Historical, Psychopathological, Neurological, and Neuropsychological Aspects of Deficit Schizophrenia: A Multicenter Study

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Objective: This multicenter study aimed to verify whether the historical and psychopathological characteristics of a large group of patients with deficit schizophrenia were consistent with those reported in previous studies. The authors also tested the hypothesis that neurological and neuropsychological indices sensitive to frontoparietal dysfunction, but not those sensitive to temporal lobe dysfunction, are more impaired in patients with deficit schizophrenia than in those with nondeficit schizophrenia.

Method: For each patient with deficit schizophrenia enrolled in the study, a matched subject with nondeficit schizophrenia was recruited. Historical, psychopathological, neurological, and neuropsychological evaluations were carried out for all patients.

Results: Patients with deficit schizophrenia, compared with patients with nondeficit schizophrenia, had a similar severity of positive symptoms and disorganization and less hostility. They had poorer premorbid adjustment during childhood and early adolescence and exhibited more impairment in general cognitive abilities. The deficit state was associated with impairment in sequencing of complex motor acts, which suggests frontoparietal dysfunction.

Conclusions: Previous reports of differences in historical, psychopathological, and neuropsychological characteristics between patients with deficit schizophrenia and those with nondeficit schizophrenia were mostly supported by the present findings. Neurological findings suggest that frontoparietal functioning is more impaired in patients with deficit schizophrenia. Deficit schizophrenia might represent a neurodevelopmental subtype of schizophrenia in which significant behavioral and cognitive impairment since childhood compromises the development of basic capacities relevant to subsequent cognitive and social functioning.

(Am J Psychiatry 2002; 159:983–990)

Research on schizophrenia has been seriously hindered by the extreme interindividual variability of the clinical manifestations of the disorder, which probably reflects a multiplicity of etiopathogenetic mechanisms (1–3). The concept of deficit schizophrenia was introduced to identify a relatively homogeneous subgroup of patients characterized by the presence of enduring primary negative symptoms: restricted affect, diminished emotional range, poverty of speech, curbing of interests, lack of a sense of purpose, and diminished social drive (4).

The prevalence of deficit schizophrenia has been reported to be about 15% among patients with first-episode schizophrenia and 25%–30% among those with chronic schizophrenia (5). Longitudinal studies have demonstrated that the deficit/nondeficit categorization is highly stable (6). Patients with deficit schizophrenia, relative to those with the nondeficit subtype, have been found to have poorer premorbid adjustment (7–9), a greater genetic load for schizophrenia (5, 10–12), a more frequently insidious onset of illness (7), a similar severity of productive symptoms and a lower severity of dysphoria (5, 13), a more

frequent resistance to antipsychotic treatment (14), and a worse long-term outcome (7).

Neuropsychological studies have reported that patients with deficit schizophrenia are significantly more impaired than those with nondeficit schizophrenia on measures sensitive to frontal and parietal lobe dysfunction but not on those sensitive to temporal lobe dysfunction (15–17). Investigations that have included a structured neurological examination have shown a greater impairment in sensory integration—but not in motor coordination or sequencing of complex motor acts—among subjects with deficit schizophrenia (8, 18). Functional brain imaging investigations have suggested cortical-striatal-thalamocortical circuit dysfunction, including prefrontal and parietal regions, as the neural basis for deficit symptoms (19–21).

Here we report the results of a large multicenter study that aimed to verify whether the historical and psychopathological characteristics of a large group of patients with deficit schizophrenia were consistent with the pattern that has emerged from previous studies. In addition, this study sought to test the hypothesis that neurological

and neuropsychological indices sensitive to frontoparietal dysfunction (attention and visuospatial abilities), but not those sensitive to frontotemporal dysfunction (verbal and visual explicit memory), are more impaired in patients with deficit schizophrenia than in those with nondeficit schizophrenia.

