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Separation of Subtypes of Depression Using Discriminant Analysis

Separation of Bipolar Endogenous Depression from Nonendogenous ("Neurotic") Depression

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Summary

We derived a discriminant function separating patients with bipolar endogenous depression ("melancholia") from patients with nonendogenous ("neurotic") depression, and showed that the difference between the groups was not one of overall severity of illness alone. The discriminant function (DF) included 5 clinical items.

We reduced the DF to a discriminant index (DI) with integral item weights, and trichotomized the DI scores into two definite classifications and an intermediate, uncertain classification. We cross-validated this DI in a separate group of patients, and found no decrease in the accuracy of classification on cross-validation. Thirty-three of 41 (80%) of the patients in the cross-validation group were classified by the DI; 26 of 33 (79%) correctly.

We also validated the DI classification against an external, biological marker, the dexamethasone suppression test (DST). The DI predicted the DST result with the same accuracy as the clinical diagnoses did, supporting the validity of the DI.

Introduction

The differentiation of "endogenous" depression ("psychotic" depression; melancholia) from nonendogenous depression (reactive depression; neurotic depression) is crucial in any research involving depressed patients. Several groups have published criteria for using clinical phenomena to make this distinction. Some

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criteria have been based on multivariate analysis of clinical data, for example the Newcastle Diagnostic Index (Carney et al. 1965), while others have been based on conventional clinical wisdom, for example the Research Diagnostic Criteria (Spitzer et al. 1975). Some investigators have found the endogenous-nonendogenous distinction impossible to make (Kendell 1968) and others have suggested alternative diagnostic schemes, such as primary-secondary (Feighner et al. 1972). We believe that some of the difficulty involved in making the endogenous-nonendogenous distinction on the basis of clinical phenomena is caused by the differences in the phenomenology of unipolar (UP) and bipolar (BP) endogenous depressions. Several researchers have shown biological differences between these groups (Beigel and Murphy 1971; Detre et al. 1972; Feinberg et al. 1982), and we have shown that the phenomenological differences can lead to errors in using the Research Diagnostic Criteria (Feinberg et al. 1979).

In a previous report (Feinberg and Carroll 1982a), we described a discriminant function (DF) which separated UP endogenous depressed (ED) patients from those with nonendogenous depression ("neurotic" depression; ND), and noted that this DF was less accurate in classifying BP patients (70% correct) than in classifying UP patients (80% correct). We have also derived a DF separating UP from BP patients on the basis of clinical phenomena (Feinberg and Carroll 1982b). In the present manuscript, we discuss the derivation of a DF separating BP from ND patients, the conversion of this DF to a discriminant index with integral weights, and the cross-validation of this discriminant index in a separate group of patients.

Patients and Methods

Patients

We included 165 inpatients and outpatients at the Clinical Studies Unit, Department of Psychiatry, University of Michigan. They were studied as part of our ongoing research on the psychobiology of depression (Carroll et al. 1980, 1981). Patients in the first (derivation) group, used to derive the discriminant functions, were seen before November, 1978. The patients in the second (cross-validation) group, used to cross-validate the discriminant functions, were evaluated between February, 1979 and April, 1980. The distribution of patients by age, sex, status (inpatient or outpatient) and diagnosis is given in Table 1. Patients in the first sample are described in Table 1a, while those in the second sample are described in Table 1b. The derivation group contained 30 BP and 36 ND patients, and the cross-validation group contained 18 BP and 25 ND patients. The UP patients listed in Table 1a were not used in deriving the DF's discussed here, but were part of our earlier papers (Feinberg and Carroll 1982a, b).

Methods

The methods used to gather, analyze, and interpret data are discussed at length in the first paper of this series (Feinberg and Carroll 1982a), and we will mention them only briefly here.

