

Classification of adolescent psychotic disorders using linear discriminant analysis

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Abstract

Background: The differential diagnosis between schizophrenia and bipolar disorder during adolescence presents a major clinical problem. Can these two diagnoses be differentiated objectively early in the courses of illness?

Methods: We used linear discrimination analysis (LDA) to classify 28 adolescent subjects into one of three diagnostic categories (healthy, $N=8$; schizophrenia, $N=10$; bipolar, $N=10$) using subsets from a pool of 45 variables as potential predictors (22 neuropsychological test scores and 23 quantitative structural brain measurements). The predictor variables were adjusted for age, gender, race, and psychotropic medication. All possible subsets composed of $k=2$ –12 variables, from the set of 45 variables available, were evaluated using the robust leaving-one-subject-out method.

Results: The highest correct classification (96%) of the 3 diagnostic categories was yielded by 9 sets of $k=12$ predictors, comprising both neuropsychological and brain structural measures. Although each one of these sets misclassified one case, each set correctly classified (100%) at least one group, such that a fully correct diagnosis could be reached by a tree-type decision procedure.

Conclusions: We conclude that LDA with 12 predictor variables can provide correct and robust classification of subjects into the three diagnostic categories above. This robust classification relies upon both neuropsychological and brain structural information. Our results demonstrate that, despite overlapping clinical symptoms, schizophrenia and bipolar disorder can be differentiated early in the course of disease. This finding has two important implications. Firstly, schizophrenia and bipolar disorder are different illnesses. If schizophrenia and bipolar are dissimilar clinical manifestations of the same disease, we would not be able to use non-clinical information to classify ('diagnose') schizophrenia and bipolar disorder. Secondly, if this study's

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findings are replicated, brain structure (MRI) and brain function (neuropsychological) used together may be useful in the diagnosis of new patients.

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1. Introduction

Recent findings of overlapping neurodevelopmental, neurocognitive, neuroanatomical and genetic alterations in schizophrenia and bipolar disorder (Kravariti et al., 2003; Kumra et al., 2004; Lochhead et al., 2004; Lyoo et al., 2004; Pillai et al., 2002) prompt a question, dating back to the times of Kraepelin and Bleuler: what are the commonalities and differences in pathogenesis of schizophrenia and bipolar disorder? The lack of pathognomonic markers for either disease (Andreasen et al., 1985) impacts clinical care since prompt diagnosis remains a cornerstone towards early intervention, when appropriate treatment may reduce alterations associated with disease progression (Cavanagh et al., 2002).

Although bipolar and schizophrenia disorders are more easily differentiated much later in the course of the disease, many features of the two diseases may overlap, particularly in the early phase (Amin et al., 1999; Azorin et al., in press; Dickerson et al., 2004; Friedman et al., 1999; Kumra et al., 1999). Unfortunately, this confusion in initial differential diagnosis may delay the optimum medical treatment (Phillips et al., 2002). Thus, the ability to aid differential diagnosis between schizophrenia and bipolar disorder in the adolescent assumes particular importance. A valid and reliable diagnostic marker would be of immediate utility (Avissar and Schreiber, 2002).

Previous psychiatric researchers have explored linear discriminant analyses (LDA) of behavioral measurements to improve differential diagnosis. Tam et al. (1998) classified correctly 75.5% of schizophrenic and bipolar cases using LDA of measurements from computerized neurocognitive tasks and later replicated the feasibility of this approach in unmedicated patients (Tam and Liu, 2004).

Studying brain structure and neurocognitive processing in healthy, schizophrenia, and bipolar disorder adolescents should provide unique insights into the course of neurodevelopmental events leading to either illness (Giedd et al., 1999). Since the symptoms and cognitive sequelae of adolescent-onset and adult-onset schizophrenia are very similar (Lay et al., 2000), the results of the LDA are likely to be of relevance to adult cases as well. These results may also highlight the

measurements most useful in differentiating the two disorders.

In this work, adolescent subjects, who were psychiatrically healthy or diagnosed with either schizophrenia or bipolar disorder, were studied using neuropsychological testing (Kenny et al., 1997) and cerebral structural Magnetic Resonance Imaging (MRI; Friedman et al., 1999). Forty-five neuropsychological and MRI measurements were available. We sought to identify subsets of these variables that could distinguish the groups of healthy, schizophrenia, and bipolar disorder using LDA. Given the known influences of demographic characteristics and medication upon neuropsychological capacities (Rahman and Wilson, 2003) and brain structure (Gur et al., 1998; Heitmiller et al., 2004; Lieberman et al., 2005), the data were adjusted for these influences prior to the LDA of each possible subset of 2–12 variables used to correctly classify subjects into the three groups. Specifically, we employed the leaving-one-subject-out method to assure high robustness of the results obtained.

