Comparing clinical and neurocognitive features of the schizophrenia prodrome to the bipolar prodrome

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ABSTRACT

Background: There is an increased interest in early intervention strategies for severe mental disorders with hopes of mitigating the emergence and impact of the illness. Individuals at clinical high-risk (CHR) for schizophrenia have been primarily identified by the presence of attenuated positive symptoms. Although bipolar disorder and schizophrenia may have overlapping etiologies, few studies have investigated the potential prodrome in bipolar disorder. We sought to determine if there is a prodrome to bipolar disorder and if clinical or neurocognitive measures could distinguish between the bipolar and schizophrenia prodromes.
Methods: We examined subjects who were initially identified as CHR for schizophrenia during the prodromal phase of the illness and followed them prospectively. Unexpectedly, eight subjects developed bipolar disorder. Baseline data from subjects who eventually developed bipolar disorder (pre-BP; N = 8), schizophrenia or a psychotic disorder (pre-SZ; N = 24) and a non-converter comparison group (NCC; N = 115) were compared.
Results: The pre-BP and pre-SZ groups did not differ on attenuated positive symptom severity, global measures of functioning or on the global neurocognitive score. Compared to NCC individuals, both pre-BP and pre-SZ patients reported more severe attenuated positive symptoms and were more likely to be on antipsychotic medication at baseline. The pre-SZ group had a significantly lower current IQ and was significantly more impaired than the NCC group on the overall neurocognitive score.
Conclusions: This study provides preliminary support for a bipolar prodrome, which may be indistinguishable from the schizophrenia prodrome based on clinical and neurocognitive measures currently used in high-risk schizophrenia programs.

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1. Introduction

Prevention has become an increasingly central interest in psychiatry. To date, research efforts have been directed at developing early interventions for schizophrenia. Although there is considerable question as to whether a clinically relevant prodromal phase of bipolar disorder can be reliably detected (Skjelstad et al., 2009), there have been a few retrospective studies showing that individuals with bipolar disorder report subsyndromal symptoms prior to developing the disorder (Conus et al., 2010; Correll et al., 2007a; Egeland et al., 2000; Mantere et al., 2008). We found that 100% of adolescents reported prodromal symptoms, which began in 51.9% over a year prior to the first manic episode and in 44.2% between one and twelve months prior (Correll et al., 2007a). Thompson et al. (2003) reported three case studies that provided a prospective account of a bipolar prodrome. There

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is also some evidence that adolescents at genetic high-risk (GHR) for an affective disorder exhibit similar neurocognitive deficits compared to adolescents at GHR for schizophrenia (Maziade et al., 2009; Seidman et al., 2006; Thompson et al., 2003). Although a number of GHR studies have been conducted (Correll et al., 2007b), no study to date has prospectively assessed individuals who are at clinical high-risk (CHR) for bipolar disorder.

The goal of this study was to provide initial findings about potential predictors of bipolar disorder in a small, but unique, sample of pre-bipolar adolescents. We hypothesized that there would be a detectable prodrome to bipolar disorder and sought to determine whether differences in the bipolar and schizophrenia prodromes could be detected based on clinical or neurocognitive measures.

2. Methods

Participants included in this report are a subset of the larger Recognition and Prevention (RAP) Program. Written, informed consent was obtained from the patients if they were ≥18 years old, or from their parent (with patient's written assent) if the patient was <18 years. The research protocol was approved by the Institutional Review Board at North Shore-Long Island Jewish Health System (NS-LIJHS). Patients were included in the study if they had a score of moderate or higher on any negative or positive symptom on the Scale of Prodromal Symptoms (SOPS; Miller et al., 1999). Subjects were excluded if they met DSM-IV criteria for an Axis I schizophrenia-spectrum disorder, major depressive disorder with psychotic features or a bipolar spectrum disorder at baseline; were non-English speaking; had a medical or neurological disorder that could affect brain functioning; drug or alcohol dependence within the past 6 months; or have an estimated IQ below 70.

