Neurocognitive Functioning as Intermediary Phenotype and Predictor of Psychosocial Functioning Across the Psychosis Continuum: Studies in Schizophrenia and Bipolar Disorder

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Objective: Neurocognitive functioning may represent an indicator of genetic risk and poor outcome in both schizophrenia and bipolar disorder. In this study, shared and nonshared characteristics in the cognitive domain in both disorders were analyzed to determine to what degree neurocognitive functioning may represent a predictor of the familial vulnerability and poor functioning that schizophrenia spectrum disorders and bipolar disorder share.

Method: Neurocognition, psychopathology, and psychosocial functioning were assessed in samples of patients with a schizophrenia spectrum disorder (n = 345) and bipolar disorder (n = 76) meeting *DSM-IV* criteria, 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 2 groups. The schizophrenia spectrum study sample was recruited between September 2004 and January 2008, and the bipolar study sample was recruited between June 2004 and July 2007.

Results: Cognitive deficits were more severe and more generalized in patients with a schizophrenia spectrum disorder compared to patients with bipolar disorder; 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.

Conclusions: 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 2 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.

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The question whether schizophrenia and bipolar disorder are truly distinct diseases is becoming increasingly important now that diagnostic boundaries are being reevaluated during the development of the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*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.[1,2] 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.[3–5] 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.[6,7] Some studies have reported cognitive alterations in first-degree bipolar relatives,[8–10] suggesting that in bipolar disorder, neurocognitive impairment may similarly be a trait marker of genetic vulnerability to the disease.[11]

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[12] 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. In a study that examined executive functioning in bipolar and schizophrenia families,[13] there were no deficits specifically related to one of both disorders. 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 2 large samples of subjects and to investigate shared and nonshared 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,[14] and it has been suggested that cognition predicts social and occupational functioning equally well as negative symptoms do[15–17] and even better than positive symptoms.[18,19] 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.[20–22] 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.

METHOD

Subjects

The subjects in this study were recruited in the context of 2 related projects: the schizophrenia spectrum study and the bipolar study.

Schizophrenia spectrum study. The study sample consisted of patients with a schizophrenia spectrum disorder, 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 fluency in the Dutch language, aged 16 to 55 years (with the exception of patients' parents), and, for patients, a diagnosis of schizophrenia spectrum psychosis according to *DSM-IV*.[25] For a patient to participate, at least 1 of his or her siblings had to take part in the study. Siblings had to be free of any lifetime nonaffective psychotic disorder and have at least 1 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 centers and psychiatric hospitals in the catchment area, namely South Limburg (The 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)[27] 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)[23] to confirm the absence of family histories of psychotic or bipolar disorders in their first-degree relatives.

The initial sample consisted of 353 patients with a schizophrenia spectrum disorder, 342 siblings of patients with a schizophrenia spectrum disorder, 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 not otherwise specified. 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, healthy first-degree relatives of patients with bipolar disorder, and controls from the general population. The sample was recruited between June 2004 and July 2007, during the baseline measurement of the BIPOLCOG study,[24] which focused on cognitive functioning in bipolar disorder.

Inclusion criteria for the BIPOLCOG study were fluency in the Dutch language, aged 18 to 60 years, and, for patients, a diagnosis of bipolar disorder according to *DSM-IV*.[25] Relatives had to be free of any lifetime bipolar or psychotic disorder and have at least 1 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 inpatient and outpatient 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 (occupational criteria for psychotic illness)[26] 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).[26] First-degree relatives and controls were clinically and diagnostically interviewed using the CASH and OPCRIT criteria to exclude individuals with a diagnosis of bipolar disorder or psychotic disorder. Healthy controls were additionally interviewed using the FIGS 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, 4 had a diagnosis of major depressive disorder (in full remission). The other relatives had no history of psychiatric disorder. One control subject had a history of major depressive 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 expanded Brief Psychiatric Rating Scale (BPRS-E).[28] This scale assesses a wide range of current psychopathology, including symptoms of depression, mania, psychosis, anxiety, and withdrawal, in the previous 2 weeks.

