Neurocognitive effects of atypical and conventional antipsychotic drugs in schizophrenia: A naturalistic 6-month follow-up study

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Abstract

The present study aimed to assess the neurocognitive effects of atypical and conventional antipsychotic drugs on neurocognition under naturalistic treatment conditions. Eighty-two patients with schizophrenia underwent a comprehensive neuropsychological assessment both at baseline during inpatient treatment and 6 months after discharge from hospital (follow-up). From this sample, we selected two subgroups of patients, which had either a continuous atypical ($n = 33$) or conventional ($n = 16$) antipsychotic medication. Twenty-seven out of 40 healthy controls were also retested to control for practice effects. Both patient groups showed a moderate and significant improvement in global cognitive functioning. The repeated measurement ANOVAs revealed no differential treatment effects for all neuropsychological domains. These results remained after controlling for potential confounders between groups. Administering antipsychotic medications in an individually optimized manner seems to have the potential to improve some aspects of neurocognition in schizophrenia, regardless of the kind of antipsychotic medication.

1. Introduction

Neurocognitive deficits are increasingly considered as essential in schizophrenia disorders. There is convincing evidence that verbal memory, executive functions, and attention are impaired in schizophrenia (Goldberg & Gold, 1995; Heinrichs & Zakzanis, 1998; Weickert et al., 2000). The neuropsychological test performance of schizophrenia patients has been reported to reach one and one half standard deviations below the mean for healthy comparison subjects (Heinrichs & Zakzanis, 1998). Comparable cognitive impairments also have been observed prior to the first manifestation of psychosis or in the first episode of psychosis and may be as severe as in chronic schizophrenia (Bilder et al., 2000; Hoff et al., 1992; Saykin et al., 1994). Certain neuropsychological deficits may even reflect a genetic vulnerability to schizophrenia (Kremen et al., 1994; Wittorf, Klingberg, & Wiedemann, 2004). These findings led to the assumption that cognitive deficits comprise a separate domain of the illness and not a secondary factor. The fact that cognitive deficits are more closely associated with functional outcome than are psychotic symptoms or any other symptom domain (Green, 1996; Green, Kern, Braff, & Mintz, 2000; Green, Kern, & Heaton, 2004; Green &

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Nuechterlein, 1999) as well as the possibly limited benefit from psychoeducational treatment due to reduced cognitive functions (Feldmann, Buchkremer, & Hornung, 2000) raises the strong interest to find ways to improve cognitive performance in schizophrenia.

The amount of studies which assess the influence of antipsychotic medication on cognitive performance increases steadily, especially since the atypical antipsychotic medication is available. Several earlier studies demonstrated only minimal positive effects of conventional antipsychotics on cognitive deficits (Blyler & Gold, 2000; Cassens, Inglis, Appelbaum, & Gutheil, 1990). A meta-analysis (Keefe, Silva, Perkins, & Lieberman, 1999) of 15 studies, which assessed the cognitive effects of clozapine und risperidone, suggested that significant improvement in cognitive functioning was found with the atypical antipsychotics. Later studies showed that olanzapine may have cognition-enhancing qualities that are at least as substantial as those reported for risperidone and clozapine (Bilder et al., 2002; Purdon et al., 2000).

However, recent considerations, such as the impact of the dose of the conventional antipsychotic comparator (Harvey & Keefe, 2001; Keefe et al., 1999), have called into question whether atypical antipsychotic drugs actually improve cognitive functioning or whether they simply afford a release from the detrimental effects, such as extrapyramidal symptoms, of inappropriately high doses of conventional antipsychotics and concomitant adjunctive agents such as anticholinergic substances (Carpenter & Gold, 2002; Keefe et al., 1999). The randomized, double-blind comparisons of the effects of olanzapine (Keefe, Goldberg, et al., 2004) and risperidone (Green et al., 2002) with low doses of haloperidol showed only small differences in cognitive benefit. Remillard, Pourcher, and Cohen (2005) found in their randomized, double blind study that risperidone and haloperidol did not differ in their effect on executive functioning as measured with the Wisconsin Card Sorting Test (WCST). Most recently, the randomized controlled CATIE trial (Keefe, Bilder, et al., 2007) found small but significant cognitive improvements for olanzapine, quetiapine, risperidone, ziprasidone, and perphenazine, with no significant differences between groups at 2 and 6 months. After 18 months of treatment, cognitive improvement was even greater in the perphenazine group than in the olanzapine and risperidone groups.