Method

Patient Group and Recruitment Procedures

The study was carried out with patients who were regularly attending the outpatient units, day-care programs, and rehabilitation centers of the University Psychiatric Departments of Naples, Milan, L'Aquila, and Pisa, Italy. Those who had a clinical diagnosis of schizophrenia and were reported to be clinically stable were tested to verify that they met the following inclusion criteria: 1) a DSM-IV diagnosis of schizophrenia, confirmed by the Structured Clinical Interview for DSM-IV (SCID); 2) age between 16 and 55 years; 3) no history of severe mental retardation, alcoholism, or drug abuse or dependence in the last 12 months and no previous ECT; 4) no significant changes in the clinical state or in drug treatment during the preceding 3 months; and 5) willingness to participate in the study procedures, expressed by providing written informed consent after complete description of the study. Patients meeting these criteria were then classified as having either deficit or nondeficit schizophrenia after being interviewed with the Schedule for the Deficit Syndrome (22).

The original version of the Schedule for the Deficit Syndrome was translated into Italian, back-translated into English by a bilingual translator, and discussed with one of the authors of the schedule (Brian Kirkpatrick), who also guided the training of the investigators. At the end of the training, there was no disagreement among eight raters (Cohen's kappa=1) in classifying one patient with nondeficit schizophrenia and two patients with deficit schizophrenia. Intraclass correlation coefficients (ICCs) showed good agreement among raters for the Schedule for the Deficit Syndrome measures of restricted affect (0.76), diminished emotional range (0.62), poverty of speech (0.67), curbing of interests (0.74), diminished sense of purpose (0.74), and diminished social drive (0.81). Investigators were also trained in the use of the SCID and the SCID Nonpatient Version. At the end of the training, there was no disagreement among eight raters (Cohen's kappa=1) in classifying two patients with schizophrenia and one as having bipolar I disorder with mood-incongruent psychotic features. The same kappa value was achieved by six raters on the nonpatient SCID.

All subjects with deficit schizophrenia according to the Schedule for the Deficit Syndrome were enrolled in the study. For each recruited patient with deficit schizophrenia, an age- and sex-matched patient with nondeficit schizophrenia was recruited. Thus, 60 deficit/nondeficit pairs were recruited. However, only those who completed most of the study procedures were included in the data analysis. The final group consisted of 58 patients with deficit schizophrenia (43 men and 15 women) and 54 patients with nondeficit schizophrenia (41 men and 13 women). The comparability between the two groups with respect to demographic and clinical variables was assessed by analyses of variance (ANOVAs) or chi-square tests, as appropriate. There were no significant differences between the deficit and nondeficit patients in terms of age (mean=35.2 years [SD=7.3] and 34.4 years [SD=7.7], respectively), education (mean=11.4 years [SD=3.1] and 11.3 years [SD=3.3]), age at onset of illness (mean=21.6 years [SD=4.5] and 21.7 years [SD=4.2]), duration of illness (mean=13.6 years [SD=7.4] and 12.8 years [SD=6.9]), or gender distribution. The mean current antipsychotic dose was significantly higher in patients with nondeficit schizophrenia (mean=645 mg/day [SD=410] in chlorpromazine equivalents) than in patients with deficit schizophrenia (mean=445 mg/day [SD=363]) (F=7.23, df=1, 106, p<0.008). There was no difference between the deficit and nondeficit patient groups as to the type of antipsychotic treatment they were receiving (novel antipsychotics: 56.9% [N=33] and 46.3% [N=25], respectively; standard neuroleptics: 25.9% [N=15] and 27.8% [N=15]; combination: 13.8% [N=8] and 24.1% [N=13]).

In two of the participating centers (Naples and Milan), a group of 26 healthy subjects (18 men and eight women)—matched to patients for age (within 3 years), education (within 3 years), handedness, and sex—was recruited through flyers from the general population for comparisons on neuropsychological indices. These comparison subjects had no personal or family history of major psychiatric disorders—as ascertained by the nonpatient SCID and the Family History Questionnaire and Relative Psychiatric History Questionnaires (23)—and no history of severe head trauma or substance-related disorders. Their mean age of 34.6 years (SD=9.4) and their mean education level of 12.7 years (SD=2.9) did not significantly differ from those of patients.

Study Procedures

Different investigators carried out historical, psychopathological, neurological, and neuropsychological evaluations to avoid "halo" effects. All of them, as well as patients and family members, were blind to the deficit/nondeficit categorization and had not been informed of the specific study aims and hypotheses.