In the schizophrenia spectrum study, patients' current symptoms were quantified using the Positive and Negative Syndrome Scale (PANSS).[29] A 5-factor model was used, generating scores on positive, negative, disorganization, excitement, and emotional distress symptom dimensions.[29] In the bipolar study, participants' current depressive and manic symptomatology was assessed using the 21-item Hamilton Depression Rating Scale (HDRS)[30] and the Young Mania Rating Scale (YMRS),[31] respectively.

Psychosocial functioning in both patient groups was assessed using the Global Assessment of Functioning (GAF).[25] 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 4-subtest version (information, block design, digit symbol coding, arithmetic) of the Dutch version of the Wechsler Adult Intelligence Scale-III.[32,33] Overall intellectual functioning in the bipolar study was estimated using 3 Groningen Intelligence Test (GIT-2) subtests (mental rotation, word analogies, mental arithmetic),[34] yielding results that are comparable to those of the Wechsler Adult Intelligence Scale-III.

The following neurocognitive tests were administered in both study samples.

Visual Verbal Learning Test. The Dutch version of the Visual Verbal Learning Test[35] was administered as a measure of verbal memory. In 3 consecutive trials, 15 monosyllabic nonrelated words had to be memorized and reproduced. The total number of words recalled over the 3 trials was used as a measure of immediate recall. Delayed recall was measured after a 20-minute delay.

Continuous Performance Test-HQ. Sustained attention was measured with the Continuous Performance Test-HQ (CPT-HQ)—a version of the continuous performance test that is also known in the literature as CPT-3–7 or CPT-AX, 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 (ie, letters) were presented in a randomized sequence at a rate of 1 per second. Each letter was presented for 150 milliseconds, after which an empty screen was presented for 850 milliseconds. The participant responded to a target by pressing the space bar of the computer's 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[36] (the present CPT-HQ is the nonchoice version mentioned in the Discussion). Outcome measures were expressed as the proportion of correct detections and the reaction time of correct detections.[37]

Flanker CPT. The Flanker continuous performance test (Flanker CPT)[38,39] is a measure of selective visual control of attention. Subjects were instructed to respond by pressing the right or left mouse button depending on whether the middle element in a display of 5 lines has an arrowhead pointing to the right or the left. There are 3 trial types: (1) neutral trials, in which the flankers are horizontal lines without arrowheads, (2) congruent trials, in which all flankers have an arrowhead pointing in the same direction as the target, and (3) 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 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 and the sum of correct trials in each condition.

Statistical Analyses

Statistical analyses were performed using STATA 10.0 (StataCorp LP, College Station, Texas).[40] 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 better performance. In both study samples, a dummy variable indicating disorder vulnerability was constructed with a value of 1 for controls, 2 for relatives, and 3 for patients (hereafter: "group").

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 a dummy variable were used to investigate the effect of group status on neurocognitive performance.

The nonindependence 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 studies and a priori adjusted for age, sex, and education by entering these variables into the equation. In bipolar disorder, these analyses were repeated excluding bipolar 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 schizophrenia spectrum patients, current symptomatology was measured by the 5 dimensions obtained in a previous factor analysis on the PANSS.[29] In bipolar 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 (1) schizophrenia spectrum and bipolar patients and (2) relatives of schizophrenia spectrum or bipolar patients.

Association between cognition and psychosocial functioning in schizophrenia spectrum and bipolar disorder. 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 schizophrenia spectrum and bipolar 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 schizophrenia spectrum patients, current symptomatology was controlled for using PANSS symptom dimensions,[29] whereas in the bipolar sample, total HDRS and YMRS scores were entered into the equation.

Analyses were then recomputed 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 Schizophrenia Spectrum Disorders

Demographic characteristics, symptom scores, and neurocognitive test scores of the sample in the schizophrenia study are presented in Table 1. Multiple regression analyses showed that schizophrenia spectrum patient status was associated with a significantly worse neurocognitive performance on all the administered tests compared to controls (Table 2). Relatives of schizophrenia spectrum patients performed significantly worse than controls on tests of Word List Learning, accuracy and reaction time of the CPT-HQ, and the reaction time measures on all 3 conditions of the Flanker CPT. For all tests, the degree of cognitive impairment was related to degree of psychosis vulnerability, with relatives of schizophrenia spectrum patients scoring intermediate to patients and controls (Table 2).