Putting together these heterogeneous findings, conventional antipsychotic drugs per se do not unavoidably seem to be the cognitive hindrances they have earlier thought to be. The main research question of this study is: Do the slightly superior effects of atypical antipsychotics on neurocognition, which have been demonstrated in some randomized trials, hold under conditions of clinical routine care? Non-randomized trials might be clinically more relevant than randomized ones as all patients get their individually optimized antipsychotic treatment.

Thus, the present exploratory study aims at examining the neurocognitive effects of atypical and conventional antipsychotic drugs in schizophrenia under naturalistic treatment conditions. An advantage to the non-random assignment of antipsychotics in our study is that if a medication is clinically more effective for certain subgroups of patients who are recognizable by health care professionals, the neurocognitive effectiveness of this treatment might be improved. The study takes into account several potential confounders for differential treatment effects like antipsychotic dose, medication side effects, compliance, and psychopathology. In order to not overestimate general effects of antipsychotic medications on neurocognition, the study also controls for practice effects.

2. Method

2.1. Patient selection

Between April 1998 and June 2001, 169 inpatients who met DSM-IV criteria for schizophrenia or schizoaffective disorder were consecutively recruited as part of a combined large-scale psychotherapy and neuropsychology study at the Tuebingen University Hospital, department of psychiatry and psychotherapy, and the Rottweil state hospital of psychiatry and psychotherapy (Germany). All patients were admitted to the hospital due to an acute episode of their psychosis. Diagnoses were determined by the German version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; Wittchen, Zaudig, & Fydrich, 1997). All patients gave written informed consent to participate in the study, which was approved positively by the local ethics committee. Patients were selected on the basis of the following inclusion criteria: (1) beginning stabilization phase of illness after an acute phase, and (2) ages between 18 and 60 years. We considered patients to be in the beginning stabilization phase if they showed a symptom reduction and voluntarily agreed to be treated at an open ward. Exclusion criteria for neuropsychological testing were: (1a) lifetime history of substance dependence (DSM-IV/SCID-I) or (1b) substance abuse (DSM-IV/SCID-I) during

the last month before recruitment; (2) neurologic disease or damage; (3) medical illnesses that may interfere with cognitive functioning; (4) history of head injury with loss of consciousness greater than five minutes; (5) mental retardation (IQ below 80 according to the MWT-B (Lehrl, 1992), a German vocabulary test measuring the premorbid intellectual level); and (6) insufficient German language skills. The diagnosis of two patients had to be changed later to a bipolar affective disorder with psychotic symptoms. These two patients were excluded from the analysis. Additional 16 patients refused to participate in the neuropsychological examination. Thus, test data of 151 patients are available at baseline (t1). Patients received medication according to their individual needs without restriction by the study protocol.

2.1.1. Selection of patients with continuous atypical versus conventional antipsychotic medications

Eighty-two out of the 151 patients underwent the comprehensive neuropsychological assessment both at baseline (t1) and 6 months after discharge from inpatient treatment (t2). With the aim of selecting patients with continuous atypical antipsychotic (PAA) or conventional antipsychotic medications (PCA), patients were excluded from the study if they cross-sectionally or longitudinally received a combination of atypical and conventional antipsychotic drugs the week before t1 or during the follow-up period. Switching of the substance within the category of atypical and conventional antipsychotics was no exclusion criterion. Antipsychotic medication was prescribed by the psychiatrist responsible for routine outpatient treatment. Three patients of the PAA group had been rehospitalized due to symptom exacerbation within 3 months prior to the planned follow-up. These individuals had been excluded from further analyses leaving 33 patients in the PAA group and 16 in the PCA group. Testing recently relapsed patients would compromise the ability to evaluate neuropsychological changes from the beginning stabilization phase to a point after sustained recovery had been achieved. These 49 patients with a continuous antipsychotic medication did not significantly differ with regard to the baseline characteristics (Table 1) from the 33 patients who had a switch of atypical and conventional antipsychotics. The mean interval from admission to hospital to baseline assessment was 27 days (S.D. = 29 days) for the PAA group and 26 days (S.D. = 21 days) for the PCA group. These intervals were not significantly different ($t(47) = 0.126$, $p = 0.900$). Thus, baseline assessment took place after an individually optimized pharmacological treatment had been initiated for approximately 4 weeks. The relatively high degree of variability regarding the interval between admission and baseline assessment (S.D. = 29 and 21 days) reflects the fact that remission of the acute psychotic symptoms varied to a great extend. To ensure that patients had been recovered, clinical and social status assessment was done on a monthly basis from the time of discharge to neuropsychological follow-up.