The personal and family history of each recruited patient was explored with the help of at least one family member (the mother, if available) by using the Family History Questionnaire and Relative Psychiatric History Questionnaires, the Obstetric Complications Scale (24), and the Premorbid Adjustment Scale (25). The psychopathological state was evaluated by the expanded Brief Psychiatric Rating Scale (BPRS), version 4.0 (26), the Scale for the Assessment of Negative Symptoms (SANS) (27), and the Scale for the Assessment of Positive Symptoms (SAPS) (28). The recent history of hospitalization and social functioning was explored by the Strauss-Carpenter Scale (29). Investigators were trained in the use of these instruments, and at the end of the training, good to excellent agreement was observed among 12 raters who assessed three patients (for the expanded BPRS, ICC=0.61–1.00; for the SANS, ICC= 0.83–0.99 [except for the alogia and attention subscales, which had coefficients of 0.59 and 0.57, respectively]; for the SAPS, ICC=0.63–1.00).

The Neurological Evaluation Scale (30), which assesses three functional areas of interest (sensory integration, motor coordination, and sequencing of complex motor acts) plus some miscellaneous items (abnormalities in eye movements, frontal release signs, and short-term memory), was used for the neurological evaluation. The presence of spontaneous or induced abnormal involuntary movements was assessed by the Abnormal Involuntary Movement Scale (AIMS) (31). Extrapyramidal signs were evaluated by the Simpson-Angus Scale (32). Investigators were trained in the use of these instruments, and at the end of the training, good to excellent agreement was observed among five raters who assessed three patients (for the Neurological Evaluation Scale indices, ICC=0.75–0.99; for the AIMS, ICC=0.95 [total score] and 0.97 [perioral region subtotal]; for the Simpson-Angus Scale average score, ICC=0.54).

Neuropsychological functioning of patients and healthy comparison subjects was evaluated by their performance on tests that assessed five functional domains: 1) general abilities (WAIS-R IQ results); 2) executive functions (number of categories and perseverative errors on the Wisconsin Card Sorting Test [33], number of interferences on the Picture Memory and Interference Test [34], the part B minus part A time on the Trail Making Test [35], and WAIS-R Digit Forward Plus Backward Test results); 3) focused/

sustained attention (WAIS-R Digit Symbol Substitution Test results and the number of errors on the Continuous Performance Test-AX [36]); 4) explicit memory (number of delayed recalls on the Auditory Verbal Learning Test [34] and the number of identifications on the Picture Memory and Interference Test [34]); and 5) visuospatial abilities (Benton Judgment of Line Orientation [37] and the WAIS-R Block Design results).

The Continuous Performance Test-AX was administered by computer; all other tests used the traditional manual method. Tests were administered in the morning (from 9:00 a.m. to 12:00 noon) in a fixed order (Auditory Verbal Learning Test, Benton Judgment of Line Orientation, Wisconsin Card Sorting Test, WAIS-R, Continuous Performance Test, Picture Memory and Interference Test, Trail Making Test [part A], Trail Making Test [part B]).

Data Analyses

Data distributions were examined for normality and homogeneity of variance. In cases in which these assumptions were violated, data were log transformed.

Categorical variables were analyzed by the chi-square test. For continuous variables, in order to deal with the problem of multiple comparisons, the following four strategies were adopted. First, for each investigated area, the lowest possible number of indices was included. Second, ANOVAs were performed, with multivariate or repeated-measures designs used when deemed appropriate. Third, Huynh-Feldt correction for multiple comparisons was used when needed. Fourth, univariate follow-up tests were carried out only when a significant main effect or interaction had been found in the multivariate test.

Psychopathological variables were reduced to eight, on the basis of previous factor analysis studies of the instruments used in this study. Measures from the SANS and SAPS were grouped into three dimensions (38–41): 1) negative symptoms (sum of global scores on the alogia, anhedonia, affective flattening, and avolition subscales of the SANS); 2) reality distortion (sum of global scores on the hallucinations and delusions subscales of the SAPS); and 3) disorganization (sum of global scores on the formal thought disorder and bizarre behavior subscales of the SAPS). Measures from the expanded BPRS were grouped into five factors (42): 1) thought disturbance (sum of scores on the conceptual disorganization, hallucinatory behavior, and unusual thought content items); 2) activation (sum of scores on the tension, mannerisms/posturing, and excitement items); 3) anxiety/depression (sum of scores on the anxiety, guilt feelings, and depressed mood items); 4) hostility/suspiciousness (sum of scores on the suspiciousness, hostility, and uncooperativeness items); and 5) anergia (sum of scores on the blunted affect, emotional withdrawal, and motor retardation items).

