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J. Klosterkötter · H. Ebel
F. Schultze-Lutter · E. M. Steinmeyer

Diagnostic validity of basic symptoms

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Abstract Although the Bonn Scale for the Assessment of Basic Symptoms (BSABS) [13] has come into use in several European countries, its diagnostic validity has not yet been sufficiently examined. That is why we have assessed BSABS items on a sample of 243 consecutive admissions to the Department of Psychiatry at the RWTH University, Aachen, and 79 psychologically healthy persons. Then, a cluster analysis was calculated to identify the empirical item-grouping. Five well-interpretable BSABS subsyndromes were found. In addition, uni- and multivariate analyses were computed to evaluate the diagnostic validity of these subsyndromes. We were able to show that every BSABS subsyndrome separates at least schizophrenic, organic mental and affective disorders from personality, neurotic and substance-induced disorders, as well as from psychological health. Furthermore, the subsyndrome “information processing disturbances” differentiates between schizophrenic and organic mental disorders, on the one hand, and affective disorders, on the other, and additionally, the subsyndrome “interpersonal irritation” between schizophrenics and all other persons examined.

Key words Schizophrenia · Basic symptoms · Diagnostic validity · Bonn Scale for the Assessment of Basic Symptoms (BSABS)

Introduction

Self-experienced neuropsychological deficits in schizophrenia as described by Huber [22] as “basic symptoms” (BS) and by Süllwold and Huber [38] as “basic disorders” were examined hitherto mostly with the “Frankfurter Beschwerdefragebogen” (FBF) [38]. From a test-theoretical point of view, the FBF is a well-constructed instrument

for self-assessment and is easy to handle. However, its broad application had led to a controversy over the question of whether the assessed deficits are sufficiently specific for schizophrenic diseases [35, 39]. Some examiners negated this and even stated that basic disorders were the expression of an overall psychophysiological disorganisation only that is found in neurotic disorders and sometimes even in psychologically healthy persons as well [24, 35, 39]. The Bonn Scale for the Assessment of Basic Symptoms (BSABS) [13] is another instrument that differs from the FBF in so far as it is an external assessment which can be used partially or fully structured, and by which the examiner can decide whether or not the described complaint meets the definition of the BSABS item in question. The interrater reliability of the BSABS has already been studied thoroughly and was proved to be satisfactory [17].

The term “basic symptoms” (BS) might be confused with Bleuler’s “fundamental symptoms”; however, the difference is clear: fundamental symptoms, and mainly also their modern operationalized successors, the negative symptoms [1], are externally observed by others on the basis of behaviour and expression, whereas BS can only be identified immediately by the person affected. But to some extent a continuum between the two symptom groups seems to exist. Some BS are probably only milder and preceding degrees of the fundamental or negative symptoms [25]. Accordingly, the correspondence in the Anglo-American symptomatology are the “early symptoms” [5] or “early signs” [4, 21]. Furthermore, correspondences are partially found in schizotypia scales of Chapman and coworkers [6, 7], especially in “Physical Anhedonia” and “Perceptual Aberration”.

The possibility of using the BSABS for the prediction of imminent schizophrenic psychoses [11, 12, 25–28, 30, 31] has made it interesting for other European research groups also. There is an Italian [14], a Spanish [15] and a Danish [16] BSABS version; a Japanese [32] and an English version are in preparation. Some BSABS items were also included in the Instrument for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS), re-

Joachim Klosterkötter (✉) · Hermann Ebel
Frauke Schultze-Lutter · Eckhard Michael Steinmeyer
Department of Psychiatry, RWTH Aachen,
Pauwelsstraße 30, D-52074 Aachen, Germany

cently developed by Häfner and coworkers [19]. But the important question raised in the controversy over the FBF concerning the specificity of the BSABS items for schizophrenia has been examined hitherto only for parts of them [28] or just on a few diagnostic groups [10]. Therefore, in the present comprehensive study we explored the distribution of all BSABS items among most ICD-10 diagnostic categories [9]. To consider the finding that BS can be found in psychologically healthy persons also [35, 39], we included a group of persons who had never received any ICD-10 diagnosis in our study. Initially, the empirical item-grouping of the BSABS items was investigated by cluster analysis. Next, the resulting BSABS subsyndromes were tested for their differentiating power for the double-digit ICD-10 categories and the included psychologically healthy persons.