Fourteen (42.4%) individuals of the PAA group received olanzapine, 12 (36.4%) clozapine, 2 (6.1%) a combination of risperidone and clozapine, 1 risperidone, 1 amisulprid, 1 sulpirid, 1 a combination of olanzapine and amisulprid, and 1 (each 3.0%) a combination of risperidone, clozapine, and olanzapine.

Six (37.3%) individuals of the PCA group received perphenazine, 6 (37.3%) perazine, 1 fluphenazine, 1 a combination of flupentixol and chlorprothixen, 1 a combination of haloperidol and fluphenazine, and 1 (each 6.3%) a combination of perazine, promethazine, and bromperidol.

Patients with a combination of two or three antipsychotics during the interval received those substances either sequentially with an overlap or simultaneously throughout the interval.

2.2. Control group

With the aim of obtaining a healthy standardization sample and to control for practice effects a control group was recruited. In order to attain a matching sample we randomly selected 40 cases out of our total patient sample ($n = 151$) as we were not able to examine 151 controls. These randomly selected patients represented the matching partners for the healthy controls. Matching criteria for the controls were age (±3 years), gender, and education (elementary, secondary, or high school). We then recruited the 40 controls through advertisements in the catchment area of the hospital. Beyond the matching criteria controls had to fulfill the following inclusion criteria: (1) no history of psychotic or affective disorders (DSM-IV/SCID-I), and (2) currently no taking of psychotropic medications. Additionally, controls qualified as non-vulnerable individuals, as they did not present any history of psychotic or affective disorders among their first-degree relatives. Exclusion criteria for the normal controls were identical with those of patients'. Further details of the recruitment of the control group have been described elsewhere (Klingberg, Wittorf, & Wiedemann, 2006). Neuropsychological reexamination (t2) of controls was scheduled 1 year after baseline testing. Unfortunately, we had not had enough staff to conduct a follow-up at 6 months. The reexamination of controls should control for learning

Table 1
Demographic and clinical psychopathologic characteristics of subjects at baseline

