**Schizophrenia Bulletin** vol. 37 no. 1 pp. 73–83, 2011
doi:10.1093/schbul/sbp034
Advance Access publication on May 14, 2009

# Neurocognitive Dysfunction in Bipolar and Schizophrenia Spectrum Disorders Depends on History of Psychosis Rather Than Diagnostic Group

**Carmen Simonsen[1–3], Kjetil Sundet[3], Anja Vaskinn[4], Astrid B. Birkenaes[2,4], John A. Engh[2,5], Ann Færden[2,5], Halldóra Jónsdóttir[2,5], Petter Andreas Ringen[2,4], Stein Opjordsmoen[2,5], Ingrid Melle[2,5], Svein Friis[2,5], and Ole A. Andreassen[2,5]**

[2]Department of Psychiatry, Oslo University Hospital, Ulleval, 0407 Oslo, Norway; [3]Department of Psychology, University of Oslo, 0317 Oslo, Norway; [4]Clinic for Mental Health, Oslo University Hospital, Aker, 0320 Oslo, Norway; [5]Institute of Psychiatry, University of Oslo, 0318 Oslo, Norway

***Objectives:*** **Neurocognitive dysfunction is milder in bipolar disorders than in schizophrenia spectrum disorders, supporting a dimensional approach to severe mental disorders. The aim of this study was to investigate the role of lifetime history of psychosis for neurocognitive functioning across these disorders. We asked whether neurocognitive dysfunction in bipolar and schizophrenia spectrum disorders depends more on history of psychosis than diagnostic category or subtype.** ***Methods:*** **A sample of individuals with schizophrenia ($n = 102$), schizoaffective disorder ($n = 27$), and bipolar disorder (I or II) with history of psychosis ($n = 75$) and without history of psychosis ($n = 61$) and healthy controls ($n = 280$), from a large ongoing study on severe mental disorder, were included. Neurocognitive function was measured with a comprehensive neuropsychological test battery.** ***Results:*** **Compared with controls, all 3 groups with a history of psychosis performed poorer across neurocognitive measures, while the bipolar group without a history of psychosis was only impaired on a measure of processing speed. The groups with a history of psychosis did not differ from each other but performed poorer than the group without a history of psychosis on a number of neurocognitive measures. These neurocognitive group differences were of a magnitude expected to have clinical significance. In the bipolar sample, history of psychosis explained more of the neurocognitive variance than bipolar diagnostic subtype.** ***Conclusions:*** **Our findings suggest that neurocognitive dysfunction in bipolar and schizophrenia spectrum disorders is determined more by history of psychosis than by *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) diagnostic category or subtype, supporting a more dimensional approach in future diagnostic systems.**

*Key words:* neurocognition/verbal memory/working memory/verbal fluency/interference control/ schizoaffective disorder

Current diagnostic systems make a categorical distinction between disorders that are primarily psychotic and disorders that are primarily affective in nature. In *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*), bipolar disorders are not included among the psychotic disorders, and the significance of psychosis in bipolar disorder remains a marker of episode severity.[1] However, psychotic and affective disorders are increasingly perceived as dimensionally different rather than categorically separate entities.[2] This is supported by recent research reporting quantitative differences in neurocognition between bipolar disorders and schizophrenia spectrum disorders, with bipolar disorder displaying a milder degree of deficits.[3,4] Subtle differences in neurocognitive dysfunction have also been reported between bipolar subtypes, with bipolar II displaying milder deficits than bipolar I on some measures,[5,6] and between schizophrenia spectrum disorders, although it remains controversial whether schizoaffective disorder has milder deficits than schizophrenia.[7,8]

Neither current affective symptoms in bipolar disorder[9] nor negative or positive symptoms in schizophrenia[10] fully explain variations in neurocognitive performance, implying that neurocognitive dysfunction is trait rather than state specific. A family history of psychosis has been related to neurocognitive dysfunction across bipolar disorder and schizophrenia probands,[11] suggesting that factors associated with susceptibility to psychotic symptoms may explain neurocognitive variations across these disorders. Thus, the reported neurocognitive differences between bipolar and schizophrenia spectrum disorders may be partly explained by lifetime history of psychosis being less prevalent in bipolar disorder (around 58%[12]) than in schizophrenia, and the subtle neurocognitive variations

[1]To whom correspondence should be addressed; Section for Psychosis Research—Thematic Organized Psychosis, Building 49, Department of Psychiatry, Oslo University Hospital, Ulleval, Kirkeveien 166, 0407 Oslo, Norway; tel: +47-23-02-73-30, fax: +47-23-02-73-33, e-mail: c.e.simonsen@medisin.uio.no

between bipolar subtypes may be partly explained by history of psychosis being less prevalent in bipolar II than in bipolar I.[5,6]

There are some studies reporting neurocognitive differences between schizophrenia, schizoaffective disorder, and bipolar disorder with a history of psychosis (psychotic bipolar disorder) but only on a limited number of functions or measures and only in remitted samples.[13] Moreover, many studies find no neurocognitive differences between these groups with a history of psychotic episodes.[13,14] However, bipolar disorder without a history of psychosis (nonpsychotic bipolar disorder) has been reported to have less severe impairment than schizoaffective disorder.[13,15] Nonpsychotic bipolar disorder also tends to have less severe neurocognitive dysfunction than psychotic bipolar disorder,[13] even after controlling for a range of clinical factors[16,17] and diagnostic subtype (bipolar I and II) in a euthymic sample.[17] There are some inconsistent findings,[18] but they may be due to small and symptomatic samples. Moreover, the 2 groups seem to share processing speed dysfunction.[13]

The few studies that have investigated neurocognition across all the above groups report more severe impairment in schizophrenia, schizoaffective disorder, and psychotic bipolar disorder compared with nonpsychotic bipolar disorder on a measure of spatial working memory[19] and 1 of 2 executive functioning measures.[20] However, both test batteries were limited. In the former study, sample sizes were small and different clinical measures were used for the various groups,[19] and in the latter study, clinical characteristics were restricted,[20] providing little control of potential confounders. Finally, neither of these studies report how many participants had severe cognitive impairment, also termed clinically significant cognitive impairment.[21]

The main purpose of the current study was therefore to investigate the role of history of psychosis for neurocognitive dysfunction across bipolar and schizophrenia-spectrum disorders, using a broad test battery and including a substantial sample of both schizophrenia, schizoaffective disorder, and psychotic and nonpsychotic bipolar disorder (I and II), rated on the same clinical assessment battery.

Based on previous reports, we predicted that neurocognitive dysfunction in bipolar and schizophrenia-spectrum disorders would be determined more by history of psychosis than by main diagnostic category or subtype: Firstly, that participants with schizophrenia, schizoaffective disorder, and psychotic bipolar disorder would display similar neurocognitive dysfunctions that were more severe and more often of clinical significance compared with participants with nonpsychotic bipolar disorder. Secondly, that within the bipolar sample history of psychosis would explain more of the variance in neurocognition than diagnostic subtype (I or II).

