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ORIGINAL PAPER

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Neurocognitive functioning in patients with first-episode schizophrenia

Results of a prospective 5-year follow-up study

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Abstract To assess the course of neuropsychological (NP) impairment in schizophrenia, 71 patients with first episode (FE) schizophrenia and 71 healthy controls were given a comprehensive battery of NP tests at index assessment, after a 2-year and after a 5-year follow-up period. By means of the *z*-score standardization, summary scores for verbal intelligence (VBI), spatial organisation (SPT), verbal fluency (VBF), Verbal learning (VBL), semantic memory (SEM), visual memory (VIM), delay/retention rate (DEL), short-term memory (STM), visuomotor processing and attention (VSM) and abstraction/flexibility (ABS) were constructed. FE schizophrenia patients showed a worse performance compared to controls in all areas investigated, most pronounced in VSM, SEM and VBL. In the majority of cognitive domains, an improvement was found over the 5-year follow-up period without differences between the two groups. However, in VBF patients slightly deteriorated whilst controls improved and in memory functions patients improved less compared to controls. When controlling for relevant confounders, neither conventional nor atypical neuroleptics showed a deleterious influence on NP performance, except on VBF. Our data suggest that NP impairment is already present at the onset of the illness and remains stable over the early course of schizophrenia.

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Introduction

Cognitive deficits are a core symptom of schizophrenia and individuals with schizophrenia demonstrate deficits in most domains of cognitive functioning compared to both psychiatric and non-psychiatric control groups. The neuropsychological (NP) profile typically consists of deficits in abstraction and executive functions, memory, psychomotor processing, attention and perceptual-motor speed. These deficits are present at the onset and prior to the onset of the illness, an assumption which has been supported by several reports on associations between poor premorbid functioning and neurocognitive dysfunction in first episode (FE) psychosis [1, 2].

Although there is substantial evidence for a widespread NP impairment, a generalized deficit, with FE schizophrenia patients scoring 1–2 standard deviations below healthy comparison subjects [3] findings are indecisive whether the most pronounced deficits in FE schizophrenia are related to memory function [3, 4], executive function [5] or both [6].

Also, there is still limited data in sufficiently large groups over sufficiently long follow-up periods as to whether NP impairment is deteriorating, stable over time, or improving. One strategy for addressing questions about progression vs. stability of NP deficits over the early course of schizophrenia is to evaluate FE patients by multiple evaluations to assess the longitudinal course of NP functions.

To the best of our knowledge, there are only four longitudinal studies covering observation periods longer than 18 months, which also assessed a control

group balanced to the patient group with regard to the most relevant confounding demographic variables, age, gender, and education [7]. Censits et al. [4] described a stable pattern of cognitive deficits over a time interval between assessment points, with a mean of 19 months.

Hoff et al. [3] found a stable pattern of cognitive dysfunction in the first 3–5 years of schizophrenia.

The results of our 2-year follow-up study [8] largely corroborate the findings of Hoff's group [3] on verbal learning and memory, supporting the view of Saykin and colleagues [9] that there is a selective and persistent deficit of schizophrenia patients in these domains.

Hill et al. [5] assessed first-episode schizophrenia patients prior to treatment with anti-psychotic medication, and again 6 weeks later to examine short-term effects. Thereafter, three additional assessments were carried out to evaluate NP function over a 2-year period. The authors reported a relatively static and generalized NP dysfunction and a decline in verbal memory after 6 weeks of treatment returning to baseline levels by the 6-months follow-up.

Summarizing the results of these follow-up studies, it appears that differences between FE patients and healthy controls are stable over time, with some areas of NP functioning improving in FE patients during the course of the illness.

NP performance and clinical measures

Although the presence of NP impairment in schizophrenia has been well documented, questions remain about whether there are unequivocal relationships between NP impairment and clinical measures. The majority of studies addressing this issue are cross-sectional studies. However, to determine whether there is a relationship between cognitive deficits and particular dimensions of psychopathology in patients with schizophrenia, longitudinal studies over a longer time frame are needed. Furthermore, such relationships should be best observable in patients with FE schizophrenia, before the effects of treatment and course of the illness might confound them.

Overall, in cross-sectional as well as in the very few longitudinal studies, no consistent relationship between positive symptoms and cognitive functioning is reported [10–12]. On the contrary, there is increasing evidence of associations between negative symptoms and cognitive functioning, although the amount of explained variance is limited [2, 12].

