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Original Article

Investigating the association between neurocognition and psychosis in bipolar disorder: further evidence for the overlap with schizophrenia

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Objectives: In schizophrenia, a distinction is made between psychosis with developmental and cognitive impairment on the one hand and psychosis without developmental impairment and positive symptoms on the other. In this study, we 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.

Methods: 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 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 nonaffective psychotic disorders suggests that this model might be extended to the continuum spanning affective and nonaffective 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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In the search for causal mechanisms of affective and nonaffective 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 (1).

Genetic and epidemiological studies suggest that there is substantial overlap in genetic risk for bipolar and nonaffective psychotic disorders (2–4), and cognitive impairment is one of the most

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frequently investigated intermediary phenotypes. The presence of neurocognitive dysfunctions in patients with bipolar disorder (BD) is well established. Although deficits are generally worse during periods of affective disturbance, two recent meta-analyses (5, 6) 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 BD (7), cognitive alterations should be detectable in subjects with a genetic vulnerability to BD, 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 (5) 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 an intermediary phenotype associated with genetic risk is much stronger for nonaffective psychotic disorders such as schizophrenia. Not only are cognitive deficits in BD less severe than those found in schizophrenia (8), relatives of patients with BD appear to have, if any, milder cognitive alterations (9) compared to relatives of patients with schizophrenia. These findings are in line with studies showing that in children destined to develop schizophrenia or BD, developmental cognitive impairment is present in the former but not the latter group (10, 11).

Any theory explaining the apparent genetic overlap between BD 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 BD is to assume that most of the cognitive impairments seen in patients are related to the ongoing illness process and its treatment, but that some are 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 BD and schizophrenia, Murray and colleagues (12) suggested that BD 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 (13), contribute to the cognitive deficits characteristic of schizophrenia. In the absence of these neurodevelopmental impairments, however, a more affective psychotic phenotype like BD 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 (14) 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 nonaffective psychosis results in testable hypotheses regarding the cognitive profile of relatives of patients with BD. 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 BD, then 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 BD 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 BD 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 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 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, were 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 inpatient and outpatient 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 Research Diagnostic Criteria (RDC) (15). 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) (16).

First-degree relatives, free from a lifetime history of BD or psychosis, were sampled through participating patients. 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 (17) and OPCRIT criteria to exclude those presenting a diagnosis of BD or psychotic disorder. Healthy controls were additionally interviewed with the Family Interview for Genetic Studies (18) in order to confirm the absence of family history 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. Eight first-degree relatives 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, five sons, and three 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 (19) and the Young Mania Rating Scale (20), respectively. To further assess the presence of psychiatric symptoms at the time of testing, the extended Brief Psychiatric Rating Scale (21) 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) http://www.cape42.homestead.com (22–24)], 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 eight rate cognitive depressive experiences. The frequency of the experience was rated on a four-point scale of 'never', 'sometimes', 'often', and 'nearly always'. The scale has been validated against clinical interview measures of schizotypy and psychosis proneness (25), and discriminatory validity was shown contrasting different patient groups (26). 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 (16). 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 (5, 6, 27–29).

Overall intellectual functioning was estimated using three Groningen Intelligence Test (30) subtests (Mental Rotation, Word Analogies, and Mental Arithmetic), yielding results that are comparable to those of the Wechsler Adult Intelligence Scale (WAIS) (31). Verbal learning and memory were assessed with the standardized Dutch version of the Visual Verbal Learning Test (32). In three consecutive trials, 15 monosyllabic, nonrelated 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 WAIS-III (33) were used as measures of attention and working memory, respectively.

Sustained attention was measured with a Continuous Performance Test (CPT) (34), 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 of correct detections, the reaction time of correct detections, and the proportion of false alarms.

The Tapping Speed Test (Cogtest plc, London, UK) 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 (35). Subjects were asked to tap a key on the keyboard with their index finger as fast as they could for eight 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, UK) (36, 37) 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 arrow pointing to the right or left. There are three trial types: (i) neutral trials, in which the flankers are just horizontal lines without arrows, (ii) congruent trials, in which all flankers have an arrow pointing in the same direction as the target, and (iii) incongruent trials, in which flankers are pointing in the 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 and the sum of correct trials in each condition.

