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Neuropsychological impairment in first-episode and chronic schizophrenic patients

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Abstract Patients with first-episode (FE) schizophrenia ($n = 40$), with chronic schizophrenia ($n = 40$) and healthy controls ($n = 40$) matched for age, gender, education and parental socioeconomic status were administered a battery of standardized neuropsychological (NP) tests. Both patient groups showed generalized impairment relative to controls and the most pronounced deficits in visual-motor processing and attention (VSM). Compared with FE patients, chronic schizophrenics performed worse in VSM and abstraction/flexibility. Our findings suggest that NP deficits are fundamental manifestations of the illness, and that mainly frontally based dysfunctions are more prominent in chronic, kraepelinian patients.

Key words Chronic schizophrenia · First-episode schizophrenia · Neuropsychological testing · Frontal dysfunction · Temporohippocampal dysfunction

Introduction

Impaired performance in standardized neuropsychological (NP) tests, mainly those involving attention, abstraction, flexibility, learning and memory, has frequently been reported in schizophrenic patients. Some authors hypothesize a generalized deficit in schizophrenic patients (Malec 1978; Braff et al. 1991; Blanchard and Neale 1994). Other investigators, while also finding generalized neuropsychological impairment, have nevertheless interpreted especially pronounced deficits on tasks related to language, verbal learning, semantic and visual memory in unmedicated chronic schizophrenic patients (Saykin et al. 1991; 1994). These deficits have been found to be independent of attentional deficits. Furthermore, several studies substantiate impaired performance of schizophrenic patients in tests measuring information processing and attention such as the Span of Apprehension Test (SAT) and the Continuous Performance Task (CPT; Nuechterlein 1991).

Although findings of impairment in abstraction/flexibility which have been proved by the Wisconsin Card-Sorting Test (WCST) have contributed to the formulation of localizable hypotheses with regard to disturbances in prefrontal functions (Weinberger et al. 1986; Goldberg et al. 1987; Fuster 1989; Morice 1990; Buchanan et al. 1994), other reports suggest a preeminent role of frontotemporal or temporohippocampal dysfunction in schizophrenia (Saykin et al. 1991; 1994; Taylor and Abrams 1984; Liddle and Morris 1991).

These diverging results can be explained at least partially by the different procedures adopted. Whereas some studies evaluate performance of schizophrenics on individual tasks as compared with normal subjects or other patient groups (Morice 1990; Everett et al. 1989; Franke et al. 1993), others grouped neuropsychological tasks by cognitive function, purportedly tapped, so as to create composite indexes prior to comparing schizophrenics with normal controls (Blanchard and Neale 1994; Saykin et al. 1991, 1994; Buchanan et al. 1994; Taylor and Abrams 1984; Heaton et al. 1994). Also, the neuropsychological tests included in the comprehensive test batteries differ considerably between studies. Moreover, the differential discriminating power of the NP tests administered, which are usually validated only in neurological populations, is a relevant factor possibly confounding test results (Chapman and Chapman 1973).

One other problem stems from the fact that a number of studies obtained NP testing in unmedicated patients, whereas others investigated patients after treatment with neuroleptics (NLs) and anticholinergic medication. Both compounds seem to influence cognitive, memory and psychomotor performance (Frith 1984; Medalia et al. 1988; Spohn and Strauss 1989; Cassens et al. 1990). On the other hand, it seems probable that neuroleptics (NLs) partially reverse attentional deficits (Spohn and Strauss 1989; Asarnow et al. 1988; Siever et al. 1990) and improve short-term verbal memory (Cleghorn et al. 1990;

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Eitan et al. 1992). In addition, information processing as assessed by the CPT does not seem to be disturbed by NLs (Braff 1993). Moreover, memory deficits have also been observed in unmedicated schizophrenic patients (Saykin et al. 1991, 1994). Despite the advantage of ruling out confounding effects of medication on NP performance, a research strategy to investigate unmedicated patients may provide results obscured by state-related factors such as positive symptoms, cognitive derailment or acute psychotic disorganization.