Subjects and methods

A total of 243 successively admitted patients of the Department of Psychiatry, RWTH Aachen, were examined. To survey as many diagnostic groups as possible, we included those who were given a sure diagnosis of one of the following double-digit ICD-10 categories [9]: F0-organic, including symptomatic, mental disorders; F1: mental and behavioural disorders due to psychoactive substance use; F2: schizophrenia, schizotypal and delusional disorders; F3: mood (affective) disorders; F4: neurotic, stress-related and somatoform disorders; and F6: disorders of adult personality and behaviour (see Table 1). To preserve appropriate group sizes, in between these main categories was no further diagnostically differentiated group. At the same time, we were able to examine 79 normal controls from the Aachen (Germany) area who never had shown signs of psychological disorders according to ICD-10, neither at the time of the interview nor before (see Table 1).

Instrument

Subjects were compared on an already advanced, and for economical reasons, shortened BSABS version, which was restricted to the qualitatively more peculiar BS of the core categories: dynamic deficiencies with and without direct minus symptoms (A and B), cognitive thought, perception and motor disturbances (C) and conasthesias (D; see Table 2).

Data assessment procedure

All patients were interviewed at the time of their admission. The interviewers were clinicians of the Department of Psychiatry, RWTH Aachen, trained on different levels. All of them took part in the prescribed rater training, but received no further introduction to the BS concept. The interrater reliability assessed in 10 patients by 22 constant

Table 1 Subject characteristics

Subjects	Age (years; median)	Gender		N
		Male	Female	
Organic mental disorders (ICD-10: F0)	53.73	11	13	24
Substance-induced disorders (ICD-10: F1)	32.44	14	7	21
Schizophrenic disorders (ICD-10: F2)	34.14	30	45	75
Affective disorders (ICD-10: F3)	53.68	20	36	56
Neurotic disorders (ICD-10: F4)	34.16	23	26	49
Personality disorders (ICD-10: F6)	26.49	6	12	18
Psychic health (normals; without any ICD-10 diagnosis)	30.44	36	43	79

raters revealed bias-corrected κ -values [37] between 0.76 and 0.80. Patients were diagnosed at the time of their discharge with respect to all findings and all informations about the clinical course. The two diagnosticians were experienced in using the ICD-10 and not identical with the BSABS raters.

Statistical procedures

We first performed a multivariate cluster analysis to identify the empirical grouping of the BSABS items. Therefore, we applied the SAS programme VARCLUS, a type of oblique component analysis related to multiple group analysis. It attempts to divide a set of variables into non-overlapping clusters so that each cluster can be interpreted as essentially unidimensional. For each cluster a first principal or centroid component is computed. VARCLUS tries to maximize the sum across cluster of the variation accounted for by the cluster components. Thus, the squared correlation of a variable with its own cluster component (R^2 own cluster) should be higher than those with any other cluster. For this reason VARCLUS also lists the highest squared correlation of a variable with a cluster component not its own (R^2 next closest). Other than in factor analysis, the variation explained by the cluster component includes contributions from only the variables in that cluster, rather than from all variables. With the option MAXEIGEN = 1 we applied an option that tends to choose clusters with a large number of variables, because that promised a result more comparable to the large categories. By this procedure we did not attempt to identify an underlying latent dimension, but to find BSABS subsyndromes that are able to explain the variation between the different groups and, doing so, are helpful in finding subsyndromes specific for schizophrenia.