## Methods

### *Participants*

Between 2003 and 2007, 265 *DSM-IV*–diagnosed participants were included in the study. Amongst these, 102 had schizophrenia, 27 had schizoaffective disorder, 80 had bipolar I disorder, and 56 had bipolar II disorder (42 bipolar I and 31 bipolar II included in previous report).[6] In the bipolar sample, 75 had a history of psychosis (83% bipolar I, 17% bipolar II) and 61 had no history of psychosis (30% bipolar I, 70% bipolar II). Additionally, 280 healthy control participants were included. The clinical participants were recruited consecutively from psychiatric units (outpatient and inpatient) in 4 major hospitals in Oslo. The healthy control participants were randomly selected from national statistical records from the same catchment area and contacted by letter inviting them to participate. The study is a part of the study Thematic Organized Psychosis Research Initiative and was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. After complete description of the study, all participants gave written informed consent.

Exclusion criteria for all groups were hospitalized head injury, neurological disorder, unstable or uncontrolled medical condition that interferes with brain function, IQ below 70, and age outside the range of 18–60 years. To assure valid neurocognitive test performance, all participants had to have Norwegian as their first language or have received their compulsory schooling in Norway and had to score 15 or above in the forced recognition trial in the California Verbal Learning Test (CVLT) II[22] (7 individuals excluded). In order to assure a healthy control sample, the control participants screened with the Primary Care Evaluation of Mental Disorders[23] were excluded if they or any of their close relatives had a lifetime history of a severe psychiatric disorder (schizophrenia, bipolar disorder, and major depression) or if they had substance abuse or dependency in the last 6 months. In order to obtain a representative clinical sample, the clinical participants were not excluded because of substance abuse or dependency in the last 6 months.

### *Clinical Assessment*

Clinical assessment was carried out by trained psychiatrists and clinical psychologists. Diagnosis was based on the Structured Clinical Interview for *DSM-IV* Axis I disorders (SCID-I).[24] Diagnostic reliability was found satisfactory[25] with overall agreement for *DSM-IV* diagnostic categories of 82% with $\kappa = 0.77$ (95% confidence interval = 0.60–0.94). Current positive and negative symptoms were rated using the Positive and Negative Symptom Scale (PANSS).[26] Interrater reliability was acceptable with intraclass correlation coefficients (ICCs [1.1][27]) for PANSS subscales ranging from .71 to .73. Participants were defined as currently psychotic if they scored 4 or

higher on any one of the following PANSS items: P1, P3, P5, P6, and G9. Current depressive symptoms were rated using the Inventory of Depressive Symptoms—Clinician Rating.[28] Current manic symptoms were rated using the Young Mania Rating Scale (YMRS).[29] Functional level was assessed with the Global Assessment of Functioning Scale, split version—function score,[30] interrater reliability was good with ICC (1.1)[27] of .86.

History of psychosis was based on information retrieved from the SCID interview; the bipolar participants were considered to have a history of psychosis if they had any previous SCID-verified psychotic episodes. Duration of illness (years since first contact with mental health services due to a primary symptom, ie, psychotic symptoms for schizophrenia group, psychotic or affective symptoms for schizoaffective and bipolar groups), number of affective and psychotic episodes, hospitalization and suicide attempts, and use of medication at time of testing were determined through clinical interview and medical charts. Substance abuse during the last 6 months was assessed with the Evaluating Substance Abuse in Persons with Severe Mental Disorders,[31] in which alcohol and drug use are rated separately as: 1 (*nonuse*), 2 (*use*), 3 (*abuse*), 4 (*dependence*), and 5 (*dependence with hospitalization*). For both alcohol and drug use, participants with abuse and dependence were collapsed into a single "abuse group." Lifetime substance abuse was based on the presence of previous *DSM-IV* substance-related diagnoses (SCID-I).

### *Neurocognitive Assessment*

Neurocognitive assessment was carried out by psychologists trained in standardized neuropsychological testing. A 3-hour test battery (including measures of estimated premorbid IQ and adequate test effort) was administered in a fixed order with 2 breaks with refreshments. Included in this study are measures previously found sensitive to dysfunction in bipolar disorder (see Simonsen et al[6] for details), as well as a measure of processing speed, which is found to differ between schizophrenia[32] and bipolar disorder.[33] *Verbal learning and memory* was tested with the Logical Memory Test (Wechsler Memory Scale [WMS] III)[34] and the California Verbal Learning Test (CVLT) II,[22] with subscore measures of verbal learning and recall. *Processing speed* was assessed with the Digit Symbol Test (Wechsler Adult Intelligence Scale [WAIS] III).[35] *Working memory* was assessed with the Digit Span Test—backward (WAIS-III)[35] and the Working Memory—Mental Arithmetic (WM-MA) Test—commissions.[36] *Verbal fluency* was measured with the Verbal Fluency Test (Delis-Kaplan Executive Function Scale [D-KEFS]),[37] with measures of phonetic fluency, semantic fluency, and semantic fluency set shift. *Interference control* was measured by the Color-Word Interference Test (D-KEFS),[37] with subscore for interference control and interference set shift. High scores equal high performance on all measures apart from the Color-Word Interference Test.

### *Group Comparisons*

Demographic and clinical group means and comparisons are presented in table 1. The schizophrenia group had more men and lower level of education and estimated premorbid IQ (National Adult Reading Test)[38] compared with healthy controls and the 2 bipolar groups. The 2 bipolar groups differed significantly from the 2 schizophrenia-spectrum groups on several clinical and functional variables. The 2 schizophrenia spectrum groups were similar apart from current negative symptoms, and the 2 bipolar groups differed only on rate of antipsychotic medication use and bipolar diagnostic subtype. When dividing the bipolar sample into 4 groups (bipolar I and bipolar II with and without a history of psychosis), these 4 groups did not differ on any demographic variables.

### *Statistical Analyses*

The Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL; version 15.0) was used. To control for the risk of running type I errors due to the large number of analyses, a multivariate analysis of variance (MANOVA) was conducted, with all 12 neurocognitive subscores entered as dependent variables and group membership entered as factor (Pillai's Trace Methods). Group differences on the individual subscores were then investigated by analyses of variance (ANOVAs) with effect sizes calculated by $\eta^2$ and with Scheffé post hoc comparisons when relevant. Proportion of clinically significant cognitive impairments (defined as scores 1.5 SDs below the healthy control group average, capturing participants performing below the normative seventh percentile level) was reported for each group on all subscores. The relative impact on neurocognition by history of psychosis and diagnostic subtype (bipolar I and II) in the bipolar sample was investigated by a 2-way MANOVA with all 12 neurocognitive subscores entered as dependent variables and history of psychosis and diagnostic subtype entered as factors (Pillai's Trace Methods). The relative impact for each subscore was investigated by 2-way ANOVA with history of psychosis and diagnostic subtype as factors.