This study tests the concept that, despite the overlap in symptoms and genetic vulnerability, schizophrenia and bipolar disorder are, indeed, two different diseases. If these disorders are really manifestations of the same disease, we will not be able to sort individual patient cases using ‘external’ non-clinical data, such as MRI and neuropsychological measurements. However, if individuals can be correctly classified by using only external measurements, schizophrenia and bipolar disorder are best conceptualized as two different diseases.

2. Methods

2.1. Subjects

Community and psychiatric clinics, community centers, and residential care facilities referred adolescent psychiatric outpatients. Advertisements posted at local hospitals facilitated recruitment of healthy subjects. All subjects ($N=28$; Table 1) were in good physical health and had an estimated intelligence quotient (IQ) of 70 or greater. Adolescent subjects and their parents or legal guardians provided written consent to participate in this

Table 1
Demographic characteristics of the 3 subject groups

Diagnosis	Number	Age (years)	Sex (male; female)	Race ^a (Eu; Afr; O)
Healthy	8	15.8	(3; 5)	(5; 2; 1)
Schizophrenia	10	14.7	(7; 3)	(6; 4; 0)
Bipolar disorder	10	15.4	(4; 6)	(10; 0; 0)

^a Eu=Euro-American; Afr=Afro-American; O=Other race.

research project conducted at the University Hospitals of Cleveland. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (Case Western Reserve University School of Medicine, Cleveland, OH) and with the Helsinki Declaration of 1975, as revised in 1983. We studied 10 patients with schizophrenia; 10 patients with bipolar disorder; and 8 healthy, medication-free control subjects.

2.2. Clinical diagnoses

One or two of the physician investigators (RLF, SCS) clinically interviewed the subjects. In addition, patients participated in a structured interview, the Schedule for Affective Disorders and Schizophrenia for School-Age Children: Epidemiological version (K-SADS-E; Orvaschel and Puig-Antich, 1987), which integrates relevant information from the subject and her/his parents. Following the diagnostic interviews, the physician investigators reached a consensus diagnosis based upon DSM-III-R criteria (American Psychiatric Association, 1987). When two investigators could not make a consensus diagnosis, a third investigator assessed the patient before the consensus diagnosis was assigned. All patients tested were clinically stable, and most were taking psychotropic medications at the time of study.

Patients meeting DSM-III-R criteria for either schizophreniform or schizoaffective disorder were included in the schizophrenia group. One of the ten subjects in the schizophrenia subject group had schizoaffective disorder. Patients meeting DSM-III-R criteria for bipolar I, with or without attention deficit disorder with hyperactivity, were included in the bipolar sample (Faraone et al., 1997). One of the ten bipolar disorder subjects had a hearing disorder. Two other bipolar disorder subjects had attention deficit/hyperactive disorder (ADHD). Control (healthy) subjects were diagnostically interviewed and assessed with either the K-SADS-E or the Schedule for Affective Disorders and Schizophrenia–Lifetime version (SADS-L; Spitzer and Endicott, 1985) and were not taking any medication.

None of the control subjects had a first-degree relative with a psychiatric disorder.

Subjects were administered neuropsychological testing (Kenny et al., 1997) and the MRI scanning (Friedman et al., 1999) within 3 months of each other. Some subjects first participated in neuropsychological testing and others first participated in the MRI scanning. We analyzed the data from subjects having both complete MRI data and complete neuropsychological data ($N=28$). All 28 subjects in the present analyses had valid and complete (i.e., without missing values) neuropsychological and brain measurement data sets. Table 1 displays the demographic variables (age, race, and gender) of the three subject groups studied. Across the three groups, demographic and medication variables were not matched, necessitating adjustment for demographic and medication influences prior to LDA, as described below.

2.3. MRI data acquisition

Details of the methods used for MRI data acquisition have been given elsewhere (Friedman et al., 1999). Briefly, subjects were scanned on a Siemens Magnetom 1.5 T MRI scanner (Erlangen, Germany), using a spin-echo double-echo sequence to create Spin-Density and T2-weighted image sets. For both image sets, the MRI axial slices obtained were 5 mm thick, with a 2 mm gap between adjacent slices.