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 reaction time ($r = -0.13$, $P = .03$) and Flanker CPT congruent condition reaction time ($r = -0.12$, $P = .05$) performance. For negative symptoms, Pearson coefficients were significant for all tests (r between −0.11 and −0.27, $P < .05$). Disorganization symptoms were also significantly correlated with most neurocognitive tests (r between −0.13 and −0.22, $P < .05$), with the exception of CPT-HQ reaction time ($r = -0.04$, $P = .48$). Symptoms of excitement only correlated significantly with CPT-HQ accuracy ($r = -0.12$, $P = .03$, 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 Bipolar Disorder

Demographic characteristics, symptom scores, and neurocognitive test scores of the bipolar study sample are presented in Table 3. Multiple regression analyses showed that bipolar 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 reaction time and Flanker CPT reaction time neutral and incongruent conditions only. However, neurocognitive performance in relatives of bipolar patients 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 of bipolar patients performed slightly better than controls.

To investigate whether cognitive dysfunction is a true trait characteristic in bipolar disorder, post hoc analyses were performed excluding bipolar 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 ($\beta = -0.18$, $P = .07$).

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

Table 1. Demographics, Symptom Scores, and Neurocognitive Test Results of the Schizophrenia Spectrum Study Sample[a]

Variable	Controls (n = 260)	Relatives of Schizophrenia Spectrum Patients (n = 331)	Schizophrenia Spectrum Patients (n = 345)
Demographic characteristic[b]			
Gender, male/female, n/n	87/173	154/177	245/100
Age range, y	16–55	16–55	16–55
Age, y	32.0 (11.9)	29.2 (9.5)	29.5 (9.4)
Level of education[c]	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, no. of cases			
Atypical antipsychotics	0	1	236
Typical antipsychotics	0	0	73
Antidepressants	6	9	76
Brief Psychiatric Rating Scale score			35.9 (13.6)
Positive and Negative Syndrome Scale score			
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)
Global Assessment of Functioning score			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)
Continuous Performance Test-HQ			
Correct detections, %	0.99 (0.04)	0.98 (0.07)	0.93 (0.12)
Reaction time 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)
Reaction time-neutral	511.1 (63.2)	521.7 (68.9)	553.0 (94.0)
Reaction time-congruent	513.8 (65.0)	523.1 (71.4)	559.3 (98.1)
Reaction time-incongruent	569.4 (62.7)	579.8 (71.4)	611.0 (101.2)

[a]Results are presented as mean (SD) unless otherwise noted.
[b]Between-group differences for demographic characteristics: gender, $\chi^2 = 89.73$, $P = .00$; age, $F = 6.34$, $P = .00$; educational level, $F = 22.69$, $P = .00$; and IQ, $F = 62.06$, $P = .00$.
[c]A 7-level variable with 1 representing lowest education and 7 highest education.

delayed recall condition of Word List Learning ($r = -0.26$, $P = .03$, other coefficients between 0.00 and −0.23). A higher HDRS 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).

Comparing Cognitive Performance in Schizophrenia Spectrum Disorders and Bipolar Disorder

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 schizophrenia spectrum patients performed significantly worse than bipolar patients on all administered tests, with the exception of CPT-HQ accuracy. Relatives of schizophrenia spectrum patients performed significantly worse than relatives of bipolar patients on both conditions of Word List Learning and Flanker CPT reaction time neutral condition. Trends toward significance were found for reaction time in the other Flanker CPT conditions (see Table 5).

Associations Between Cognitive Functioning and Psychosocial Functioning

In schizophrenia spectrum 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: $\beta = 0.16$, $P = .00$; delayed recall: $\beta = 0.20$, $P = .00$). Accuracy on the CPT-HQ was no longer significantly predictive of GAF ($\beta = .06$, $P = .18$), whereas the association with the reaction time was reduced but still significant ($\beta = 0.13$, $P = .01$). The previously significant associations of Flanker CPT with GAF disappeared (all beta values between 0.03 and 0.07, *P* values > .15).

