Supplementary Methods

Clinical Rater Training and Maintenance

Clinical raters went through extensive training and certification prior to contributing ratings to the study, as well as ongoing training throughout the course of the study. Initial competency was established by on site didactic training for all clinical assessments and data collection procedures (SCID-I/P, SIDP-IV, YMRS, MADRS, PANSS, SFS, SBS, clinical history and demographics), followed by a pencil and paper competency evaluation (100% accuracy required), and finally the establishment of inter-rater reliability. Inter-rater reliability was accomplished using a train-to-criterion protocol with recorded patient interviews (for symptom scales all total scores were required to be within 2 points of the standardized score and all individual item scores were required to be within 1 point of the standardized score; for diagnostic assessments 100% agreement was required for the primary diagnosis). Remediation and additional training was provided as needed on a case-by-case basis until competency was achieved; clinical raters were not otherwise allowed to contribute data to the study. In order to maintain competency and reduce "drift," in-person didactic re-training sessions were conducted annually and inter-rater reliability established at 6 month intervals. Additionally, monthly diagnostic consensus calls (SCID-I, SIDP, SBS) were held throughout the course of the study, allowing for ongoing assessment monitoring and training.

Data Management

Diagnostic and clinical assessment data were collected on paper forms or entered directly into an electronic data entry system constructed in MS Access. Each site maintained an electronic data entry system comprised of the local data and utilized the local site's data storage and security routines. Data were transferred to the Data Center using a secure FTP server. The data received at the Data Center were stored on a secure server for all data processing. The data were verified and passed through an editing process to check for logical inconsistencies

within the data. Any discrepancies were described and an e-mail sent to the appropriate site personnel for resolution where a suitable correction would be made in the local database. Weekly conference calls were conducted to convey information and to resolve problems in regard to data collection, entry, and processing.

Raw data files were processed into analysis ready files using SAS 9.3. Data processing included data cleaning, missing value coding, data formatting, and variable labeling, as well as instrument scoring, data merges, and construction of data dictionaries. Processing of the analysis ready files was accomplished through written programs stored for review and future use. The processed analysis ready files were purged of any unnecessary identifying or administrative information before being disseminated for analysis.

Evaluation of Family History of Psychiatric Illness

Family history of psychiatric illness was obtained using a modified version of the psychiatric family history interview (29). The family history evaluations were completed by experienced clinical raters at each site who underwent initial and maintenance training on this assessment tool. Probands and all available relatives within each pedigree were interviewed. The information on the following psychiatric diagnoses was collected: schizophrenia/schizoaffective disorder, bipolar disorder, depressive disorder, suicide/suicide attempts, alcoholism, illicit substance abuse/dependence, other mental illness (including anxiety disorders, eating disorders, dementia, unspecified mental disorder, etc.). The questions were asked separately about 1st degree, 2nd degree, and distant (3rd degree and above) relatives. In addition, within each degree of relationship, specific relatives who had psychiatric illness were reported: 1st degree, mother, father, sibling, child; 2nd degree: half-sibling, aunt, uncle, nephew, niece, grandparent, grandchild; distant relatives, cousin, great-grandparent, etc. Since the family history method has limitations, including underreporting and lower specificity (29), we used two thresholds indicating the rater's confidence in the reported diagnosis: 1=the diagnosis is definite

[e.g., confirmed by medical records, a report of a formal diagnosis (e.g., “schizophrenia”) treated with a specific medication (e.g., Haldol)], and 2=the diagnosis is probable (e.g., the subject describes a symptomocomplex characteristic for a specific diagnosis but no medical records are available to confirm this report). Both threshold ratings required clarifying questions to ascertain as detailed and reliable clinical information as possible. The final judgments on the diagnoses were made based on all available historical information from the proband and the proband’s relative(s).