Because most of the demographic and clinical group differences (table 1) were considered illness specific, they were not entered as covariates in the main neurocognitive comparisons, but follow-up analyses explored the impact of these variables on the main findings. Correlation analyses (Spearman $\rho$) explored whether neurocognition was associated with demographic variables (across all 5 groups) or clinical variables (separately for schizophrenia spectrum and bipolar disorder samples). Three separate multivariate analyses of covariance (MANCOVAs) investigated if group differences

**Table 1.** Demographic and Clinical Characteristics

| | 1, Schizophrenia (n = 102) | 2, Schizoaffective (*n* = 27) | 3, Psychotic Bipolar (*n* = 75) | 4, Nonpsych Bipolar (*n* = 61) | 5, Healthy Control (*n* = 280) | ANOVA/Chi-Square Analysis | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | $F/\chi^2$ | *P* | Post hoc |
| Demographics | | | | | | | | |
| Gender *n* (% males) | 62 (61) | 8 (30) | 36 (48) | 24 (39) | 136 (49) | $\chi^2 = 12.0$ | .017 | 1>2,3,4,5 |
| Age (years) | 32.4 (9.8) | 33.7 (9.9) | 35.7 (11.7) | 36.0 (10.3) | 35.9 (10.5) | F = 2.4 | .053 | |
| Education | 12.4 (2.1) | 12.7 (2.4) | 13.3 (2.6) | 14.2 (2.1) | 14.1 (2.2) | $F = 17.6$ | <.001 | 1<3,4,5 |
| NART IQ[a] | 103.4 (4.4) | 104.3 (4.7) | 105.4 (4.5) | 106.5 (3.7) | 106.6 (4.0) | $F = 12.5$ | <.001 | 1<3,4,5 |
| Symptom rating scales | | | | | | | | |
| IDS-C[b] | 15.3 (10.9) | 17.5 (11.8) | 14.9 (10.8) | 19.0 (12.2) | — | $F = 1.8$ | .143 | |
| YMRS[c] | 5.3 (5.1) | 6.0 (4.4) | 3.0 (3.9) | 3.3 (3.7) | — | $F = 6.2$ | <.001 | 3<1,2 |
| PANSS positive total[d] | 14.3 (5.1) | 14.7 (5.1) | 10.1 (3.2) | 9.6 (2.5) | — | $F = 26.4$ | <.001 | 3,4<1,2 |
| PANSS negative total[d] | 15.7 (6.2) | 12.4 (5.2) | 10.6 (4.2) | 9.9 (3.1) | — | $F = 23.0$ | <.001 | 2,3,4<1 |
| Current psychosis *n* (% yes) | 56 (55) | 17 (62) | 11 (15) | 0 (0) | — | $\chi^2 = 75.4$ | <.001 | |
| Functional level | | | | | | | | |
| GAF functioning[e] | 43.8 (10.4) | 44.3 (10.9) | 55.0 (13.2) | 59.2 (10.2) | — | $F = 30.9$ | <.001 | 1,2<3,4 |
| Illness course[f] | | | | | | | | |
| Duration of illness (years) | 5.5 (6.2) | 7.3 (7.0) | 8.4 (10.5) | 6.7 (7.4) | — | $F = 2.0$ | .117 | |
| Number of episodes | | | | | | | | |
| Depressive | 1.0 (2.8) | 4.6 (8.3) | 6.7 (12.7) | 7.9 (9.2) | — | $F = 9.1$ | <.001 | 1<3,4 |
| Hypomanic | 0.1 (1.0) | 0.7 (2.9) | 4.3 (13.1) | 13.2 (23.9) | — | $F = 12.4$ | <.001 | 1,2,3<4 |
| Manic | 0.1 (0.5) | 0.9 (1.2) | 2.4 (5.1) | 1.4 (4.3) | — | $F = 6.8$ | <.001 | 1<3 |
| Mixed | 0.0 (0.0) | 0.0 (0.2) | 0.2 (0.8) | 0.2 (0.7) | — | $F = 2.0$ | .122 | |
| Psychotic | 2.3 (2.5) | 3.2 (3.0) | 2.2 (2.2) | 0.0 (0.0) | — | $F = 20.7$ | <.001 | 4<1,2,3 |
| Hospitalizations | 3.0 (3.6) | 3.8 (3.7) | 2.8 (3.7) | 0.9 (1.5) | — | $F = 7.4$ | <.001 | 4<1,2,3 |
| Suicide attempts | 0.8 (2.4) | 0.7 (1.0) | 0.6 (1.2) | 0.8 (1.8) | — | $F = 0.2$ | .912 | |
| Medication *n* (%) | | | | | | | | |
| Antipsychotic[g] | 93 (91) | 25 (93) | 50 (67) | 12 (20) | — | $\chi^2 = 96.6$ | <.001 | |
| Antiepileptic | 16 (16) | 9 (33) | 35 (47) | 25 (42) | — | $\chi^2 = 22.4$ | <0.001 | |
| Lithium | 0 (0) | 2 (7) | 13 (17) | 6 (10) | — | $\chi^2 = 18.1$ | <0.001 | |
| Antidepressants | 34 (33) | 9 (33) | 24 (32) | 30 (50) | — | $\chi^2 = 5.9$ | .116 | |
| Combination therapy[h] | 53 (52) | 18 (67) | 45 (60) | 25 (42) | — | $\chi^2 = 6.6$ | .085 | |
| Substance abuse *n* (%) | | | | | | | | |
| Last 6 months | | | | | | | | |
| Alcohol abuse | 11 (11) | 2 (7) | 8 (11) | 8 (13) | — | $\chi^2 = 0.7$ | .885 | |
| Drug abuse | 14 (14) | 3 (11) | 7 (9) | 3 (5) | — | $\chi^2 = 3.3$ | .343 | |
| Lifetime | | | | | | | | |
| Alcohol abuse | 23 (23) | 2 (7) | 8 (11) | 14 (23) | — | $\chi^2 = 7.3$ | .063 | |
| Drug abuse | 27 (27) | 5 (19) | 13 (17) | 7 (12) | — | $\chi^2 = 5.9$ | .118 | |
| Bipolar diagnostic subtype | | | | | | | | |
| Bipolar type (I/II) | — | — | 62/13 | 18/43 | — | $\chi^2 = 39.3$ | <.001 | |

*Note*: Means (SDs) are reported unless otherwise specified. ANOVA, analysis of variance.
[a]NART IQ, Estimate of premorbid IQ, measured by the National Adult Reading Test; number of missing scores for group 1 = 4, group 2 = 3, group 3 = 4, group 4 = 1.
[b]IDS-C, Inventory of Depressive Symptoms—Clinician rating; number of missing scores for group 1 = 8, group 2 = 2, group 3 = 7, group 4 = 3.
[c]YMRS, Young Mania Rating Scale; number of missing scores for group 2 = 1.
[d]PANSS, Positive and Negative Symptom Scale; number of missing scores for group 2 = 1.
[e]GAF, Global Assessment of Functioning.
[f]Number of missing for illness course variables (depending on variable) was up to 6 participants in group 1, 1 participant in group 2, up to 4 participants in group 3, and up to 5 participants in group 4.
[g]Number with atypical primary antipsychotic medication; group 1 = 83, group 2 = 24, group 3 = 46, group 4 = 10.
[h]Combination of 2 or more different psychotropic medications.

in neurocognitive performance remain significant when (1) demographic variables, (2) current symptom measures, or (3) illness course variables were entered as covariates (Pillai's Trace Methods). Two-way MANOVAs investigated whether the effect of group membership on neurocognition remains significant when either *gender*, *current psychosis*, *antiepileptic medication*, *lithium use*, or *antipsychotic medication* were included as second