Next, we computed pairwise group comparisons for the clusters to get information about their validity for schizophrenia. We did that within the framework of General Linear Models (SAS programme GLM). The group mean of positive statements in the BSABS subsyndromes were used as classification variables. We chose the option

Table 2 Basic symptoms: BSABS categories and empirical shift to BSABS subsyndromes (for abbreviations see Fig.1); squared correlations with the own and the next closest cluster

From To	BSABS items	R ² own cluster	R ² next closest
C.1–BIP	Disturbances of comprehension of symbols (concretism)	0.8127	0.5905
C.1–BIP	Disturbances of receptive speech	0.7888	0.6111
C.1–BIP	Interference of thought	0.7291	0.5572
C.1–BIP	Subjective blocking of thought	0.7223	0.5930
C.1–BIP	Obsessional perseveration of thought	0.7175	0.5745
C.1–BIP	Disturbances of discrimination between ideas and perception	0.6875	0.5651
C.1–BIP	Pressure of thought	0.6870	0.5490
C.1–BIP	Disturbances of expressive speech	0.6796	0.5755
C.1–BIP	Disturbance of long-term memory	0.6133	0.5940
C.1–BII	Tendency to delusion of reference	0.6555	0.5675
C.1–BA	Disturbances of thought initiative or "thought energy"	0.7829	0.5497
C.1–BA	Retardation and impediment of thought processes	0.7700	0.4252
C.1–BA	Disturbances of short-term memory	0.7083	0.4466
C.1–BA	Disturbances of immediate recall	0.6954	0.4561
C.1–BA	Disturbances of concentration	0.6603	0.3760
C.2–BIP	Partial seeing	0.9680	0.7156
C.2–BIP	Pseudomovements of optic stimuli	0.9678	0.7168
C.2–BIP	Diplopia, oblique vision	0.9615	0.7150
C.2–BIP	Disintegration of the linearity of objective contours	0.9602	0.7147
C.2–BIP	Near and tele-vision	0.9593	0.7060
C.2–BIP	Micropsia, macropsia	0.9574	0.7051
C.2–BIP	Metamorphopsia	0.9408	0.6947
C.2–BIP	Changes in the perception of the face/body of others	0.9400	0.6909
C.2–BIP	Abnormally long-lasting remains of optic stimuli	0.9332	0.6870
C.2–BIP	Changes in the perception of the intensity or quality of acoustic stimuli	0.9318	0.7129
C.2–BIP	Changes in colour vision	0.9239	0.6859
C.2–BIP	Blurred vision	0.9219	0.6772
C.2–BIP	Sensitivity to light or optic stimuli	0.9108	0.6604
C.2–BIP	Disturbances of the estimation of distances	0.9090	0.6539
C.2–BIP	Maintenance of acoustic stimuli	0.8969	0.6737
C.2–BIP	Photopsia	0.8968	0.6622
C.2–BIP	Changes in the perception of the own face	0.8957	0.6601
C.2–BIP	Captivation by details of perception	0.8762	0.7031
C.2–BIP	Disturbances of perception of olfactory, gustatory or sensible stimuli	0.8617	0.7134
C.2–BIP	Aroused state of perceptual awareness	0.8264	0.7514
C.2–BIP	Acoasms	0.7605	0.6332
C.2–BIP	Sensitivity to noises	0.7492	0.5831
C.3–BIP	Loss of automatic skills, psychomotor retardation	0.9118	0.8259
C.3–BIP	Motor interference	0.8150	0.7279
C.3–BIP	Motor blockages	0.8624	0.7754
D–BC	Kinesthetic sensation	0.9637	0.7838
D–BC	Electric sensations	0.9587	0.7644
D–BC	Vestibular sensations	0.9549	0.7722

Table 2 (continued)

