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Relationship of Neurocognitive Deficits to Diagnosis and Symptoms across Affective and Non-Affective Psychoses

Kathryn E. Lewandowski^{a,b}, Bruce M. Cohen^{a,b}, Matcheri S. Keshavan^{b,c}, and Dost Öngür^{a,b}

^aSchizophrenia and Bipolar Disorder Program, McLean Hospital, 115 Mill St., Belmont, MA, 02478 USA

^bHarvard Medical School, Department of Psychiatry, Landmark Ctr., 401 Park Dr., Boston, MA, 02215, USA

^cBeth Israel Deaconess Medical Center, 330 Brookline Ave., Boston, MA, 02215, USA

Abstract

Introduction—Neurocognitive dysfunction is believed to be a core feature of schizophrenia and is increasingly recognized as a common symptom dimension in bipolar disorder. Despite a copious literature on neurocognition in these disorders, the relationship amongst neurocognition, symptoms, and diagnosis remains unclear. We examined neurocognitive functioning in a cross-diagnostic sample of patients with psychotic disorders. Based on previous findings, it was hypothesized that neurocognitive functioning would be impaired in all three patient groups, and that groups would be similarly impaired on all neuropsychological measures. Additionally, we predicted that negative symptoms but not positive, general, or mood symptoms, would be associated with neurocognitive functioning.

Method—Neurocognitive functioning and symptoms were assessed in participants with schizophrenia ($n=25$), schizoaffective disorder ($n=29$), or bipolar disorder with psychosis ($n=31$), and in healthy controls ($n=20$).

Results—Neurocognitive functioning was significantly impaired in all patient groups, and groups did not differ by diagnosis on most measures. A series of linear regressions revealed that negative symptoms (but no other clinical symptom) predicted poorer executive functioning across groups. Diagnosis was not a significant predictor of any neurocognitive variable.

Discussion—Neurocognitive deficits were pronounced in this cross-diagnostic sample of patients with psychotic disorders, and did not differ by diagnosis. Neurocognitive dysfunction may represent a symptom dimension that spans diagnostic categories, and may reflect shared pathogenic processes. As neurocognitive dysfunction is among the strongest predictors of outcome in patients, efforts to treat these deficits, which have shown promise in schizophrenia, should be extended to all patients with psychosis.

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Corresponding Author: Dr. Kathryn E. Lewandowski AB307, Mail Stop 108 McLean Hospital 115 Mill St, Belmont, MA 02478
klewandowski@mclean.harvard.edu Phone : 617-855-2866 Fax : 617-855-2895.

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Keywords

Bipolar; Schizophrenia; Schizoaffective; neurocognitive; comparative

1. Introduction

Neurocognitive dysfunction is a core feature of schizophrenia (SZ) and related disorders, and is increasingly recognized as a prominent feature of bipolar disorder (BD). Cognitive functioning is among the strongest predictors of outcome in patients with SZ or BD (Barch, 2009, Green, 1996, Green, 2006, Martino et al., 2009, Tabares-Seisdedos et al., 2008). Despite a copious literature on neurocognition in SZ and a growing literature in BD, comparisons of neurocognition across disorders have yielded inconsistent findings, and the relationships amongst cognitive and other symptom domains across disorders remain unclear.

Comparisons of cognitive impairment between diagnoses have produced mixed results (see (Lewandowski et al., 2011) for review). Several reports indicate that patients with BD or schizoaffective disorder (SZA) exhibit a similar pattern of deficits to patients with SZ, but with levels of functioning between patients with SZ and healthy controls (Altshuler et al., 2004, Daban et al., 2006, Heinrichs et al., 2008, Krabbendam et al., 2005, Reichenberg et al., 2009, Schretlen et al., 2007, Stip et al., 2005). A cross-diagnostic comparison of patients with SZ, SZA, BD and MDD found neurocognitive deficits in all patient groups, but patients with SZ were most severely impaired (Reichenberg et al., 2008). However, other reports show no qualitative or quantitative neurocognitive differences between BD and SZ patients (Balanza-Martinez et al., 2005, McClellan et al., 2004, McGrath et al., 1997, Mojtabai et al., 2000, Morice, 1990, Simonsen et al., 2011), or amongst patients with SZ, SZA or BD with psychosis (Glahn et al., 2006, Simonsen et al., 2011, Smith et al., 2009). Lastly, patient groups may differ on some neurocognitive measures but not others. A study comparing patients with SZA, SZ, and BD reported that patients with SZA performed similarly to patients with SZ on some tasks, but that on other tasks scores fell along a continuum from SZ to SZA to BD (Szoke et al., 2008).

Cognitive functioning is most commonly associated with negative symptoms in SZ (Andreasen et al., 1990, Berman et al., 1997, Leeson et al., 2009, Nieuwenstein et al., 2001). Patients with primarily positive symptoms or paranoid subtype perform better on neurocognitive tasks relative to negative symptom or disorganized subtype patients in most (Brazo et al., 2002, Cvetic and Vukovic, 2006, Dominguez et al., 2009, Hill et al., 2001, Wang et al., 2008, Zalewski et al., 1998), although not all (Tam and Liu, 2004) studies. In BD, history of psychosis has been associated with poorer cognitive functioning (Glahn et al., 2007, Glahn et al., 2006, Martinez-Aran et al., 2008, Simonsen et al., 2011), as are factors such as earlier age of onset (Osugi and Cullum, 2005) and manic or mixed states (Dixon et al., 2004, Sweeney et al., 2000). A recent report comparing patients with SZ, BD I, BD II or SZA found that all patients with psychosis performed worse than patients with no history of psychosis or controls, but did not differ from each other (Simonsen et al., 2011). Again, these findings do not always replicate (Sanchez-Morla et al., 2009, Selva et al., 2007).