However, which NP areas of functioning are associated with negative symptoms is still subject to debate. One group observed the most consistent correlation between anhedonia and performance in abstraction, attention, spatial memory, language and spatial abilities [4], others found that more severe negative symptoms were related to more impairment in each of the cognitive domains evaluated [13]. Heydebrand et al. [12], found that severity of negative symptoms was associated with deficits in memory, verbal fluency, psychomotor speed and executive function. Gold et al. [14] reported an association between changes in negative symptoms and performance changes in verbal intelligence quotient (IQ) and full-scale IQ. A treatment study showed that higher negative symptom recovery was associated with improvement of cognitive performance in verbal fluency and attention, whereas low or no negative symptom improvement was associated with stable or decreased cognitive performance [15].

With the exception of negative symptoms the relationships reported between clinical and neurocognitive indices are scarce, suggesting that the two domains are relatively independent. Although the relationship between negative symptoms and NP areas of functioning awaits further clarification, negative symptoms have to be considered as potentially confounding clinical variables when assessing NP performance.

NP functioning and medication

There have been numerous articles written about the superiority of the new atypical neuroleptics (Nls) with regard to clinically significant improvements in attention, executive function and several other domains of cognitive function compared to typical Nls [16–18]. A summary of cognitive changes to clozapine treatment has suggested domain-specific gains on tests of motor and mental speed, visual spatial orientation and new verbal learning [19] whilst Meltzer & Megun [20] postulated a most robust effect of clozapine on attention, verbal fluency, and executive function.

Although treatment-related research on the effects of conventional vs. atypical Nls on neurocognitive functioning seems to prove that atypical Nls are superior to conventional Nls, studies has been subject to criticism because of methodological weaknesses, such as the lack of adequate blinding, or the use of non-standard outcome measures [21]. Furthermore, the validity of some of these studies can be criticized due to small sample sizes, choice of cognitive measures and—because the vast majority of these studies were acute treatment studies—questionable clinical stability among the subjects. Several reports on changes in NP functioning are so-called by-packages to acute treatment studies designed to show clinical efficacy in which relevant confounding variables such as gender, age, and education are not controlled. Other criticized aspects related to the limited sensitivity of the treatment designs are that the detection of change may be due to treatment duration or the use of supplemental medications. Furthermore, neurocognitive improvement reported in studies, in which

patients treated with conventional agents are tested, switched to an atypical anti-psychotic and then tested again, may be to some degree due to practice effects due to repeated test administration [19]. In the majority of studies comparing the clinical and NP effects of classical and atypical Nls, the dosages of conventional Nls administered were high, up to 20 mg Haloperidol [18], far beyond dosages administered in clinical practice and likely to induce EPS. Therefore, superiority of atypical Nls could be at least partially accounted for by a negative effect of high-dose conventional Nls on psychomotor speed due to extrapyramidal side effects (EPS). Also, when comparing conventional and atypical Nls the negative association with anti-cholinergics, quite frequently used as concomitant medication with conventional Nls has to be taken into account. It is well established that anti-cholinergics impair learning and memory. Reviewing the literature, Cirillo and Seidman [22] concluded that typical Nls had very little effect on verbal declarative memory (VDM) other than that accounted for by anti-cholinergic effects and even a small positive effect on VDM at certain doses.

In addition, a meta-analysis of the effects of conventional Nls on cognition in schizophrenia [23] showed that conventional Nls provided modest to moderate gains in multiple cognitive domains, and only motor function was impacted adversely. Studies using low-dose conventional Nls as comparator showed improved NP performance in schizophrenia patients without significant difference between typical and atypical Nls after 3 months of treatment [24] and after a 2-year treatment period with risperidone compared to low-dose treatment with haloperidol [25].

Having in mind these possible pitfalls, the overall purpose of this study is to examine the longitudinal course of cognitive functioning and its relationship to clinical symptoms and medication in FE schizophrenia. This is the largest cohort of FE schizophrenia patients and matched healthy comparison subjects, assessed at first hospital admission and followed over a 5-year period reported as yet.

The use of a sufficiently large sample of FE patients, a matched and well-characterised control group and an extensive NP battery, allows testing of the specificity and severity of NP dysfunction in schizophrenia, and obtaining further information on the neuropsychology of FE schizophrenia. In the present study, we tried to assess the following issues:

1. Which cognitive domains remain stable, deteriorate or improve over a 5-year-period?
2. How is the change in NP functioning compared with that of matched healthy controls?
3. What associations are between clinical symptoms and NP functioning at 5-year follow-up?
4. How is medication status associated with NP performance at 5-year follow-up?

Methods

Participants

Participants were FE psychosis patients during their index hospitalisation between 1993 and 1997 at the District Hospital of Haar due to schizophrenia, schizophreniform disorder, schizoaffective disorder, psychotic disorder not otherwise specified (NOS), delusional disorder, bipolar disorder, or depression. After complete description of the study, patients gave informed consent to participate at the study, which was voted positively by the local Ethics Committee.

Patients were enrolled when meeting the following inclusion criteria: FE of the above mentioned disorders (DSM-III R/DSM-IV 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, no disturbances in vision and hearing and no lifetime treatment with Nls for more than 8 weeks.