In the RAP program, 29 CHR patients converted to a schizophrenia spectrum disorder (pre-SZ group; i.e., schizophrenia: N = 19; schizoaffective disorder: N = 2; schizophreniform disorder: N = 2; delusional disorder: N = 1; and psychotic disorder NOS: N = 5) and 8 converted to a bipolar spectrum disorder (pre-BP group; bipolar I: N = 6; and bipolar NOS: N = 2). Five of the 8 pre-BP subjects reported psychotic features at the time of the first manic episode. Participants missing data from at least 33% of the neurocognitive variables (pre-SZ: N = 5) were excluded from the

analysis. One hundred and fifteen CHR patients who did not convert to either disorder and who had no missing data were included as a control sample (NCC group). Thus, the final sample consisted of 24 pre-SZ subjects, 8 pre-BP subjects, and 115 NCC subjects.

All participants were assessed at baseline with clinical measures (Table 1) and neurocognitive tests (Table 2). Neurocognitive scores from a healthy control sample (N = 38) were used to create a global neuropsychological z-score that was

Table 1
Clinical measures.

Clinical measure	Assessment
Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version (K-SADS-E; Orvaschel and Puig-Antich, 1994)	Axis I diagnoses
Structured Interview for Prodromal Syndromes (SIPS) and the Scale of Prodromal Symptoms (SOPS; McGlashan et al., 2001; Miller et al., 1999)	Prodromal symptoms
Global Assessment of Functioning scale (GAF; Hall, 1995)	Global functioning
Global Functioning: Social scale (GFS; Auther et al., 2006; Cornblatt et al., 2007)	Social functioning
Global Functioning: Role scale (GFR; Cornblatt et al., 2007; Niendam et al., 2006)	Role functioning

Table 2
Neurocognitive tests and dependent measures.

Test	Dependent measure
IQ measures	
Premorbid IQ	
WRAT-3 (Wilkinson, 1993)	Age scaled score for words read correctly.
Current IQ [a]	
WISC-III (Wechsler, 1991)/WAIS-R (Wechsler, 1981)	Sum of age scaled score for Vocabulary and Block Design subscales.
Neurocognitive battery	
Boston Naming Test (Kaplan et al., 1983)	Number of correctly named items.
CVLT Adult (Delis et al., 1987)	
CVLT Child (Delis et al., 1994)	
Total for trials 1–5	Words recalled in trials 1–5.
Short delay free recall	Words recalled after delay
CPT-IP (Cornblatt and Keilp, 1994) 2-, 3-, 4-digits and shapes	d′ (for all stimulus sets).
COWAT (Benton and Hamsher, 1989)	Words produced in three 60 s trials.
Finger Tapping Test, Dominant and Nondominant Hand Scores (Reitan, 1979)	Taps in 10 s, over 5 trials.
Grooved Pegboard Test, Dominant and Nondominant Hand Scores (Matthews and Klove, 1964)	Time to place pegs.
Judgment of Line Orientation (Benton et al., 1983)	Lines accurately matched.
Letter-Number Span (Gold et al., 1997)	Number of correct trials.
Ruff Figural Fluency Test (Ruff, 1987)	Number of unique designs generated.
Trail Making Test, Parts A and B (Reitan, 1979)	Time to complete trails.
WAIS-R/WISC-III (Wechsler, 1981, 1991)	
Digit Span, Forward and Backward	Digit sequences recalled.
Block Design	Correctly reconstructed blocks to recreate patterns on cards.
Vocabulary	Number of words correctly defined.
Information	Number of correct responses.
WMS-R (Wechsler, 1987)	
Logical Memory, Immediate and Delayed	Story elements recalled.
Visual Reproduction, Immediate and Delayed	Number of correctly reproduced figures.
WSCT (Heaton et al., 1993)	Number of perseverative errors.
WRAT-3 (Wilkinson, 1993)	Total score for words read correctly.

WRAT-3, Wide-Range Achievement Test, 3rd Edition; WISC-III, Wechsler Intelligence Scale for Children, 3rd Edition; WAIS-R, Wechsler Adult Intelligence Scale, Revised; CVLT, California Verbal Learning Test; CPT-IP, Continuous Performance Test-Identical Pairs; COWAT, Controlled Oral Word Association Test; WMS-R, Wechsler Memory Scale, Revised; WSCT, Wisconsin Card Sorting Test, Version 2.