Positive and Negative Syndrome Scale negative (beta values between −0.23 and −0.29, *P* values < .00), disorganization (beta values between −0.14 and −0.21, *P* values < .02), and emotional distress (beta values between −0.16 and −0.18, *P* values < .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 bipolar disorder patients, significant associations were found between neurocognitive performance and GAF score for reaction time in the neutral and congruent conditions of the Flanker CPT (neutral: $\beta = 0.27$, $P = .03$; congruent: $\beta = .23$,

Table 2. Associations Between Neurocognitive Performance and Group Status in the Schizophrenia Spectrum Study[a]

	Relatives of Schizophrenia Spectrum Patients		Schizophrenia Spectrum Patients	
Cognitive Variable[b]	β	*P*	β	*P*
Word List Learning				
Immediate recall	−0.10	.01	−0.33	.00
Delayed recall	−0.07	.04	−0.28	.00
Continuous Performance Test-HQ				
Correct detections, %	−0.06	.04	−0.24	.00
Reaction time correct detections	−0.12	.00	−0.25	.00
Flanker CPT				
Correct-neutral	−0.01	.69	−0.26	.00
Correct-congruent	−0.01	.62	−0.29	.00
Correct-incongruent	−0.02	.63	−0.29	.00
Reaction time-neutral	−0.13	.00	−0.34	.00
Reaction time-congruent	−0.12	.00	−0.35	.00
Reaction time-incongruent	−0.12	.00	−0.33	.00

[a]Controls were used as reference category. All analyses adjusted for age, sex, and education.
[b]Higher values indicate better performance.

Table 3. Demographics, Symptom Scores, and Neurocognitive Test Results of the Bipolar Study Sample[a]

Variable	Controls (n = 61)	Relatives of Bipolar Patients (n = 37)	Bipolar Patients (n = 76)
Demographic characteristic[b]			
Gender, male/female, n/n	23/38	20/17	35/41
Age range, y	25–56	18–58	27–60
Age, y	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, no. of cases			
Antipsychotics	0	0	23
Anticonvulsants	0	0	43
Lithium	0	0	37
Antidepressants	0	2	14
Brief Psychiatric Rating Scale score	25.0 (1.7)	26.8 (3.2)	33.4 (6.4)
Hamilton Depression Rating Scale score	0.23 (0.9)	0.41 (1.0)	4.03 (4.3)
Young Mania Rating Scale score	0.07 (0.3)	0.30 (0.9)	1.61 (2.5)
Global Assessment of Functioning score	89.7 (3.3)	84.7 (5.5)	67.2 (10.7)
Previous psychotic, n (%)[c]			38 (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)
Continuous Performance Test-HQ			
Correct detections, %	0.99 (0.02)	0.99 (0.02)	0.95 (0.07)
Reaction time 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)
Reaction time-neutral	647.2 (65.1)	636.6 (65.6)	669.1 (86.9)
Reaction time-congruent	644.2 (55.8)	640.7 (60.8)	669.7 (85.3)
Reaction time-incongruent	706.3 (64.6)	704.0 (75.5)	721.7 (82.7)

[a]Results are presented as mean (SD) unless otherwise noted.
[b]Between-group differences for demographic characteristics: gender, $\chi^2 = 2.57$, $P = .28$; age, $F = 4.09$, $P = .02$; educational level, $F = 3.14$, $P = .05$; and IQ, $F = 6.23$, $P = .00$.
[c]Based on 75 patients.

P = .05), whereas trends toward significance were reported for reaction time in the incongruent condition (β = 0.23, *P* = .06) and for CPT-HQ reaction time (β = 0.20, *P* = .09). A better cognitive performance was associated with a higher GAF score.

Associations were reduced but did not disappear after additionally entering symptom measures into the equation (CPT-HQ reaction time: β = 0.17, *P* = .10; Flanker CPT reaction time-neutral: β = .27, *P* = .03; Flanker CPT reaction time-congruent: β = 0.20, *P* = .07; Flanker CPT reaction time-incongruent: β = 0.22, *P* = .10). Higher HDRS depression ratings were consistently associated with lower GAF scores (beta values between −0.42 and −0.46, *P* values < .01), whereas YMRS mania/hypomania symptoms were not significantly predictive of GAF scores (beta values between −0.05 and −0.17, *P* values > .12).