Out of the initial sample of 83 schizophrenia patients, who met DSM-III R criteria for schizophrenia at index, 5 could not be traced, 13 refused to participate and 7 had committed suicide. Therefore, from this initial sample a total of 58 patients were investigated at 5-year follow-up. Because another 13 patients who had met DSM-III R criteria for schizoaffective disorder and schizophreniform disorder at index met DSM-IV criteria for schizophrenia at 5-year follow-up, a total of 71 patients meeting diagnostic criteria for schizophrenia could be investigated at 5-year follow-up. Altogether, the degree of non-participation of eligible patients was 30%, a reasonable low percentage for a 5-year follow-up design. Moreover, when comparing the study patients with the original intake sample, there were no significant differences in gender, age, neurocognitive performance or symptoms at index between those that completed the assessment and those that did not.

At baseline evaluation, all patients were treated with butyrophenones, the then standard treatment in our hospital. At the time of the 5-year follow-up, 15 patients were not taking any medication, 16 were taking classical Nls, with a mean daily Chlorpromazine equivalence dosage (CPE) of 246 (±236), 40 were taking atypical Nls with a mean daily CPE equivalence dosage of 227 (±131). In addition, 23 patients had anti-cholinergics, 19 benzodiazepines at index testing, whilst at 5-year follow-up, 4 patients had anti-cholinergics, 5 benzodiazepines as concomitant medication.

Healthy controls were recruited through advertisement and word by mouth and matched pairwise to the patients on the basis of age, gender, education, and parental socio-economic status. They had no family history of psychiatric disorders, no history of psychiatric treatment and no Axis I disorder based on Structured Clinical Interview for DSM-III-R/DSM-IV (SCID) criteria. Patient and controls were investigated three times: at baseline, at 2-year follow-up [8] and at 5-year follow-up. Patients and controls got travel expenses reimbursed and €25.00 financial reward.

Due to drop outs of both, patients and healthy controls, controls and patients could not be matched pairwise anymore at 5-year follow-up. However, the two groups were still balanced with regard to gender (36 male, 35 female in each group), mean age (controls: 29.9 + 9.2 years, schizophrenia patients: 29.74 + 9.13 years), education (controls: 23 elementary/18 secondary/30 high school; schizophrenia patients: 23 elementary/13 secondary/35 high school) and parental socio-economic status (controls: 3 lower lower/17 lower upper/24 lower middle/23 middle middle/4 upper middle class; schizophrenia patients: 4 lower lower/17 lower upper/26 lower middle/20 middle middle/4 upper middle class).

During index hospitalisation, at 2-year and at 5-year follow-up assessments, patient diagnoses according to the criteria of the

Diagnostic and Statistical Manual of Mental Disorders were derived from a structured interview, the SCID [26, 27], a systematic review of the medical record and clinician information. Besides detailed and extensive checking and reviewing of all medical data of each subject (medical records from all in- and outpatient treatments) also patients' and relatives' reports were gathered to obtain reliable data on diagnostic classification and course of illness for the 5-year period. Two expert clinicians, unaware of the NP data, reviewed all available information to determine consensus diagnoses. Inter-rater reliability was determined by 100% agreement on the diagnosis and at least 80% agreement for symptom presence.

For assessment of psychopathology, the Brief Psychiatric Rating Scale (BPRS, [28]), the Hamilton Rating Scale for Depression [29], the Clinical Global Impressions Scale (CGI, [30]) and the Global Assessment of Functioning (GAF) were administered for global rating. The Scale for the Assessment of Negative Symptoms (SANS; [31]) and the Positive and Negative Syndrome Scale (PANSS; [32]) was used to obtain ratings for positive and negative symptoms. At the 5-year follow-up assessment, absence or presence of the deficit syndrome (Strauss-Carpenter Deficit Syndrome, SDS; [33]) was also evaluated.

Neuropsychological assessment

Patients and healthy controls were given a comprehensive NP battery, which was administered at baseline [34], at 2 years [8] and at 5 years. Baseline assessment was carried out 26 ± 8 days after index admission at the time of best remission, when psychopathological improvement was shown by a reduction of at least 50% of BPRS total score.