[a] Estimated current full-scale IQ was derived from the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) for three subjects (BP: N = 1; SZ: N = 2).

Table 3
Demographic data means ± standard deviations for the pre-BP, pre-SZ and NCC groups.

	Pre-BP group (N=8)	Pre-SZ group (N=24)	NCC group (N=115)	F/t/χ²	p	Post hoc tests (p-value)		
						Pre-BP vs. Pre-SZ	Pre-BP vs. NCC	Pre-SZ vs. NCC
Age	15.85 ± 1.87	17.11 ± 2.17	16.03 ± 2.18	2.61	ns	–	–	–
Sex, N (%) male	5 (62.5%)	20 (83.3%)	76 (66.1%)	2.90	ns	–	–	–
Ethnicity, N (%) Caucasian	6 (75%)	17 (70.8%)	96 (83.5%)	3.33	ns	–	–	–
Current IQ	94.50 ± 23.21	96.30 ± 12.51	104.96 ± 16.67	3.77	<0.05	ns	ns	<0.05
Premorbid IQ	103.12 ± 14.54	102.38 ± 15.65	106.43 ± 11.75	1.19	ns	–	–	–
Age of disorder onset	18.43 ± 3.08	18.41 ± 2.29	N/A	0.02	ns	–	–	–
Disorder onset after identified as high-risk (days)	941.88 ± 641.24	475.50 ± 447.20	N/A	2.29	<0.05	–	–	–
On antipsychotic at baseline, N (%)	4 (50%)	14 (58.3%)	17 (14.8%)	23.96	<0.001	ns	<0.01	<0.001
On antidepressant at baseline, N (%)	2 (25%)	5 (20.8%)	28 (24.3%)	0.14	ns	–	–	–
On mood stabilizer at baseline, N (%)	1 (12.5%)	1 (4.2%)	4 (3.5%)	1.56	ns	–	–	–
On stimulant at baseline, N (%)	1 (12.5%)	0 (0.0%)	8 (7%)	2.27	ns	–	–	–
On anxiolytic at baseline, N (%)	2 (25%)	4 (16.7%)	10 (8.7%)	3.04	ns	–	–	–

BP, bipolar disorder; SZ, schizophrenia; NCC, non-converter comparison group; ns, non-significant; N/A, Not Applicable.

calculated from individual test variables. In all cases, data were statistically evaluated using SPSS (Chicago, Illinois, USA, Version 16.0). Comparisons of demographic, clinical, and neurocognitive variables were performed with an analysis of variance (ANOVA) with group (pre-BP, pre-SZ, NCC) as the between-subjects factor, independent sample t-tests and chi-square analyses. Because there was unequal variance among the three groups and unequal sample size, post hoc tests were performed using the Games–Howell test of contrasts (Kirk, 1995). Means (and standard deviations) for individual SOPS positive symptom items are presented in Table 5.

3. Results

All results are presented in Tables 3 and 4. There were no differences among the groups on age, gender or ethnicity. The pre-SZ group had a significantly lower current IQ than the NCC group ($p < 0.05$); however, there was no difference between the pre-BP and pre-SZ groups, nor between the pre-BP and NCC groups' premorbid or current IQ. When comparing the pre-BP and pre-SZ groups, the age of disorder onset was similar; however, pre-BP subjects took longer to develop the full-blown disorder after being identified as a high-risk subject than the pre-SZ subjects ($p < 0.05$). The pre-BP and pre-SZ groups did not differ on what medication they were taking at baseline, but the NCC group was significantly less likely to be on an antipsychotic medication at baseline.

Both the pre-BP and pre-SZ groups reported significantly more severe positive symptoms than the NCC group ($p < 0.05$

and $p < 0.001$, respectively), without differences between the pre-BP and pre-SZ groups. There were no group differences on the functioning measures, with the exception of a trend ($p = 0.09$) toward the pre-SZ group having a lower GAF score than the NCC group.