Another element confounding the interpretation of findings is that NP performance is related to the stage of illness (Heaton et al. 1986; Filskov and Catanese 1986). To address some of the variables potentially influencing NP performance, i.e. long-term medication and chronicity, patients experiencing their first episode (FE) of psychosis have been studied more recently. Several authors report that NP deficits are already present at the early stages of the disorder (Hoff et al. 1992; Sweeney et al. 1992; Saykin et al. 1994), and are more pronounced in later stages of the illness (Saykin et al. 1994; Bilder et al. 1992; Sweeney et al. 1992). Other important variables which are known to influence NP performance, such as age, education and socioeconomic background (Mortensen and Gade 1993; Goldstein and Shemansky 1995), have not been controlled appropriately in the majority of studies published thus far. Thus, interpretation of the literature is limited by a number of methodological issues including variation of group-matching procedures, test selection, differential test sensitivity, medication and psychopathological status of the patients investigated.

Given these problems, the present study was designed to evaluate NP functioning of patients with FE and chronic schizophrenia, and thereby reexamine several potentially confounding factors. The neuropsychological evaluation was used to assess a variety of functions thought to be impaired in schizophrenia, and to allow the evaluation of test profiles to differentiate between a general and/or specific deficit in relation to normal controls. The comparison of FE and chronic schizophrenia allows conclusions about potential profile differences between chronic, kraepelinian patients and FE patients, a sample comprising subjects with milder forms of the illness. The control group was matched perfectly with regard to relevant demographic characteristics such as age, gender, education and parental socioeconomic status. To prevent potentially confounding effects of an acute psychotic disorganization on complex tests, we carried out the investigation at the time of the best possible remission after treatment with NLs during the index admission in FE schizophrenics. Also chronic schizophrenic subjects were tested when clinically and pharamcologically in stable conditions.

We addressed the following questions:

1. Is a generalized deficit already present in FE schizophrenic patients or only in patients with chronic schizophrenia?

2. Are NP deficits in FE and chronic schizophrenia similar or do they support the assumption of a differential deficit?

3. Is NP performance in patients treated with NLs at the time of best possible remission comparable to or different from other studies of NL-free patients using a nearly identical test battery?

Subjects and methods

A total of 40 patients with FE schizophrenia were recruited consecutively from acutely admitted inpatients of the State Mental Hospital Haar. Also, 40 chronic schizophrenic patients were recruited from a behaviour therapy unit of the same hospital. The normal control subjects (n = 40) were matched to the groups of schizophrenics with regard to gender, age, education and parental socioeconomic status.

All subjects were screened with a medical history questionnaire to exclude the following: history of moderate or severe head trauma or other neurological disorders, current alcohol or other substance abuse and systemic medical diseases which are likely to affect central nervous system (CNS) functions.

With reference to another first-onset study (Lieberman et al. 1993), the following inclusion criteria for FE schizophrenic patients were applied: FE schizophrenics meeting DSM-III-R criteria for schizophrenia (n = 30), or schizophreniform disorder (n = 10) with no cumulative lifetime treatment with neuroleptics (NLs) for longer than 12 weeks prior to admission.

In both patient samples the diagnosis of schizophrenia was assigned on the basis of a structured interview based on DSM-III-R criteria (SCID; Spitzer et al. 1987). Psychopathological status was evaluated by trained and experienced raters through a semistructured interview which was videotaped to control for interrater reliability and rated by means of the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1976) Raters were blind with regard to diagnoses and medication. Table 1 summarizes the demographic and clinical characteristics of the three groups investigated.

Neuropsychological assessment

All subjects underwent a battery of neuropsychological tests designed to tap a broad range of functions in a standardized fashion by two trained and experienced psychometrists. In selecting the neuropsychological tests we focussed on the NP ability areas which are regarded as relevant in studies of schizophrenia: verbal intelligence and language, spatial organization, verbal memory and learning, visual memory, short-term memory, visual-motor processing and selective attention, language, information processing and attention and abstraction/flexibility.

Verbal intelligence and language (VBL) were measured by the two subtests, "Information" and "Similarities", of the HAWIE-R (Wechsler 1981). To test verbal fluency a lexicographic subtest of the LPS (Horn 1983) and the semantic Supermarket test (Genzel 1991), which is adopted from the Dementia Rating Scale (Mattis 1976), were administered. In the Supermarket test probands are asked to name as many items as possible which can be bought in a supermarket. The number of items as well as the number of categories (fruits, beverages, etc.) are scored.