For the Neurological Evaluation Scale, the score on each of the three factors was included in the analysis; they were preferred to the total score as they test different functions of the CNS.

Independent two-way ANOVAs for repeated measures on SANS/SAPS dimensions, expanded BPRS factors, and Neurological Evaluation Scale factors were used to test group differences between patients with deficit schizophrenia and patients with nondeficit schizophrenia (group, between; dimension/factor, within). A repeated-measure ANOVA was not deemed appropriate for the Premorbid Adjustment Scale, since the subscores were obtainable only for epochs preceding the age at illness onset, which was different for different subjects, yielding missing data for many of them for some epochs. In this case, a Bonferroni correction was applied (p=0.05/5=0.01).

Neuropsychological variables were grouped into the five aforementioned functional domains. To deal with the problem of multiple comparisons, a multivariate analysis of variance (MANOVA) on all neuropsychological indices was used to assess group differences among subjects with deficit schizophrenia, subjects with

FIGURE 1. Premorbid Adjustment Scale Scores of Patients With Deficit Schizophrenia and Patients With Nondeficit Schizophrenia
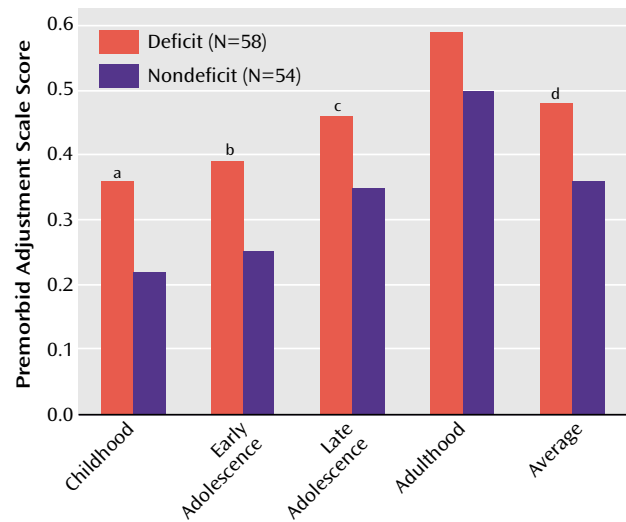
[a] Significantly worse premorbid adjustment seen in patients with deficit schizophrenia (F=14.9, df=1, 104, p=0.0002).
[b] Significantly worse premorbid adjustment seen in patients with deficit schizophrenia (F=18.1, df=1, 104, p=0.00005).
[c] Significantly worse premorbid adjustment seen in patients with deficit schizophrenia (F=7.5, df=1, 100, p=0.007).
[d] Significantly worse premorbid adjustment seen in patients with deficit schizophrenia (F=16.9, df=1, 104, p=0.0001).

nondeficit schizophrenia, and healthy comparison subjects. Only in the presence of a MANOVA significant group effect were follow-up two-way ANOVAs for repeated measures performed on each neuropsychological domain, with diagnosis (deficit schizophrenia, nondeficit schizophrenia, healthy comparison) as a between-group factor and test as a within-group factor. Analyses of covariance (ANCOVAs), with general abilities (the summed age-corrected scores on the WAIS-R vocabulary and picture completion subscales) entered as a covariate, were planned to exclude the influence of group IQ differences on the other tested functions (43). For those domains showing significant group effects or interactions, follow-up analyses of simple effects were planned to locate the source of the main effect or interaction.

For measures showing significant differences between patients with deficit schizophrenia and patients with nondeficit schizophrenia, a further question was addressed, i.e., whether the deficit state remained significantly associated with these measures when combinations of several confounding variables (demographic or clinical) were simultaneously controlled. To this aim, stepwise multiple regression analyses were performed in which the deficit/nondeficit categorization, the SANS/SAPS dimensions, age, education, duration of illness, the Simpson-Angus average score, and the chlorpromazine-equivalent doses were entered as independent variables.