The present study aimed to examine neuropsychological functioning in a cross-diagnostic sample of patients with SZ, SZA or Bipolar I Disorder with psychosis (PBD) and the relationship of cognition to diagnosis and clinical symptoms. Based on past studies, we hypothesized that a) patients with SZ, SZA and PBD would exhibit neuropsychological deficits relative to healthy controls but would not differ from each other, and b) negative

symptoms – but not mood, positive, or general symptoms – would be associated with poorer neuropsychological functioning.

2. Method

2.1 Participants

Patients with diagnoses of SZ, SZA, or PBD, and healthy controls between the ages of 18 and 55 were eligible to participate. Participants were recruited through the Schizophrenia and Bipolar Disorder Program (SBDP) at McLean Hospital, and all procedures were approved by the McLean IRB. The present sample consisted of participants with SZ ($n=25$), SZA ($n=29$) or PBD ($n=31$) and 20 control participants. Participants were recruited through inpatient units after stabilization or via fliers posted at the hospital. Controls were recruited from the SBDP or through online advertisements. All patients endorsed past or current psychosis. All participants with PBD were manic or hypomanic at the time of assessment; all participants with SZA had bipolar subtype. All SZA patients had a chronic psychotic illness and six had YMRS scores >20 at the time of testing. Participants had no lifetime history of substance dependence, no substance abuse within the past three months, and no history of seizure disorder or history of head injury with loss of consciousness. Diagnosis was established using the Structured Clinical Interview for DSM-IV-TR (First et al., 1996) completed through patient interview, medical record review, and – when possible – consultation with the participant's treatment provider(s).

2.2 Materials

Participants were administered clinical and neuropsychological assessments and a diagnostic interview. The neuropsychological battery included: Trails A and B (Trails; processing speed, executive functioning); Brief Visuospatial Memory Test (BVMT; visuospatial learning and memory); Stroop Color and Word Test Color and Color-Word forms (Stroop; attention, processing speed, executive functioning); Hopkins Verbal Learning Test – Revised (HVLT; verbal learning and memory); Category Fluency (verbal fluency). Raw scores were converted to standard scores using published normative data (Benedict, 1997, Benedict et al., 1998, Gladsjo et al., 1999, Golden, 1978, Selnes et al., 1991). Standardized scores were converted to z-scores for ease of comparison. A neuropsychological composite score reflecting overall neuropsychological performance was calculated by averaging the above z-scores.

The SCID was administered by trained clinicians to diagnose primary mood and psychotic disorders and comorbid substance use or anxiety disorders. The SCID was never administered by the same study staff conducting the cognitive assessments. SCID interviewers met routinely for reliability exercises and to discuss difficult cases and arrive at a consensus diagnosis. The assessment also included the Positive and Negative Syndrome Scale (PANSS; (Kay et al., 1987)), the Young Mania Rating Scale (YMRS; (Young et al., 1978)), and the Montgomery-Asberg Depression Rating Scale (MADRS; (Montgomery and Asberg, 1979)) to evaluate current psychotic and mood symptoms.

Information about medications at time of assessment was obtained from the discharge medication list (inpatients) or by patient report (outpatients). For participants with complete data, chlorpromazine (CPZ) equivalent dose was calculated; some data (e.g. dosage information) were missing in 9 subjects. For typical antipsychotics, we calculated CPZ equivalents based on the Schizophrenia Patient Outcomes Research Team (PORT) recommendations (Lehman and Steinwachs, 1998). For most atypical antipsychotics, we used the CPZ equivalent doses published by Woods (Woods, 2003). For risperidone and paliperidone, we used guidelines by Gardner et al. (2010).

2.3 Procedures

All participants completed the above assessment lasting approximately 3 hours. The SCID was administered during the first session and the neurocognitive assessment during a second session. Clinical symptoms were assessed during either the first or second session. In most cases sessions were conducted within one week of each other. If the neuropsychological assessment was conducted more than one week after the clinical assessment, symptom measures were re-administered and the more recent data used in order to ascertain state clinical symptoms at the time of neuropsychological testing. While diagnostic interviews and neuropsychological assessments were conducted by different staff members, neuropsychological and symptom assessments were often conducted by the same study staff, and staff members were not always able to remain blind to group membership.

2.4 Statistical Approach

Groups were compared on clinical and neurocognitive measures using ANOVAs, first including patient groups and controls, then including only patient groups. We examined both the neuropsychological composite score and individual domain scores to determine whether specific domains differed by diagnosis, even if the overall composite did not. When significant differences were detected amongst the three patient groups, pair-wise *t*-tests were conducted. This approach was taken to reduce the number of pair-wise comparisons and the risk for Type I errors. A series of linear regressions was conducted examining the effects of diagnosis on neurocognitive outcomes after controlling for demographic variables (age, sex, education), lifetime illness and state symptom severity (lifetime hospitalizations and treatment setting at testing (inpatient vs. outpatient)), and CPZ equivalents. We then examined the effects of positive, negative, and mood symptom ratings on neurocognitive outcomes after accounting for the above demographic and severity measures and diagnosis. While we ran a number of comparisons, we did not correct for multiple comparisons because we 1) anticipated modest effects which – given the sample size – are unlikely to withstand multiple comparisons corrections creating a potential for Type II errors, and 2) tested *a priori* hypotheses regarding specific relationships of diagnosis and clinical symptoms to neurocognitive variables.