Compiling the NP test we focused on NP areas that have shown to be affected in schizophrenia and tasks that have proven to be sensitive measures of cognitive dysfunction in schizophrenia. Our comprehensive NP test battery covered the following NP ability areas: Verbal intelligence (VBI) was evaluated by the Wechsler Adult Intelligence Scale (WAIS)—subtests Information and Similarities; Spatial organization (SPT) by the WAIS-subtests Block design and Picture Completion [35]; Verbal fluency (VBF) was evaluated by the Supermarket test, which is adopted from the Dementia Rating Scale [36] and by a lexicographic subtest of the Leistungsprüfsystem (LPS; [37]); Verbal learning (VBL) was measured with the California Verbal Learning Test (CVLT; [38]) and the "Paired Associate Learning Test", a subtest of the revised Wechsler Memory Scale (WMS-R; [39]); Semantic memory (SEM) was evaluated by the "Logical memory" passages (immediate and delayed recall) of the WMS-R; Visual memory (VIM) was evaluated by the "Visual reproduction" subtest (immediate and delayed recall) of the WMS-R; delay/retainment (DEL) was defined as percentage of items retained at delayed recall compared to immediate recall for both, the "Logical memory" passages and the "Visual reproduction" subtest of the WMS-R; Short-term memory (STM) was assessed by using the Reading Span [40], and the Digit Span, a subtest of the WAIS; Visual-motor processing and attention (VSM), was assessed with the Digit Symbol Test, a subtest of the WAIS, the Trailmaking test, part B (TMT; [41]) and the Color-Word-Interference test [42], one of the most widely used paradigms for the evaluation of selective attention; Abstraction and conceptual flexibility (ABS) were assessed by means of the modified Wisconsin Card Sorting Test (number categories and perseverative errors; WCST, [43]), which is considered to be a specific measure of dorsolateral prefrontal cortex (DLPFC) function.

At all three time points, the NP test battery was administered by the same two trained psychometricians. At all NP assessments, the psychometricians were blind to the diagnoses of the patients. At index assessment, two counterbalanced test sequences were administered at two successive days to control for potential order effects. At 2- and 5-year follow-up, the two test sequences were administered at the same day in the same order as administered at index, with an approximately 2-h break in between.

Statistical methods

In a first step, two different *z*-scores were calculated for the patient group: for index and for 5-year follow-up assessment, all patients' raw scores in each test were converted to *z*-scores based on the means and standard deviations of the control group at index assessment. In addition, patients' raw scores at 5-year follow-up were converted to *z*-scores based on the means and standard deviations of the control group at 5-year follow-up. Alike, controls' raw scores for 5-year follow-up assessment were converted to *z*-scores based on the means and standard deviations of the control group at index assessment. Thereafter, *z*-scores were grouped by function (mean scores), thereby generating the neurocognitive composite scores VBI, SPT, VBF, VBL, SEM, VIM, DEL, STM, VSM and ABS (see Table 1). The organization of test variables was modified according to Saykin et al. [9].

Group differences

To evaluate differences between FE schizophrenia patients and healthy controls, repeated measure analyses of variance (ANOVAs) were carried out with group as between-subjects factor and time and cognitive domain as within-subjects factors using *z*-score standardization based on the means and standard deviations of the control group at index assessment (t1).

Effect of medication

For evaluation of medication effects we used the difference of the *z*-scores at 5-year follow-up (t5) and the *z*-scores at index (t1) as outcome variable. As the effect of medication can only be assessed in patients, the control group was used only for standardisation. *Z*-scores were standardized on the scores of the control group at the same time point to adjust for time effects. Since our study design did not allow for a randomised clinical trial, controlling of possibly confounding variables is essential when assessing the effect of medication. The following 10 variables according to present knowledge likely to influence NP performance were considered as potential confounders:

Age, gender, education, overall severity of illness (GAF, CGI), number of relapses within the 5-year follow-up, severity of positive symptoms (PANS) and severity of negative symptoms (PANS, SANSS Composite Score, Strauss-Carpenter Deficit Syndrome, SDS).

From these variables the confounder model was selected for each cognitive domain by means of a general linear model. A backward procedure was used, i.e. starting with a full model with all confounders, and the least significant variable was removed. Then, with the remaining variables another linear model analysis of variance was performed, again, the least significant variable removed, until only the variables with a statistical significant (5%-level) association remained. This selection was done without considering the main variable of interest, i.e. medication status.

Thereafter, for each cognitive domain, the association with medication status on performance was analysed by means of a univariate analysis of variance, controlling for the confounders revealed to be significant by the backward procedure.

Results

Demographic data

There were no statistically significant differences between the control group and the FE schizophrenia patients regarding age, gender, hand dominance, education, or parental socioeconomic status. There was also no significant difference in pre-morbid IQ

Table 1 *Z*-scores and standard deviation of *z*-scores (SD) on cognitive domains at index (t1) and 5-year follow-up (t5) for healthy controls and FE schizophrenia patients