Results

Historical, Psychopathological, and Neurological Evaluations

A family history of schizophrenia was more frequent in patients with deficit schizophrenia (15.5%, N=9) than in those with nondeficit schizophrenia (11.1%, N=6), and a family history of affective disorders was less frequent

TABLE 1. Psychopathology Among Patients With Deficit Schizophrenia and Patients With Nondeficit Schizophrenia

| | Score | | | | | |
| | Patients With Deficit Schizophrenia (N=58) | | Patients With Nondeficit Schizophrenia (N=54) | | Analysis[a] | |
Psychopathology Measure	Mean	SD	Mean	SD	F (df=1, 110)	p
Expanded BPRS factors						
Thought disturbance	7.6	3.2	8.7	3.6	3.0	0.08
Activation	4.7	1.9	4.8	1.9	0.0	0.88
Anxiety/depression	6.3	2.2	6.1	2.9	0.1	0.71
Hostility/suspiciousness	4.9	2.0	5.8	2.7	4.4	0.04
Anergia	11.1	3.4	8.0	2.7	27.8	0.00005
SANS/SAPS dimensions						
Negative symptoms	13.1	3.1	10.0	3.2	28.2	0.00005
Reality distortion	3.8	2.6	4.1	3.0	0.3	0.62
Disorganization	2.8	2.3	3.0	1.9	0.3	0.57

[a] Follow-up univariate tests conducted after repeated-measure ANOVAs showed a significant group-by-factor interaction (F=13.0, df=4, 440, p=0.0001, with Huynh-Feldt correction for multiple comparisons) for the five factors of the expanded Brief Psychiatric Rating Scale (BPRS) and a significant group-by-dimension interaction (F=24.4, df=2, 220, p=0.00005, with Huynh-Feldt correction for multiple comparisons) for the three dimensions of the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS).

TABLE 2. Neurological Characteristics of Patients With Deficit Schizophrenia and Patients With Nondeficit Schizophrenia

| | Score | | | | | |
| | Patients With Deficit Schizophrenia (N=58) | | Patients With Nondeficit Schizophrenia (N=54) | | Analysis[a] | |
Neurological Evaluation Scale Factor	Mean	SD	Mean	SD	F (df=1, 109)	p
Sensory integration	2.72	2.60	1.72	1.82	5.5	0.03
Motor coordination	2.65	3.10	1.57	2.17	4.5	0.04
Sequencing of complex motor acts	4.27	4.26	2.60	2.87	5.6	0.02

[a] Follow-up univariate tests conducted after a repeated-measure ANOVA showed significant main effects of group (F=7.1, df=1, 109, p=0.009) and factor (F=16.2, df=2, 218, p=0.00005, with Huynh-Feldt correction for multiple comparisons).

(10.3% [N=6] versus 13.0% [N=7], respectively), but these differences did not reach statistical significance. The two patient groups were also not significantly different with respect to the frequency of pre- and perinatal complications.

ANOVAs on Premorbid Adjustment Scale scores revealed that patients with deficit schizophrenia, as compared with those with nondeficit schizophrenia, had worse premorbid adjustment during childhood and early and late adolescence; they also had a poorer average premorbid adjustment (Figure 1). Premorbid Adjustment Scale scores for childhood and early adolescence in the nondeficit schizophrenia group were comparable to those reported in the literature for groups of healthy subjects (25).

The two repeated-measure ANOVAs on the expanded BPRS factors and the SANS/SAPS dimensions (Table 1) showed significant group-by-dimension/factor interactions. Follow-up univariate tests showed that patients with deficit schizophrenia had higher scores on the expanded BPRS anergia factor and the SANS negative dimension, and lower scores on the expanded BPRS hostility factor, than did patients with nondeficit schizophrenia (Table 1). For Strauss-Carpenter Scale scores, there was a significant group-by-item interaction (F=5.77, df=3, 327, p<0.01), which was due to fewer social contacts among patients with deficit schizophrenia (mean=1.2, SD=1.4) than among patients with nondeficit schizophrenia (mean=1.8, SD=1.5) (F=4.60, df=1, 109, p=0.03).