3. Results

Table 1 presents demographic data by diagnosis. Patient groups did not differ in age, education, sex, or ethnicity. Control participants had significantly higher educational attainment than any patient group. Patients differed in treatment setting at enrollment (inpatient: PBD>SZ>SZA) and number of lifetime hospitalizations (SZA>SZ>PBD). All patients were taking at least one psychiatric medication at the time of testing. Groups differed on rates of antidepressant medication ($X^2 = 8.30, p = 0.016$; SZ = 44%; SZA = 46%; PBD = 14%). Groups did not differ in rates of antipsychotic (typical or atypical), mood stabilizer, or benzodiazepine use; however, groups did differ in terms of CPZ equivalents (SZ, SZA>PBD; Table 1). Three participants were taking an anticholinergic medication (benztropine).

Table 2 presents clinical symptom data by group. Patient groups differed on YMRS and PANSS N scores. *T*-tests revealed that the SZ and SZA groups differed from the PBD group on YMRS scores ($t=-4.41, p<.001$, and $t=-4.44, p<.001$, respectively) but did not differ from each other ($t=0.05, p=.96$). The SZ group scored higher on the PANSS N than the SZA ($t=2.32, p<.05$) or PBD ($t=3.80, p<.001$) groups; the SZA group scored higher than the PBD group ($t=-2.01, p<.05$). Groups did not differ on any other clinical measure.

Control participants scored within 0.4 standard deviations of the mean on the neuropsychological composite and on all measures except the Stroop Color score (-0.86). The distribution of scores does not suggest that this finding is being driven by one or more outliers. Given that controls performed at the level that would be expected on all other neurocognitive measures and that patients also scored lower on this measure than on any other test, the normative data used for standardization appear elevated relative to our sample. Controls performed significantly better than all patient groups on all measures (Figure 1). Patient groups did not differ on the neurocognitive composite ($F=2.20$; $p=0.12$). In terms of individual tasks, groups differed only on Trails B (SZ < SZA, PBD) ($t=-2.58$, $p<.05$, and $t=-2.91$, $p<.01$, respectively). The SZA and PBD groups did not differ from each other ($t=-0.27$, $p=.79$).

We examined the effects of diagnosis and symptoms on neurocognitive outcomes using a series of linear regressions. Several demographic and symptom severity variables were predictive of neurocognitive functioning. Increasing age and lower educational attainment predicted worse performance on Trails B ($t=-3.08$, $p=.003$ and $t=4.02$, $p<.001$, respectively) and Stroop Color-Word ($t=-2.40$, $p=.02$ and $t=2.07$, $p=0.04$, respectively), and age significantly predicted the composite ($t=-2.42$, $p=.02$). Inpatient status and more prior hospitalizations predicted poorer BVMPT scores ($t=-2.42$, $p=.02$ and $t=-2.23$, $p=.03$, respectively), and treatment setting predicted the composite and Category Fluency scores ($t=-2.15$, $p=.04$ and $t=-2.13$, $p=.03$, respectively). Sex predicted Category Fluency and Stroop Color-Word scores ($t=-2.29$, $p=.03$ and $t=-2.79$, $p=.007$, respectively), with males performing better. CPZ predicted Trails A scores ($t=-2.19$, $p=.03$), but did not predict any other neuropsychological variable or the composite.

After controlling for age, sex, education, number of lifetime hospitalizations, treatment setting, and CPZ equivalents, diagnosis was not a significant predictor of any neurocognitive variable. Negative symptoms predicted Stroop Color-Word ($t=-2.43$, $p=.018$) and Trails B ($t=-2.59$, $p=.012$) – both measures of executive functioning – after controlling for demographic and severity confounders and diagnosis (Figure 2). Depression, mania, positive and general symptoms were not predictive of any neurocognitive outcome.

4. Discussion

The present study examined neurocognitive functioning in patients with SZ, SZA and PBD across multiple cognitive domains including verbal and visuospatial learning and memory, verbal fluency, executive functioning and processing speed. Our sample was adequately powered to detect medium effects using well-validated measures in patients with psychotic disorders. We aimed to reduce heterogeneity within groups by selecting for symptoms that may be relevant to neurocognitive functioning: all participants had a history of psychosis; all participants with SZA had bipolar subtype; all participants with PBD were in a manic or hypomanic episode at the time of testing. All patient groups performed worse than controls on all measures, and between one and two standard deviations below the mean on all measures except Trails A. Groups did not differ by diagnosis on most neurocognitive variables. Patients with SZ performed worse than patients with PBD or SZA on one measure of executive functioning (Trails B) but not another (Stroop Color-Word). We did not find evidence of domain-specific deficits within or among diagnoses.