Supplemental Table S1. The Psychosis, Affective Symptoms, and Social Functioning Overlap between the Proband Groups

	Within 1 SD of SZP Mean Scores	Within 2 SD of SZP Mean Scores
PANSS Total		
SADP	71.1%	98.9%
BDP	65.2%	100.0%
YMRS		
SADP	75.3%	89.9%
BDP	82.3%	88.5%
MADRS		
SADP	60.0%	77.8%
BDP	57.1%	86.6%
SFS Total		
SADP	67.6%	90.1%
BDP	59.8%	94.6%

SZP – probands with schizophrenia, SADP – probands with schizoaffective disorder, BDP – probands with psychotic bipolar I disorder, SD – standard deviation, PANSS – the Positive and Negative Schizophrenia Syndrome Scale, YMRS – the Young Mania Research Scale, MADRS – the Montgomery–Asberg Depression Rating Scale, SFS – the Birchwood Social Functioning Scale

Supplemental Table S2. Medication Use by Probands (SZP, SADP, BDP), Relatives (SZR, SADR, BDR) and Normal Controls (NC) shows percent (number) of cases using this medication.

	SZP (n=397)	SADP (n=224)	BPP (n=312)	SZR (n=415)	SADR (n=280)	BPR (n=360)	NC (n=459)
Unknown Medication History, % (n)	10.6 (42)	2.7 (6)	6.7 (21)	6.0 (25)	5.7 (16)	5.8 (21)	7.0 (32)
Medication data below are for subjects with medication history reported	**n=355**	**n=218**	**n=291**	**n=390**	**n=264**	**n=339**	**n=427**
No Medication taken, % (n)	2.3 (8)	3.2 (7)	3.4 (10)	31.5 (123)	29.5 (78)	27.1 (92)	55.3 (236)
Not on Psychotropic Medications, % (n)	5.4 (19)	5.5 (12)	5.8 (17)	75.9 (296)	68.2 (180)	65.5 (222)	96.3 (411)
Antiparkinsonian, % (n)	18.9 (67)	12.8 (28)	7.9 (23)	1.8 (7)	0.8 (2)	0.3 (1)	0.0 (0)
Antidepressant (Any), % (n)	38.9 (138)	56.9 (124)	44.0 (128)	14.6 (57)	22.3 (59)	23.3 (79)	1.4 (6)
A. Tricyclic	0.8 (3)	1.4 (3)	2.7 (8)	0.5 (2)	1.5 (4)	0.6 (2)	0.0 (0)
B. Other (SSRI, SNRI, tetracyclic, other)	37.7 (134)	55.5 (121)	41.2 (120)	14.4 (56)	20.8 (55)	22.7 (77)	1.4 (6)
Antipsychotic (Any), % (n)	91.6 (325)	86.7 (189)	70.1 (204)	9.7 (38)	9.1 (24)	7.1 (24)	0.0 (0)
A. Typical	13.0 (46)	10.1 (22)	5.1 (15)	1.5 (6)	1.5 (4)	0.0 (0)	0.0 (0)
B. Atypical	78.6 (279)	76.2 (166)	65.0 (189)	8.2 (32)	7.6 (20)	7.1 (24)	0.0 (0)
Anxiolytic/Hypnotic, % (n)	20.3 (72)	32.1 (70)	33.7 (98)	7.7 (30)	11.0 (29)	10.9 (37)	0.0 (0)
Mood Stabilizer (Any), % (n)	21.7 (77)	51.4 (112)	71.1 (207)	3.6 (14)	9.5 (25)	10.3 (35)	0.0 (0)
A. Lithium	5.4 (19)	9.6 (21)	23.0 (67)	1.0 (4)	2.3 (6)	2.7 (9)	0.0 (0)
B. Other	16.3 (58)	41.7 (91)	48.1 (140)	2.6 (10)	7.2 (19)	6.8 (23)	0.0 (0)
Miscellaneous, Centrally Active, % (n)	0.3 (1)	0.5 (1)	0.7 (2)	0.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Stimulants, % (n)	4.2 (15)	5.5 (12)	11.0 (32)	0.5 (2)	3.4 (9)	5.0 (17)	0.5 (2)