2.4. MRI image processing

Image processing software (Lim and Pfefferbaum, 1989) enabled segmentation and volume measurements of the head and brain MRI data. Additionally, custom software permitted calculation of fluid and tissue thresholds (Friedman et al., 1999). The maximum circumferences of the head, skull, and brain were then calculated. Specific landmarks determined the boundaries of eight intracranial slices for the following region-of-interest (ROI) analyses; details of the boundaries of the areas measured are given in Friedman et al. (1999). ROI boundaries were restricted to these eight slices, not the entire cranial vault. The following ROIs were measured: left and right cerebral tissue volume; percentage of fluid in left and right intracranial volume; percentage of ventricular fluid volume for left and right hemispheres; and percentage volume of fluid in left and right of frontal, temporal, and occipital cortices; and indices of coronal volumes using anterior, middle, posterior, and total coronal sections from brain index boundaries. ROI boundaries for the entire left and right

thalamic tissue volumes are given in [Dasari et al. \(1999\)](#). The MRI slices for the hippocampus were acquired in the sagittal plane with a TR=40, TE=10, slice thickness=2.5, gap=0; FOV=256, and Matrix=256×256 (1 pixel=1 mm²); they were re-sliced in the coronal plane with a 2 mm thickness and an in-plane resolution of 1×1 mm. Measurements of the re-sliced data were performed on these 2 mm thick image slices. The measurement of the hippocampus started at 4 mm anterior (2 slices) to the crus of the fornix and ended 10 mm posterior (5 slices) to the anterior commissure.

2.5. Neuropsychological variables

Table 2 lists the neuropsychological tests used in our analyses to assess the neurocognitive abilities of maintaining set, abstract thinking, auditory arithmetic, cognitive flexibility, eye–hand coordination, general knowledge, performance intelligence quotient (IQ), verbal fluency, planning, processing speed, recall memory for content, receptive vocabulary, selective attention, semantic verbal fluency, verbal memory, visuospatial construction, visuospatial perception, and working memory with distraction. Details of these tests are given in [Kenny et al. \(1997\)](#).

3. Statistical analyses

3.1. Preprocessing: Multiple linear regression

Of the 45 variables obtained, 22 were neuropsychological test scores and 23 were structural brain measurements. Prior to the LDA, multiple regression analyses were used to (1) determine significant factors of medication, age, race, and gender; and (2) adjust the data for these factors prior to LDA. The effects of medications and demographic factors upon each of the 45 variables were assessed using stepwise multiple linear regression to obtain the significant coefficients (BMDP/Dynamic: BMDP Statistical Software Inc., Los Angeles CA, 1992). Independent variables were re-evaluated at each step and (re)entered or removed according to a default statistical *F*-test criterion; tolerance for collinearity was set to 0.01. The dependent variable was a given measurement, and independent variables were the following: age (continuous variable), gender (coded as single binary variable), race (coded as combinations of 2 dummy binary variables, since there were 3 races; see [Table 1](#)), and medication (coded as 14 binary variables, i.e., presence or absence of: any psychotropic medication,