The Strategic Target Detection Task (STDT; Cogtest plc, London, UK) (38) 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 being given feedback, thereby modifying their future responses. This is an aspect of the STDT 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 (Cogtest plc, London, UK) (39), subjects are asked to respond as quickly 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 three 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 (40). Statistical analyses were performed using STATA 10.0 (41).

In order to reduce the number of dependent neuropsychological variables in the analyses (42), 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 the relationship between a history of psychosis in the patients and neurocognition in the relatives, using multilevel regression analyses. A history of psychosis was coded as a dichotomous ('yes' or 'no') variable defined by the lifetime presence of at least one positive psychotic symptom in OPCRIT (16).

Subsequently, to investigate the second hypothesis, multilevel random regression analyses with group × 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 similarly 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 1. Demographics, clinical characteristics, and results of neurocognitive assessment

	Control subjects (n = 61)		First-degree relatives (n = 39)		Bipolar disorder patients (n = 76)	
	Mean	SD	Mean	SD	Mean	SD
Demographics						
Gender M/F (n)	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
Backward	6.9	2.0	7.6	2.5	5.9	1.9
Flanker CPT						
Correct-neutral	45.7	3.0	46.3	1.9	43.9	5.3
Correct-congruent	46.4	2.1	46.4	1.7	44.0	5.6
Correct-incongruent	43.2	4.1	44.1	3.2	39.9	8.0
RT-neutral	634.2	53.0	623.4	58.5	679.6	86.5
RT-congruent	632.6	49.2	629.3	60.7	679.6	84.7
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
% 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
Number incorrect	24.3	11.0	22.1	6.4	24.8	10.3
Perseverative errors	4.1	3.3	4.7	2.5	4.6	2.9
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
Start imitation RT	378.9	47.9	406.0	57.1	429.8	65.8
End imitation RT	344.4	61.6	349.6	72.7	386.5	81.4
Start reversal RT	385.1	48.9	419.1	50.3	442.6	72.8
End reversal RT	340.4	56.6	348.3	72.9	382.7	93.2
Imitation errors	0.82	1.1	0.83	0.94	1.4	1.5
Reversal errors	0.93	1.1	0.98	1.2	1.6	1.9
Fine motor speed						
Finger tapping test						
Tap rate right	180.2	22.6	178.1	22.2	184.4	26.1
Tap rate left	192.7	23.7	190.9	27.9	204.1	29.5
Total hits right	279.4	35.3	282.0	32.9	272.5	39.5
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 CAPE, which were administered only in the second session.

GIT = Groningen Intelligence Test; BPRS = Brief Psychiatric Rating Scale; HDRS = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale; CAPE = Community Assessment of Psychic Experiences; CPT = Continuous Performance Test; RT = reaction time; STDT = Strategic Target Detection Test; SST = Set Shifting Test.

Table 2. Component composition and loadings after principal component analysis with varimax rotation

Component	1	2	3	4	5	6	7	8
WLT immediate 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 recognition	0.0057	−0.1346	0.2839	0.0300	0.3886	−0.1480	0.0889	−0.2527
CPT HQ, % correct	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 neutral	−0.0215	0.0286	0.4869	−0.0072	−0.0620	0.0373	−0.0122	0.0765
Flanker count congruent	0.0266	−0.0164	0.4969	0.0372	−0.0097	0.0317	−0.0034	0.0236
Flanker count incongruent	0.0215	−0.0125	0.4879	−0.0266	−0.0144	0.0839	−0.0367	0.0274
Flanker RT neutral	−0.0176	0.0011	0.0433	0.5437	−0.0145	0.0269	0.0016	−0.0251
Flanker RT congruent	0.0014	−0.0074	0.0181	0.5399	0.0016	0.0245	0.0080	−0.0467
Flanker RT incongruent	−0.0429	−0.0210	−0.0355	0.5552	−0.0525	−0.0162	−0.0185	0.0335
STDT correct	0.1009	−0.0588	−0.0690	0.0361	0.1302	−0.0884	−0.4218	0.2241
STDT incorrect	0.0232	−0.0238	−0.0891	0.0558	0.0207	0.0041	0.6260	0.0635
STDT perseverative errors	0.0010	0.0360	0.0613	−0.0553	0.0227	−0.0358	0.6049	0.0579
STDT RT correct	−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 imitation RT	0.0238	0.4982	−0.0586	0.0151	−0.0049	0.1370	0.0304	−0.0197
SST end imitation RT	−0.0180	0.4911	−0.0163	−0.0170	0.0126	−0.0465	0.0252	−0.0018
SST start reversal RT	0.1005	0.3511	−0.0008	0.0127	0.0916	−0.0481	−0.0314	0.0204
SST end reversal RT	−0.0429	0.4280	0.0424	−0.0194	0.0498	−0.1443	0.0505	0.0255
SST imitation errors	0.0186	0.0050	0.0341	0.0327	0.0457	0.6016	0.0571	−0.0222
SST reversal 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.
WLT = Word Learning Test; CPT = Continuous Performance Test; RT = reaction time; STDT = Strategic Target Detection Test; SST = Set Shifting Task; TST = Tapping Speed Test; DS = Digit Span.