As hypothesized, negative symptoms, but no other clinical symptoms, predicted neurocognitive outcomes. Negative symptoms predicted measures of executive functioning and selective attention, but were not associated with visual or verbal learning and memory, verbal fluency, or processing speed. The association between negative symptoms and executive deficits remained significant even after accounting for diagnosis, suggesting that

negative symptoms themselves are associated with poorer executive performance. While groups differed in terms of negative symptoms, within diagnoses negative symptoms were similarly associated with executive deficits. A post-hoc correlation analysis examining the 7 items from the PANSS Negative Symptom subscale and executive functioning scores revealed that Blunted Affect, Emotional Withdrawal, and Abstract Thinking were modestly correlated with Stroop Color-Word ($r = -0.25$, -0.27 , and -0.32 , respectively), and Spontaneity/Flow of Conversation and Abstract Thinking were modestly to moderately correlated with Trails B ($r = -0.24$ and -0.41 , respectively). All other correlations were trivial to small, and non-significant ($p > .05$). No single, large correlation drove the relationship between executive functioning/selective attention and negative symptoms, although, not surprisingly, abstract thinking was correlated with both neurocognitive scores.

The association between neurocognitive deficits and negative symptoms is often reported in SZ but not in BD, perhaps due to the assumption that negative symptoms are absent or minimal in BD. Toomey et al. (1998) found that both positive and negative factors generalized to mood disorders groups. We found that negative symptoms were present in PBD, albeit at lower levels than SZ, and that they were associated with poorer executive functioning. Across psychotic disorders, negative symptoms appear to be associated with executive dysfunction.

Within psychotic disorders, neurocognitive dysfunction appears to represent an illness dimension that is detectable in cross-diagnostic samples and is associated with specific symptom dimensions (i.e. negative symptoms). These findings have implications for treatment and may inform investigations of the pathophysiology of psychotic disorders. The relationship between negative symptoms and executive deficits may reflect a shared neurobiology that is not specific to SZ, and may be indicative of maldevelopment of specific neural pathways. For instance, dopamine hypoactivity in PFC may relate to both negative symptoms and neurocognition (e.g. Alves Fda et al., 2008, Goldman-Rakic and Selemon, 1997, Knable and Weinberger, 1997). Identification of a specific relationship between executive deficits and negative symptoms in a cross-diagnostic sample supports hypotheses regarding a shared neurobiology related to these outcomes in broader populations than just SZ.

Cognitive impairments are associated with poorer functional outcomes in SZ and BD, and longer time to recovery after a first episode in BD patients (Barch, 2009, Bowie et al., 2010, Green, 1996, Green, 2006, Gruber et al., 2008, Martino et al., 2009, Tabares-Seisdedos et al., 2008). While neurocognitive dysfunction is increasingly recognized as a key treatment target in patients with SZ, our findings indicate that this symptom dimension is an important target in patients with SZA and BD with psychotic features, as well.

The present study has several limitations. First, our sample was experiencing substantial symptoms at the time of testing; thus, it is not clear that our participants are representative of all patients with psychotic disorders or would continue to share similar levels of neurocognitive dysfunction after recovery. Our participants' symptom scores were at the level that would be expected of patients with psychosis who experience periodic symptom exacerbations, making these findings generalizable to patients experiencing an acute episode or more severe chronic illness. Follow-up studies tracking participants through both acute and remitted phases of illness will help to clarify these questions.

We examined relationships amongst neuropsychological variables and CPZ equivalents, but we did not control for all medication effects. While some findings suggest that second generation antipsychotics are associated with small improvements in neurocognitive functioning in SZ (Harvey and Keefe, 2001, Harvey et al., 1990, Keefe et al., 2007,

Woodward et al., 2005), polypharmacy and high dosing appear to be associated with poorer cognitive performance (Elie et al., 2010). Similarly, antipsychotics, lithium, and anticonvulsants may be associated with poorer cognitive performance in patients with BD (Balanza-Martinez et al., 2010, Donaldson et al., 2003, Stip et al., 2000, Wingo et al., 2009). Our groups differed in CPZ equivalents; however, we found that CPZ was associated only with Trails A scores and did not affect the relationship between diagnosis and neurocognitive outcomes. While medications may have affected performance on some tasks, it does not appear that medication effects account for the relationships between neurocognitive and clinical measures.

Substantial evidence exists of shared genetic liability between SZ and BD (e.g. (Craddock et al., 2006, Kendler et al., 1998, Torrey, 1999, Tsuang et al., 1980, Valles et al., 2000)). The identification of symptom dimensions such as neurocognitive dysfunction that are shared across related disorders supports increasing skepticism of stark Kraepelinian boundaries between SZ and affective disorders (e.g. (Craddock and Owen, 2007)). Study of the expression and course of major features of illness may help clarify aspects of specific pathological processes that are shared or distinct in these disorders. Additionally, the present findings indicate that treatments targeting cognitive deficits such as cognitive remediation, which has shown promise in patients with SZ (Bell et al., 2007, Bell et al., 2008, Eack et al., 2009, Fisher et al., 2009, Kurtz et al., 2007, McGurk and Wykes, 2008, Medalia and Choi, 2009, Wykes, 2008) and SZA (Lewandowski et al 2011), should be extended to all patients with psychosis. Finally, our findings support the view that translational studies of cross-cutting domains of neural dysfunction as envisioned in the R-DoC concept (Insel et al 2010) are likely to help us better understand complex psychiatric disorders better than categorical approaches alone.