Table 2
Neuropsychological variables

Neuropsychological measurements	Abbreviations	Cognitive abilities
Judgment of Line Orientation (Benton)	Line	Visuospatial perception
Wisconsin Card Sorting Test: Categories completed (Heaton)	WCST-Cat	Cognitive flexibility; maintaining set; abstract thinking
Wisconsin Card Sorting Test: Percent Perseverative Errors	WCST-%PE	Same as above
Verbal List Learning—Immediate Recall (Buschke Selective Reminding)	VLL-IR	Verbal auditory memory
Verbal List Learning—Delayed Recall (Buschke Selective Reminding)	VLL-DR	Verbal auditory memory after delay
Digit Span Distraction Test	DSDT	Working memory of digits during distraction
Paced Auditory Serial Addition Test 1 (slowest presentation rate)	PASAT 1	Auditory arithmetic; working memory
Paced Auditory Serial Addition Test 2	PASAT 2	Auditory arithmetic; working memory
Paced Auditory Serial Addition Test 3	PASAT 3	Auditory arithmetic; working memory
Paced Auditory Serial Addition Test 4 (fastest presentation rate)	PASAT 4	Auditory arithmetic; working memory; processing speed
Primary Memory Test (Brown–Peterson Consonant Trigram Interference)	PRIMEM	Working memory with distraction
Wechsler Intelligence Scale—Children: Coding	Coding	Eye–hand coordination
Wechsler Intelligence Scale—Children: Block Design	Block Design	Visuospatial construction and perception
Wechsler Intelligence Scale—Children: Information	Info	General knowledge
Wechsler Intelligence Scale—Children: Similarities	Simil	Abstract reasoning
Wechsler Intelligence Scale—Children: Maze	Maze	Planning; visuospatial perception
Phonological Fluency Test (Letters: F, A, S)	Phon Flu	Phonological verbal fluency
Semantic Fluency Test (Categories: animals, fruits and vegetables, and objects in the street)	Sem Flu	Semantic verbal fluency
Stroop Test (Golden)	Stroop	Selective attention; suppress reading
Wechsler Memory Scale—Logical Memory subtest: <i>Immediate</i> Recall	Logmem-IR	Recall memory for content; verbal memory
Wechsler Memory Scale—Logical Memory subtest: <i>Delayed</i> Recall	Logmem-DR	Recall memory for content; verbal memory
Peabody Picture Vocabulary Test—Revised	PPVT	Abstract thinking; receptive vocabulary; general knowledge

neuroleptics, typical neuroleptics, atypical neuroleptics, anticholinergics, any antidepressant, selective serotonin reuptake inhibitor antidepressants, tricyclic antidepressants, mixed-mode antidepressants, stimulants, anticonvulsants, lithium, anxiolytics, and beta-blockers). The stepwise multiple linear regression yielded a final set of regression coefficients which had a statistically significant effect ($p < 0.05$) on the given dependent variable. These coefficients were then used to adjust the data for demographic and medication influences prior to LDA. Since these factors were not the same across the three groups, this was an important step in the data analysis.

3.2. Classifying each subject to one of the 3 groups: Linear Discriminant Analysis (LDA)

We applied LDA (Green, 1978) on the data already adjusted for demographic and medication effects to classify a subject to a specific group. We used LDA to test the power of different groups of variables when used in combination, to correctly classify each subject. Since we did not know a priori which variables would be most powerful for discriminating the groups, we decided to acquire as much information as possible, i.e., to maximize our variable pool. The 45 variables were the pool out of which only a limited number of variables was used at any time, with a maximum of 12 variables; in this last case, the ratio of individuals to be classified/variables to classify them was 2.5:1. Specifically, we evaluated all combinations of $k=2-12$ predictors (out of the 45 available) using the leaving-one-subject-out method (IMSL Fortran 90 MP Library, Version 4.01, Visual Numerics, Houston, TX, 1999). In this method, discriminant classification functions are computed using $N-1$ ($=27$) subjects and then applied to classify the subject omitted. As shown in Fig. 1, this procedure is repeated systematically for all subjects, such that the resulting classification matrix is based on classification functions to which the subject classified did not contribute. This is the basis for the robustness (i.e., cross-validation) of the result.

A key aspect of our analysis was the evaluation of all possible subsets for various subset sizes ($k=2-12$). The number M of such subsets is given by the following formula:

$$M = \frac{V!}{k!(V-k)!}$$

where $V=45$ is the total set of variables and k is the subset size. For $k=2$, $M=990$, whereas for $k=12$, M is in the billions. These computations were performed using a 64-processor IBM (White Plains, NY) Linux cluster.

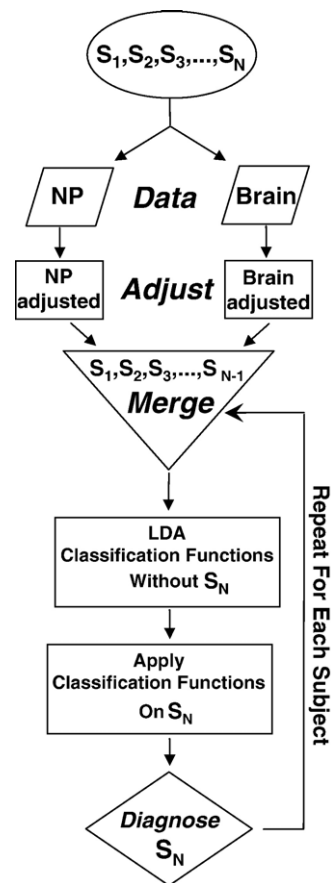


Fig. 1. Flowchart of linear discriminant analysis (LDA using the leaving-one-subject-out method. S=subject; NP=22 neuropsychological measurements; Brain=23 MRI cerebral measurements; Adjust=data are adjusted for demographic and medication influences as determined by multiple regression analyses from all subjects; Merge=all adjusted data are merged for all but one subject, S_N , LDA=linear discriminant analyses using all possible combinations of subset sizes containing 2–12 of the 45 measurements.