Controls			FE schizophrenia patients		
	z-scores t1 (SD)	*z*-scores t5 (SD)	*z*-scores t1 (controls t1) (SD)	*z*-scores t5 (controls t1) (SD)	*z*-scores t5 (controls t5) (SD)
Verbal intelligence (VBI)	0 (0.00)	0.38 (0.86)	−0.37 (1.08)	−0.05 (0.98)	−0.42 (0.95)
Spatial organisation (SPT)	0 (0.00)	0.24 (0.93)	−0.76 (0.87)	−0.54 (0.95)	−0.68 (0.83)
Verbal fluency (VBF)	0 (0.00)	0.10 (0.82)	−0.61 (0.87)	−0.71 (0.98)	−0.84 (1.02)
Verbal learning (VBL)	0 (0.00)	0.17 (0.92)	−1.24 (1.22)	−1.11 (1.19)	−1.19 (1.15)
Semantic memory (SEM)	0 (0.00)	0.40 (0.86)	−1.35 (1.15)	−1.22 (1.24)	−1.82 (1.40)
Visual memory (VIM)	0 (0.00)	0.47 (0.89)	−0.90 (1.85)	−0.71 (1.72)	−1.24 (1.76)
Delay/retention rate (DEL)	0 (0.00)	0.15 (0.62)	−0.90 (1.47)	−0.43 (1.18)	−0.75 (1.42)
Short-term memory (STM)	0 (0.00)	0.32 (0.98)	−0.59 (0.79)	−0.42 (0.86)	−0.63 (0.75)
Visuomotor proc. and attention (VSM)	0 (0.00)	0.27 (0.90)	−1.49 (1.00)	−1.13 (1.07)	−1.30 (1.00)
Abstraction/flexibility (ABS)	0 (0.00)	−0.05 (0.75)	−0.74 (1.87)	−0.81 (1.69)	−0.88 (1.92)
Profile mean	0 (0.00)	0.25 (0.52)	−0.89 (0.82)	−0.71 (0.84)	−0.97 (0.86)

Z-scores t5 of controls are derived from the comparison of the controls' performance at 5-year follow-up to the controls' performance at index (t1); *z*-scores of FE schizophrenia patients at t5 (*z*-scores t5) are derived from the comparison of patients' performance at 5-year follow-up to the controls' performance at index (controls t1) as well as from the comparison of patients' performance at 5-year follow-up to the controls' performance at 5-year follow-up (controls t5)

between healthy controls (IQ = 104.89 + 6.52) and FE schizophrenia patients (IQ = 101.80 + 8.10).

Clinical data

As can be derived from Table 2, overall FE schizophrenia patients at 5-year follow-up rated low in measures of positive or negative symptoms, and depression. In global ratings, patients were considered to be mildly to moderately ill and their level of social functioning was reasonably well. Compared to index assessment, patients were improved with regard to their psychopathological status. The CPE equivalent dosage of Nls taken at 5-year follow-up was remarkably lower compared to the time of index testing. During the 5-year follow-up period, patients had an average of 1.7 ± 1.7 relapses and were an average of 211 ± 262 days treated as inpatients.

Group differences

As can be derived from Table 3 and Fig. 1, there were highly significant effects for group in all cognitive domains investigated, indicating that FE schizophrenia patients performed worse than controls on all NP ability areas at 5-year follow-up. ANOVA results on the comparison between changes from index-performance to 5-year follow-up assessment (time effect) showed that during the follow-up period, both groups improved significantly in the majority of cognitive domains and remained stable in VBF and ABS. A significant difference in time course was found between healthy controls and FE schizophrenia patients in VBF ($F = 4.31$; $P < .04$), where FE patients showed a slight deterioration whilst controls improved. Also, a trend towards differences between FE patients and controls was found for SEM ($F = 3.09$, $P < 0.08$) and DEL ($F = 2.86$; $P < 0.09$), where controls showed more pronounced improvement than FE schizophrenia patients during the follow-up period.

Medication and other confounder variables

As can be derived from Table 4, education is the most relevant confounder, influencing performance in the majority of NP areas, except verbal learning, semantic memory and retainment. The higher pre-morbid education, the better was performance. Also, gender had a significant impact on verbal intelligence, spatial ability, verbal fluency and verbal learning with males performing better in verbal intelligence and spatial organization, and worse in verbal fluency and verbal learning compared to females.

Examining the association between medication and NP performance, patients without medication showed a significant better performance in verbal fluency than both medication groups. In all other NP areas investigated, the association between medication and NP performance was negligible.

The examination of associations between clinical symptoms and cognition at 5-year follow-up demonstrated, that patients with negative symptoms performed poorly in verbal fluency, verbal learning, semantic memory, retainment and visuomotor processing and attention. Much less pronounced effects on NP performance were seen for positive symptoms. Higher scores in positive symptoms were only related to a worse performance in verbal learning, however affected no other NP area investigated.