Spatial organization (SPT), used in measuring nonverbal intelligence, was assessed with the Block Design and Picture Completion tests, both subtests of the HAWIE-R.

Verbal memory and learning (VBM) were evaluated by the "Logical memory" subtest of the revised Wechsler Memory Scale (WMS-R; Wechsler 1987). Probands listen to two stories and are asked to recall them thereafter (immediate recall) and 30 min after (delayed recall). The California Verbal Learning test (CVLT; Delis et al. 1987), a learning test of single items, and the "Paired Associate Learning test", an additional subtest of WMS-R, were administered to evaluate verbal learning.

Visual memory (VIM) was evaluated by the "Visual reproduction" subtest of the revised Wechsler Memory Scale (WMS-R), where probands are shown four geometric designs and are then

Table 1 Demographic and clinical characteristics of patients. FE first episode; NL neuroleptics; CPE chlorpromazine equivalents. BPRS Brief Psychiatric Rating Scale; ANOVA analysis of variance

	FE schizophrenia (n = 40) Mean + SD	Chronic schizophrenia (n = 40) Mean + SD	Controls (n = 40) Mean + SD	*df*	*F* ANOVA	*P*
Mean age (years)	30.9 + 7.5	30.8 + 6.4	30.7 + 7.8	2	0.01	0.99
Age at first hospitalization (years)	30.8 + 10	22.3 + 5.7		1	4.56	0.05
No. of hospitalizations		6.1 + 3.8				
Total length of hospitalization (months)		29.5 + 37.8				
Daily dosage of NL (CPE)	487 + 201	533 + 374		1	1.93	0.16
BPRS (18 items) total	27.1 + 7.6	34.8 + 8.9		1	16.21	0.0001
Anxiety/depression	6.3 + 2.4	7.3 + 4.0		1	1.75	0.19
Anergia	7.3 + 3.2	9.7 + 3.8		1	8.59	0.004
Thought disturbance	6.1 + 2.6	7.7 + 3.4		1	5.34	0.02
Activation	3.3 + 0.9	4.9 + 1.8		1	21.56	0.0001
Hostility	4.1 + 1.4	5.1 + 2.3		1	5.26	0.02
Gender	Number	Number	Number		Chi-square	
Male/female	24/16	24/16	24/16	2	0.0000	1.00
Education						
Elementary school	10	10	10	4	0.0000	1.00
Secondary school	10	10	10			
High school	20	20	20			
Social class						
Lower lower	1	1	1	8	6.50	0.59
Upper lower	6	11	9			
Lower middle	20	16	12			
Middle middle	9	6	13			
Upper middle	4	6	5			

asked to draw them from memory immediately after presentation and 30 min after.

Short-term memory (STM) was assessed by the "Digit-Span" subtest of the HAWIE-R and the reading span test. In the reading-span test the probands must recall the last words of a successively increasing number of phrases to which they have listened.

The Color-Word-Interference test (Stroop 1989), a test of selective attention, the Trailmaking test (TMT; Reitan 1958), a number-number and number-letter sequencing task, as well as the Digit Symbol test, a subtest of the HAWIE-R, are considered to test speeded visual-motor processing and selective attention (VSM).

Techniques used to assess information processing and attention dysfunctions in schizophrenic patients are the Continuous Performance task (CPT; Rosvold et al. 1956) and the Span of Apprehension (SAT; Neale 1971). The SAT is a measure of the number of stimuli that can be attended to, apprehended and reported on a single brief exposure. In the CPT subjects are asked to attend to a series of numbers and to detect an intermittently presented target stimulus presented along with other numbers.

Abstraction- and conceptual flexibility (ABS) were assessed using the modified WCST, a test version of 48 response cards. Since its introduction as a neuropsychological test (Heaton 1981), the WCST has been increasingly regarded as the best single measure of prefrontal cortical function.

The total battery of tests usually took 3–4 h to complete and was generally administered on two occasions to an individual patient over a period of 2–3 days.

