de familieleden van bipolaire patiënten, en dat ze significant slechter presteerden op taken naar verbaal geheugen en snelheid van selectieve aandacht.
Bij patiënten met schizofrenie bestond er een duidelijke samenhang tussen betere cognitieve testprestaties en een beter psychosociaal functioneren, terwijl bij bipolaire patiënten alleen een maat van selectieve aandacht geassocieerd was met functioneren. Bij patiënten met schizofrenie was symptomatologie even sterk geassocieerd met psychosociaal functioneren als cognitie, terwijl bij de bipolaire patiënten depressieve symptomatologie het sterkst met functioneren samenhing. Samenvattend, hoewel cognitieve stoornissen bij zowel schizofrenie als de bipolaire stoornis voorkomen, lijken de ernst en de gevolgen ervan gedeeltelijk te verschillen tussen de twee ziektebeelden.

In eerder onderzoek werden associaties gevonden tussen cognitieve endofenotypen van schizofrenie en het COMT gen. COMT is echter nog nauwelijks onder-

zocht in relatie tot cognitief functioneren bij de bipolaire stoornis. Gegeven de mogelijke overlap tussen schizofrenie en de bipolaire stoornis werden in **hoofdstuk 4** verschillende functionele polymorfismen en haplotypes van het catechol-O-methyltransferase (COMT) gen onderzocht in relatie tot de bipolaire stoornis en cognitief functioneren. Neurocognitie werd gemeten bij patiënten met een bipolaire stoornis en gezonde controleproefpersonen. Genetisch materiaal werd verzameld met behulp van speekselstalen. De resultaten van het onderzoek toonden dat het risico allel van COMT polymorfisme rs165599 geassocieerd was met een diagnose bipolaire stoornis en dat variatie in markers rs165599 en rs737865 samenhing met cognitief functioneren, onafhankelijk van diagnose. Haplotypes waren niet geassocieerd met een kwetsbaarheid voor de bipolaire stoornis en marker rs165599 was een sterkere voorspeller van bipolaire status dan de verschillende haplotypes. Dit suggereert dat variatie in COMT polymorfisme rs165599 kan leiden tot een toename in kwetsbaarheid voor de bipolaire stoornis en een grotere kans op cognitieve afwijkigen.

In **Hoofdstuk 5** wordt de samenhang tussen psychotische symptomen en neurocognitief functioneren bij de bipolaire stoornis onderzocht. Een consistente bevinding bij schizofrenie is dat er geen associaties bestaan tussen neurocognitieve stoornissen en de positieve symptomen van psychose. In dit hoofdstuk werd onderzocht of dit onderscheid in twee onafhankelijke symptoom dimensies ook bij de bipolaire stoornis kunnen worden gevonden. Hiertoe werden neurocognitie en psychopathologie gemeten bij patiënten met een bipolaire stoornis, hun eerstegraads familieleden en gezonde controleproefpersonen. De resultaten van het onderzoek toonden aan dat bipolaire patiënten cognitieve stoornissen vertoonden op verschillende cognitieve domeinen, terwijl de prestatie van hun familieleden vergelijkbaar was met die van de controlegroep. Dit suggereert dat het bewijs voor neurocognitie als endofenotype, geassocieerd met genetisch risico voor de bipolaire stoornis, niet sterk is. Wel werd gevonden dat familieleden van bipolaire patiënten met een psychose in de voorgeschiedenis een betere cognitieve prestatie hadden en dat er in de groep familieleden een associatie bestond tussen de aanwezigheid van subklinische psychotische symptomen en een beter cognitief functioneren. Bij de bipolaire stoornis werden dus vergelijkbare psychose - cognitie associaties gevonden als bij schizofrenie. Dit ondersteunt het idee van een overlappende kwetsbaarheid voor deze twee stoornissen.

Hoofdstuk 6 beschrijft een studie waarin werd onderzocht of cognitieve afwijkingen in groepen met een toenemend risico op psychose geassocieerd zijn met de expressie van psychopathologie en met dagelijks functioneren. Neurocognitie,

psychopathologie en *functional outcome* werden gemeten in patiënten met non-affectieve psychotische stoornissen, een groep niet-psychotische eerstegraads familieleden en proefpersonen met een psychometrische psychose kwetsbaarheid. Er werd een dosisrespons relatie gevonden tussen toenemend risico op psychose en het niveau van cognitief functioneren, wat suggereert dat cognitie beschouwd kan worden als een indicator van psychose kwetsbaarheid langs het gehele psychose continuüm. Bovendien werd er in de twee hoogrisico groepen een significante associatie gevonden tussen cognitief functioneren en *functional outcome*. Dit duidt er op dat cognitieve endofenotypen niet slechts neutrale indicatoren van genetisch risico zijn, maar een directe invloed lijken te hebben op het ontstaan van psychopathologie en een veranderd functioneren.

Hoofdstuk 7 beschrijft een longitudinaal onderzoek waarbij in een groep patiënten met affectieve en non-affectieve psychose de voorspellende waarde van cognitie werd vergeleken met die van symptomen in relatie tot *'functional outcome'*. Ook werd onderzocht of cognitie voorspellende waarde heeft op de lange termijn door de samenhang met veranderingen in *'functional outcome'* te bekijken. Cross-sectioneel werd er een zwakke associatie gevonden tussen cognitieve informatieverwerkingssnelheid en *'functional outcome'*, maar de longitudinaal voorspellende associaties waren zwak en zelfs helemaal afwezig nadat gecontroleerd was voor het basisniveau van functioneren. Zowel cross-sectioneel als longitudinaal was de samenhang tussen cognitie en *'functional outcome'* niet sterker dan de associaties met psychopathologie. De zwakke cross-sectionele associaties gecombineerd met de afwezigheid van specifieke longitudinale associaties suggereren dat cognitieve informatieverwerkingssnelheid een onafhankelijke dimensie is van ziekte-ernst in plaats van een causale invloed op de *'functional outcome'* van patiënten met psychotische stoornissen.

In **hoofdstuk 8** worden de resultaten van de studies in dit proefschrift samengevat. Er wordt getracht de overeenkomsten en verschillen in etiologische en voorspellende waarde van cognitief functioneren bij schizofrenie en de bipolaire stoornis te verklaren binnen het continuüm idee van '*severe mental illness'*. Er wordt beargumenteerd dat de cognitieve stoornissen bij schizofrenie en de bipolaire stoornis een gedeeltelijk andere oorzaak lijken te hebben. Tenslotte worden klinische implicaties en aanbevelingen voor verder onderzoek besproken.

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CURRICULUM VITAE

Nienke Jabben werd geboren op 11 september 1980 in Sittard. In 1998 behaalde ze het VWO diploma aan de Philips van Horne scholengemeenschap in Weert en verhuisde ze naar Maastricht om daar de studie psychologie aan de Universiteit Maastricht te volgen. Ze studeerde in 2003 af in de biologische psychologie, afstudeervarianten neuropsychologie en psychopathologie. Vervolgens ging ze werken als onderzoeksmedewerker bij de vakgroep Psychiatrie en Neuropsychologie van de faculteit Geneeskunde van de Universiteit Maastricht. In maart 2005 begon zij als assistent in opleiding (AiO) aan haar promotieonderzoek naar neurocognitief functioneren bij de bipolaire stoornis en schizofrenie bij de sectie Sociale Psychiatrie en Psychiatrische Epidemiologie. Daarnaast werkte ze als psycholoog binnen een 'Assertive Community Treatment' team van Psycope Maastricht. Per september is ze werkzaam in de functie van postdoc bij GGZ inGeest in Amsterdam.

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