Discussion

In interpreting our findings we are aware about the strengths and limitations of our study. The study's

Table 2 Clinical data at index and at 5-year follow-up: BPRS = Brief Psychiatric Rating Scale; HAMD = Hamilton Depression Scale; SANS = Scale for the Assessment of Negative Symptoms; PANSS = Positive and Negative Syndrome Scale; SDS = Scale of Deficit Symptoms

Ratings	Scores	Index assessment t1		5-year follow-up t5	
		Mean (SD)	Range	Mean (SD)	Range
GAF		–	–	60.3 (12.0)	30–85
CGI 1		3.9 (1.0)	2–6	4.2 (1.7)	1–7
CGI 2		1.7 (0.8)	1–4	2.4 (1.3)	1–7
BPRS	Total score 18	28.8 (8.3)	19–56	29.3 (11.0)	18–61
	Total score 24	35.4 (9.2)	24–62	37.4 (13.3)	24–79
SANS	Composite score	35.6 (23.6)	0–112	30.6 (27.0)	0–100
	Summary score	7.7 (5.1)	0–23	6.6 (6.0)	0–23
PANSS	Positive score	10.7 (4.4)	7–22	11.4 (6.0)	7–28
	Negative score	13.4 (7.7)	7–45	11.9 (6.5)	7–34
	Difference score	−2.7 (8.6)	−34 to +15	−0.5 (8.2)	−23 to 20
HAMD	17-item-score	5.2 (4.2)	2–13	5.6 (5.8)	0–28
SDS global		–	–	1.1 (1.5)	0–4
SDS deficit	Yes/no	–	–	50/21	0–1
Strauss carpenter prognosis scale		–	–	25.5 (7.5)	9–39
N patients benzodiazepines		19/71		5/71	
N patients anti-cholinergics		23/71		4/71	
CPE standard NIs		449.6 (443)	150–750	238 (222)	30–750
CPE atypical NIs				223 (127)	50–600
Dosis stable (weeks)				71 (74)	6–261

Table 3 Repeated measures analyses of variance (ANOVA) comparing performance of healthy controls ($N = 71$) and FE schizophrenia patients ($N = 71$) at index and at 5-year follow-up. Effects of group, time and interaction group × time

Cognitive domain	Group		Time (t5–t1)		Interaction group × time	
	F	*P*	*F*	*P*	*F*	*P*
Verbal intelligence (VBI)	7.19	0.008	49.77	0.000	0.43	0.51
Spatial organisation (SPT)	31.01	0.000	16.83	0.000	0.12	0.91
Verbal fluency (VBF)	24.87	0.000	0.001	0.97	4.31	0.04
Verbal learning (VBL)	59.98	0.000	4.79	0.03	0.09	0.76
Semantic memory (SEM)	83.57	0.000	12.61	0.001	3.09	0.08
Visual memory (VIM)	25.04	0.000	7.76	0.006	1.45	0.23
Delay/retention rate (DEL)	23.30	0.000	10.57	0.001	2.86	0.09
Short-term memory (STM)	25.35	0.000	13.43	0.000	1.29	0.26
Visuomotor proc. and attention (VSM)	96.56	0.000	25.94	0.000	0.55	0.46
Abstraction/flexibility (ABS)	14.37	0.000	0.218	0.64	0.01	0.91
Profile mean	69.05	0.000	38.65	0.000	0.83	0.36

main strength is the large size of the study group and the parallel assessment of an initially pair wise matched comparison group over a 5-year follow-up period. The study's main limitation is that this study was conducted in a naturalistic open-label design. Therefore, it is not possible to draw firm conclusions about differential indications and effects of conventional vs. atypical anti-psychotics on clinical and NP measures.

Consistent with other studies, our study of FE schizophrenia patients followed over a 5-year period showed a pattern of widespread NP deficits compared to healthy controls. This deficit was already present at index admission and throughout the 5-year follow-up period, during which FE schizophrenia patients remained 0.42 (verbal intelligence) to 1.82 (semantic memory) standard deviations below healthy controls. The most pronounced deficits were found in the NP areas of visuomotor processing and attention (VSM), which other authors summarize under executive functions, which is compiled of the Trail-Making-Test, the Stroop Test, and the Digit Symbol test, in semantic memory (SEM), compiled of the logical memory passages of the Wechsler Memory Scale, and in verbal learning (VBL), compiled of the California verbal learning test and the pair association test. Impairment in semantic memory and verbal learning seems to be due to parietal–temporal dysfunctions [44] and represent a different deficit compared to that which is represented in VSM. The tests used to measure VSM seem to evaluate selective attention, i.e. the ability to enhance the processing of relevant and to limit the processing of irrelevant stimuli. Neuroimaging studies suggest that mainly the anterior cingulate gyrus and the prefrontal cortex are involved during performance of the Stroop test [45]. At index assessment, VSM was the most impaired area of