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Table 4. Associations Between Neurocognition and Group Status in the Bipolar Study[a]

	Relatives of Bipolar Patients		Bipolar Patients	
Cognitive Variable[b]	β	*P*	β	*P*
Word List Learning				
Immediate recall	0.03	.70	−0.20	.01
Delayed recall	0.07	.43	−0.23	.01
Continuous Performance Test-HQ				
Correct detections, %	−0.02	.60	−0.37	.00
Reaction time correct detections	−0.09	.31	−0.03	.76
Flanker CPT				
Correct-neutral	−0.04	.53	−0.20	.03
Correct-congruent	−0.10	.13	−0.26	.01
Correct-incongruent	−0.04	.43	−0.24	.01
Reaction time-neutral	−0.03	.66	−0.16	.07
Reaction time-congruent	−0.06	.39	−0.20	.03
Reaction time-incongruent	−0.05	.48	−0.12	.19

[a]Controls were used as reference category. All analyses adjusted for age, sex, and education.
[b]Higher values indicate better performance.

Table 5. Mean *z* Scores of Neurocognitive Performance in the Research Groups and Schizophrenia-Bipolar Comparisons[a]

	Relatives of Bipolar Patients (n = 37)		Relatives of Schizophrenia Spectrum Patients (n = 329)		Relatives of Bipolar Patients vs Relatives of Schizophrenia Spectrum Patients[c]		Bipolar Patients (n = 76)		Schizophrenia Spectrum Patients (n = 345)		Bipolar Patients vs Schizophrenia Spectrum Patients[d]	
Cognitive Variable[b]	Mean	SD	Mean	SD	β	*P*	Mean	SD	Mean	SD	β	*P*
Word List Learning												
Immediate recall	0.23	1.3	−0.25	1.0	−0.23	.00	−0.52	1.1	−0.98	1.2	−0.32	.00
Delayed recall	0.28	1.1	−0.19	0.9	−0.28	.00	−0.57	1.2	−0.85	1.1	−0.18	.01
Continuous Performance Test-HQ												
Correct detections, %	0.06	0.9	−0.23	1.8	−0.06	.34	−1.59	2.9	−1.34	3.2	−0.04	.61
Reaction time correct detections	−0.18	1.1	−0.13	1.0	−0.01	.94	−0.04	1.1	−0.38	1.1	−0.21	.01
Flanker CPT												
Correct-neutral	0.20	0.6	−0.06	1.1	0.02	.75	−0.46	1.6	−1.07	2.3	−0.18	.00
Correct-congruent	−0.01	0.8	−0.04	1.2	0.08	.14	−0.74	1.9	−1.22	2.5	−0.14	.02
Correct-incongruent	0.22	0.7	−0.06	1.1	−0.00	.94	−0.61	1.7	−0.99	1.7	−0.15	.02
Reaction time-neutral	0.16	1.0	−0.17	1.1	−0.17	.02	−0.34	1.3	−0.66	1.5	−0.33	.00
Reaction time-congruent	0.06	1.1	−0.14	1.1	−0.14	.08	−0.46	1.5	−0.70	1.5	−0.28	.00
Reaction time-incongruent	0.04	1.2	−0.17	1.1	−0.14	.08	−0.24	1.3	−0.66	1.6	−0.33	.00

[a]All analyses adjusted for age, sex, and education.
[b]Higher values indicate better performance.
[c]For relatives of bipolar patients versus relatives of schizophrenia spectrum patients, the former were used as the reference category.
[d]For bipolar patients versus schizophrenia spectrum patients, the former were used as the reference category.