For each subset of variable tested, the LDA classification process: (1) assigned each individual to a group and (2) determined the likelihood of correct assignment (posterior probabilities).

4. Results

Of the subset sizes evaluated ($k=2-12$), only the highest one ($k=12$) yielded $>90\%$ correct classification rates. Specifically, there were 9 such subsets each of which misclassified just 1/28 subjects for an overall classification rate of 96.4%. It should be noted that only the leaving-one-subject-out method was used in these analyses, and that, therefore, these results are robust.

Of these 9 subsets, all classified schizophrenia subjects correctly, 8/9 classified control subjects

correctly, and 1/9 classified bipolar subjects correctly. We assessed the quality of subject classification further by examining the posterior probabilities associated with each classification decision and by taking into account the nature of misclassified cases. Of note, although the functions derived from these subsets misclassified single subjects, these same functions also were perfect in classifying different types of subjects. For, example if a subset led to an incorrect classification of one schizophrenia subject as a bipolar subject, that subset would still perfectly classify each control subject. We found that within these 9 subsets, there existed one or more subset(s) that perfectly classified each subject type (schizophrenia, bipolar disorder, and control). Posterior probabilities were then used to select the best subset for each diagnostic group.

This procedure identified 3 final subsets, one for each diagnostic group, from the 9 subsets, as follows. Each of the 3 final subsets (see Table 3) perfectly classifies a different diagnostic group and is named by the type of perfect classification (not the misclassification). The *control* set classified correctly all control subjects and did not misclassify any schizophrenia or bipolar subject as control; the posterior probabilities for correct classification were >0.99 for each subject. The *schizophrenia* set classified correctly all schizophrenia

subjects and did not misclassify any control or bipolar subject as having schizophrenia; the posterior probabilities for correct classification were 1.0 for 8/10, >0.99 for 1/10, and >0.93 for 1/10 subjects. Finally, the *bipolar* set classified correctly all bipolar subjects and did not misclassify any control or schizophrenia subject as bipolar; the posterior probabilities for correct classification were 1.0 for 7/10, >0.99 for 2/10, and >0.73 for 1/10 subjects. Thus, a joint consideration of all 3 subsets together would provide perfect classification with zero misclassification for each of the three diagnostic groups. This suggests a tree-based decision procedure as illustrated in Fig. 2.

The composition of the 3 final subsets above is given in Table 3. In each subset 8/12 variables were neuropsychological measurements, whereas the remaining 4/12 variables were from quantitative brain measurements. Interestingly, 7 of the 8 neuropsychological measurements were the same in all 3 subsets, as was one of the 4 brain measurements.

5. Discussion

Our high classification results confirmed our hypothesis that schizophrenia and bipolar disorder are different illnesses, which can be differentiated with

Table 3
Three final subsets that each classify one diagnosis perfectly

Control subset	Bipolar disorder subset	Schizophrenia subset	Cognitive ability
LINE	LINE	LINE	Visual spatial perception
WCST_PP	WCST_PP	WCST_PP	Cognitive flexibility; perseveration
DSDT	DSDT	DSDT	Working memory of digits during distraction
STROOP	STROOP	STROOP	Suppressing alternative response
LOGMEM_DR	LOGMEM_DR	LOGMEM_DR	Delayed memory for story details
PASAT2	PASAT2	PASAT2	Online auditory arithmetic—2nd slowest
PASAT4	PASAT4	PASAT4	Online auditory arithmetic—fastest
		VLL_IR	Memory for word list
PASAT3			Online auditory arithmetic—intermediate
	SIMIL		Verbal abstract reasoning
			BRAIN MRI VOLUMES
TRFL	TRFL	TRFL	
ORFL	TLFL	POSTVOL	
ANTVOL	ANTVOL	TOTVOL	
POSTVOL	HippR	HippR	