**Table 2.** Neurocognitive Performance

| | 1, Schizophrenia ($n$ = 102) | 2, Schizoaffective ($n$ = 27) | 3, Psychotic Bipolar ($n$ = 75) | 4, Nonpsych Bipolar ($n$ = 61) | 5, Healthy Control ($n$ = 280) | ANOVA | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | $F$[a] | $P$ | $\eta^2$ | Post hoc |
| Verbal learning and memory | | | | | | | | | |
| Logical memory (WMS-III) | | | | | | | | | |
| Learning | 21.2 (7.0) | 23.0 (6.7) | 22.4 (6.3) | 27.6 (6.5) | 26.8 (5.9) | 22.02 | **.001** | 0.14 | 1, 2, 3 < 4, 5 |
| Recall | 17.4 (7.2) | 18.3 (8.6) | 19.1 (7.8) | 24.5 (6.5) | 24.0 (6.6) | 24.29 | **.001** | 0.15 | 1, 2, 3 < 4, 5 |
| CVLT-II | | | | | | | | | |
| Learning | 47.6 (11.3) | 48.9 (9.9) | 53.1 (10.2) | 58.3 (11.1) | 57.7 (9.1) | 24.10 | **.001** | 0.15 | 1 < 3, 4, 5 \| 2 < 4, 5 \| 3 < 5 |
| Recall | 11.0 (3.2) | 10.3 (3.2) | 12.3 (2.9) | 13.3 (3.1) | 13.4 (2.5) | 19.33 | **.001** | 0.13 | 1, 2 < 4, 5 |
| Processing speed | | | | | | | | | |
| Digit symbol (WAIS-III) | | | | | | | | | |
| Correct number | 56.1 (14.5) | 57.1 (13.3) | 63.7 (16.2) | 69.3 (16.1) | 76.0 (13.8) | 43.65 | **.001** | 0.24 | 1 < 3, 4, 5 \| 2 < 4, 5 \| 3, 4 < 5 |
| Working memory | | | | | | | | | |
| Digit span (WAIS-III) | | | | | | | | | |
| Backward | 4.2 (1.0) | 4.3 (1.0) | 4.4 (1.3) | 4.9 (1.1) | 5.1 (1.2) | 13.32 | **.001** | 0.09 | 1 < 4, 5 \| 2, 3 < 5 |
| WM-MA | | | | | | | | | |
| 2-Back[b] | 11.3 (7.0) | 11.0 (7.7) | 12.6 (5.5) | 14.1 (4.6) | 15.4 (3.7) | 16.55 | **.001** | 0.11 | 1 < 4, 5 \| 2, 3 < 5 |
| Verbal fluency | | | | | | | | | |
| Verbal fluency (D-KEFS) | | | | | | | | | |
| Phonetic | 37.8 (12.3) | 39.0 (11.5) | 39.1 (13.1) | 42.9 (10.8) | 44.9 (10.8) | 9.64 | **.001** | 0.07 | 1, 3 < 5 |
| Semantic | 39.0 (10.6) | 37.7 (7.3) | 40.8 (11.3) | 45.4 (8.3) | 48.1 (8.4) | 26.54 | **.001** | 0.16 | 1, 2 < 4, 5 \| 3 < 5 |
| Set shifting | 12.0 (2.5) | 11.8 (2.9) | 12.6 (3.1) | 14.2 (2.7) | 14.7 (2.7) | 24.93 | **.001** | 0.16 | 1, 2, 3 < 4, 5 |
| Inhibition | | | | | | | | | |
| C-W interference (D-KEFS) | | | | | | | | | |
| Interference | 63.5 (18.9) | 64.9 (12.0) | 59.0 (15.5) | 53.0 (13.4) | 50.1 (10.5) | 24.68 | **.001** | 0.15 | 1, 2 < 4, 5 \| 3 < 5 |
| Set shifting | 69.4 (17.8) | 66.9 (13.8) | 54.2 (16.3) | 57.6 (11.4) | 56.3 (12.1) | 20.13 | **.001** | 0.13 | 1 < 4, 5 \| 2, 3 < 5 |

*Note*: Means (SDs) are reported. Bold = $P < .05$. ANOVA, analysis of variance; WMS-III, Wechsler Memory Scale III Revision; CVLT-II, California Verbal Learning Test—Revised; WAIS-III, Wechsler Adult Intelligence Scale III Revision; WM-MA, Working Memory—Mental Arithmetic Test; C-W Interference, Color-Word Interference; D-KEFS, Delis-Kaplan Executive Functioning System.
[a]$df$ = 4, 540.
[b]Control group $n$ = 274 and schizophrenia group = 100, due to missing data ($df$ = 4, 532).

independent variables (Pillai's Trace Methods). Because only controls were excluded on substance abuse last 6 months at inclusion, follow-up analyses were carried out excluding participants with substance abuse last 6 months (21 with schizophrenia, 4 with schizoaffective, 14 with psychotic bipolar disorder, 10 with nonpsychotic bipolar disorder). All analyses (except $\chi^2$) were 2 tailed.

## Results

### *Neurocognitive Performance Across Groups With and Without a History of Psychosis*

A significant overall difference in neurocognitive performance between the groups was detected (MANOVA: $F_{48,2092}$) = 4.96, $P < .001$) with a medium effect size[39] ($\eta^2$ = 0.10). The group mean performance for each neurocognitive subscore and the respective univariate ANOVA along with post hoc comparisons are presented in table 2. Univariate ANOVA revealed significant differences between the groups in all neurocognitive subscores, with small to large effect sizes. Overall, the 3 groups with a history of psychosis performed significantly poorer than healthy controls on all subscores (apart from psychotic bipolar disorder on CVLT-recall and schizoaffective disorder on phonetic fluency). The nonpsychotic bipolar disorder group did not differ significantly from the healthy control group on any neurocognitive subscore apart from digit symbol where they performed poorer. The 3 groups with a history of psychosis did not differ from each other on any subscores (apart from the schizophrenia group performing significantly poorer than psychotic bipolar group on CVLT learning and digit symbol). The groups with a history of psychosis performed poorer than the nonpsychotic bipolar group on a number of measures (the schizophrenia group on 12 subscores, the schizoaffective group on 8 subscores, and the psychotic bipolar group on 3 subscores).

Clinically significant cognitive impairment across tests was present in 33% (21%–49%) of the schizophrenia group, 31% (19%–48%) of the schizoaffective group,