Table 6. Associations Between Neurocognitive Performance and Psychosocial Functioning Measured by the Global Assessment of Functioning in the Schizophrenia Spectrum and Bipolar Patient Groups[a]

	Schizophrenia Spectrum Patients		Bipolar Patients	
Cognitive Variable[b]	β	*P*	β	*P*
Word List Learning				
Immediate recall	0.21	.00	0.10	.45
Delayed recall	0.22	.00	0.16	.27
Continuous Performance Test-HQ				
Correct detections, %	0.19	.01	0.13	.23
Reaction time correct detections	0.20	.00	0.20	.09
Flanker CPT				
Correct-neutral	0.13	.02	0.05	.63
Correct-congruent	0.12	.02	0.05	.71
Correct-incongruent	0.14	.02	0.09	.47
Reaction time-neutral	0.19	.00	0.27	.03
Reaction time-congruent	0.23	.00	0.23	.05
Reaction time-incongruent	0.20	.00	0.23	.06

[a]All analyses adjusted for age, sex, and education.
[b]Higher values indicate better performance.

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 spectrum patients, the associations between neurocognition and GAF were significant only for tests of verbal memory and reaction time 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

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

attention. Bipolar patients similarly showed impairment in all 3 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 Schizophrenia Spectrum Disorders and Bipolar Disorder

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[1,41,42] and confirms the idea of cognitive impairment as a core feature of the disorder.[43,44] 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[45–47] and adds further evidence to the suggestion that neurocognitive impairments are putative markers of the genetic vulnerability to schizophrenia.[48,49]

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.[22,50–52] Although cognitive alterations in verbal memory and attention in relatives of bipolar patients have been found in some studies,[8,10] 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[11] that neurocognitive impairments represent candidate intermediary phenotypes for bipolar disorder. However, the more recent systematic review of Balanzá-Martínez et al[53] showed that the evidence in support of neurocognitive deficits in bipolar relatives is sparse, and a recent quantitative meta-analysis[6] showed that differences between relatives and controls were generally small and significant only for the domain of executive control.

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[43,54–57] comparing neurocognitive functioning in schizophrenia and bipolar disorder have yielded variable results but the broad conclusion that cognitive impairment in schizophrenia and bipolar disorder is qualitatively similar but quantitatively more marked in schizophrenia[58,59] seems justified.

Relatives of schizophrenia spectrum patients in this study had a poorer cognitive performance than relatives of bipolar patients, 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[13,60–62] that have compared the cognitive performance of relatives of schizophrenia and bipolar patients, namely that in general there is a more severe and generalized pattern of cognitive impairment in schizophrenia relatives.

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.[63–65] In line with previous suggestions,[66] 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 neurocognition-outcome associations in schizophrenia.[14,19] 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.[15,67,68] 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.[15,16]

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 RT 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 neurocognition-outcome associations in bipolar disorder; some showed positive associations between cognitive functioning on memory and executive functioning tests and GAF score in bipolar patients.[22,69,70] 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,[71] be more predictive of psychosocial outcome than cognition,[72] but cognition may also be more strongly related to functional outcome during depression or mania/hypomania than in the euthymic state.[73]

Neurocognition-outcome associations seem stronger in schizophrenia than in bipolar disorder,[72,87] and are possibly restricted to more selective cognitive deficits in bipolar disorder.[74] 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 2 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.[75] 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 preschizophrenia children but not in prebipolar subjects,[76] findings of lower premorbid IQ estimation in schizophrenia as compared to bipolar disorder,[77] and other developmental delays, as well as pregnancy and birth complications in schizophrenia[78] but not in bipolar disorder,[79] are in line with this suggestion. The finding that in bipolar disorder, cognitive deficits are associated with severity and progression of the illness[80] and studies showing that the presence of cognitive alterations is more marked in relatives of schizophrenia patients than in relatives of bipolar patients adds further credence to this idea. A recent review[81] on the causes of neurocognitive dysfunction in bipolar disorder suggested that the evidence was more in favor of a neurodegenerative model rather than a neurodevelopmental one.

On the other hand, the qualitatively similar pattern of neurocognitive dysfunctions in both disorders may also suggest partial etiological overlap. Previous studies[52,82] 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. In the context of a continuum model spanning affective and nonaffective psychosis, it can be suggested that this subgroup of bipolar subjects may be more toward the nonaffective, neurodevelopmental 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 (eg, Keefe[83]). 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 the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition/*International Classification of Diseases, Eleventh Revision*.[84] 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 2 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 toward 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,[85] and some atypical antipsychotic drugs even seem to improve cognitive functioning.[86] 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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Drug name: lithium (Eskalith, Lithobid, and others).
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