Variables in capitalized in bold are common to the 3 subsets. Each classifies perfectly one of the 3 diagnostic categories: *Control*, *Bipolar Disorder*, and *Schizophrenia*. Variables present in the 3 sets are from the neuropsychological tests of LINE: Judgment of Line Orientation; WCST-PP: Wisconsin Card Sorting Test—Percent Perseverative Errors; DSDT: Auditory Digit Span with Distraction Test; Stroop: naming the color of the ink of the of incongruent color names; LOGMEM_DR: Wechsler Memory Scale—Logical Memory subtest: *Delayed* Recall for story details; PASAT 2, 3, 4: Paced Auditory Serial Arithmetic [speeded addition of the last two auditorily presented numbers as numbers are continually presented at a pre-defined rate]; VLL_IR: Verbal List Learning—Immediate Recall of words presented auditorily; SIMIL: Wechsler Intelligence Scale—Children: Similarities subtest; and the Cerebral MRI Volume measurements of TRFL: Right Temporal Lobe Fluid; POSTVOL: Volume of Posterior Coronal Section; ORFL: Right Occipital Lobe Fluid; TLFL: Left Temporal Lobe Fluid; TOTVOL: Total Volume of Anterior, Middle, and Posterior Coronal Sections; ANTVOL: Volume of Anterior Coronal Section; and HippR: Right Hippocampus Volume.

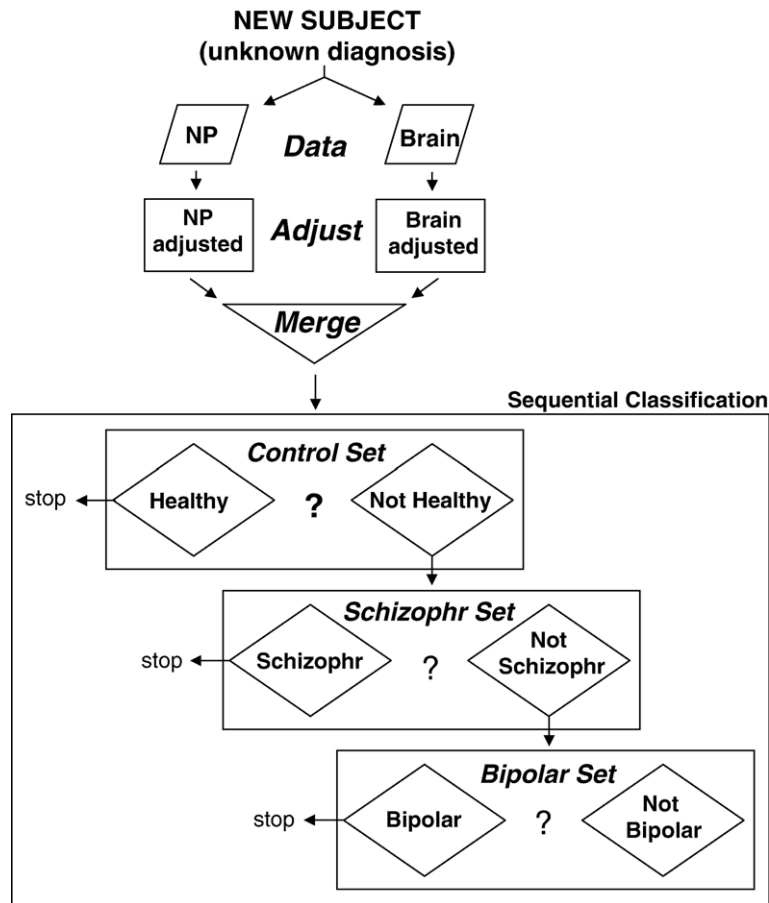


Fig. 2. Procedure to classify a new subject (NP=22 neuropsychological measurements of the new subject; Brain=23 MRI cerebral measurements of the new subject; Adjust=adjustment of NP and Brain measurements for demographic and medication using the group data). Sequential Classification uses the adjusted data from the New Subject and the 3 sets of 12 variables, which classify perfectly control, schizophrenia (Schizophr), and bipolar subjects, respectively, to classify the new subject.

objective measurements of brain structure and function. We found that the different subsets of 12 variables yielding the best classification produced different incorrect (and, consequently, correct) classifications such that a combination of these classifications can be used sequentially in a tree-type design to correctly classify all subjects.