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References

- Altshuler LL, Ventura J, van Gorp WG, Green MF, Theberge DC, Mintz J. Neurocognitive function in clinically stable men with bipolar I disorder or schizophrenia and normal control subjects. *Biol. Psychiatry*. 2004; 56:560–569. [PubMed: 15476685]
- Alves Fda S, Figue M, Vamelsvoort T, Veltman D, de Haan L. The revised dopamine hypothesis of schizophrenia: evidence from pharmacological MRI studies with atypical antipsychotic medication. *Psychopharmacol. Bull*. 2008; 41:121–132. [PubMed: 18362875]
- Andreasen NC, Flaum M, Swayze VW 2nd, Tyrrell G, Arndt S. Positive and negative symptoms in schizophrenia. A critical reappraisal. *Arch. Gen. Psychiatry*. 1990; 47:615–621. [PubMed: 2360855]
- Balanza-Martinez V, Selva G, Martinez-Aran A, Prickaerts J, Salazar J, Gonzalez-Pinto A, Vieta E, Tabares-Seisdedos R. Neurocognition in bipolar disorders - A closer look at comorbidities and medications. *Eur. J. Pharmacol*. 2010; 626:87–96. [PubMed: 19836378]
- Balanza-Martinez V, Tabares-Seisdedos R, Selva-Vera G, Martinez-Aran A, Torrent C, Salazar-Fraile J, Leal-Cercos C, Vieta E, Gomez-Beneyto M. Persistent cognitive dysfunctions in bipolar I disorder and schizophrenic patients: a 3-year follow-up study. *Psychother. Psychosom*. 2005; 74:113–119. [PubMed: 15741761]
- Barch DM. Neuropsychological abnormalities in schizophrenia and major mood disorders: similarities and differences. *Curr. Psychiatry Rep*. 2009; 11:313–319. [PubMed: 19635240]
- Bell M, Fiszdon J, Greig T, Wexler B, Bryson G. Neurocognitive enhancement therapy with work therapy in schizophrenia: 6-month follow-up of neuropsychological performance. *J. Rehabil. Res. Dev*. 2007; 44:761–770. [PubMed: 17943687]
- Bell MD, Zito W, Greig T, Wexler BE. Neurocognitive enhancement therapy with vocational services: work outcomes at two-year follow-up. *Schizophr. Res*. 2008; 105:18–29. [PubMed: 18715755]

- Benedict, RH. Brief Visuospatial Memory Test—Revised. Psychological Assessment Resources, Inc; Odessa, FL: 1997.
- Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test-Revised: Normative data and analysis of inter-form and test-retest reliability. *Clin. Neuropsychologist*. 1998; 12:43–55.
- Berman I, Viegner B, Merson A, Allan E, Pappas D, Green AI. Differential relationships between positive and negative symptoms and neuropsychological deficits in schizophrenia. *Schizophr. Res.* 1997; 25:1–10. [PubMed: 9176922]
- Bowie CR, Depp C, McGrath JA, Wolyniec P, Mausbach BT, Thornquist MH, Luke J, Patterson TL, Harvey PD, Pulver AE. Prediction of real-world functional disability in chronic mental disorders: a comparison of schizophrenia and bipolar disorder. *Am. J. Psychiatry*. 2010; 167:1116–1124. [PubMed: 20478878]
- Brazo P, Marie RM, Halbecq I, Benali K, Segard L, Delamillieure P, Langlois-Thery S, Van Der Elst A, Thibaut F, Petit M, Dollfus S. Cognitive patterns in subtypes of schizophrenia. *Eur. Psychiatry*. 2002; 17:155–162. [PubMed: 12052576]
- Craddock N, O'Donovan MC, Owen MJ. Genes for schizophrenia and bipolar disorder? Implications for psychiatric nosology. *Schizophr. Bull.* 2006; 32:9–16. [PubMed: 16319375]
- Craddock N, Owen MJ. Rethinking psychosis: the disadvantages of a dichotomous classification now outweigh the advantages. *World Psychiatry*. 2007; 6:84–91. [PubMed: 18235858]
- Cvetic T, Vukovic O. Cognitive deficit in schizophrenia: comparative analysis of positive and negative subtype and predictors of positive subtype. *Psychiatr. Danub.* 2006; 18:4–11. [PubMed: 16804494]
- Daban C, Martinez-Aran A, Torrent C, Tabares-Seisdedos R, Balanza-Martinez V, Salazar-Fraile J, Selva-Vera G, Vieta E. Specificity of cognitive deficits in bipolar disorder versus schizophrenia. A systematic review. *Psychother. Psychosom.* 2006; 75:72–84. [PubMed: 16508342]
- Dixon T, Kravariti E, Frith C, Murray RM, McGuire PK. Effect of symptoms on executive function in bipolar illness. *Psychol. Med.* 2004; 34:811–821. [PubMed: 15500302]
- Dominguez, Mde G, Veichtbauer W, Simons CJ, van Os J, Krabbendam L. Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations. *Psychol. Bull.* 2009; 135:157–171. [PubMed: 19210058]
- Donaldson S, Goldstein LH, Landau S, Raymont V, Frangou S. The Maudsley Bipolar Disorder Project: the effect of medication, family history, and duration of illness on IQ and memory in bipolar I disorder. *J. Clin. Psychiatry*. 2003; 64:86–93. [PubMed: 12590629]
- Eack SM, Greenwald DP, Hogarty SS, Cooley SJ, DiBarry AL, Montrose DM, Keshavan MS. Cognitive enhancement therapy for early-course schizophrenia: effects of a two-year randomized controlled trial. *Psychiatr. Serv.* 2009; 60:1468–1476. [PubMed: 19880464]
- Elie D, Poirier M, Chianetta J, Durand M, Gregoire C, Grignon S. Cognitive effects of antipsychotic dosage and polypharmacy: a study with the BACS in patients with schizophrenia and schizoaffective disorder. *J. Psychopharmacol.* 2010; 24(7):037–44.
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). American Psychiatric Press, Inc.; Washington, DC: 1996.
- Fisher M, Holland C, Subramaniam K, Vinogradov S. Neuroplasticity-Based Cognitive Training in Schizophrenia: An Interim Report on the Effects 6 Months Later. *Schizophr. Bull.* 2010; 36(4): 869–879. [PubMed: 19269924]
- Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. *Am. J. Psychiatry*. 2010; 167:686–693. [PubMed: 20360319]
- Gladysjo JA, Schuman CC, Evans JD, Peavy GM, Miller SW, Heaton RK. Norms for letter and category fluency: demographic corrections for age, education, and ethnicity. *Assessment*. 1999; 6:147–178. [PubMed: 10335019]
- Glahn DC, Bearden CE, Barguil M, Barrett J, Reichenberg A, Bowden CL, Soares JC, Velligan DI. The neurocognitive signature of psychotic bipolar disorder. *Biol. Psychiatry*. 2007; 62:910–916. [PubMed: 17543288]