Statistical analysis

For the tests where data from large normative samples were available (see Table 2), the raw scores on the NP tests were converted to T-scores (TMT A + B, CVLT, verbal fluency, Stroop test). In a second step, all test scores were converted to Z-scores based on the data of the control group which was matched perfectly with regard to age, gender, education and parental socioeconomic status to the patient groups. Then Z-scores were grouped by function (mean scores).

Multivariate analysis of variance (MANOVA) was carried out to evaluate profile level and shape, with diagnosis (FE, chronic schizophrenia) as the between-group factor and neuropsychological function as the within-subject factor. For each contrast the score for a particular function was compared with the mean of the remaining functions in the profile. This procedure allows the determination of areas of selective deficit by testing for between-group differences in profile shape. In significance testing of the contrasts the Bonferroni procedure was employed.

Results

Profile analysis

The Z-score profile of the neuropsychological battery for both patients groups is shown in Fig. 1. By definition, the control group mean is represented by the zero line with SD = 1 for all functions. The MANOVA indicated an overall difference in performance, with chronic schizophrenic patients (df 8,111; $F = 10.33$, $P < 0.001$) as well as FE patients (df 8,111; $F = 5.85$, $P < 0.01$) scoring lower than controls. This can be seen by the fact that the entire profile lies well below zero in both patient groups, significantly lower in the chronic group as compared with FE schizophrenics (df 8,111; $F = 3.71$, $P < 0.01$). There is also a diagnoses x function interaction indicating differences in the shape of the profile between FE schizophren-

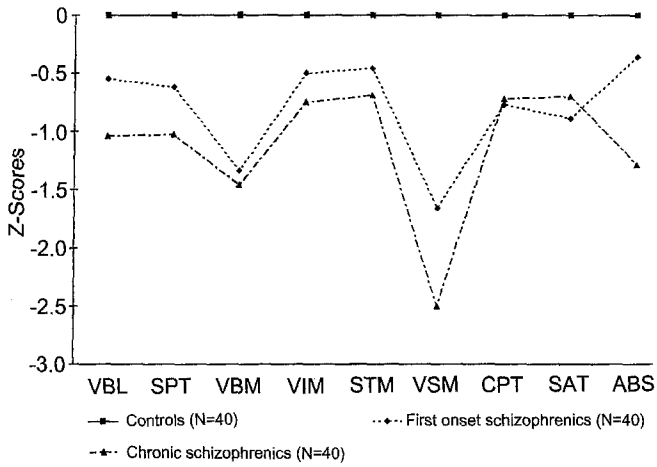

Fig. 1 Neuropsychological profile for chronic schizophrenic patients (n = 40) and patients with first-episode schizophrenia (n = 40) relative to healthy controls (n = 40) whose performance is set to zero (+ 1 SD). Functions are verbal intelligence and learning (VBL), spatial organization (SPT), verbal memory and learning (VBM), visual memory (VIM), short-term memory (STM), visual-motor processing and selective attention (VSM), information processing and attention (SAT, CPT) and abstraction/flexibility (ABS)

ics and controls (df 8,71; F = 4.68, $P < 0.01$), chronic schizophrenics and controls (df 8,71; F = 8.33, $P < 0.001$) and FE and chronic schizophrenics (df 8,71; F = 3.47, $P < 0.01$). Chronic schizophrenics were significantly more impaired as compared with FE schizophrenics in VSM (df 1,117; F = 7.95, $P < 0.05$) and ABS (df 1,117; F = 7.64, $P < 0.05$).

Profile contrasts of FE schizophrenia

The profile contrasts sequentially comparing each function to the profile mean of FE schizophrenia revealed significantly more pronounced impairment in visual-motor processing and attention (VSM; df 1,39; F = 11.99, $P < 0.01$) as well as in verbal memory and learning (VBM; df 1,39; F = 10.38, $P < 0.01$). Significantly less impaired performance as compared with the profile mean was found in abstraction/flexibility (ABS; df 1,39; F = 7.63, $P < 0.05$), this area not being significantly different from controls.