From To	BSABS items	R ² own cluster	R ² next closest
D–BC	Sensations of extension, diminution, shrinking, enlargement or constriction	0.8986	0.7149
D–BC	Sensations of abnormal heaviness, lightness or emptiness, of falling or sinking, levitation or elevation	0.8871	0.6864
D–BC	Somatopsychic depersonalization	0.8735	0.7063
D–BC	Thermic sensations	0.8645	0.6723
D–BC	Dysesthetic crises	0.8489	0.6399
D–BC	Sensations of motor weakness	0.8434	0.6442
D–BC	Sensations of numbness and stiffness and feeling strange	0.8384	0.6255
D–BC	Migrating sensations	0.8325	0.6236
D–BC	Sensations of movement, pulling or pressure inside the body or on its surface	0.7524	0.5293
D–BC	Circumscribed sensations of pain	0.7460	0.5247
B.1 + A.8 – BV	Decreased psychic tolerance with respect to unusual, unexpected or specific novel demands	0.8590	0.3568
B.1 + A.8 – BV	Decreased psychic tolerance with respect to working under pressure or time or rapidly changing different demands	0.8210	0.3729
B.1–BV	Decreased psychic tolerance with respect to physical and/or psychic stress when working	0.7920	0.4005
B.1 + A.8 – BV	Decreased psychic tolerance with respect to certain social situations of everyday life that are primarily emotionally neutral	0.7707	0.3983
A.8–BV	Inability to device one's attention adequately	0.5416	0.3804
B.2–BII	Increased impressionability due to being personally affected by the behaviour of others	0.6308	0.3420
B.2–BII	Increased impressionability due to everyday events	0.7523	0.4592
B.2–BII	Increased impressionability due to misfortunes of others	0.6830	0.4480
A.6–BA	Decrease in the need for contact with others	0.5820	0.3692
A.6–BA	Changes in basic mood and emotional reactivity	0.5773	0.3961
A.6–BIP	Incapacity to discriminate between different kinds of emotions	0.5649	0.5131
A.7–BII	Decrease in the ability to contact others in the presence of a desire for such contacts	0.5324	0.3698
A.7–BII	Disturbances in presenting her- or himself	0.6343	0.5206

Waller [40], which performs k-ratio *t*-test and controls not only α , but β also. Calculations were performed on a general α -level of 1% over all subsyndromes adjusted according to Hager's [20] severe criteria for mean differences for each subsyndrome.

In the last step, multivariate discrimination analyses were calculated for the five subsyndromes on item level to

receive further information about the differentiating quality for schizophrenia of each of these subsyndromes. We applied the SAS programme CANDISC for canonical discrimination analyses based on quantitative variables that derive linear combinations of the variables that have the highest possible multiple correlations with the group (canonical components). Such linear combinations are of great interest for diagnostic purposes, especially because canonical components are uncorrelated whether the correlation is calculated from the total sample or from a pooled within-group correlations. CANDISC computes probability levels associated with the F statistic testing hypothesis that group means are equal in the population, and gives the group means on the canonical components.

Results

BSABS subsyndromes

The multivariate cluster analysis led to a solution of five clusters that explain 53.25% of the variation (see Table 2). The first cluster (BSABS subsyndrome) resulted from cognitive thought, perception and motor disturbances, and was named BSABS subsyndrome “*information processing disturbances*” (BIP). The only addition to cognitive BS in this cluster was “incapacity to discriminate between different kinds of emotions” from the category of affective disturbances which correlates less than any other subsumed BS with the BIP (see Table 2).

Whereas perceptive and motor disturbances were completely included in the BIP, six BS of the category of thought disturbances entered other clusters. These BS were “tendency to delusion of reference”, on the one hand, and disturbances of concentration, of short-term memory, of immediate recall and of thought initiative, as well as re-

tardation and impediment of thought processes, on the other hand (see Table 2). These latter BS describe primarily dynamic aspects of thinking and form the majority of the fourth cluster. Supplementary items in cluster 4 originally belonged to the category of disturbances of affect and contact (see Fig. 1 and Table 2). Because all BS of this cluster are marked by reduced psychological dynamics, this BSABS subsyndrome was given the name “*adynamia*” (BA).

The second cluster was identical to the conasthetic category; therefore, this BSABS subsyndrome kept the name “*conasthesias*” (BC) (see Fig. 1 and Table 2).

Cluster 3 was built by five BS from the category of stressor sensitivity; all of them are characterized by a reduced psychological stress tolerance. It was named BSABS subsyndrome “*vulnerability*” (BV), because each of the BS included delineates a high susceptibility to overstrain (see Fig. 1 and Table 2).