**Table 3.** Bipolar Subgroups—History of Psychosis and Diagnostic Subtype

| | Psychotic Bipolar Disorder | | Nonpsychotic Bipolar Disorder | | ANOVA | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | History of Psychosis | | | Diagnostic Subtype | | | Psychosis × Subtype | | |
| | Bipolar I ($n$ = 62) | Bipolar II ($n$ = 13) | Bipolar I ($n$ = 18) | Bipolar II ($n$ = 43) | $F^a$ | $P$ | $\eta^2$ | $F^a$ | $P$ | $\eta^2$ | $F^a$ | $P$ | $\eta^2$ |
| Verbal learning and memory | | | | | | | | | | | | | |
| Logical memory (WMS-III) | | | | | | | | | | | | | |
| Learning | 21.9 (6.4) | 24.5 (5.2) | 27.1 (7.1) | 27.8 (6.3) | 10.3 | **.002** | 0.07 | 1.6 | .209 | 0.01 | 0.5 | .466 | 0.00 |
| Recall | 18.2 (7.9) | 23.1 (5.7) | 23.5 (5.9) | 24.9 (6.8) | 5.9 | **.017** | 0.04 | 4.6 | **.034** | 0.03 | 1.3 | .256 | 0.01 |
| CVLT-II | | | | | | | | | | | | | |
| Learning | 52.5 (10.4) | 56.1 (8.8) | 56.4 (13.4) | 59.1 (10.0) | 2.5 | .113 | 0.02 | 2.1 | .149 | 0.02 | 0.1 | .842 | 0.00 |
| Recall | 12.0 (3.0) | 13.7 (2.2) | 12.7 (3.5) | 13.6 (2.9) | 0.2 | .636 | 0.00 | 4.6 | **.035** | 0.03 | 0.4 | .564 | 0.00 |
| Processing speed | | | | | | | | | | | | | |
| Digit symbol (WAIS-III) | | | | | | | | | | | | | |
| Correct number | 63.4 (16.9) | 65.2 (13.2) | 68.9 (13.8) | 69.4 (17.2) | 2.1 | .152 | 0.02 | 0.1 | .732 | 0.00 | 0.0 | .840 | 0.00 |
| Working memory | | | | | | | | | | | | | |
| Digit span (WAIS-III) | | | | | | | | | | | | | |
| Backward | 4.4 (1.2) | 4.2 (1.3) | 4.7 (1.2) | 4.9 (1.1) | 4.8 | **.030** | 0.04 | 0.1 | .957 | 0.00 | 1.1 | .290 | 0.01 |
| WM-MA | | | | | | | | | | | | | |
| 2-Back | 13.1 (5.4) | 10.3 (5.3) | 13.4 (5.2) | 14.3 (4.4) | 4.2 | **.042** | 0.03 | 0.8 | .385 | 0.01 | 3.1 | .081 | 0.02 |
| Verbal fluency | | | | | | | | | | | | | |
| Verbal fluency (D-KEFS) | | | | | | | | | | | | | |
| Phonetic | 39.9 (13.2) | 35.5 (12.1) | 43.3 (10.9) | 42.7 (10.9) | 4.4 | **.038** | 0.03 | 1.0 | .327 | 0.01 | 0.6 | .458 | 0.00 |
| Semantic | 40.9 (11.4) | 39.8 (10.9) | 44.5 (6.4) | 45.8 (9.0) | 5.2 | **.024** | 0.04 | 0.1 | .978 | 0.00 | 0.4 | .550 | 0.00 |
| Set shifting | 12.5 (3.0) | 13.1 (3.4) | 14.0 (3.2) | 14.0 (2.5) | 4.9 | **.029** | 0.04 | 0.5 | .490 | 0.00 | 0.1 | .817 | 0.00 |
| Inhibition | | | | | | | | | | | | | |
| C-W interference (D-KEFS) | | | | | | | | | | | | | |
| Interference | 58.3 (15.7) | 62.2 (14.5) | 50.22 (11.7) | 54.2 (14.0) | 7.0 | **.009** | 0.05 | 1.7 | .197 | 0.01 | 0.1 | .984 | 0.00 |
| Set shifting | 63.5 (16.6) | 67.3 (15.1) | 57.7 (9.9) | 57.6 (12.0) | 6.8 | **.010** | 0.05 | 0.5 | .541 | 0.00 | 0.5 | .505 | 0.00 |

*Note*: Means (SDs) are reported. Bold = $P < .05$. ANOVA, Analysis of variance; WMS-III, Wechsler Memory Scale III Revision; CVLT-II, California Verbal Learning Test—Revised; WAIS-III, Wechsler Adult Intelligence Scale III Revision; WM-MA, Working Memory—Mental Arithmetic Test; D-KEFS, Delis-Kaplan Executive Functioning System; C-W Interference, Color-Word Interference.
[a]$df$ = 1, 132.

and 23% (16%–29%) of the psychotic bipolar group. In the nonpsychotic bipolar group and the healthy control group, clinically significant cognitive impairment occurred in 10% (5%–21%) and 7% (5%–9%), respectively.

### *History of Psychosis Vs Bipolar Diagnostic Subtype Within the Bipolar Disorder Sample*

Within the bipolar sample, a 2-way MANOVA revealed a trend like main effect for history of psychosis ($F_{11,122} = 1.86$, $P = .052$) with large effect size ($\eta^2 = 0.14$). No significant main effect was revealed for diagnostic subtype ($F_{11,122} = 1.42$, $P = .172$, $\eta^2 = 0.11$) nor for the interaction effect between history of psychosis and diagnostic subtype ($F_{11,122} = 0.83$, $P = .616$, $\eta^2 = 0.07$). As illustrated in table 3, history of psychosis had significant main effects on all subscores apart from the CVLT subscores and the digit symbol subscore, while diagnostic subtype only had significant main effects on the 2 verbal recall subscores. There were no interaction effects on any subscores.

### *Follow-up Analyses*

Follow-up analyses were used to investigate the impact of possible demographic and clinical confounders on the neurocognitive group differences. Significant positive correlations were revealed across all subscores between neurocognitive measures and premorbid IQ ($r$ = .20–.39, $P < .001$) and education ($r$ = .16–.32, $P < .001$). Significant negative correlations between neurocognition and age were revealed only on the 2 CVLT subscores and digit symbol ($r$ = −.14 to −.17, $P = .001$). Women performed significantly better than men across all neurocognitive subscores ($t$ = −6.66 to −4.13, $P$ = .001–0.022) apart from on the WM-MA Test. However, the group differences in neurocognition remained significant when entering premorbid IQ, education, and age as covariates in a MANCOVA ($F = 4.53$, $P < .001$, $\eta^2 = 0.10$) and

when including *gender* as a second independent variable in a 2-way MANOVA ($F = 4.84$, $P < .001$, $\eta^2 = 0.10$).

As illustrated in table 4, few significant correlations were revealed between neurocognitive measures and clinical variables in the schizophrenia spectrum sample, although negative symptoms correlated on 5 subscores. In the bipolar sample, only number of psychotic episodes and hospitalizations correlated with the majority of neurocognitive subscores. Furthermore, clinical group differences in neurocognition remained significant when all current symptom measures (see table 1) were included as covariates in a MANCOVA ($F = 1.81$, $P = .003$, $\eta^2 = 0.09$) and when all illness course variables (see table 1) were included as covariates in a MANCOVA ($F = 2.23$, $P < .001$, $\eta^2 = 0.12$). None of these clinical variables significantly affected neurocognition.

The effects of clinical group membership on neurocognition remained significant when *current psychosis* ($F = 1.96$, $P = .001$, $\eta^2 = 0.09$), *antiepileptic medication* ($F = 2.08$, $P < .001$, $\eta^2 = 0.09$), or *lithium use* ($F = 1.78$, $P = 0.004$, $\eta^2 = 0.08$) were included as second independent variables in separate 2-way MANOVAs. Neither of these clinical variables significantly affected neurocognition, and there were no significant interaction effects. The overall effect of group membership on neurocognitive performance did not remain significant when controlling for *antipsychotic medication* ($F = 1.00$, $P = .467$, $\eta^2 = 0.05$), but *antipsychotic medication* did not have an overall significant main effect either ($F = 1.65$, $P = .078$, $\eta^2 = 0.07$), and there was no interaction effect ($F = 0.69$, $P = .917$, $\eta^2 = 0.03$) in a 2-way MANOVA. Because use of *antipsychotic medication* almost completely overlaps with history of psychosis, it is not possible to disentangle the effect of *antipsychotic medication* from the effect of history of psychotic episodes. Group differences remained significant across all subscores when clinical participants with substance abuse or dependency were excluded from the analyses ($F = 4.25$, $P < .001$, $\eta^2 = 0.10$).

In sum, these follow-up analyses reveal that the impact of group membership on neurocognitive function remains significant despite controlling for demographic and clinical variables, apart from *antipsychotic medication,* which is almost congruent with a history of psychotic episodes.