Table 2 Neuropsychological test battery: Mean values and SD of each test (raw scores). WAIS-R Wechsler Adult Intelligence Scale; WCST Wisconsin Card-Sorting Test; LPS Leistungs-Prüf System, verbal fluency test; WMS-R Wechsler Memory Scale; CPT Continuous Performance Task; SAT Span of Apprehension Test; TMT Trailmaking test

	FE schizophrenics (n = 40) Mean + SD	Chronic schizophrenics (n = 40) Mean + SD	Controls (n = 40) Mean + SD
WAIS-R (HAWIE-R)			
Information	11.2 + 2.5	9.8 + 2.5	12.1 + 2.3
Similarities	11.4 + 2.2	10.4 + 2.8	12.1 + 1.9
Digit-symbol test	7.8 + 1.9	7.7 + 2.7	11.8 + 2.1
Digit-span	9.6 + 2.6	9.7 + 2.3	10.9 + 3.2
Picture completion	9.2 + 3.0	8.9 + 3.9	11.3 + 2.2
Block design	10.8 + 2.2	9.1 + 3.1	11.5 + 2.4
WCST			
Categories	6.1 + 1.5	5.0 + 1.6	6.4 + 1.1
Perseverative responses	3.5 + 5.9	5.8 + 4.3	1.9 + 3.1
LPS Subtest 6	33.9 + 8.1	30.7 + 8.2	38.6 + 9.6
Supermarket test Max: number words	23.8 + 6.6	20.8 + 7.2	29.9 + 6.2
WMS-R			
Logical memory, immediate	24.1 + 7.1	22.3 + 6.5	30.9 + 5.9
Logical memory, delayed	20.4 + 7.3	18.8 + 7.7	28.3 + 6.7
Paired associate learning	18.0 + 4.2	18.2 + 3.9	21.2 + 2.4
Design reproduction, immediate	35.6 + 5.1	34.4 + 5.6	36.7 + 2.8
Design reproduction, delayed	32.9 + 6.3	32.6 + 6.8	35.3 + 3.7
California Verbal Learning Test Sum of trail 1-5	9.0 + 1.8	8.9 + 2.2	11.7 + 1.6
TMT			
Part A (s)	36.7 + 10.6	52.2 + 19.4	27.9 + 8.9
Part B (s)	86.3 + 29.4	144.7 + 73.4	59.5 + 16.9
Stroop test (time)			
Words	33.6 + 5.5	38.6 + 9.6	28.3 + 4.7
Colour	55.1 + 12.6	60.5 + 15.8	42.7 + 6.3
Word-Colour interference	99.3 + 22.4	98.2 + 29.1	73.0 + 13.3
Reading span	3.0 + 1.1	2.6 + 1.1	3.5 + 1.0
CPT			
d'	1.9 + 0.6	2.0 + 0.8	2.6 + 0.8
SDR2 (false alarm, %)	4.9 + 5.3	5.0 + 5.7	2.8 + 3.4
SAT			
3-Letter version, % hits	87.1 + 13.1	88.7 + 10.8	94.5 + 7.1
8-Letter version, % hits	72.6 + 11.8	74.1 + 8.1	79.2 + 8.8

Profile contrasts of chronic schizophrenic patients.

The profile contrasts of chronic schizophrenic patients revealed a significantly more impaired performance in the area of visual-motor processing and attention (VSM; *df* 1,39; $F = 12.92$, $P < 0.01$) compared to the profile mean.

Discussion

The results reported herein support the assumption of an underlying generalized NP impairment in schizophrenic patients (Malec 1978; Braff et al. 1991, Blanchard and Neale 1994). A generalized impairment is indicated by our finding that besides abstraction/flexibility in FE schizophrenia, every composite index of higher-order cognitive function of both patients groups was far below the profile mean relative to healthy controls of comparable age, gender, education and parental socioeconomic status. Although the interpretation of this finding is limited by the fact that two different groups were investigated, rather than the same group being tested twice during different stages of the illness, our data suggest that generalized NP dysfunction is already present in FE schizophrenics and more pronounced in chronic schizophrenic patients. This is in line with the results of other investigators who report more pronounced deficits in chronic schizophrenic patients and deficit schizophrenic patients as compared with nondeficit schizophrenics and FE schizophrenics (Saykin et al. 1994; Taylor and Abrams 1984; Cassens et al. 1990; Bilder et al. 1992; Sweeney et al. 1992).