- Glahn DC, Bearden CE, Cakir S, Barrett JA, Najt P, Serap Monkul E, Maples N, Velligan DI, Soares JC. Differential working memory impairment in bipolar disorder and schizophrenia: effects of lifetime history of psychosis. *Bipolar Disord.* 2006; 8:117–123. [PubMed: 16542181]
- Golden, CJ. Stroop Color and Word Test. Stoelting Company; Chicago, IL: 1978.
- Goldman-Rakic PS, Selemon LD. Functional and anatomical aspects of prefrontal pathology in schizophrenia. *Schizophr. Bull.* 1997; 23:437–458. [PubMed: 9327508]
- Green M. What are the functional consequences of neurocognitive deficits in schizophrenia? *American Journal of Psychiatry.* 1996; 153:321–330. [PubMed: 8610818]
- Green MF. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *J. Clin. Psychiatry.* 2006; 67:e12. [PubMed: 17107235]
- Gruber SA, Rosso IM, Yurgelun-Todd D. Neuropsychological performance predicts clinical recovery in bipolar patients. *J. Affect. Disord.* 2008; 105:253–260. [PubMed: 17524493]
- Harvey PD, Keefe RS. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *Am. J. Psychiatry.* 2001; 158:176–184. [PubMed: 11156796]
- Harvey PD, Keefe RS, Moskowitz J, Putnam KM, Mohs RC, Davis KL. Attentional markers of vulnerability to schizophrenia: performance of medicated and unmedicated patients and normals. *Psychiatry Res.* 1990; 33:179–188. [PubMed: 2243895]
- Heinrichs RW, Ammari N, McDermid Vaz S, Miles AA. Are schizophrenia and schizoaffective disorder neuropsychologically distinguishable? *Schizophr. Res.* 2008; 99:149–154. [PubMed: 18031992]
- Hill SK, Ragland JD, Gur RC, Gur RE. Neuropsychological differences among empirically derived clinical subtypes of schizophrenia. *Neuropsychology.* 2001; 15:492–501. [PubMed: 11761038]
- Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am. J. Psychiatry.* 2010; 167:748–751. [PubMed: 20595427]
- Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 1987; 13:261–276. [PubMed: 3616518]
- Keefe RS, Bilder RM, Davis SM, Harvey PD, Palmer BW, Gold JM, Meltzer HY, Green MF, Capuano G, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Davis CE, Hsiao JK, Lieberman JA. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Arch. Gen. Psychiatry.* 2007; 64:633–647. [PubMed: 17548746]
- Kendler KS, Karkowski LM, Walsh D. The structure of psychosis: latent class analysis of probands from the Roscommon Family Study. *Arch. Gen. Psychiatry.* 1998; 55:492–499. [PubMed: 9633666]
- Knable MB, Weinberger DR. Dopamine, the prefrontal cortex and schizophrenia. *J Psychopharmacol. (Oxf).* 1997; 11:123–131.
- Krabbendam L, Arts B, van Os J, Aleman A. Cognitive functioning in patients with schizophrenia and bipolar disorder: a quantitative review. *Schizophr. Res.* 2005; 80:137–149. [PubMed: 16183257]
- Kurtz MM, Seltzer JC, Shagan DS, Thime WR, Wexler BE. Computer-assisted cognitive remediation in schizophrenia: what is the active ingredient? *Schizophr. Res.* 2007; 89:251–260. [PubMed: 17070671]
- Leeson VC, Barnes TR, Hutton SB, Ron MA, Joyce EM. IQ as a predictor of functional outcome in schizophrenia: a longitudinal, four-year study of first-episode psychosis. *Schizophr. Res.* 2009; 107:55–60. [PubMed: 18793828]
- Lehman AF, Steinwachs DM. Translating research into practice: the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations. *Schizophr. Bull.* 1998; 24:1–10. [PubMed: 9502542]
- Lewandowski KE, Cohen BM, Ongur D. Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. *Psychol. Medicine.* 2011; 41(2):225–41.
- Lewandowski KE, Eack SM, Hogarty SS, Greenwald DP, Keshavan MS. Is cognitive enhancement therapy equally effective for patients with schizophrenia and schizoaffective disorder? *Schizophr. Res.* 2011; 125:291–294. [PubMed: 21167689]

