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ORIGINAL PAPER

Margot Albus · Werner Hubmann · Josef Scherer · Bettina Dreikorn · Susanne Hecht · Norbert Sobizack · Fritz Mohr

A prospective 2-year follow-up study of neurocognitive functioning in patients with first-episode schizophrenia

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Abstract To investigate the temporal stability, or progressivity, of neuropsychological (NP) impairment in schizophrenia, 50 patients with first episode (FE) schizophrenia and 50 healthy controls were given a battery of tests at the outset of the study and after a two-year interval. Both patient and control groups were balanced with respect to age, gender, education and parental socioeconomic status. Summary rating scales for semantic memory (SEM), visual memory (VIM), verbal learning (VBL), visual-motor processing and attention (VSM) and abstraction/flexibility (ABS) were constructed. FE schizophrenics showed improvement in VBL, stability of function in SEM, VSM and ABS and absence of improvement in VIM. While performance in VSM and VIM is influenced by medication status, SEM seems to be trait-related and stable; VBL, however, seems to be state-related. Our data suggest that there is no proof for the assumption of progressive deterioration in NP functioning during the first few years of illness.

Key words first episode schizophrenia · follow-up · neuropsychological functions

Introduction

Cognitive impairment in a variety of functions is consistently reported in schizophrenia, and there is evidence that marked cognitive abnormalities are already present at the onset of the illness (Bilder et al. 1992; Goldberg et al. 1993; Hoff et al. 1992; Nopoulos et al. 1994; Saykin et al. 1994; Albus e t al., 1996; Bilder et al. 2000).

Follow-up studies after an acute episode of schizophrenia, of recent onset schizophrenia or FE schizophrenia, carried out so far, reported either stability of neuropsychological (NP) deficits (Bilder et al. 1991; Hoff et al. 1992; Rund et al. 1997, 1998; Nopoulos et al. 1994; Gold et al. 1999; Hoff et al. 1999; Rosmark et al. 1999; Heaton et al. 2001) or even improvement in motor functions, learning and memory (Bilder et al. 1991), complex attention and executive functions (Nopoulos et al. 1994) concentration, motor speed and overall global functioning (DeLisi et al. 1995), free recall of memory test scores, flexibility of cognitive set and performance IQ (Gold et al. 1999). These findings support a model of neurodevelopmental deficits and state-dependent NP deficits. These hypotheses were supported by recent studies (Russell et al. 1997; Kremen et al. 1998; Cosway et al. 2000) which demonstrated that the deficits in intellectual functions of schizophrenic patients predate the onset of schizophrenia.

In principle, prospective follow-up studies are the best design to determine whether cognitive impairment reflects underlying traits or clinical states.

The confounding variables that have to be considered are the reliability and validity of diagnoses, the effects of medication, and the practice effects in test-retest studies.

The influence of medication in follow-up studies is of particular importance, because NLs apparently improve some cognitive functions and deteriorate others (Rund et al. 1997; Friedman et al. 1999). Gold et al. (1999) reported that medication dose at the 5-year follow-up significantly correlated with improvement in performance IQ, and accounted for 7 % of the variance. Some studies point at different influences of typical and atypical NLs on NP performance: Purdon et al. (2000) reported a significantly greater benefit on the general cognitive index derived from six different cognitive domains after one year treatment with Olanzapine relative to both Risperidone and Haloperidol. Other authors also conclude that

M. Albus (✉) · W. Hubmann · J. Scherer · B. Dreikorn · S. Hecht · N. Sobizack · F. Mohr
Division of Teaching and Research
District Hospital Haar
Vockestr. 72
85540 Haar, Germany
Tel.: +49-89/45 62-32 36
Fax: +49-89/45 62-32 11
E-Mail: margot.albus@krankenhaus-haar.de

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atypical NLs have either a less negative or even a positive impact on NP performance than typical ones (McGurk, 1999; Keefe et al. 1999; Gallhofer et al. 1999), although a more recent study (Green et al. 2002) failed to provide support for neurocognitive advantages of Risperidon over low-dose Haloperidol medication.

Previous longitudinal studies – except Hoff et al. (1999) – highlight methodological shortcomings that include testing mixed groups of FE, recent onset and chronic schizophrenic patients (Nopoulos et al. 1994; Censits et al. 1997; Gur et al. 1998; Gold et al. 1999). The absence of normal control subjects (Hoff et al. 1992; DeLisi et al. 1995; Nopoulos et al. 1994; Gold et al. 1999) obscures the influence of demographic variables, and the effects of repeated testing. Failure to address the influence of medication status (DeLisi et al. 1995) and investigating small groups degrades statistical significance (Hoff et al. 1992; Nopoulos et al. 1994).