At first glance, patients with schizophrenia and bipolar disorders show abnormalities in many of the same general areas: neurodevelopment of microcircuitry (Benes, 2000; Lewis and Lieberman, 2000), common cerebral tissue loss in certain brain regions, and deficits in higher brain function. Shared and unique disease mechanisms still need further elucidation at the micro and macro levels of inquiry. For the purpose of psychiatric classification, using more than one type of measure increases the predictive power considerably (Davidson et al., 1999). The preponderance of neuro-

psychological variables in all of the robust sets has external validity and relevance since neurocognitive deficits are correlated in schizophrenia with social problem solving and skill acquisition (Green, 1996) and in bipolar disorder with functional impairment (Zarate et al., 2000). Altshuler et al. (2004) found these neurocognitive deficits to be present even in clinically stable male patients with bipolar disorder or schizophrenia. The common MRI variable across sets, right temporal lobe fluid (TRFL) is consistent with studies of abnormal right temporal lobe gyrification in schizophrenia (Harris et al., 2004).

We measured brain function and structure in adolescents and applied LDA to differentiate between schizophrenia, bipolar disorder, and no mental illness. Prior to LDA, we also incorporated adjustments for demographic and medication variables for each subject's data to optimize proper diagnostic assignment.

Using an LDA approach has the advantage of exploiting the interrelatedness of the 45 parameters used in subsets. Moreover, the posterior probabilities for each robust subset reflect the certainty or likelihood of correct classification for each particular subset.

In the future, a comprehensive strategy including MRI and neurocognitive measurements, as well as proper medication and demographic adjustments, could augment the early diagnostic process for an individual patient. The time period just preceding the first episode of schizophrenia and the first 2 years of the disease constitute a critical period for pharmacological intervention (Lieberman, 1999). The differential diagnosis between schizophrenia versus bipolar disorder guides the choice of pharmacological treatments (Toren et al., 1998; Rush et al., 2003; Bauer et al., 2003). In fact, early intervention can actually postpone onset of psychosis (Phillips et al., 2002) and optimize longitudinal outcome (Lieberman, 1999). Since these two illnesses can be differentiated objectively, pharmacological research should develop disease-specific treatments for early and later stages of the disease.

Applying LDA to more targeted neurocognitive (Posner, 1986) and neuroanatomical (McCarley et al., 1999) measures might amplify the power of this comprehensive approach to further probe selective attention, memory, arithmetic and other cognitive processes assayed by the neuropsychological measurements in the final 3 subsets (Table 3). Multiple PASAT subtests in each final subset suggest key brain mechanisms are recruited differentially as a function of task rate. Yet, the wide range of performance on neurocognitive measures (Pardo et al., 2000; Kieseppä et al., 2005), and the large intra-group variance in cerebral MRI measurements (McIntosh et al., 2004) for all groups does imply that the classifying power in our study arises from the interaction of key variables (Baare et al., 1999) present in the LDA classification functions.

Once the key components of the most robust sets are further refined and replicated, clinicians can evaluate the cost-effectiveness and utility of ordering neurocognitive testing and a head MRI scan at intake and then using LDA classification functions to aid in the differential diagnosis of schizophrenia versus bipolar disorder. Presently, neuropsychological testing and MRI volumetric analysis require local expertise. In the future, select neurocognitive tests could be converted into a series of user-friendly, computer-administered programs to test a new patient. Likewise, once a refined set of select MRI cerebral measurements is developed, the set of clinical MRI images of a new patient could be analyzed off-site by a laboratory or company expert in

software image segmentation and parcellation. Influences of new medications would need to be routinely incorporated into the analyses so the sorting algorithms could be optimized for each presenting patient. Future efforts using this approach may prove useful in diagnosing and treating symptomatic, prepsychotic patients (Bartók et al., 2005; Lencz et al., 2003).

Upcoming studies using this approach should also address the following limitations of the present study: small sample size; uneven gender and race distributions across diagnostic groups; presence of co-morbidities; no handedness information; limited medication information; and lack of longitudinal follow-up of diagnostic stability. In addition to the measures used for the present study, future related studies will likely include neurocognitive measures targeted to assay specific brain mechanisms (Albright et al., 2000; Posner and Rueda, 2002) and more detailed MRI measurements, such as cortical thickness (Kuperberg et al., 2003). Adding genetic measures (Rybakowski et al., 2003; Tsuang et al., 2005) may further augment the classification of these two disease processes. The conceptual framework of disease classification directly impacts upon clinical care and research. Results of the present study illustrate the power of combining multiple types of measurements to address key questions of psychiatric nosology.

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