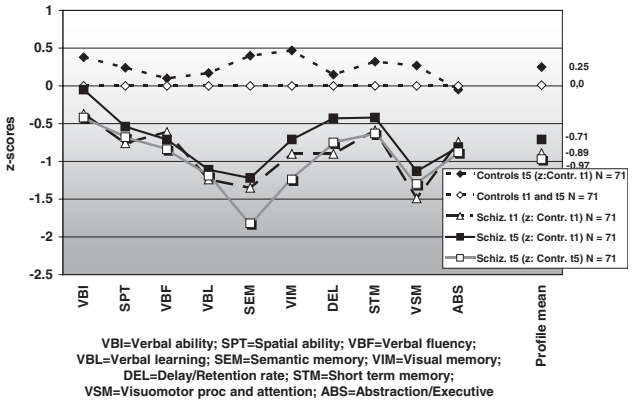

Fig. 1 NP performance of controls and FE schizophrenia patients at index and at 5-year follow-up, based on the performance of controls at index (Contr. t1) and at 5-year follow-up (contr. t5) in verbal ability (VBI), spatial ability (SPT), verbal fluency (VBF), verbal learning (VBL), semantic memory (SEM), visual memory (VIM), delay/retention rate (DEL), short term memory (STM), visuomotor processing and attention (VSM) and abstraction/flexibility (ABS)

functioning in FE schizophrenia patients and was also shown to be the most impaired area in chronic schizophrenia patients, suggesting that prefrontal dysfunctions are one of the core symptoms underlying NP impairment in schizophrenia [34].

In summary, our findings of most pronounced deficits in semantic memory, verbal learning and executive functions support the hypothesis of selective deficits in neurocognition of schizophrenia [9, 34] as well as the assumption of prefrontal and parietal–temporal localized dysfunction in FE schizophrenia. Our data are also in accordance with earlier studies showing impairment of executive functions [5], prominent deficits in memory and executive functions [6], and with studies concluding that verbal memory tends to be the cognitive task that patients with schizophrenia are significantly impeded [3, 4].

Focusing on the course of NP deficits in FE schizophrenia, our results are consistent with the reports of other groups that these deficits seem to be stable over time [3, 5, 6, 8, 14]. However, the time course of NP functioning must be looked at more thoroughly. There is a significant improvement in the majority of subtests in both, FE schizophrenia patients and controls. Therefore, our data suggest that neurocognitive deficits, present already at the onset of the disorder, are stable or slightly improving over time and do not match with the hypothesis of neurodegeneration of CNS. This interpretation is in line with the conclusions drawn in other follow-up studies on FE schizophrenia published as yet [3, 5, 6, 14].

The gains over time are higher in the control group compared to FE schizophrenia, most pronounced in verbal fluency, semantic memory and retention rate. As a different influence of reward can be excluded, this difference may mainly reflect practice and medication effects. As there is no relevant association between medication and the domains of SEM and DEL, our data support the hypothesis, that one of the core cognitive symptoms of schizophrenia is impairment in memory functions, which make it more difficult for schizophrenia patients to recognize, to store and memorize information. Impairments in such a fundamental cognitive domain, essential for everyday functioning, have important implications for treatment and rehabilitation programs in schizophrenia.

The interdependence of changes in NP functioning over time and the comparator used, i.e. the performance of a control group, has only been addressed briefly by Hoff and colleagues [3]. Our findings point at the importance of a carefully matched healthy control group, tested at the same intervals as the patients to control for differences in time course and training effects.

The importance of such a control group is also underlined by another important finding of our study. NP performance is strongly associated with education, a confounding variable which has a statistically highly significant impact on 7 out of 10 NP areas investigated. Therefore, control of this confounding variable, not adequately dealt with in the majority of follow-up studies published so far [3, 4, 6, 14] is essential. It is noteworthy that in our study patients and controls were matched with regard to the highest level of education achieved, not with regard to the highest level of education completed. This approach was chosen to avoid the effect of overmatching on education, a variable, which frequently is not independent of the illness, because of the early age at onset of schizophrenia. This problem is known as the matching fallacy [46]. As well, the proportion of gender has to be balanced because gender is also a moderating variable with a high impact on verbal intelligence, verbal fluency, spatial organization and visuomotor intelligence. This could already be shown at baseline evaluation [7].