The pre-BP group did not differ from either the pre-SZ or NCC groups on the global neurocognitive score. However, the pre-SZ group was significantly more impaired than the NCC group (Table 3, Fig. 1), even when covarying for current IQ (F (2,142) = 5.78, $p < 0.01$).

4. Discussion

This is the first study to assess clinical and neurocognitive characteristics during the prodromal phase of bipolar disorder compared to the prodromal phase of schizophrenia. There was no difference between the pre-BP and pre-SZ subjects on total positive symptom scores at baseline. Although most individual items were similar across the two groups (Table 5), grandiosity was low in the pre-BP group. On average, the pre-BP group reported more perceptual abnormalities, whereas the pre-SZ group reported more disorganized communication. Overall, the NCC group scored lower on the total positive symptom score compared to both groups and was less likely to be on an antipsychotic at baseline. These trends may be informative for future research to differentiate risk for bipolar disorder and schizophrenia.

All three groups were impaired on social and role functioning. Overall, these findings are consistent with the

Table 4
Clinical data means ± standard deviations for the pre-BP, pre-SZ and NCC groups.

	Pre-BP group (N=8)	Pre-SZ group (N=24)	NCC group (N=115)	F	p	Post hoc tests (p-value)		
						Pre-BP vs. pre-SZ	Pre-BP vs. NCC	Pre-SZ vs. NCC
SOPS total positive score	10.88 ± 3.40	13.25 ± 7.04	7.25 ± 5.01	13.48	<0.001	ns	<0.05	<0.001
GAF score	48.62 ± 12.34	41.78 ± 10.32	46.80 ± 8.53	3.28	<0.05	ns	ns	=0.09
Global Functioning: Role score	5.25 ± 2.96	5.29 ± 2.16	5.63 ± 2.17	0.32	ns	ns	ns	ns
Global Functioning: Social score	6.12 ± 2.75	5.42 ± 1.35	6.04 ± 1.40	1.83	ns	ns	ns	ns
Global neurocognitive score	−2.85 ± 3.86	−2.32 ± 2.18	−0.73 ± 1.69	10.12	<0.001	ns	ns	<0.01

BP, bipolar disorder; SZ, schizophrenia; NCC, non-converter comparison group; SOPS, Scale of Prodromal Symptoms; GAF, Global Assessment of Functioning; ns, non-significant.
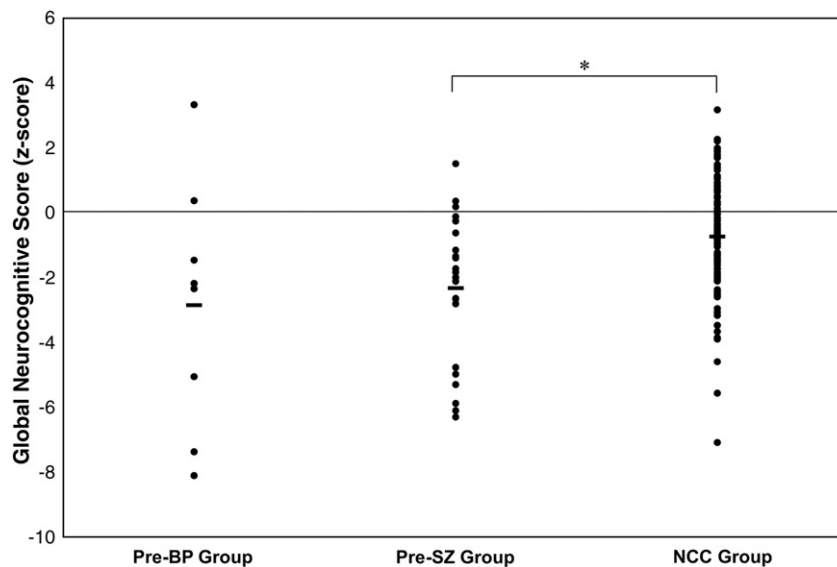
Fig. 1. Individual global neurocognitive scores for pre-BP, pre-SZ and NCC subjects. Group means are represented by a solid horizontal bar. The line at the zero z-score indicates the mean for the healthy control group used to normalize the data. The asterisk indicates that the pre-SZ group had significantly lower global neurocognitive scores than the NCC group ($p < 0.01$).

literature, which shows that individuals in the prodromal phase of schizophrenia have impaired social and role functioning (Cornblatt et al., 2007). Additionally, bipolar disorder patients do exhibit some variability in social and role functioning (Goldberg and Harrow, 2004). Thus, the data show that deficits in functioning are present prior to the development of the full-blown disorder; however, these deficits were not specific to conversion in this sample.