- Martinez-Aran A, Torrent C, Tabares-Seisdedos R, Salamero M, Daban C, Balanza-Martinez V, Sanchez-Moreno J, Manuel Goikolea J, Benabarre A, Colom F, Vieta E. Neurocognitive impairment in bipolar patients with and without history of psychosis. *J. Clin. Psychiatry*. 2008; 69:233–239. [PubMed: 18232725]
- Martino DJ, Marengo E, Igoa A, Scapola M, Ais ED, Perinot L, Strejilevich SA. Neurocognitive and symptomatic predictors of functional outcome in bipolar disorders: a prospective 1 year follow-up study. *J. Affect. Disord*. 2009; 116:37–42. [PubMed: 19033081]
- McClellan J, Prezbindowski A, Breiger D, McCurry C. Neuropsychological functioning in early onset psychotic disorders. *Schizophr. Res*. 2004; 68:21–26. [PubMed: 15037336]
- McGrath J, Scheldt S, Welham J, Clair A. Performance on tests sensitive to impaired executive ability in schizophrenia, mania and well controls: acute and subacute phases. *Schizophr. Res*. 1997; 26:127–137. [PubMed: 9323343]
- McGurk SR, Wykes T. Cognitive remediation and vocational rehabilitation. *Psychiatr. Rehabil. J*. 2008; 31:350–359. [PubMed: 18407885]
- Medalia A, Choi J. Cognitive remediation in schizophrenia. *Neuropsychol. Rev*. 2009; 19:353–364. [PubMed: 19444614]
- Mojtabai R, Bromet EJ, Harvey PD, Carlson GA, Craig TJ, Fennig S. Neuropsychological differences between first-admission schizophrenia and psychotic affective disorders. *Am. J. Psychiatry*. 2000; 157:1453–1460. [PubMed: 10964862]
- Montgomery S, Asberg M. A new depression scale designed to be sensitive to change. *Br. J. Psychiatry*. 1979; 134:382–389. [PubMed: 444788]
- Morice R. Cognitive inflexibility and pre-frontal dysfunction in schizophrenia and mania. *Br. J. Psychiatry*. 1990; 157:50–54. [PubMed: 2397362]
- 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. [PubMed: 11377441]
- Osugi JJ, Cullum CM. Cognition in bipolar disorder. *Psychiatr. Clin. North Am*. 2005; 28:427–241. [PubMed: 15826741]
- Reichenberg A, Harvey PD, Bowie CR, Mojtabai R, Rabinowitz J, Heaton RK, Bromet E. Neuropsychological Function and Dysfunction in Schizophrenia and Psychotic Affective Disorders. *Schizophr. Bull*. 2008; 35:1022–1029. [PubMed: 18495643]
- Reichenberg A, Harvey PD, Bowie CR, Mojtabai R, Rabinowitz J, Heaton RK, Bromet E. Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. *Schizophr. Bull*. 2009; 35:1022–1029. [PubMed: 18495643]
- Sanchez-Morla EM, Barabash A, Martinez-Vizcaino V, Tabares-Seisdedos R, Balanza-Martinez V, Cabranes-Diaz JA, Baca-Baldomero E, Gomez JL. Comparative study of neurocognitive function in euthymic bipolar patients and stabilized schizophrenic patients. *Psychiatry Res*. 2009; 169:220–228. [PubMed: 19758705]
- Schretlen DJ, Cascella NG, Meyer SM, Kingery LR, Testa SM, Munro CA, Pulver AE, Rivkin P, Rao VA, Diaz-Asper CM, Dickerson FB, Yolken RH, Pearlson GD. Neuropsychological functioning in bipolar disorder and schizophrenia. *Biol. Psychiatry*. 2007; 62:179–186. [PubMed: 17161829]
- Selnes OA, Jacobson L, Machado AM, Becker JT, Wesch J, Miller EN, Visscher B, McArthur JC. Normative data for a brief neuropsychological screening battery. Multicenter AIDS Cohort Study. *Percept. Mot. Skills*. 1991; 73:539–550. [PubMed: 1766784]
- Selva G, Salazar J, Balanza-Martinez V, Martinez-Aran A, Rubio C, Daban C, Sanchez-Moreno J, Vieta E, Tabares-Seisdedos R. 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. [PubMed: 16762369]
- Simonsen C, Sundet K, Vaskinn A, Birkenaes AB, Engh JA, Faerden A, Jonsdottir H, Ringen PA, Opjordsmoen S, Melle I, Friis S, Andreassen OA. Neurocognitive dysfunction in bipolar and schizophrenia spectrum disorders depends on history of psychosis rather than diagnostic group. *Schizophr. Bull*. 2011; 37(1):73–83. [PubMed: 19443616]