TABLE I

CLINICAL DATA

	N	Mean ± SD	Age range (yr)	Sex ratio M : F	Status [c]		Hamilton Rating Score Mean ± SD
					I	O	
1a. Patients in the first (derivation) sample							
UP [a]	46	52 ± 17 [b]	20–84	0.50	16	30	22.3 ± 4.5
BP	30	44 ± 14	24–75	0.87	10	20	18.6 ± 5.2
ND	37	35 ± 13	20–75	0.44	9	28	16.9 ± 4.4
1b. Patients in the second (cross-validation) sample							
BP	18	45 ± 15 [b]	25–82	0.29	11	8	22.0 ± 6.2
ND	25	34 ± 13	19 66	0.56	3	22	15.4 ± 3.8

[a] UP = unipolar endogenous depression; BP = bipolar endogenous depression; ND = nonendogenous ("neurotic") depression.

[b] All mean ages differ from each other, $P < 0.02$, analysis of variance.

[c] I = inpatient; O = outpatient.

Diagnoses were made as described by Carroll et al. (1980), and were based on the total clinical material available, including both open clinical interviews and a structured interview. The diagnoses were not explicitly based on the clinical item scores, nor were they necessarily the same as the RDC diagnoses (Spitzer et al. 1975), which were based on item scores. Rather, the diagnoses represent a pattern or Gestalt seen by the staff psychiatrist making the diagnosis. This study is thus an attempt to quantify that Gestalt and show that it is consistent across time and clinicians in our Unit. The patient groups included all patients with a score of 10 or higher on the 17-item Hamilton rating scale for depression (HRS) (Hamilton 1960; 1967) who had received a diagnosis of bipolar endogenous depression (BP) or of nonendogenous depression (ND). BP patients had had one or more episodes of mania or hypomania.

The discriminant function was derived using canonical discriminant analysis, and the weights were multiplied by 10 and rounded to the nearest integer to form a discriminant index (DI) similar to the Newcastle Diagnostic Index (Carney et al. 1965) and to that discussed in our earlier manuscript. The discriminant analysis was performed a second time, using clinical variable scores adjusted for overall severity of illness, to rule out the possibility that the difference between the groups was one of severity alone. The method used is described in our earlier manuscript (Feinberg and Carroll 1982a). We cross-validated the DI in a separate group of patients, the "cross-validation" sample. These patients were seen after those in the derivation group, and were selected using the same inclusion criteria. Any diagnostic bias was avoided by the separation of duties in our Unit; one of us (MF) had done the data analysis without sharing the results with his colleagues who assigned the diagnoses.

We also studied the effects of age and sex on diagnosis, to determine whether these variables alone could account for the differences in the symptom profiles of the

two groups. We used stepwise multiple regression analysis, with diagnosis (BP or ND) as the dependent variable. We added the DF score to the regression equation last, after the variance due to age and sex had been accounted for.

Results

Clinical data are shown in Table 1, which includes information about both the first (derivation) and second (cross-validation) groups. The diagnostic groups differed in age, in a manner consistent with published data for age of onset of endogenous (ED) (Angst et al. 1973; Loranger and Levine 1978) and nonendogenous (Spicer et al. 1973) depression (ND).

(1) Discriminant functions

We used the DF described in our earlier paper (Feinberg and Carroll 1982a) to classify BP patients as endogenously depressed (that is, UP) or as nonendogenously depressed. The results (Table 2) show that BP patients are classified less accurately than UP patients, and support our decision to consider them separately. We derived several DF's separating BP from ND patients. The most powerful of these used the item "Precipitants Present" and weighted it more heavily than any clinical phenomenon of the present state. We were concerned that the rating of this item, scored as either present or absent, might easily be biased by the clinician's opinion about the diagnosis. Therefore, we derived a DF which excluded this item, and used it in the rest of the work described here. This DF is shown in Table 3, along with the DF derived using item weights adjusted for overall severity of illness. There was a slight increase in the accuracy of classification when the adjusted item weights were used (Table 4). This increase (78–85%) was not statistically significant, but supports our assumption that ED and ND patients differ in the pattern of symptoms they present, and not simply in overall severity of illness, as suggested by Kendell (1968).

As we would expect from the data in Table 1, age at the time of study differentiated between the BP and ND patients, while sex did not. However, the DF score remained highly significant when added to a multiple regression analysis after age and sex had been accounted for ($P < 0.0001$).