On the Neurological Evaluation Scale, a repeated-measure ANOVA showed significant main effects of group and factor; follow-up univariate tests showed that patients with deficit schizophrenia were significantly more impaired than patients with nondeficit schizophrenia on each of the three factors (Table 2). No between-group differences were found on the AIMS and Simpson-Angus scores.

Neuropsychological Evaluation

MANOVA revealed a significant overall group effect for neuropsychological test performance (Wilks's lambda ratio=0.54; F=3.0, df=28, 234, p<0.00005).

ANOVA showed significantly lower IQ in patients with deficit schizophrenia versus patients with nondeficit schizophrenia (F=4.4, df=1, 106, p<0.04) and in each patient group versus healthy comparison subjects (Table 3). In light of these differences, statistical analyses for the remaining four neuropsychological function domains were carried out by ANCOVAs in which the general abilities domain was used as covariate.

Two-way repeated-measure ANCOVAs showed significant group effects or group-by-test interactions for each of the evaluated domains except visuospatial abilities (group effects seen for executive functions [F=4.7, df=2, 127, p<0.01] and explicit memory [F=8.0, df=2, 127, p<0.0007]; group-by-test interactions seen for executive functions [F=8.0, df=8, 512, p<0.00005], focused/sustained attention

TABLE 3. Neuropsychological Performance of Patients With Deficit Schizophrenia, Patients With Nondeficit Schizophrenia, and Healthy Comparison Subjects

Neuropsychological Function Domain and Test Measure	Score						Analysis[a]					
	Patients With Deficit Schizophrenia (N=58)		Patients With Nondeficit Schizophrenia (N=54)		Healthy Comparison Subjects (N=26)		Patients With Deficit Schizophrenia Versus Healthy Comparison Subjects			Patients With Nondeficit Schizophrenia Versus Healthy Comparison Subjects		
	Mean	SD	Mean	SD	Mean	SD	F	df	p	F	df	p
General abilities: WAIS-R IQ	76.2	12.9	81.9	15.1	94.5	13.9	33.0	1, 78	0.00005	12.6	1, 78	0.0006
Executive functions[b]												
WAIS-R Digit Forward Plus Backward Test	7.8	3.6	8.4	3.2	10.5	3.4	0.1	1, 78	0.73	1.2	1, 78	0.28
Flexibility index (Trail B minus Trail A)	86.1	53.0	77.7	57.5	34.4	18.4	9.9	1, 75	0.002	7.8	1, 76	0.007
Picture Memory and Interference Test (number of interferences)	15.0	13.0	11.6	9.3	5.7	4.6	3.6	1, 75	0.06	6.1	1, 76	0.01
Wisconsin Card Sorting Test												
Number of categories	3.0	2.3	3.2	2.2	4.8	1.6	1.5	1, 75	0.23	4.7	1, 77	0.03
Number of perseverative errors	28.3	19.7	26.4	19.7	18.0	11.4	0.2	1, 75	0.64	0.3	1, 77	0.60
Focused/sustained attention[c]												
Continuous Performance Test-AX (number of errors)	5.2	6.1	3.4	5.0	1.5	2.3	2.5	1, 75	0.12	0.2	1, 76	0.62
WAIS-R Digit Symbol Substitution Test	4.0	1.8	5.2	2.7	8.6	2.7	41.5	1, 75	0.00005	18.1	1, 77	0.0001
Explicit memory[d]												
Auditory Verbal Learning Test (number of delayed recalls)	8.3	3.2	8.3	3.1	12.1	2.2	15.0	1, 75	0.0002	19.6	1, 76	0.00005
Picture Memory and Interference Test (number of identifications)	49.5	12.1	52.4	12.4	63.1	5.3	11.4	1, 75	0.006	9.8	1, 76	0.002

[a] Follow-up univariate tests conducted after repeated-measure ANOVAs showed either a significant main effect of group or a significant group-by-test interaction.

[b] Significant group effects and significant group-by-test interactions were seen for analyses involving patients with deficit schizophrenia and healthy comparison subjects (F=8.9, df=1, 75, p=0.004, and F=19.1, df=4, 304, p=0.00005 [with Huynh-Feldt correction for multiple comparisons], respectively) and those involving patients with nondeficit schizophrenia and healthy comparison subjects (F=9.3, df=1, 76, p=0.003, and F=11.4, df=4, 308, p=0.0003 [with Huynh-Feldt correction for multiple comparisons]).