To test if there is stability over time, or change of either a generalized neuropsychological deficit or of various NP deficits with respect to first episode schizophrenia, throughout the illness, we compared NP functioning in FE schizophrenics and in healthy controls with a 2-year prospective follow-up

In addressing these questions (hypotheses), we tried to control several factors that are known to influence NP function:

- At index, all FE patients were investigated at the time of best possible remission (remission of positive symptoms and stability of psychopathological status for at least two weeks, defined as a reduction in BPRS-total score of at least 50 % compared to index admission) to control for the influence of state-related factors such as cognitive derailment and acute psychotic disorganization.
- As treatment with butyrophenones was at the time of index assessment standard treatment in our hospital we could control for the different impacts of typical and atypical NLs on NP performance at index.
- The NP battery was also administered twice during the 2-year interval to healthy subjects to control for effects of repeated administration, (i. e., learning effects) to have a reference for the comparison of the course of NP performance with that of schizophrenic patients.
- The NP battery was administered on two different occasions with both test blocks presented at random to control for order effects and fatigue.
- Patients and controls were balanced with regard to age, gender, education and parental socioeconomic status, to control for demographic parameters of demonstrated significance on NP function (Albus et al. 1997).

Methods

Subjects

The sample described is a sub-sample of 138 consecutively recruited patients with first admission to the District Hospital of Haar between 1993 and 1997 due to schizophrenia, schizophreniform disorder, schizoaffective disorder, psychotic disorder NOS, delusional disorder, bipolar disorder, or depression. Patients were enrolled when meeting the following inclusion criteria: first episode of the above mentioned disorders (DSM-III R criteria), age below 60, no history of moderate or severe head injury and systemic medical diseases which are likely to affect central nervous system functions, no alcohol or other substance dependency, no current alcohol or other substance abuse, and no lifetime treatment with NLs for more than eight weeks (Table 1). All patients gave informed consent to participate at the study, which was voted positively by the local Ethics Committee.

Out of this sample, 66 patients met DSM-III criteria for schizophrenia either at index admission (N = 58) or at 2-year follow-up (N = 8). Out of the sample of 58 schizophrenic patients, who already met DSM-III R criteria for schizophrenia at index, 3 could not be traced, 6 refused to participate and 5 had committed suicide. Therefore, a total of 52 patients had been investigated at two-year follow-up. As the healthy controls, pairwise matched to each patient at index had been partially recruited months to years later than the patients, we decided to analyze the data as soon as follow-up data of 50 healthy controls were available and to drop the last two patients from analysis.

At baseline evaluation, all patients were treated with butyrophe-

Table 1 Demographic and clinical characteristics (*SD* standard deviation; *N* Number; *FE* first episode

	Controls N = 50	FE-Schiz. N = 50	F	Chi^2	dF	P
Gender	23 m, 27 f	26 m, 24 f		0.36	1	0.55
	Mean ± SD	Mean ± SD				
Mean age (years) at index assessment	31.6 ± 9.6	29.0 ± 9.3	1.97		1.99	0.16
Age at first symptoms (years)		22.8 ± 8.6				
SANS-Composite Score		37.9 ± 21.3				
PANSS Negative Score		13.5 ± 7.0				
Education	N	N				
Elementary school	14	17		2.61	2	0.27
Secondary school	16	9				
High school	20	24				
Social class (Strauss-Carpenter)						
Lower class	14	14		0.50	2	0.78
Lower middle class	17	20				
Upper middle class	19	16				

nones, at the time of the index assessment the then standard initial acute treatment in our hospital. At 2-year follow-up: 9 patients were taking no medication; 23 were treated with typical neuroleptics (NLs) with a mean daily CPE equivalence dosage of 375 ± 396 mg; 18 were treated with Clozapine with a mean daily dosage of 148 ± 86 mg. Healthy controls (23 male, 27 female, mean age 31.6 ± 9.6 years) were also investigated twice: once at baseline and then at a 2-year follow-up.

Procedures: assessment of course and psychopathology

During index hospitalization and at 2-year follow-up assessment, all patients underwent evaluation with a structured interview, the SCID (Spitzer et al. 1987), the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1989), the Scale for the Assessment of Positive and Negative Symptoms (PANSS, Kay et al. 1989) and the Clinical Global Impressions Scale (CGI, Guy & Bonato, 1976). At the 2-year follow-up assessment, absence or presence of the deficit syndrome (Kirkpatrick et al. 1989) was evaluated. To control for memory biases due to the retrospective assessment of course, detailed and extensive checking and review of all medical data from each subject (medical records from all in- and outpatient treatments by psychiatric hospitals, psychiatrists and other treatment facilities), including patients' and relatives' reports were gathered to obtain reliable data on diagnostic classification and course of illness for the 2-year period.