The three remaining BS from the category of increased stressor sensitivity were subsumed in the fifth cluster. There they joined up with “decrease in the ability to contact others in the presence of a desire for such contact”, “disturbances in presenting oneself” and “tendency to delusion of reference” (see Fig. 1 and Table 2).

A person with a disturbed sense of presenting her/himself subjectively lacks control over her/his expressive behaviour, especially over facial and bodily gestures, and feels as if she/he no longer can adequately express feelings and affections. A “tendency to delusion of reference” causes the diffuse feeling that actions and statements of others around are related to oneself. In such a case, contrary to real delusion of reference, the affected person is still aware – at the same time or shortly after – that this feeling is not realistic. Thus, cluster 5 was given the name BSABS subsyndrome “*interpersonal irritation*” (BII), because every included BS describes an irritation especially in social situations.

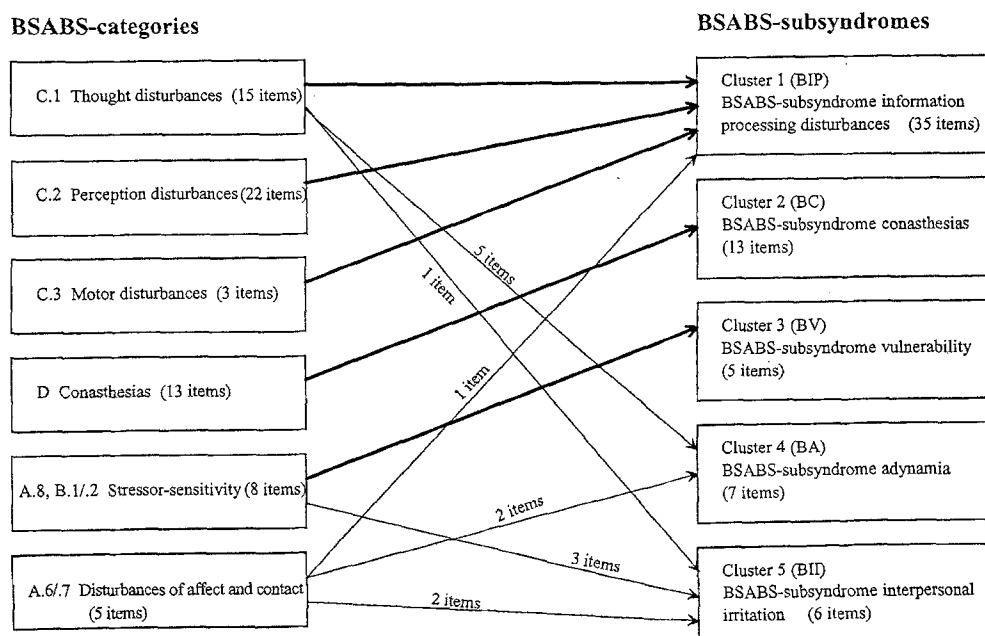


Fig. 1 Cluster analytical grouping of basic symptoms

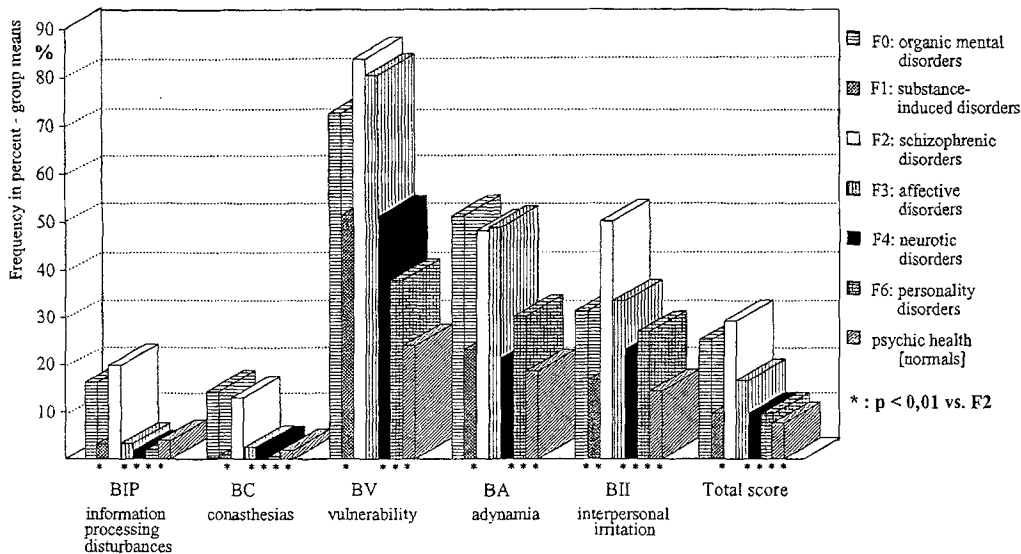


Fig. 2 BSABS subsyndromes: mean comparison of groups

Group comparison

Given the various group means in percentage of all possible items per subsyndrome or in total by reason of homogeneous presentation, the relations shown in Fig. 2 result. BS in total are significantly the most frequent in F2 ($\bar{x} = 19.19$, $s = 16.86$) and F0 ($\bar{x} = 16.58$, $s = 17.48$). Furthermore, there are significant differences between F3 ($\bar{x} = 10.91$, $s = 5.32$) and the other clinical groups (F1: $\bar{x} = 6.38$, $s = 5.79$; F4: $\bar{x} = 6.37$, $s = 5.60$; F6: $\bar{x} = 6.33$, $s = 5.11$) and the psychologically healthy group ($\bar{x} = 4.98$, $s = 4.30$). Neither these latter three clinical groups nor the psychologically healthy group show any further significant differences in total BS frequencies.