## Discussion

The main result of the present study is that neurocognitive dysfunction in bipolar and schizophrenia spectrum disorders appears to be determined more by history of psychosis than by *DSM-IV*–defined diagnostic category or subtype.

Our first set of findings shows that while the bipolar group with a lifetime history of psychosis had neurocognitive dysfunction similar to that of the schizophrenia and schizoaffective disorder groups, the bipolar group without previous psychotic episodes had neurocognitive function similar to the normal controls, apart from in processing speed where they performed poorer. To our knowledge, this is the first time this has been shown in an adequately powered study comprising broad diagnostic groups assessed with the same clinical rating scales and a comprehensive neuropsychological test battery. Moreover, our findings reveal that the group mean differences in neurocognition have clinical significance, as severe impairment was more common in the groups with a history of psychosis. On average, clinically significant cognitive impairment occurred in approximately one-third with schizophrenia spectrum disorders, one-fourth with psychotic bipolar disorder, but only in one-tenth with nonpsychotic bipolar disorder.

Overall, this first set of findings, in which groups with a history of psychosis have more severe neurocognitive dysfunction than the bipolar group without a history of psychosis, is consistent with but expands on a line of previous findings.[13–17,19,20] However, inconsistent with this overall picture yet consistent with some previous reports,[13] we found poorer verbal memory and processing speed in schizophrenia compared with psychotic bipolar disorder. Furthermore, we found more severe impairment in the psychotic bipolar group compared with the nonpsychotic bipolar group across more measures (verbal fluency and interference control) than many previous studies, although, there is at least one previous report of poorer interference control in a psychotic compared with a nonpsychotic bipolar group.[18] Our nonpsychotic bipolar group was only impaired in processing speed, which has been related to the clinical expression of bipolar disorder.[33] Thus, unlike many previous studies, our nonpsychotic bipolar group was generally unimpaired. There are however reports of relatively intact neurocognitive function for nonpsychotic bipolar disorder in at least one earlier study.[15] The present lack of impairment could be explained by the relatively small deficit effect sizes across our sample. Alternatively, the participants in this group may be impaired compared with their premorbid functioning despite performing above the normative seventh percentile level.

Because the psychotic bipolar group had more bipolar I participants and the nonpsychotic bipolar group had more bipolar II participants, there is partial overlap between history of psychosis and diagnostic subtype. Our second set of findings however revealed that history of psychosis explains the neurocognitive variance in the bipolar sample better than diagnostic subtype. History of psychosis had effect on most neurocognitive measures even when controlling for bipolar diagnostic subtype, while diagnostic subtype only had effect on the two verbal recall measures. This indicates that the difference in neurocognitive dysfunction between psychotic and nonpsychotic bipolar groups are not due to diagnostic subtype, ie, severity of elated states. Nevertheless, because psychosis can occur during either mania or depression in bipolar I and by definition only during phases of depression in bipolar II, psychosis may be qualitatively

**Table 4.** Relationship Between Neurocognitive Performance and Current Symptoms and Number of Episodes

| | Schizophrenia Spectrum Groups | | | | | | | | | Bipolar Groups | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Current Symptoms | | | | Number of Episodes | | | | | Current Symptoms | | | | Number of Episodes | | | | |
| | IDS-C | YMRS | Positive | Negative | Dep | Hypom | Mani | Psych | Hosp | IDS-C | YMRS | Positive | Negative | Dep | Hypom | Mani | Psych | Hosp |
| Verbal learning and memory | | | | | | | | | | | | | | | | | | |
| Logical memory (WMS-III) | | | | | | | | | | | | | | | | | | |
| Learning | .03 | −.03 | −.04 | −.22* | .18 | .16 | .05 | .08 | −.09 | −.04 | .19* | .10 | −.07 | −.04 | .05 | −.29** | −.31** | −.27** |
| Recall | −.00 | .05 | −.03 | −.18* | .11 | .07 | −.01 | .01 | −.13 | −.07 | .15 | .07 | −.14 | .04 | .12 | −.27** | −.31** | −.27** |
| CVLT-II | | | | | | | | | | | | | | | | | | |
| Learning | .03 | −.09 | −.06 | −.26** | .01 | .18* | −.04 | .05 | −.13 | −.07 | .03 | .03 | −.15 | .07 | .12 | −.29** | −.27** | −.27** |
| Recall | .05 | −.04 | .03 | −.15 | −.02 | .19* | −.13 | .03 | −.20* | −.03 | .03 | .05 | −.10 | .19* | .19* | −.27** | −.27** | −.27** |
| Processing speed | | | | | | | | | | | | | | | | | | |
| Digit symbol (WAIS-III) | | | | | | | | | | | | | | | | | | |
| Correct number | −.14 | −.01 | −.13 | −.21* | −.02 | −.03 | .01 | .04 | −.08 | −.13 | .08 | .13 | −.21* | .07 | −.05 | −.19* | −.19* | −.15 |
| Working memory | | | | | | | | | | | | | | | | | | |
| Digit span (WAIS-III) | | | | | | | | | | | | | | | | | | |
| Backward | .05 | .04 | −.05 | −.14 | .00 | −.00 | −.06 | .12 | −.03 | .07 | −.03 | .02 | −.02 | .02 | .10 | −.12 | −.20* | −.13 |
| WM-MA | | | | | | | | | | | | | | | | | | |
| 2-Back | −.15 | −.07 | −.18* | −.12 | −.09 | −.02 | .96 | .14 | −.08 | .01 | .01 | .03 | −.14 | .05 | −.03 | −.01 | −.12 | −.20* |
| Verbal fluency | | | | | | | | | | | | | | | | | | |
| Verbal fluency (D-KEFS) | | | | | | | | | | | | | | | | | | |
| Phonetic | −.07 | .12 | .16 | −.14 | .02 | .02 | .07 | .09 | −.14 | −.15 | .02 | .08 | −.22* | .10 | −.01 | −.00 | −.15 | −.05 |
| Semantic | −.13 | −.07 | .08 | −.25** | −.05 | −.03 | −.06 | .25** | −.07 | −.12 | .09 | .08 | −.28** | .06 | .10 | −.09 | −.28** | −.27** |
| Set shifting | −.14 | .09 | .01 | −.13 | −.14 | −.02 | −.10 | .12 | −.04 | −.10 | −.3 | .01 | −.27** | .10 | .11 | −.11 | −.37** | −.28** |
| Inhibition | | | | | | | | | | | | | | | | | | |
| C-W interference (D-KEFS) | | | | | | | | | | | | | | | | | | |
| Interference | −.05 | −.02 | .21* | .14 | .04 | .08 | .14 | −.08 | .03 | .17* | −.31 | −.05 | .17 | −.07 | .06 | .08 | .24** | .19* |
| Set shifting | −.00 | −.10 | .06 | .14 | −.02 | .09 | .07 | −.10 | .07 | .26** | .01 | .11 | .27** | −.02 | .01 | .13 | .17 | .16 |

*Note*: Spearman ρ is reported. IDS-C, Inventory of Depressive Symptoms—Clinician Rating; YMRS, Young Mania Rating Scale; Positive and Negative symptoms from Positive and Negative Symptom Scale; Dep, depression; Hypom, hypomania; Mani, mania; Psych, psychosis; Hosp, hospitalization ;WMS-III, Wechsler Memory Scale III Revision; CVLT-II, California Verbal Learning Test—Revised; WAIS-III, Wechsler Adult Intelligence Scale III Revision; WM-MA, Working Memory—Mental Arithmetic Test; D-KEFS, Delis-Kaplan Executive Functioning System; C-W Interference, Color-Word Interference.
*$P < .05$; **$P < .01$.

different in bipolar I and II participants. Therefore, we cannot rule out that the predominance of bipolar I in our psychotic bipolar group may have in some way influenced this group's neurocognitive performance.