Pre-SZ subjects had significant neurocognitive deficits compared to NCC subjects, yet the NCC subjects were almost one standard deviation below healthy controls. This is consistent with the literature, with some neurocognitive deficits in CHR subjects, but more extensive neurocognitive deficits in subjects who eventually converted to psychosis (Eastvold et al., 2007; Keefe et al., 2006; Lencz et al., 2006). However, we did not find a difference between pre-BP subjects and the NCC group on neurocognitive function. On average, though, the pre-BP group performed worse than the NCC group. It is difficult to know the extent to which neurocognitive

deficits are a characteristic of the bipolar prodrome. Furthermore, the data from the bipolar group had a large degree of variance, which is consistent with what is observed in cognitive performance in bipolar patients (Martino et al., 2008).

The main limitation of this study is its small sample size, particularly in the pre-BP group. Most of the pre-BP subjects received their diagnosis less than 6 months after disorder onset (2 subjects were diagnosed over 2 years later), therefore long-term follow-up is also needed to confirm the diagnosis of bipolar disorder and not schizoaffective disorder. Further limitations include an ascertainment bias toward individuals who were recruited for a study assessing the prodrome to schizophrenia, and limited measures specific to bipolar disorder. However, the results are strengthened by the fact that they are based on prospective data in adolescents with a *true* prodrome. Given that only 35% of CHR individuals develop psychosis (Cannon et al., 2008), results from other high-risk studies are likely skewed by false-positives.

Results from this study support the notion that patients can be identified during the bipolar prodrome, and that at least some of its features may overlap clinically and neurocognitively with the schizophrenia prodrome. Although not the central focus of this paper, we found that individuals who convert to full-blown bipolar disorder or schizophrenia can be differentiated from non-converters based on clinical severity, and in the case of schizophrenia, neurocognitive deficits. Overall, these data are preliminary, but they suggest that the CHR approach is feasible in bipolar disorder, and calls for the need to develop prodromal measures specific for defining CHR for bipolar disorder.

Table 5
SOPS positive symptom item means ± standard deviations for the pre-BP, pre-SZ and NCC groups.

	Pre-BP group (N = 8)	Pre-SZ group (N = 24)	NCC group (N = 115)
SOPS unusual thought content	2.88 ± 2.23	2.67 ± 2.35	1.77 ± 1.88
SOPS suspiciousness	3.25 ± 1.75	3.88 ± 2.23	2.36 ± 1.71
SOPS grandiose ideas	0.25 ± 0.46	1.67 ± 1.93	0.44 ± 1.09
SOPS perceptual abnormalities	3.25 ± 2.87	2.54 ± 2.21	1.50 ± 1.93
SOPS disorganized communication	1.25 ± 1.58	2.50 ± 1.72	1.18 ± 1.40

BP, bipolar disorder; SZ, schizophrenia; NCC, non-converter comparison group; SOPS, Scale of Prodromal Symptoms.

analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Doreen M. Olvet undertook the statistical analysis and wrote the manuscript. Walter H. Stearns assisted in writing the manuscript. Danielle McLaughlin collected the data and edited the manuscript. Andrea M. Auther designed the study, collected the data and edited the manuscript. Christoph U. Correll designed the study and edited the manuscript. Barbara A. Cornblatt designed the study and edited the manuscript.

Conflict of interest

Dr. Correll has been a consultant and/or advisor to Actelion, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Janssen/J&J, GSK, Hoffmann-La Roche, Lundbeck, Otsuka, Pfizer, Schering-Plough, Supernus, Takeda and Vanda. Dr. Cornblatt was the original developer of the CPT-IP and has been an advisor for Merck. All other authors declare that they have no conflicts of interest.

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