[c] Significant group-by-test interactions were seen for analyses involving patients with deficit schizophrenia and healthy comparison subjects (F=33.8, df=1, 76, p=0.00005) and those involving patients with nondeficit schizophrenia and healthy comparison subjects (F=15.0, df=1, 77, p=0.0002).

[d] Significant group effects and significant group-by-test interactions were seen for analyses involving patients with deficit schizophrenia and healthy comparison subjects (F=14.9, df=1, 75, p=0.0002, and F=19.2, df=1, 76, p=0.00005, respectively) and those involving patients with nondeficit schizophrenia and healthy comparison subjects (F=14.5, df=1, 76, p=0.0003, and F=9.3, df=1, 77, p=0.003).

[F=16.4, df=2, 128, p<0.00005], and explicit memory [F=8.1, df=2, 128, p<0.0005]).

Follow-up ANCOVAs revealed no significant group effect for the comparisons between patients with deficit schizophrenia and patients with nondeficit schizophrenia. A significant group-by-test interaction was observed only for the focused/sustained attention domain (F=6.1, df=1, 103, p<0.01), for which follow-up analyses did not reveal a meaningful source. Comparisons between each patient group and healthy comparison subjects are shown in Table 3. On executive function tests, patients with nondeficit schizophrenia showed less flexibility and poorer ability to suppress interference and to form categories than healthy comparison subjects. Patients with deficit schizophrenia were significantly different from healthy comparison subjects only on the flexibility index. Both patient groups performed significantly worse than healthy comparison subjects on the WAIS-R Digit Symbol Substitution Test of the focused/sustained attention domain and on both tests of the explicit memory domain.

Stepwise Multiple Regression Analyses

To further investigate whether worse premorbid adjustment and more impaired neurological state are specifi-cally associated with the deficit state after removing the effect of potential confounding variables, stepwise multiple regression analyses were performed on Premorbid Adjustment Scale and Neurological Evaluation Scale scores. The deficit/nondeficit categorization, the SANS/SAPS dimensions, age, education, duration of illness, the Simpson-Angus average score, and the chlorpromazine-equivalent doses were entered as independent variables.

The deficit/nondeficit categorization was significantly associated with Premorbid Adjustment Scale scores in childhood (F=13.8, df=1, 102, p<0.001; R^2=0.12) and early adolescence (F=17.5, df=1, 102, p<0.001; R^2=0.15). After removing this effect, the early adolescence Premorbid Adjustment Scale score did not show further significant associations, while the childhood Premorbid Adjustment Scale score was associated with education (F=6.7, df=1, 102, p<0.05; R^2=0.05). The late adolescence Premorbid Adjustment Scale score was significantly associated with the negative symptom dimension (F=11.6, df=1, 102, p<0.001; R^2=0.11); after removing this effect, it showed a further significant association with age (F=4.9, df=1, 102, p<0.05; R^2=0.04).

For the Neurological Evaluation Scale factors, the Simpson-Angus average score was significantly associated with

sensory integration (F=26.0, df=1, 102, p<0.001; R^2=0.20), motor coordination (F=38.1, df=1, 102, p<0.001; R^2=0.27), and complex motor sequences (F=21.2, df=1, 102, p<0.001; R^2=0.17). After removing this effect, the sensory integration factor showed a further significant association with the negative symptom dimension (F=9.1, df=1, 102, p<0.01; R^2=0.07), while the sequencing of complex motor acts factor was significantly associated with the deficit/nondeficit categorization (F=5.8, df=1, 102, p<0.05; R^2=0.04).

Discussion

The pattern of historical, psychopathological, and neuropsychological characteristics previously reported in patients with deficit schizophrenia relative to those with the nondeficit subtype (7, 8, 10, 17) is mostly supported by the findings of the present study. This finding confirms that the deficit/nondeficit categorization, guided by the Schedule for the Deficit Syndrome after an appropriate training of the investigators, is replicable and reliable and allows the identification of patients with consistent clinical characteristics across independent studies. At odds with previous reports (9, 13), however, our patients with deficit schizophrenia and patients with nondeficit schizophrenia did not significantly differ on the expanded BPRS anxiety/depression factor.