Neuropsychological assessment

All subjects underwent a battery of neuropsychological (NP) tests covering the following NP ability areas: semantic memory (SEM) was evaluated by the "Logical memory" passages (immediate and delayed recall) of the revised Wechsler Memory Scale (WMS-R; Wechsler, 1987); visual memory (VIM) was evaluated by the "Visual reproduction" subtest (immediate and delayed recall) of the WMS-R; verbal learning (VBL), was measured with the California Verbal Learning Test (CVLT; Delis et al. 1987) and the "Paired Associate Learning Test", another subtest of the WMS-R; visual-motor processing and attention (VSM), was assessed with the Color-Word-Interference test (Stroop, 1989), the Trailmaking test, part B (TMT; Reitan, 1958) and the Digit Symbol Test, a subtest of the HAWIE-R (Wechsler, 1981); abstraction and conceptual flexibility (ABS) were assessed using the modified Wisconsin Card Sorting Test (number of categories and perseverative responses)(WCST, Heaton, 1981).

Data analysis

For index and for 2-year follow-up assessment all raw scores (Table 2) were converted to z-scores based on the means and standard deviations of the control group at index assessment. Then, z-scores were grouped by function (mean scores),

Change scores were obtained according to the recommendations of Chapman & Chapman (1989) as follows: for each score at index-assessment (t1), the predicted retest-score (t2) was calculated, using the equation for the regression of t2 on t1 which was computed for the normal comparison sample. Thus, only scores of the control sample were used in the regression analyses to evaluate differences in change scores of the FE sample relative to change scores of the control group. Differences between predicted and observed retest-scores were considered as residual scores. These residuals were transformed into standard equivalents (z-scores) by using the mean values and standard deviations of the control group (standardized residual scores). This procedure fixes the mean of control group change scores to zero with a standard deviation of ±1. Negative change scores reflect a deterioration of NP performance during the follow-up period, and positive scores indicate an improvement.

Repeated measures multivariate analyses of variance (MANOVAs) were performed with diagnosis (FE schizophrenia vs healthy controls) to establish a group factor. Multivariate and univariate analyses of covariance were performed for each neuropsychological function separately with gender, education and medication group at 2-year follow-up (e. g., patient without medication, patients treated with atypical NLs, and patients treated with classical NLs at 2-year follow-up) as group factors. To control for the impact of NP functioning and of psychopathology at index on NP functioning at follow-up, NP scores at index, CGI, PANS and SANSS were used as covariates.

Results

Demographic and clinical data

There were no statistically significant differences between the control group and the FE schizophrenics with respect to age, education, gender, or parental socioeconomic status (see Table 1). It is important to note that with regard to education the highest educational level

Table 2 Neurospsychological test scores: raw scores (mean ± standard deviation) for the tests administered at index and at 2 year follow-up (2 yr f-up) assessment for the NP areas SEM (semantic memory), VIM (visual memory), VBL (verbal learning), VSM (visual motor processing), ABS (abstraction/flexibility)

Tests	NP area	Controls		FE schizophrenia	
		Index	2 yr f-up	Index	2 yr f-up
Wechsler Memory Scale					
Logical Memory, immediate recall	SEM	31.24±6.51	31.86±6.04	23.94±7.99	25.08±8.04
Logical Memory, delayed recall	SEM	28.60±7.37	29.62±6.99	19.08±8.52	19.98±8.66
Visual Memory, immediate recall	VIM	36.76±2.92	38.12±3.01	34.97±5.69	35.00±5.99
Visual Memory, delayed recall	VIM	35.30±3.77	37.18±3.08	31.75±8.50	32.36±7.83
Paired Association Learning Test	VBL	21.09±2.58	20.58±3.14	18.76±3.83	20.22±3.74
California Verbal Learning Test					
Sum of trial 1–5	VBL	11.61±1.57	11.56±1.85	9.14±1.98	10.06±2.00
Trail Making Test					
Time Part B	VSM	60.66±16.53	58.72±19.34	86.36±31.37	88.18±47.10
Wechsler Adult Intelligence Scale					
Digit Symbol Test	VSM	12.40±2.30	13.56±2.32	8.48±2.29	9.28±3.12
Stroop Test					
Time Color-Word-Interference Test	VSM	71.72±13.84	69.30±13.29	99.22±26.94	90.54±26.29
Wisconsin Card Sorting Test					
Number Categories	ABS	6.50±0.87	6.56±1.09	6.02±1.48	6.12±1.21
Number perseverative responses	ABS	1.67±2.49	2.28±4.03	4.34±6.55	3.90±4.42

ever reached, however, not the highest level successfully completed, was scored.