Regarding the contributions of the five-cluster analytically received BSABS subsyndromes to this distribution profile, "information processing disturbances" (BIP) are found significantly the most frequent among F2 ($\bar{x} = 6.95$, $s = 10.71$) and F0 ($\bar{x} = 5.67$, $s = 9.74$) as well, but other than in the total score F3 ($\bar{x} = 1.14$, $s = 1.75$), does not significantly differ from the other clinical groups and the psychologically healthy group in this cognitive field. The same relations of frequencies as in BIP are found in the conasthetic subsyndrome (BC) where again F2 and F0 differ significantly from F3 and all other groups. Vulnerability features (BV) as well as adynamia features (BA) are also significantly more frequent in F2 and F0 than in F1, F4, F6 and psychologically healthy persons. But of these affective-dynamic symptoms, BV features occur nearly as often in F3 ($\bar{x} = 4.02$, $s = 1.12$) as in F2 ($\bar{x} = 4.19$, $s = 1.31$), and BA features even slightly more often in F3 ($\bar{x} = 3.41$, $s = 2.26$) than in F2 ($\bar{x} = 3.36$, $s = 2.25$).

Finally, features of "interpersonal irritation" (BII) are significantly more frequent in F2 ($\bar{x} = 3.00$, $s = 1.90$) than in any other group. Furthermore, patients with a F0- ($\bar{x} = 1.88$, $s = 2.03$) or F3 diagnosis ($\bar{x} = 2.00$, $s = 1.85$) presented BII features significantly more often than those

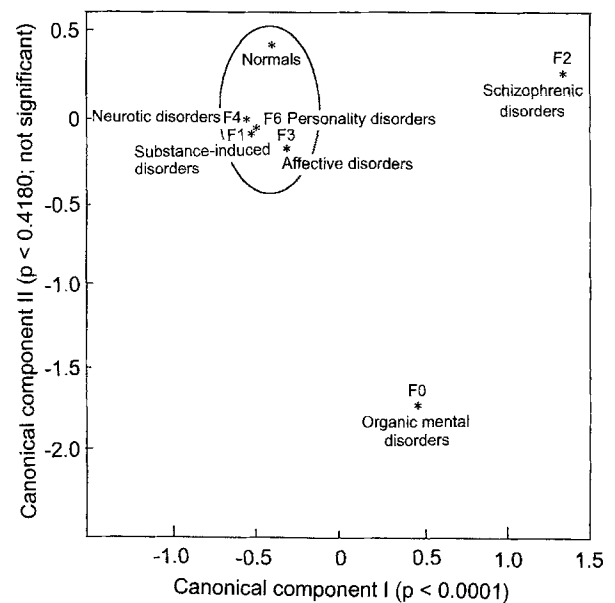


Fig. 3 Discrimination space of the BSABS subsyndrome "information processing disturbances" (BIP): group means on canonical components. Oval shape indicates a common space for groups on the first canonical component