Several important confounding variables were eliminated in this study by the design and the subject characteristics: patients with deficit schizophrenia and patients with nondeficit schizophrenia were matched for age and sex, had a comparable duration of illness, had been clinically stable for at least 3 months before the study procedures, and had a comparable severity of psychotic symptoms and disorganization. Furthermore, all the examiners, as well as interviewed patients and family members, were blind to the deficit/nondeficit categorization and were uninformed regarding the specific study aims and hypotheses. Different researchers performed the historical, psychopathological, neurological, and neuropsychological evaluations.

Our findings suggest that premorbid adjustment during childhood and early adolescence is poor in patients with deficit schizophrenia but not in patients with nondeficit schizophrenia. Actually, a significant association between poor premorbid adjustment and either negative symptoms or the deficit state has repeatedly been reported (8, 44, 45); however, to our knowledge, no attempt has been made to disentangle the respective contribution of negative symptoms and the deficit state to Premorbid Adjustment Scale score variance. Our data indicate that the association between the deficit state and poor premorbid adjustment is not due to the presence of more pronounced negative symptoms in the deficit group. These findings are consistent with Buchanan et al.'s hypothesis that patients with deficit schizophrenia represent a schizophrenic subgroup characterized by an early-onset disease process in which poor premorbid adjustment during childhood and early adolescence might represent the onset of deficit symptoms (8).

Patients with deficit schizophrenia exhibited more impairment on the Neurological Evaluation Scale than did those with nondeficit schizophrenia. The results of the stepwise multiple regression indicated that, after partialling out the influence of extrapyramidal symptoms, the deficit/nondeficit categorization was the only clinical variable entering the regression equation on the sequencing of complex motor acts factor, while the negative symptom dimension was associated with the sensory integration factor. The association of deficit schizophrenia with an impairment of sequencing of complex motor acts is in line with current hypotheses on the neural basis of the syndrome (19–21); both frontal and parietal deficits have been found in association with an impairment on sequencing of motor acts (46). At odds with our findings, a previous study has concluded that deficit schizophrenia is associated with an impairment of sensory integration, which was based on the results of separate multiple regressions that included either the deficit/nondeficit characterization or negative symptoms (18). The inclusion of different independent variables in the regression analysis might partly account for the discrepancy between the two studies. However, no direct comparison between our findings and those by Arango et al. (18) can be made. In their study, evaluation of the positive, negative, and disorganization symptoms was based on the BPRS (instead of the SANS and SAPS), only the conceptual disorganization was taken into account, and no evaluation of extrapyramidal symptoms was included.

As for neuropsychological results, in line with the Neurological Evaluation Scale findings that suggested frontoparietal dysfunction in subjects with deficit schizophrenia, when comparing patients with deficit and nondeficit schizophrenia, a significant group-by-test interaction was found only for the focused/sustained attention domain, which is thought to involve frontoparietal circuits.

When comparing each patient group with healthy subjects, patients with nondeficit schizophrenia exhibited more impairment in executive functions than did those with deficit schizophrenia. A greater impact of general abilities on the performance of subjects with deficit schizophrenia is actually responsible for such a finding (data not shown). These results are in agreement with Buchanan et al.'s finding of a strong influence of general abilities on neuropsychological performance in patients with deficit schizophrenia (15). Both the data of Buchanan et al. and our set of findings suggest that differences in intelligence/general abilities can no longer be regarded as just a "nuisance" requiring control. Low IQ has been found in association with negative symptoms, neurological signs, and poor premorbid adjustment and is increasingly recognized as a risk factor for schizophrenia (47, 48). Low IQ and other signs of cognitive and motor dysfunction have been re-

peatedly reported as childhood precursors of schizophrenia (48–51), although their presence seems to characterize only a minority of children who will develop schizophrenia (52, 53).

Deficit schizophrenia might represent a neurodevelopmental subtype of schizophrenia in which a significant behavioral and cognitive impairment since childhood compromises the development of basic capacities that contribute to subsequent cognitive and social functioning.

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