Neuropsychological performance

To control for multiple testing, the Bonferroni procedure was used in univariate comparisons by dividing the critical p value of 0.05 by the number of comparisons.

A comparison between FE schizophrenics and healthy controls is shown in Fig. 1.

There was a significant group effect (Pillai's Trace 0.450, dF = 5; F = 15.40; p < 0.000) indicating that all the FE schizophrenics performed worse on the NP ability areas at index and at 2-year follow-up. Univariate tests revealed the largest differences in VSM (dF 1,98; F = 70.82, p < 0.000), SEM (dF 1,98; F = 37.68, p < 0.000) and VBL (dF 1,98; F = 19.02, p < 0.000) followed by VIM (dF 1,98; F = 12.91, p < 0.001) and ABS (dF 1,98; F = 7.04, p < 0.01)

A significant time effect was found (Pillai's Trace 0.20, dF = 5, F = 4.70, p < 0.001) owing to – as shown by univariate tests – an improvement in VSM (dF 1,98, F = 12.69, p < 0.01) in both groups and an improvement in VBL (dF 1,98; F = 11.20, p < 0.01) in the FE schizophrenics.

Of the group factors chosen, the medication group at 2-year follow-up and education had significant impacts on NP scores at 2-year follow-up. Of the covariates chosen, NP performance at index had a highly significant influence on the different areas of NP functioning at 2-year follow up (see Table 3). On the contrary, none of the clinical variables (CGI, SANS, PANSS) had a significant influence on NP functioning.

Comparing change scores between controls and FE schizophrenics, multivariate analysis of variance showed a significant group effect (Pillai's Trace.351, dF = 5; F = 10.18, p < 0.01). Univariate tests showed that FE schizophrenics exhibited significant improvement after 2-years in VBL (dF 1,98; F = 11.81; p = < 0.01), but no significant changes in SEM, VSM, and ABS and a deterioration in VIM (dF 1,98; F = 13.36; p = < 0.01) (Fig. 2).

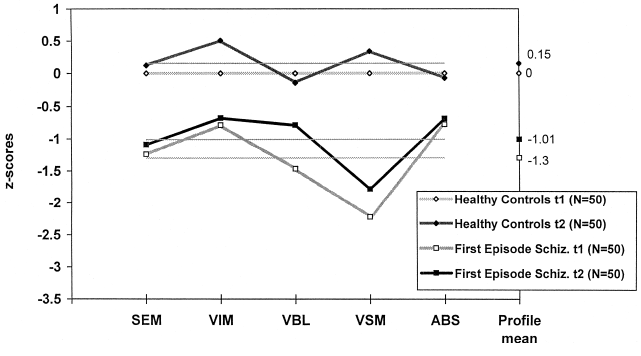

Fig. 1 Performance at index and at 2-year follow-up assessment in semantic memory (SEM), visual memory (VIM), verbal learning (VBL), visual-motor processing and attention (VSM), and abstraction/flexibility (ABS) of patients with first episode (FE) schizophrenia and healthy controls

Table 3 Univariate analyses of covariance: impact of CPE, medication group, education, NP performance at index on NP performance at 2-year follow-up (standardized z-scores). Total sample: N = 50

Dependent variables	SEM	VIM	VBL	VSM	ABS
Independent variables: Education (dF 1,42)					
F		5.68	5.21	12.8	
P	n. s.	0.05	0.05	0.01	n. s.
ABS at index (dF 1,42)					
F			7.99		12.74
P	n. s.	n. s.	0.01	n. s.	0.01
VIM at index (dF 1,42)					
F		12.20			
P	n. s.	0.01	n. s.	n. s.	n. s.
VBL at index (dF 1,42)					
F	6.40		28.91		
P	0.05	n. s.	0.01	n. s.	n. s.
VSM at index (dF 1,42)					
F			5.40	19.65	
P	n. s.	n. s.	0.05	0.01	n. s.
Med. Group at 2-years (dF 2,45)					
F		3.72		8.49	5.97
P	n. s.	0.05	n. s.	0.01	0.05