Overall, this second set of findings supports and expands on a recent study, which found that bipolar diagnostic subtype did not have significant influence on neurocognitive measures and thus could not explain the differences they found between psychotic and nonpsychotic bipolar groups.[17] The current report of bipolar diagnostic subtype only influencing verbal recall measures is in line with our earlier report where bipolar I and II were only significantly different on verbal memory measures.[6] A consistency in findings was expected as the first sample covers approximately half of the current bipolar sample.

Our follow-up analyses indicate that none of the demographic and clinical differences between groups can fully explain the group differences in neurocognition. Thus, it seems that the psychotic bipolar group is neurocognitively closer to the schizophrenia spectrum disorders, than to the nonpsychotic bipolar group. Firstly, and in line with previous reports,[40] we found few differences in demographic and clinical characteristics between the psychotic and nonpsychotic bipolar groups. Secondly, although demographic variables were associated with neurocognitive function, group differences in neurocognitive performance remained significant despite controlling for gender, age, premorbid IQ, and education. Thirdly, in line with Glahn et al,[19] we found few associations between neurocognitive and clinical measures. Associations were primarily found between neurocognition in the bipolar sample and number of psychotic episodes and hospitalizations, both of which are related to history of psychosis. Moreover, group differences in neurocognition remained significant despite controlling for all current symptom measures and in line with previous reports[10]; current psychosis did not influence neurocognitive performance. Group differences also remained significant after controlling for all illness course variables.

Due to the study design, we cannot disentangle the effects of medications from the effect of illness severity causing medication use. As there was no difference between our groups in proportion with antidepressants and combination therapy, they were not considered likely confounders. The effects on neurocognition from antiepileptic medication are considered minimal[41] and the effect of lithium unclear.[42,43] Moreover, group differences in neurocognitive performance remained significant despite controlling for antiepileptic medication and lithium use; thus, these medications are not considered likely confounders. Because the use of antipsychotic medication naturally has a very high degree of association with a history of psychosis, it is impossible to disentangle their effect from that of history of psychosis. However, because most recent findings also seem to indicate, if any, an improved cognitive function associated with typical as well as atypical antipsychotic medication,[44,45] we do not find it likely that the use of antipsychotics explains our main findings. Finally, because all group differences remained significant after excluding clinical participants with substance abuse last 6 months from the analyses, we argue that substance abuse last 6 months cannot explain our main findings.

The present findings have several implications. Firstly, they imply that future neurocognitive research needs to study individuals with bipolar disorder with a history of psychosis separately from those without. Secondly, in line with neuroimaging and genetic studies,[46,47] they indicate that individuals with a history of psychosis might share common neurobiological substrates across the major *DSM-IV* schizophrenia and bipolar spectrum distinctions. Thus, in line with recent reports,[33,48] this suggests neurocognition as an endophenotypic marker for these disorders. We argue that our findings support a more dimensional view of mental disorders in line with that of Vieta and Phillips,[1] proposing that future diagnostic systems should incorporate dimensional consideration of a range of clinical symptoms beyond those of the primary symptom that determines main category belonging and that psychotic symptoms should be part of the diagnostic criteria for bipolar disorder.

The main limitation of the present study is that not all diagnostic participants were asymptomatic. Because we might be less likely to find differences between these groups during symptomatic phases,[13] we might find differences between the 3 groups with a history of psychosis in an entirely remitted sample. That the psychotic bipolar group had more participants with bipolar I disorder than the nonpsychotic bipolar group may be considered a limitation. But as it is in line with other samples,[17] it may in fact represent subtype-specific differences. Finally, future studies should examine whether neurocognitive dysfunction is related to type or severity of psychotic history, including whether there is a difference between mood-congruent and mood-incongruent psychosis, between psychosis during mania and psychosis during depression, or between hallucinations and delusions.[49]

In conclusion, neurocognitive dysfunction in bipolar and schizophrenia spectrum disorders seems to be more related to history of psychosis than to *DSM-IV*–defined diagnostic category or subtype. From a neurocognitive point of view, this suggests that the major diagnostic distinction between disorders that are predominantly psychotic and predominantly affective is too simplistic, supporting a more dimensional approach in future diagnostic systems.

## Funding

Eastern Norway Health Authority (2005-115, 2004-123); Research Council of Norway (Storforsk grant 167153); Thematic Organized Psychosis study group.

## Acknowledgments

Birkenaes has received the annual, 2005 research grant from Eli Lilly, Norway, participated as a national

investigator in one drug trial initiated by Bristol-Myer Squibbs, and is also an advisory board member of this company. Andreas Ringen has received the annual, 2004 research grant from Lundbeck, Norway, and is an advisory board member of Eli-Lilly, Norway. He has also received travel funding from Pfizer, Norway. Opjordsmoen has participated as a clinical investigator in drug trials initiated by Astra Zeneca and Janssen-Cilag and is also an advisory board member for Bristol-Myer Squibbs, Norway. Melle has been a speaker at meetings arranged by the Norwegian departments of Lundbeck, Astra Zeneca, Bristol-Myer Squibbs, Pfizer, Wyeth, Eli Lilly, and Janssen-Cilag. She has also received travel funding from Eli Lilly and Astra Zeneca, Norway, Andreassen has been a speaker at meetings arranged by the Norwegian departments of Lundbeck, Astra Zeneca, Bristol-Myer Squibbs, Pfizer, Wyeth, Eli Lilly, and Janssen-Cilag. He has also received travel funding from Eli Lilly and Lundbeck, Norway. Simonsen has been a speaker at a meeting arranged by the Norwegian department of GlaxoSmithKline. Sundet, Vaskinn, Færden, Engh, Jónsdóttir, and Friis report no competing interests.