	Patients with atypical antipsychotics (PAA) $n=33$	Patients with conventional antipsychotics (PCA) $n=16$	Controls (CON) $n=40$	p		
				PAA vs. PCA	PAA vs. CON	PCA vs. CON
Age[a] M (S.D.)	32.7 (9.8)	36.2 (9.9)	33.3 (9.7)	0.246	0.821	0.306
Gender[b]						
Female	16 (48.5%)	9 (56.3%)	20 (50.0%)	0.762	>0.999	0.771
Male	17 (51.5%)	7 (43.8%)	20 (50.0%)			
Education[b]						
Elementary/secondary school	22 (66.7%)	10 (62.5%)	25 (62.5%)	>0.999	0.808	>0.999
Elementary/high school	11 (33.3%)	6 (37.5%)	15 (37.5%)			
Diagnoses (DSM-IV/SCID-I)[b]						
Schizophrenia, paranoid type	13 (39.4%)	9 (56.3%)	–	0.361	–	–
PANSS standard-scales[a] (Kay et al., 1987), baseline (t1)						
Positive-syndrome, mean item score (S.D.)	1.9 (0.7)	2.0 (0.6)	–	0.906	–	–
Range	1.0–3.7	1.1–3.0				
Sum score (S.D.)	13.6 (5.1)	13.8 (4.2)				
Negative-syndrome, mean item score (S.D.)	2.4 (1.0)	1.9 (0.7)	–	0.044	–	–
Range	1.0–4.1	1.0–3.9				
Sum score (S.D.)	16.9 (7.1)	13.4 (4.6)				
General score, mean item score (S.D.)	1.9 (0.5)	1.8 (0.4)	–	0.595	–	–
Range	1.1–2.8	1.1–2.6				
Sum score (S.D.)	30.9 (7.9)	29.2 (6.1)				
Total score, mean item score (S.D.)	2.1 (0.6)	1.9 (0.4)	–	0.244	–	–
Range	1.0–3.0	1.2–2.7				
Sum score (S.D.)	60.8 (15.9)	56.3 (11.1)				
First episode patients[b]	12 (36.4%)	2 (12.5%)	–	0.017	–	–
Age at onset of illness (first psychotic symptoms)[a], M (S.D.)	26.5 (8.8)	27.4 (9.2)		0.744	–	–
Number of previous hospitalizations[a], Md/M (S.D.)	2.0/2.6 (3.0)	2.0/4.8 (7.3)		0.254	–	–
Duration of prev. hospitalization (weeks)[a], Md/M (S.D.)	23.0/31.5 (40.2)	18.5/49.6 (77.6)		0.285	–	–
Medication, baseline (t1)						
CPE at day of testing[a], M (S.D.)	416 (221)	597 (358)	–	0.044	–	–
Extrapyramidal Symptoms Scale[c], mean sum score (S.D.)	3.0 (3.7)	2.9 (5.2)	–	0.480	–	–
Compliance Rating Scale[c], mean item score (S.D.)	5.4 (1.4)	5.3 (1.7)		0.840		
Lifetime duration of neuroleptic treatment (months)[a], M (S.D.)	30.9 (45.4)	71.1 (113.3)		0.190		
Patients with anticholinergic co-medication[b]	7 (21.2%)	6 (37.5%)	–	0.304	–	–

PANSS: Positive and Negative Syndrome Scale; CPE: chlorpromazine-equivalents; Md: median.

[a] t-Test (two-tailed).

[b] Fisher's Exact Test (two-tailed).

[c] U-Test (two-tailed).

and practice effects. Thirteen of the controls refused the reexamination (non-completers) leaving 27 controls at t2 (completers).

2.3. Demographic and clinical characteristics

Table 1 shows the demographic and clinical psychopathologic characteristics of the three groups. Patient groups (PAA and PCA) and controls showed no significant differences with regard to age, gender, and education. The clinical symptom assessment in patients had to be completed within 2 weeks prior to neuropsychological testing. The interviewers used the Positive and Negative Syndrome Scale (PANSS, Kay, Fiszbein, & Opler, 1987). Table 1 shows the ranges for the mean item scores along with the sum scores for the PANSS scales at t1. The moderate level of the PANSS scores implies that patients were neuropsychologically assessed at the beginning of their stabilization phase. With regard to the negative-syndrome, the PAA group had a significantly higher mean item score than the PCA group. Further, the PAA group showed a significantly higher proportion of first-episode patients.

Antipsychotic dosages were transformed into chlorpromazine-equivalents (CPE). With regard to conventional antipsychotics, CPE were calculated according to Davis (1974). Atypical antipsychotics were transformed in line with Mueller (1999) and information of the pharmaceutical industry. The following potency factors were applied to the atypical substances: olanzapine 20.0, clozapine 2.0, risperidone 100.0, amisulprid 1.0, and sulpirid 0.5. The PCA group showed significantly higher CPE at t1 than the PAA group. Medication adherence was assessed using the seven point observer-rated Compliance Rating Scale (CRS, Kemp, Hayward, Applewhaite, Everitt, & David, 1996; Kemp, Kirov, Everitt, Hayward, & David, 1998). This scale assesses whether medication was taken as prescribed and takes into account the patient's interest in collaboration with antipsychotic treatment. Both the PAA and the PCA group had mean item scores slightly higher than five on the CRS indicating at least "passive acceptance" of the antipsychotic medication. Thus, medication adherence in both patient groups was satisfying and not significantly different. Further, the patient groups did not differ significantly in their extrapyramidal symptoms assessed with the Extrapyramidal Symptoms Scale (EPS, Simpson & Angus, 1970). The proportion of patients co-medicated with anticholinergics (biperiden) was comparable between the two patient groups.