TABLE 2

CLASSIFICATION OF BIPOLAR DEPRESSED PATIENTS AS UNIPOLAR DEPRESSED (UP) OR AS NONENDOGENOUS DEPRESSED (ND) BY A DISCRIMINANT FUNCTION DERIVED FROM THE UP AND ND GROUPS ONLY

Clinical diagnosis	Discriminant function classification		
	UP	ND	% Correct
UP	37	9	80
BP	21	9	70
ND	4	32	89

TABLE 3

ITEM WEIGHTS FOR DISCRIMINANT FUNCTIONS SEPARATING BIPOLAR ENDOGENOUS DEPRESSED PATIENTS FROM NONENDOGENOUS DEPRESSED PATIENTS

Symptom	Raw data	Adjusted data [b]
Guilt [a]	0.77258	0.97982
Retardation [a]	0.49065	0.62208
Decreased appetite	0.36324	0.46041
Loss of reactivity	0.25914	0.28933
Work and interests [a]	0.18625	0.21603

[a] These items were taken from the Hamilton rating scale for depression.
[b] Raw item scores were adjusted for severity of illness as described by Feinberg and Carroll (1982a).

(2) Discriminant index

The DF derived from raw item weights was converted to a discriminant index (DI) by multiplying the weights by 10 and rounding to the nearest integer (Table 5). We divided the DI scores into 3 classifications by inspection of a histogram of the scores (Fig. 1), using the strategy set forth in our earlier paper. We are thus able to classify patients as nonendogenous, uncertain, or BP endogenous. The corresponding ranges for the BP-ND DI scores are < 22, 22–27, and > 27. We were able to classify 27 of 30 (90%) BP patients, 21 of 27 (78%) correctly, and 29 of 37 (78%) ND patients, 24 of 29 (83%) correctly. Overall, we classified 56 of 67 patients (84%), 45 of 56 (80%) correctly (Table 6). Kappa (Cohen 1960) for the resulting 2×2 table is 0.60, showing good agreement between DI classification and clinical diagnosis.

(3) Cross-validation of the discriminant index

We cross-validated the discriminant index in a separate group of 43 patients studied after the patients in the original sample (Table 1b and Methods). Forty-one of these patients had complete data on the items used in the DI. The trichotomous distribution of the scores for the cross-validation group is shown in Table 7. Using the DI scores, we classified 33 of 41 patients as definitely BP or ND (80%), 26 of 33

TABLE 4

DISCRIMINANT FUNCTION CLASSIFICATIONS

Clinical diagnosis	Raw data		Adjusted data [a]	
	BP	ND	BP	ND
BP	22	8	25	5
ND	7	30	5	32
	78% correct		85% correct	
	Kappa = 0.56		Kappa = 0.70	

[a] Raw item scores were adjusted for severity of illness as described by Feinberg and Carroll (1982a).

TABLE 5

A DIAGNOSTIC INDEX FOR SEPARATING PATIENTS WITH BIPOLAR ENDOGENOUS DEPRESSION FROM THOSE WITH NONENDOGENOUS DEPRESSION

Clinical item	Weight	Scoring range
Guilt [a]	8	0–4
Retardation [a]	5	0–4
Decreased appetite	4	0 2
Loss of reactivity	3	0–2
Work and interests [a]	2	0–4

[a] This item is taken from the Hamilton rating scale.

TABLE 6

BP-ND DISCRIMINANT INDEX: DERIVATION GROUP

Clinical diagnosis	Discriminant index score for BP-ND discrimination		
	< 22	22–27	> 27
BP	6	3	21
ND	24	8	5
Total	30	11	26
% correctly classified	80	–	81

correctly (79%). This can be compared with the performance of the DI in the derivation group, where 84% of the patients were classified and 80% of the classifications were correct. There was a slight drop in the portion of patients classified on cross-validation (84–78%), and almost no change in the portion of

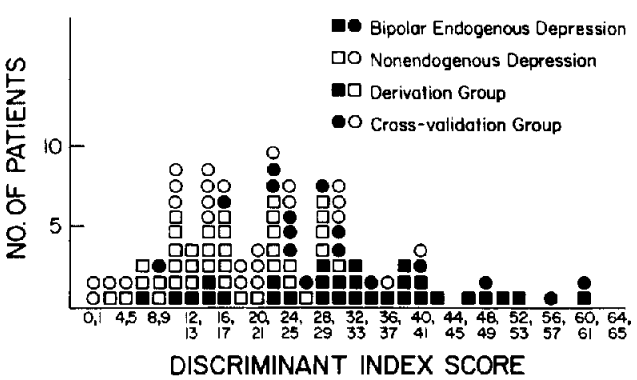

Fig. 1. Histogram of patient scores on the discriminant index.