Paralleling prior research, our results show that negative symptoms have a relatively consistent pattern of association with neurocognitive deficits. In our study, negative symptoms were associated with verbal fluency, verbal learning, semantic memory and retainment, but not with short-term memory, visual memory and abstraction/flexibility, spatial organisation and verbal intelligence, suggesting that these might constitute unique syndromal elements. On the contrary, positive symptoms did not appear to substantially modulate neurocognitive function. These findings are in line with those of Brazo et al. [10], Heydebrand et al. [12] and Milev et al. [13], who also found no associations between cognition and positive symptoms, however a range of associations between negative symptoms and cognition, as well as between negative symptom changes and changes in cognition [2, 4, 15]. It is important to note that these associations account for only a minor portion of the variance. The missing links between positive symptoms

Table 4 Effect of medication on NP performance by controlling for the significant confounder variables found by means of the backward procedure separately for each cognitive domain. Medication group was defined categorical as no NIs ($N = 15$), conventional NIs ($N = 16$) and atypical NIs ($N = 40$)

Variable	Confounder/medication group	df	F	P	Variance explained (R^2)
Verbal intelligence (VBI)	Education	2.70	10.355	0.000	0.394
	Gender	1.70	5.696	0.020	
	Medic. group	2.70	2.657	0.078	
Spatial ability (SPT)	Education	2.70	19.020	0.000	0.447
	Gender	1.70	13.429	0.001	
	Medic. group	2.70	0.968	0.385	
Verbal fluency (VBF)	Education	2.70	7.495	0.001	0.479
	Negative sympt.	1.70	7.301	0.009	
	Gender	1.70	2.812	0.098	
	Medic. group	2.70	4.145	0.020	
Verbal learning (VBL)	Negative sympt.	1.70	10.118	0.002	0.253
	Age	1.70	5.982	0.017	
	Positive symp.	1.70	5.302	0.025	
	Gender	1.70	4.119	0.047	
	Medic. group	2.70	0.121	0.887	
Semantic memory (SEM)	Negative sympt.	1.70	10.850	0.002	0.152
	Medic. group	2.70	0.067	0.935	
Visual memory (VIM)	Education	2.70	7.243	0.001	0.215
	Medic. group	2.70	1.809	0.172	
Delay/retainment (DEL)	Negative sympt.	1.70	8.310	0.005	0.128
	Medic. group	2.70	0.178	0.838	
Short-term memory (STM)	Education	2.70	8.575	0.000	0.211
	Medic. group	2.70	1.020	0.366	
Visuomotor processing and attention (VSM)	Education	2.70	4.120	0.021	0.295
	Negative sympt.	1.70	4.276	0.043	
	Medic. group	2.70	1.680	0.194	
Abstraction/flexibility (ABS)	Education	2.70	5.215	0.008	0.152
	Medic. group	2.70	1.066	0.350	

and cognition together with consistent, although weak associations between negative symptoms and impairment mainly in verbal fluency, attention, memory and executive functions support the contention that modulation of cognition and positive symptoms may proceed with considerable independence.

Another important finding emerges from our study: when controlling possible moderating variables like education, gender and negative symptoms by means of a regression analyses, the association between medication and NP performance was found to be significant only for verbal fluency and showed a trend towards significance in verbal intelligence. In all other NP areas investigated, NP performance was not associated with medication status.

This finding might be considered at odds with conclusions presented elsewhere in the literature, that atypical Nls including Clozapine are ameliorating neurocognitive deficits in schizophrenia patients [18, 19, 20]. We want to stress, that our finding obtained in a sample of outpatients, the majority of whom was treated with low dosages of conventional or atypical Nls stable over weeks to months, cannot be put on a level with the results of treatment studies comparing the effects of conventional and atypical Nls on cognition in acutely ill schizophrenia inpatients.

However, we also want to stress, that this finding allows the conclusion that both, conventional and atypical Nls, administered in lower doses than in the vast majority of acute treatment studies do not appear to impair NP performance to a relevant extent. Also, this finding casts doubt on the assumption that atypical Nls are superior to conventional Nls with regard to cognitive functioning, at least in longer observation periods than those usually chosen for acute treatment studies. These conclusions drawn are supported by other studies [24, 25]. Also, in a comprehensive review, Cirillo and Seidman [22] stated that typical Nls have, besides the effect accounted for by anti-cholinergics, little negative effect on verbal memory. Moreover, a meta-analysis led to the surprising result that conventional Nls provided modest to moderate gains in multiple cognitive domains [23].

Several authors have discussed a dose dependent deleterious effect of classical Nls on different NP areas of functioning [21, 25]. In line with the results of Mishara and Goldberg [23], we did not detect such an effect in our study. This can be due to the fact that our sample size did not provide adequate statistical power to detect advantages of low dose treatment. With regard to the doses applied, they were both, low and within a relatively narrow range. Thus it is not clear whether there might be significant dose effects across a wider medication dose range.

VBF is the only cognitive domain where a negative effect of both, conventional and atypical Nls, and a deterioration over time was found. In contrast, FE schizophrenia patients off medication performed

nearly as good as controls in VBF. Even when taking into account that patients without medication at 5-year follow-up are the least severely impaired patient group, the difference in time course exclusively existing in the two medication groups, exclusively in this domain, renders a negative effect of medication itself likely.

It remains to be demonstrated whether cognitive impairment in this group of FE patients, make a substantial difference in patients' social and vocational functioning.

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