- 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. [PubMed: 18786811]
- 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. [PubMed: 11074103]
- Stip E, Sepehry AA, Prouteau A, Briand C, Nicole L, Lalonde P, Lesage A. Cognitive discernible factors between schizophrenia and schizoaffective disorder. *Brain Cogn.* 2005; 59:292–295. [PubMed: 16125294]
- Sweeney JA, Kmiec JA, Kupfer DJ. Neuropsychologic impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. *Biol. Psychiatry.* 2000; 48:674–684. [PubMed: 11032979]
- Szoke A, Meary A, Trandafir A, Bellivier F, Roy I, Schurhoff F, Leboyer M. Executive deficits in psychotic and bipolar disorders - implications for our understanding of schizoaffective disorder. *Eur. Psychiatry.* 2008; 23:20–25. [PubMed: 18083013]
- Tabares-Seisdedos R, Balanza-Martinez V, Sanchez-Moreno J, Martinez-Aran A, Salazar-Fraile J, Selva-Vera G, Rubio C, Mata I, Gomez-Beneyto M, Vieta E. Neurocognitive and clinical predictors of functional outcome in patients with schizophrenia and bipolar I disorder at one-year follow-up. *J. Affect. Disord.* 2008; 109:286–299. [PubMed: 18289698]
- Tam WC, Liu Z. Comparison of neurocognition between drug-free patients with schizophrenia and bipolar disorder. *J. Nerv. Ment. Dis.* 2004; 192:464–470. [PubMed: 15232316]
- Toomey R, Faraone SV, Simpson JC, Tsuang MT. Negative, positive, and disorganized symptoms dimensions in schizophrenia, major depression, and bipolar disorder. *J. Nerv. Ment. Dis.* 1998; 186:470–476. [PubMed: 9717864]
- Torrey EF. Epidemiological comparison of schizophrenia and bipolar disorder. *Schizophr. Res.* 1999; 39:101–106. discussion 159–160. [PubMed: 10507519]
- Tsuang MT, Winokur G, Crowe RR. Morbidity risks of schizophrenia and affective disorders among first degree relatives of patients with schizophrenia, mania, depression and surgical conditions. *Br. J. Psychiatry.* 1980; 137:497–504. [PubMed: 7214104]
- Valles V, Van Os J, Guillamat R, Gutierrez B, Campillo M, Gento P, Fananas L. Increased morbid risk for schizophrenia in families of in-patients with bipolar illness. *Schizophr. Res.* 2000; 42:83–90. [PubMed: 10742646]
- Wang X, Yao S, Kirkpatrick B, Shi C, Yi J. Psychopathology and neuropsychological impairments in deficit and nondeficit schizophrenia of Chinese origin. *Psychiatry Res.* 2008; 158:195–205. [PubMed: 18243336]
- Wingo AP, Wingo TS, Harvey PD, Baldessarini RJ. Effects of lithium on cognitive performance: a meta-analysis. *J. Clin. Psychiatry.* 2009; 626:87–96.
- Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J. Clin. Psychiatry.* 2003; 64:663–667. [PubMed: 12823080]
- Woodward ND, Purdon SE, Meltzer HY, Zald DH. A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. *Int. J. Neuropsychopharmacol.* 2005; 8:457–472. [PubMed: 15784157]
- Wykes T. Review: cognitive remediation improves cognitive functioning in schizophrenia. *Evid. Based Ment. Health.* 2008; 11:117. [PubMed: 18952966]
- Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br. J. Psychiatry.* 1978; 133:429–435. [PubMed: 728692]
- Zalewski C, Johnson-Selfridge MT, Ohriner S, Zarrella K, Seltzer JC. A review of neuropsychological differences between paranoid and nonparanoid schizophrenia patients. *Schizophr. Bull.* 1998; 24:127–145. [PubMed: 9502551]

Figure 1. Neurocognitive Measures by Diagnosis

* = $p < .05$

Note: control participants differed significantly from all patient groups on all cognitive measures: Composite: $p < .001$; BVMT: $p < .01$; HVLT: $p < .001$; Trails A: $p < .001$; Trails B: $p < .001$; Category Fluency: $p < .01$; Stroop Color: $p < .001$; Stroop Color-Word: $p < .001$

Figure 2.
Negative Symptoms and Neurocognitive Score by Diagnosis

Table 1

Demographic Variables by Diagnosis

	SZ(n=25)	SZA(n=29)	PBD(n=31)	Control(n=20)
Age	37.8 (11.4)	38.3 (9.1)	33.9 (11.6)	40.4 (8.7)
Education ^a	4.2 (1.4)	4.5 (1.7)	5.0 (1.2)	6.1 (1.4) ***
% Female	40%	55%	65%	45%
% Caucasian	68%	79%	71%	70%
# Lifetime				
Hospitalizations	4.0 (2.2)	4.8 (1.8)	3.5 (1.8) *	n/a
% Inpatient	68%	48%	87% **	n/a
CPZ Equivalent	650 (435)	606 (499)	304 (271) **	n/a

p<.001

**
p<.01

*
p<.05

^aEducation is coded based on the SCID Education and Work History scale: 1 = grade 6 or less; 2 = grade 7–12 (without graduating); 3 = high school grad or equivalent; 4 = part college; 5 = graduated 2 year college; 6 = graduated 4 year college; 7 = part graduate/professional school; 8 = completed graduate/professional school

Table 2

Symptom Scales by Diagnosis

	SZ(n=25)	SZA(n=29)	PBD(n=31)	F-statistic	Control(n=20) ^a
YMRS	13.8 (10.5)	13.7 (12.2)	29.3 (14.7)	14.52***	0.6 (0.8)
MADRS	11.1 (7.5)	13.6 (9.4)	11.7 (7.2)	0.69	1.3 (1.9)
PANSS P	20.5 (8.1)	17.5 (8.0)	19.8 (8.2)	1.05	7.1 (0.4)
PANSS N	15.2 (5.5)	12.2 (4.5)	9.6 (5.6)	8.20**	7.4 (0.7)
PANSS G	29.2 (8.0)	28.1 (8.6)	31.6 (10.1)	1.19	16.7 (1.3)

**
p<.01

p<.001

^a control participants differed significantly from all patient groups on all clinical measures (p<.001)