TABLE 7

BP-ND DISCRIMINANT INDEX: CROSS-VALIDATION

Clinical diagnosis	Discriminant index score > 27	22–27	< 22		
	Discriminant class			Total	Correct classification
	BP	?	ND		
BP	9	5	2	16	9/11 (82%)
ND	5	3	17	25	17/22 (77%)
Total	14	8	19	41	26/33 (79%)

patients correctly classified (80–78%). We have shown that the DF separating UP from ND patients classified BP patients less accurately than it did UP patients. We therefore made the analogous test of the BP-ND DI, and examined the classification of the unipolar patients in the cross-validation group (Feinberg and Carroll 1982a) using the DI separating BP and ND patients. Sixteen of 26 patients were classified as ED (i.e., BP), 5 as uncertain, and 5 as ND.

We used the dexamethasone suppression test (DST) (Carroll et al. 1981) as an external criterion of the validity of the DI classification of BP and ND patients, as we had done in our earlier work on the separation of UP and ND patients. We administered either 1 or 2 mg of dexamethasone, and drew blood at 16.00 (outpatients) or at 08.00, 16.00, and 23.00 (inpatients) after dexamethasone. These modifications of dexamethasone dose and sampling time lower the sensitivity of the DST (Carroll et al. 1981). In the cross-validation group, 31% of the patients clinically diagnosed as having BP endogenous depression had abnormal DST's, i.e. they failed to suppress cortisol synthesis for 24 h following oral dexamethasone. In other words, the sensitivity of the DST was 0.31. Twenty-three of the 25 ND patients in this group (92%) had normal responses to dexamethasone (specificity = 0.92). If the DI classifications of patients in the cross-validation group are used, rather than the clinical diagnoses, the corresponding figures are: sensitivity of the DST = 0.23, and specificity = 0.89. The drop in sensitivity reflects one BP patient with an abnormal DST who was not classified by the DI, and one who was misclassified as ND. This difference is not significant.

Discussion

The differential diagnosis of patients with depressed mood has long been a major problem in psychiatric research and clinical practice. With the availability of digital computers, several groups brought multivariate statistical procedures to bear on the problem, using factor analysis to describe diagnostic groups (Mendels and Cochrane 1968), discriminant analysis (DA) to validate diagnostic groupings (Demel et al.

1973; Prusoff and Klerman 1974), and cluster analysis to find new diagnostic classes or to confirm older ones (Andreasen 1979; Blashfield and Morey 1979). This methodology has been partly succeeded by "decision trees", with diagnostic classifications made on the basis of successive yes-no decisions (Spitzer et al. 1974) as in the RDC. This technique rests in part on data gathered in structured interviews, with item definitions and the wordings of questions carefully defined.

However, both the multivariate studies and the symptom lists have tended to lump unipolar (UP) and bipolar (BP) endogenous depression. Leonhard (1957) suggested that endogenous depressed patients be classified as bipolar if they had been hospitalized for mania, or as unipolar if they had not. Several groups have described differences between the phenomenology of unipolar and bipolar ED (Beigel and Murphy 1971; Detre et al. 1972; Himmelhoch et al. 1976; Feinberg et al. 1982) and on differences between members of these groups which are not state-dependent (von Zerssen 1977). We have used discriminant analysis to confirm earlier findings of differences in phenomenology between UP and BP patients (Feinberg and Carroll 1982b) and have constructed two diagnostic indices (DI's) for use in classifying depressed patients. The first was described in our previous publication (Feinberg and Carroll 1982a), and the second is described here. The second DI, separating BP depressed patients from ND patients, initially would seem to be of academic interest only, since BP patients have a history of mania or (in our classification) hypomania which clearly sets them apart. However, we not infrequently see a young depressed person with an unclear history of hypomania, or none, and might tend to diagnose that patient as having a neurosis or personality disorder because he or she lacks typical endogenous (i.e. unipolar) features. Since both bipolar affective disorder and ND frequently occur in patients under 30 (Angst et al. 1973; Spicer et al. 1973; Loranger and Levine 1978), this problem is one of real clinical significance. More important, the DI can be used to define homogenous groups for use in research. This operational definition of our bipolar group will help other workers to extend our work with the DST.