## References


1. Vieta E, Phillips ML. Deconstructing bipolar disorder: a critical review of its diagnostic validity and a proposal for DSM-V and ICD-11. *Schizophr Bull*. 2007;33:886–892.
2. Craddock N, Owen MJ. Rethinking psychosis: the disadvantages of a dichotomous classification now outweigh the advantages. *World Psychiatry*. 2007;6:84–91.
3. Daban C, Martinez-Aran A, Torrent C, et al. Specificity of cognitive deficits in bipolar disorder versus schizophrenia. A systematic review. *Psychother Psychosom*. 2006;75:72–84.
4. Krabbendam L, Arts B, van OJ, Aleman A. Cognitive functioning in patients with schizophrenia and bipolar disorder: a quantitative review. *Schizophr Res*. 2005;80:137–149.
5. Torrent C, Martinez-Aran A, Daban C, et al. Cognitive impairment in bipolar II disorder. *Br J Psychiatry*. 2006;189: 254–259.
6. Simonsen C, Sundet K, Vaskinn A, et al. Neurocognitive profiles in bipolar I and bipolar II disorder: differences in pattern and magnitude of dysfunction. *Bipolar Disord*. 2008;10: 245–255.
7. Evans JD, Heaton RK, Paulsen JS, McAdams LA, Heaton SC, Jeste DV. Schizoaffective disorder: a form of schizophrenia or affective disorder? *J Clin Psychiatry*. 1999;60:874–882.
8. Heinrichs RW, Ammari N, McDermid VS, Miles AA. Are schizophrenia and schizoaffective disorder neuropsychologically distinguishable? *Schizophr Res*. 2008;99:149–154.
9. Robinson LJ, Thompson JM, Gallagher P, et al. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J Affect Disord*. 2006;93:105–115.
10. Nieuwenstein MR, Aleman A, de Haan EH. Relationship between symptom dimensions and neurocognitive functioning in schizophrenia: a meta-analysis of WCST and CPT studies. Wisconsin Card Sorting Test. Continuous Performance Test. *J Psychiatr Res*. 2001;35:119–125.
11. Tabares-Seisdedos R, Balanza-Martinez V, Salazar-Fraile J, Selva-Vera G, Leal-Cercos C, Gomez-Beneyto M. Specific executive/attentional deficits in patients with schizophrenia or bipolar disorder who have a positive family history of psychosis. *J Psychiatr Res*. 2003;37:479–486.
12. Goodwin F, Jamison K. *Manic-Depressive Illness.* New York, NY: Oxford University Press; 2006.
13. Bora E, Yucel M, Fornito A, Berk M, Pantelis C. Major psychoses with mixed psychotic and mood symptoms: are mixed psychoses associated with different neurobiological markers? *Acta Psychiatr Scand*. 2008;118:172–187.
14. Smith MJ, Barch DM, Csernansky JG. Bridging the gap between schizophrenia and psychotic mood disorders: relating neurocognitive deficits to psychopathology. *Schizophr Res*. 2009;107:69–75.
15. Torrent C, Martinez-Aran A, Amann B, et al. Cognitive impairment in schizoaffective disorder: a comparison with non-psychotic bipolar and healthy subjects. *Acta Psychiatr Scand*. 2007;116:453–460.
16. Glahn DC, Bearden CE, Barguil M, et al. The neurocognitive signature of psychotic bipolar disorder. *Biol Psychiatry*. 2007;62:910–916.
17. Martinez-Aran A, Torrent C, Tabares-Seisdedos R, et al. Neurocognitive impairment in bipolar patients with and without history of psychosis. *J Clin Psychiatry*. 2008;69:233–239.
18. Selva G, Salazar J, Balanza-Martinez V, et al. Bipolar I patients with and without a history of psychotic symptoms: do they differ in their cognitive functioning? *J Psychiatr Res*. 2007;41:265–272.
19. Glahn DC, Bearden CE, Cakir S, et al. Differential working memory impairment in bipolar disorder and schizophrenia: effects of lifetime history of psychosis. *Bipolar Disord*. 2006;8:117–123.
20. Szoke A, Meary A, Trandafir A, et al. Executive deficits in psychotic and bipolar disorders—implications for our understanding of schizoaffective disorder. *Eur Psychiatry*. 2008;23:20–25.
21. Thompson JM, Gallagher P, Hughes JH, et al. Neurocognitive impairment in euthymic patients with bipolar affective disorder. *Br J Psychiatry*. 2005;186:32–40.
22. Delis DC, Kramer JH, Kaplan E, Ober BA. *California Verbal Learning Test: CVLT-II.* Stockholm, Sweden: Pearson Assessment; 2004.
23. Spitzer RL, Williams JB, Kroenke K, et al. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *JAMA*. 1994;272:1749–1756.
24. First M, Spitzer R, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders: Patient Edition (SCID-P), Version 2.* New York, NY: Biometrics Research, New York State Psychiatric Institute; 1995.
25. Ringen PA, Lagerberg TV, Birkenaes AB, et al. Differences in prevalence and patterns of substance use in schizophrenia and bipolar disorder. *Psychol Med*. 2008;38:1241–1249.
26. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13:261–276.
27. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull*. 1979;86:420–428.
28. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med*. 1996;26:477–486.
29. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133:429–435.

30. American Psychiatric Association. *Diagnostic and Statistical manual of Mental Disorders: DSM-IV 1994;Washington, DC: APA.*
31. Drake RE, Mueser KT, McHugo GJ. Clinician rating scales. In: Sederer LI, Dickey B, eds. *Outcomes Assessment in Clinical Practice.* Baltimore, Md: Williams & Wilkins; 1996: 113–116.
32. Dickinson D, Ramsey ME, Gold JM. Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Arch Gen Psychiatry*. 2007;64:532–542.
33. Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J Affect Disord*. 2009;113:1–20.
34. Wechsler D, Wycherley RJ, Benjamin L. *Wechsler Memory Scale: WMS-III.* Stockholm, Sweden: Pearson Assessment; 2008.
35. Wechsler D. *Wechsler Adult Intelligence Scale: WAIS-III.* Stockholm, Sweden: Pearson Assessment; 2003.
36. Hugdahl K, Rund BR, Lund A, et al. Brain activation measured with fMRI during a mental arithmetic task in schizophrenia and major depression. *Am J Psychiatry*. 2004; 161:286–293.
37. Delis DC, Kaplan E, Kramer JH. *The Delis-Kaplan Executive Function System: D-KEFS.* Stockholm, Sweden: Pearson Assessment; 2005.
38. Sundet K, Vaskinn A. Estimating premorbid IQ with the National Adult Reading Test (NART) [article in Norwegian, abstract in English]. *J Norwegian Psychological Assoc*. 2008; 45:1108–1115.
39. Cohen J. *Statistical Power Analysis for the Behavioural Sciences.* Hillsdale, NJ: Erlbaum; 1988.
40. Keck PE, Jr, McElroy SL, Havens JR, et al. Psychosis in bipolar disorder: phenomenology and impact on morbidity and course of illness. *Compr Psychiatry*. 2003;44:263–269.
41. Devinsky O. Cognitive and behavioral effects of antiepileptic drugs. *Epilepsia*. 1995;36:(suppl 2):S46–S65.
42. Engelsmann F, Katz J, Ghadirian AM, Schachter D. Lithium and memory: a long-term follow-up study. *J Clin Psychopharmacol*. 1988;8:207–212.
43. Stip E, Dufresne J, Lussier I, Yatham L. A double-blind, placebo-controlled study of the effects of lithium on cognition in healthy subjects: mild and selective effects on learning. *J Affect Disord*. 2000;60:147–157.
44. Keefe RS, Bilder RM, Davis SM, et al. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Arch Gen Psychiatry*. 2007;64:633–647.
45. Mishara AL, Goldberg TE. A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book. *Biol Psychiatry*. 2004;55:1013–1022.
46. Potash JB. Carving chaos: genetics and the classification of mood and psychotic syndromes. *Harv Rev Psychiatry*. 2006;14:47–63.
47. Strasser HC, Lilyestrom J, Ashby ER, et al. Hippocampal and ventricular volumes in psychotic and nonpsychotic bipolar patients compared with schizophrenia patients and community control subjects: a pilot study. *Biol Psychiatry*. 2005;57:633–639.
48. Gur RE, Calkins ME, Gur RC, et al. The consortium on the genetics of schizophrenia: neurocognitive endophenotypes. *Schizophr Bull*. 2007;33:49–68.
49. Engh JA, Friis S, Birkenaes AB, et al. Delusions are associated with poor cognitive insight in schizophrenia [published online ahead of print January 27, 2009]. *Schizophr Bull*. 2009. doi:10.1093/schbul/sbn193.