It has been concluded that NP impairment in schizophrenia is caused by an attentional deficit (Nuechterlein 1991). However, the performance in information processing and attention as measured by CPT and SAT in both patient groups, where both groups were not more or even less impaired as compared with the profile mean, renders this explanation unlikely.

Differences in the shapes of ND profiles between FE and chronic schizophrenics are found exclusively in the area of abstraction/flexibility. The absence of differences in the shapes of NP profiles in all other neuropsychological areas investigated, which is also reported by other authors (Bilder et al. 1992; Sweeney et al. 1992; Saykin et al. 1994), suggests a consistency of pattern of deficits, rather than a differential deficit across the different stages of schizophrenia.

When focusing on selective NP impairment, the profile contrasts revealed a significantly more impaired performance in verbal memory and learning in FE schizophrenics and in the area of visual-motor processing and attention (VSM) in FE as well as in chronic schizophrenic patients. As Chapman and Chapman (1973) noted, the differential discriminating power of the tests used could account for these selective impairments as compared with other functions. However, the magnitude of the difference of the profile mean in FE as well as in chronic patients as compared with a perfectly matched control group, as well as the fact that three different tests were grouped together, renders an interpretation of this finding as an exclusively psychometric artefact unlikely.

In FE schizophrenics a sample consisting of patients who will develop different courses of the disorder, ranging from experiencing only one episode to developing a chronic course of the illness, verbal memory and learning (VBM), which is indicative of dysfunctions in the temporal-hippocampal system (Saykin et al. 1994), was nearly as impaired as performance in VSM, which is indicative of dysfunctions in frontal lobe functioning (Buchanan et al. 1984; Hoff et al. 1992). However, abstraction/flexibility as measured by the WCST-R was significantly less impaired in FE schizophrenia. Assuming that the WCST is the best single measure of prefrontal functioning (Goldberg et al. 1987; Morice 1990), disturbances in prefrontal functioning in FE schizophrenics are not substantiated by our data. Because two tests assessed to evaluate VSM (the Stroop test and the TMT) are considered to tap frontal lobe functions (Buchanan et al. 1984; Fuster 1989; Morice 1990; Hoff et al. 1992), the findings of the present study support the assumption that frontal dysfunction is an important underlying deficit in FE as well as in chronic schizophrenia. There are reports of fixed frontally based dysfunctions (Braff et al. 1990) as well as no improvement in cognitive functions, despite an improvement of psychotic symptoms, in chronic schizophrenic patients (Goldberg et al. 1993). Therefore, the more pronounced impairment of chronic schizophrenics as compared with FE schizophrenics in VSM as well as in ABS favours a developmental model in prefrontal and frontal lobe deficits in patients with a chronic course of the illness. Because cross-sectional studies cannot determine whether patients' conditions deteriorate, longitudinal studies will be necessary to examine temporal stability and disease trajectories.

Saykin et al. (1991, 1994), who administered nearly the identical test battery for assessing VSM and VBM as we did, reported that verbal memory and learning were compromised selectively relative to other functions while visual-motor processing and attention were also selectively impaired, but to a lesser extent. This is partially in contrast to our findings where chronic schizophrenics had most pronounced deficits in VSM. When comparing the Z-scores of the samples investigated, it is evident that Saykins' patients were far below the performance of our patients in verbal memory and learning. In contrast, Z-scores were similar in the area of visual-motor performance and attention. Differences in medication and psychopathological status of the patients investigated may account for these different findings. In this context we have to mention the limitations of the present study: Because in our study patients were tested under NLs to control for state-related factors, such as cognitive derailment and acute psychotic disorganization, effects of NLs on test performance cannot be excluded. Although the dosage of neuroleptics both patient group received at the time of testing is comparable, differential effects of NP performance due to the longer duration of NL exposure as well as to poorer treatment response in the chronic sample cannot be ruled out.

In conclusion, our data suggest that NP deficits are fundamental manifestations of schizophrenia, and that mainly frontally based dysfunctions seem to reflect a trait variable underlying the disease process, being more pronounced in chronic, kraepelinian patients.

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