with a diagnosis of F1 ($\bar{x} = 1.00$, $s = 1.43$) or psychologically healthy persons ($\bar{x} = 0.86$, $s = 1.19$). Among the latter, BII features occur significantly less frequently than in F6 ($\bar{x} = 1.61$, $s = 1.42$) also.

Analyses of discriminance

Computing multivariate analyses for each of the five BSABS subsyndromes to find out about their discrimination power for F2, the following resulted: For the BIP items one significant canonical component was calculated (see Fig. 3). Here, F2 and F0 are each separated from the other six groups with F2 having the highest group mean on the canonical component, and F0 the second highest.

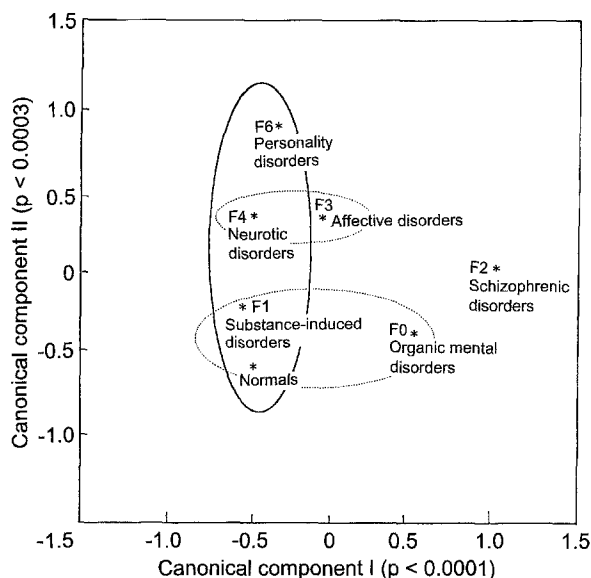


Fig. 4 Discrimination space of the BSABS subsyndrome “interpersonal irritation” (BII): group means on canonical components. *Solid oval shape* indicates a common space for groups on the first canonical component; *Dotted oval shape* indicates a common space for groups on the second canonical component

No significant canonical component resulted for the BC items. For the BV two highly significant canonical components were found. F6 having low group means is separated from all other groups on both components ($p < 0.001$ each). But also in this case F2 and F0 score high on both dimensions. For the BA one significant canonical component was chosen ($p < 0.0001$) discriminating the psychotic groups (F0, F2, F3) from all other groups. Here again, F2 and F0 score highest on the component, but do not differ significantly from F3. For the BII two highly significant canonical components were found which both separate F2 from all other groups (see Fig. 4).

Discussion

To test the diagnostic validity of BS, in this study we first tried to identify BSABS subsyndromes by cluster analysis. The resulting five cluster solution seems to be quite plausible and easy to interpret. Especially interesting is the empirical shift of the uncharacteristic, dynamic thought disturbances to the BSABS subsyndrome “adynamia” (BA) where they are connected with other dynamic deficiencies. This shift appears as a clearance of the main category of cognitive disturbances. Thus, the BSABS subsyndrome “information processing disturbances” (BIP) includes only the qualitatively more peculiar BS of the cognitive thought, perception and motor disturbances, and is mainly represented by optic perception disturbances. Plausible also is the partition of BS of the category “stressor sensitivity” into those indicating a low psychological stress tolerance and those characterized by a high emotional impressionability towards external events. These latter entered the BSABS subsyndrome “in-

terpersonal irritation” (BII). Here, BS are subsumed which affect mainly the quantity and quality of social contacts and could be regarded as an expression of a reduced self-confidence or a decreased ego strength [36].