Pairwise comparisons

Forty-two pairs of patients and siblings 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 consistently suggested 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 the 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 ß between −0.13 and 0.11, p > 0.21).

Does subclinical psychosis affect relative-control differences?

There were significant two-way group × 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

Table 3. Association between neurocognitive functioning and the group variable reflecting risk for bipolar disorder (BD)[a]

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

[a]Controls were used as reference category. All analyses a priori adjusted for age, sex, and session.
[b]For all outcome measures: higher values indicate better performance.
[c]All ß 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.

Table 4. Group × Community Assessment of Psychic Experiences (CAPE) trait psychosis interactions[a]

	CAPE subclinical psychosis[b]				
Outcome measure	−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–reaction time	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–accuracy[c]	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–reaction time	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 p = 0.02 CI: 0.23, 2.11
Set shifting–accuracy[c]	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[c]	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
Attention–working memory[c]	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.
[a]In relatives, controls as reference category.
[b]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.
[c]Group × CAPE trait interactions were nonsignificant (all ß between −0.12 and 0.37, p > 0.38).
CI = 95% confidence interval.

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.

Discussion

Summary of findings

The results of this study can be summarised as follows. Patients with BD showed impaired performance on multiple cognitive domains, whereas 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 (43–46), attention (47–49), and executive functioning (50–53). 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 (54) 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 (55), who also found deficits in relatives on an attentional shift task but not in verbal memory. The absence of alterations on other cognitive functions is inconsistent with studies reporting cognitive alterations in relatives in verbal memory (56–58), attention, and psychomotor speed (29, 59, 60). In a recent review and meta-analysis of studies on cognition in relatives, individuals at risk for BD differed from controls, but effect sizes were small and present only for executive control and immediate verbal memory (5).

Cognitive alterations and positive psychotic symptoms

In line with our first hypothesis, the presence of a history of positive psychotic symptoms in patients with BD 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 the best of our knowledge, the first study investigating the association between positive psychotic symptoms in patients with BD 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 BD, but results are inconsistent (46, 61–63). Some studies found that a history of psychosis was associated with impaired verbal memory (46) and executive control functioning (63), whereas other studies failed to find an association with neurocognition (62, 64).

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 BD 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 is in relatives, if at all present, the genetic expression of developmental impairment.

Based on the current study, the evidence for cognitive alterations as an intermediary phenotype associated with genetic risk for BD is not strong, at least not for the broad range of phenotypical expressions of BD. 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 BD and schizophrenia (2–4), 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) (14, 65) might be extended to the continuum spanning affective and nonaffective psychosis (12). The finding of a similar psychosis-cognition association in BD, as implied by the two pathways leading to nonaffective psychotic disorders (14), is in line with the idea of a partially overlapping vulnerability to BD 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 BD appears to be due to genetic effects that are shared to a small degree with schizophrenia and are 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 (12). 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, which 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 every patient had a participating sibling may have caused a lack of power in the pairwise sibling-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 (66, 67) and valproate (68, 69) are not consistent. In addition, in the current paper the focus was on relatives who did not use medication.

Conclusions

Given the suggested genetic overlap between BD 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 nonaffective psychosis. This is in line with the idea of a partially overlapping vulnerability to BD 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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