We derived a discriminant function (DF) separating BP from ND patients (Table 3), and used it to classify these patients with good accuracy (Table 4). When we used item scores adjusted for overall severity of illness to derive the DF, the accuracy of classification increased slightly (Tables 3 and 4), showing that the difference between the endogenous and nonendogenous groups is not one of severity alone, but represents a different profile of signs and symptoms. We converted the DF to a discriminant index (DI) modelled on the Newcastle Diagnostic Index of Carney et al. (1965) and divided the scores into 3 ranges, classifying patients as BP, uncertain, or ND (Tables 5 and 6). This division into 3 groups made little change in the accuracy of classification of the derivation group (c.f. Tables 4 and 6), but did increase slightly the accuracy of classification on cross-validation. While 30 of 41 patients in the latter group were classified correctly by the DF (73%), 26 of 33 patients (79%) were classified correctly when the scores were trichotomized. This was not unexpected, since Fig. 1 shows clearly that patients with both diagnoses have DI scores at the middle of the range.

Inspection of Fig. 1 shows good separation of BP and ND patients. The distribu-

tion is not clearly bimodal, but the small number of patients makes it difficult to test this mathematically.

We compared the DI classification of the cross-validation group with an external, biological marker for endogenous depression, the dexamethasone suppression test (DST) (Carroll et al. 1981). The sensitivity and specificity of the DST, using clinical diagnosis as a standard, were 0.31 and 0.92. These figures are quite similar to those obtained when the DST is compared with DI classifications excluding the unclassified patients, 0.23 and 0.89. As Carroll et al. (1980) have suggested, this comparison with an external, biological marker supports the validity of the DI classifications. The sensitivity of the DST in this group of bipolar patients (0.31) is lower than that usually reported. The low sensitivity is due to the use of 2 mg of dexamethasone in some patients and the inclusion of outpatients, from whom only 1 plasma sample was drawn. The sensitivity of the DST was slightly, but not significantly, higher in those bipolar patients who were classified as BP by the DI: it was 0.38.

We have discussed the differences in the phenomenology of UP and BP depression, and the need for separate criteria to separate each of these from nonendogenous depression. The clinical items used in the DF (or DI) separating BP from ND patients are not the same as those in the DF separating UP from ND patients (Feinberg and Carroll 1982a). (This DF/DI used the items decreased appetite, guilt, agitation, delusions, work and interests, retardation, loss of pleasure, and presence of precipitants.) BP patients are classified slightly more accurately by the former (c.f. Tables 2 and 3), while UP patients are classified more accurately by the latter. Twenty of 27 UP patients were classified as UP (74%), 5 as uncertain, and 2 as ND using the earlier UP-ND DI, while 16 of 26 (62%) were classified as endogenous (BP) by the BP-ND DI. (One of the 27 UP patients had incomplete data, and was not classified by the BP-ND DI). This decrement in accuracy supports the previously cited differences in the clinical phenomenology of UP and BP endogenous depressed patients (Beigel and Murphy 1971; Himmelhoch et al. 1976; Feinberg and Carroll 1982b).

We can draw several conclusions based on our work with discriminant analysis of clinical features. First, our results support the earlier conclusion of other groups that endogenous and nonendogenous depression are clinically distinct (Carney et al. 1965; Mendels and Cochrane 1968; Kiloh et al. 1972). We believe also that UP and BP endogenous depression are clinically distinct, although there is certainly some controversy about this. We suggest that, because of this possible difference in clinical presentation, classification schemes (symptom lists, lists of diagnostic criteria, etc.) meant to distinguish between ED and ND should deal with UP and BP endogenous depression separately, rather than lumping patients with and without a history of mania or hypomania. Finally, we think that biological markers are a valuable addition to clinical practice, and will be of most benefit in helping to diagnose those patients whose clinical presentations are unclear.

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