In subsequent group comparisons, these subsyndromes turned out to be distributed differently. Features of BII were found significantly more often among schizophrenic, delusive and schizoaffective patients – as subsumed in the ICD-10-category “F2” – than in any other group. About the same difference in frequencies also occurred in all other subsyndromes, with the exception of organic mental disorders in the BIP and the BSABS subsyndrome “conasthesias” (BC), and both, organic mental and affective disorders, in the BA and the BSABS subsyndrome “vulnerability” (BV). In total, BS occur highly significantly more often in schizophrenic and organic mental disorders than in affective disorders. In the latter they are highly significantly more frequent than in neurotic, personality or substance-induced disorders, as well as in the common fluctuations of the state of psychological health found in healthy persons within a normal range. Thus, this symptomatology, although externally assessed with the BSABS spreads over the whole range of psychological disorders and occurs in psychologically healthy persons also. Nevertheless, according to our results, it cannot be regarded simply as the expression of an overall psychophysical impairment, as in the controversy over the FBF [24, 35, 39]. Even BV and BA features that are the least specific for schizophrenia occur significantly more often in those disorders which are traditionally entitled “psychoses” – endogenous or physically based – than in any other group. Thereby, these relatively unspecific BS resemble the schizophrenic negative symptoms according to Andreasen [1, 2]. For these negative symptoms also, it could be shown that they are significantly more frequent in schizophrenic disorders than in neurotic or personality disorders, but that they do not differ in frequency in schizophrenic, organic mental and affective disorders [3, 8, 28, 29, 33].

Negative symptoms as broadly understood by Häfner [18] in the Mannheim ABC schizophrenia study as well as BS [22, 25, 30] are proved to appear even years before the first positive symptoms characteristic for schizophrenia. Therefore, it would be beneficial to be able to make an early diagnosis and to initiate an early treatment based on these symptoms. With regard to this perspective, the results of our discrimination analyses are of interest. According to them, at least two BSABS subsyndromes separate significantly schizophrenia from all other groups. Basic symptoms of BII seem to discriminate schizophrenic disorders best. Along with the “tendency of delusion of reference”, they are closest to the positive symptoms. Their discrimination power is indeed as good as it has been reported for positive symptoms that are characteristic for schizophrenia [37]. Recently, we also found positive symptoms to be of far greater diagnostic validity for schizophrenia when compared with negative symptoms [29].

Basic symptoms of BIP also separate schizophrenia as well as organic mental disorders from all other groups,

and even schizophrenia from organic mental disorders. This fact is probably the most important for early diagnosis and treatment, because this subsyndrome includes by far the most items, and according to current results of BS research [22, 25, 30], the subsumed thought, perception and motor disturbances appear earlier in course than BS of BII. By reason of their cognitive nature, it is not surprising that BIP items differentiate worse between schizophrenic and organic mental disorders than between schizophrenia and other disorders. In BS research [22] this small difference is traditionally regarded as supporting the (broadly accepted) hypothesis that schizophrenic disorders are also physically based. At any rate, the practical value of this subsyndrome for the early recognition of schizophrenia is not limited by the differentiation problem between these two disorders. In diagnostic practice a definite organic factor initiating and maintaining the disturbances just has to be excluded to use the evidence of "information processing disturbances" for the early diagnosis of a schizophrenic disorder. In our prospective early recognition study [26, 27, 30, 31], the results thus far indicate that BIP features are indeed predictive of a subsequent development of positive symptoms.

Thus, to the question of the diagnostic validity of BS, a general answer cannot be given. Some BSABS items – namely, BA and BV items – are neither more nor less specific for schizophrenia than negative symptoms. But there are BSABS items – namely, BIP and BII items – that reach a degree of specificity for schizophrenia close to or even the same as the positive symptoms which are typical for schizophrenic disorders. Consequently, the development of the BSABS to a dependable instrument for the prediction of schizophrenia has to focus on these latter subsyndromes.

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