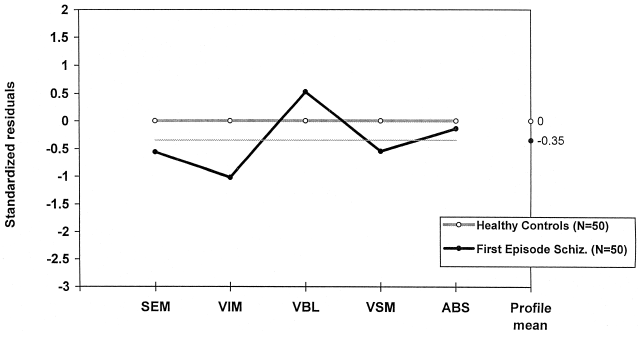

Fig. 2 Change scores for semantic memory (SEM), visual memory (VIM), verbal learning (VBL), visual-motor processing and attention (VSM), and abstraction/flexibility (ABS) in patients with first episode schizophrenia and healthy controls

Discussion

Our data indicate that NP impairment is already present at the onset of illness and throughout a two-year follow-up, during which FE schizophrenics remained 0.68 to 1.79 standard deviations below controls in all NP areas investigated. These findings agree with most previously published follow-up studies (Hoff et al, 1992; Rund et al. 1993; Nopoulos et al. 1994; DeLisi et al. 1995, Rosmark et al. 1999; Hoff et al. 1999; Heaton et al. 2001). Marked cognitive impairment that is already present at the onset of illness is no indication of further deterioration after FE. Thus, our data do not support a model of progressive deterioration of NP functioning in schizophrenia. On the contrary, our observations of stability in SEM, VSM and ABS results, support a hypothesis of static encephalopathy based on neurodevelopmental deficits associated with schizophrenia. That is, NP deficits are apparently enduring features in schizophrenia, which are already

present at the first manifestation of the illness and remain stable beyond FE.

The observed deterioration in VIM scores for schizophrenics, at a 2-year follow-up, seems to contradict the findings of other authors (DeLisi et al. (1995), who report that schizophrenics remain stable post FE. This, however, is explained by the improvement in VIM for healthy volunteers, which implies a relative deterioration for schizophrenic patients. This underlines the necessity of including a control group in follow-up studies to separate absolute change, i. e., deterioration from relative changes, i. e., inability to benefit from repeated practice. The improvement in VBL at 2-year follow-up for FE schizophrenics, compared to index assessment, supports the conclusion that VBL is an episodic indicator, associated with certain features of schizophrenic symptomatology, e. g., a state dependent factor.

This global finding needs to be specified when considering the variables influencing NP performance. The overall strong impact of education and NP performance at index on NP performance at 2-year follow-up is suggestive of functional stability with time. On the other hand, a strong impact of medication on VIM, VSM and ABS was found. Because treatment was not controlled, it is possible that other confounding variables compromise the results, e. g. some patients might receive high potent typical NLs or higher NL dosages because their treating psychiatrists consider them to be more severely ill. Clearly, the effects of confounding variables are greatest on the VIM and VSM tests. On the contrary, performance in SEM, which is independent of education and medication, and is temporally stable, seems to reflect an underlying trait variable. Thus, SEM impairment is apparently a strong indicator of the disorder, separable from psychiatric symptomatology and medication status. This conclusion is supported by the findings of Hoff et al. (1999) of a lack of improvement in verbal memory scores during a 2 to 5 year follow-up, and the finding of Saykin et al. (1994), who concluded in a cross-sectional comparison between FE schizophrenics and chronic schizophrenic patients that verbal memory is a selective deficit in schizophrenia.

There are several limitations to our study. After discharge from index admission, patients were referred to a variety of private practice psychiatrists. Therefore, treatment during the 2-year interval was not experimentally controlled and patients received a variety of NLs in variable dosages. In addition, there are many uncertainties about the reasons for changes in the medications received, despite an extensive studying of medical records. Some patients were switched to atypical NLs, while others were kept on typical NLs, or were withdrawn from treatment. The group size was only moderately large, providing relatively weak statistical power and therefore the possibility of false-negative results.

In conclusion, there is evidence for improvement in VBL, lack of improvement in VIM and stability of NP function in SEM, VSM and ABS. These observations support the hypothesis that impairments in cognition are a consequence of neurodevelopmental deficits which most likely predate FE schizophrenia (Russell et al. 1997; Kremen et al. 1998; Cosway et al. 2000). The considerable variance in change-scores suggests that there might be a subgroup of FE schizophrenics who may exhibit deteriorating NP deficits during the course of time. Therefore, future work on larger samples for longer follow-up periods are necessary to detect a core group of FE schizophrenics who can be discriminated from other schizophrenics by the remarkable severity and/or progression of their impairments.

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