2.4. Neuropsychological testing

The following battery of tests was administered to assess neuropsychological functions that have been found to be impaired in schizophrenia patients: Computerized Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993); Degraded Stimulus Continuous Performance Test (dsCPT; Nuechterlein & Asarnow, 1996); Trail Making Test A/B (TMT; Reitan, 1992); Digit-Symbol and Digit-Span from the German version of the Wechsler Adult Intelligence Scale (WAIS; Tewes, 1994); Rey Complex Figure Test (RCFT; Meyers & Meyers, 1995); Verbal Fluency (Horn, 1983); and the German version of the Rey Auditory Verbal Learning Test (AVLT; Heubrock, 1992) with a paralleled version. Retests with paralleled versions showed a fluctuation of less than one word and high retest stability in normal controls (Lezak, 1995).

We previously conducted a principal components analysis (PCA) on the neuropsychological data of the total patient sample ($n = 151$) at t1 (Klingberg et al., 2006). Thus, we assume that this factor structure applies also to the 49 patients of the present study, which are part of our total sample. PCA was followed by orthogonal (Varimax) rotation. The PCA extracted three components, which accounted for 59% of variance. We interpreted the three factors as representing the following constructs. Factor 1 (39.2% of total variance): memory (AVLT and RCFT); factor 2 (10.1%): attention (TMT A/B, Digit-Symbol, Digit-Span, dsCPT, and Verbal Fluency); and factor 3 (9.6%): abstraction (WCST). Details of the PCA procedure and the construction of the factor scores have been described elsewhere (Klingberg et al., 2006).

The sequence of the test application was always the same: (1) AVLT, (2) RCFT, (3) Verbal Fluency, (4) Digit-Symbol, (5) Digit Span, (6) TMT, (7) WCST, and (8) dsCPT. Regarding the AVLT, patients and controls got the same paralleled versions at baseline and follow-up (design wise). Completion of the test battery took approximately 75–90 min. The tests were applied by a trained psychological assistant with more than 10 years of experience in conducting psychological testing. This assistant was independent from the study team and not aware of the study's aims. The test application was supervised by a Ph.D. level senior clinical psychologist.

Neuropsychological follow-up of the PAA group was done on an average of 257 days (S.D. = 47) after baseline testing. The interval for the PCA group (254 days, S.D. = 43) was not significantly different ($t(47) = 0.183$, $p = 0.56$).

Neuropsychological re-examination of the 27 controls took place 418 days (S.D. = 53) after baseline testing. This interval was significantly longer than for the PAA and PCA group respectively ($p < 0.01$). Table 2 presents the neuropsychological raw scores of both patient groups and the control group at baseline and follow-up. With one exception (WCST—failure to maintain set), change in the individual measures was consistently positive for both patient groups. The positive changes for the RCFT—delayed recall and some of the WCST variables in the control group imply practice effects.

2.5. Standardization of the test battery and control for repeated testing

To calculate neuropsychological factor scores (function scores) raw test scores of all probands were first transformed to standard equivalents (z-scores) using the means and standard deviations of the control group. All standard scores were computed with higher values indicating better performance.

The follow-up (t2) control sample has been demonstrated to be representative of the complete sample: no significant differences regarding both the demographic characteristics (Table 1) and the neuropsychological variables at baseline resulted between the 27 controls with reexamination (completers) and the 13 refusing controls (non-completers). Thus, we standardized the patients' scores at t1 by the scores of the total control group at t1. The patients' scores of t2 were standardized by the scores of the controls at t2. Thus, resulting z-scores of t2 will not be confounded by the effect of repeated testing. This method of standardization and control for repeated testing has been published elsewhere (Klingberg, Wittorf, Sickinger, Buchkremer, & Wiedemann, 2008).

Factor scores were created by averaging z-scores within each empirical domain. Finally, we computed a total score of cognitive functioning by averaging z-scores of the three factor scores. By definition, the control group mean is represented by the zero line with S.D. = 1 for all domains.

2.6. Statistics

The study is a controlled, repeated measures analysis of neuropsychological functioning. In addition to descriptive statistics, we calculated repeated measurement ANOVAs with differences at t1 between the two patient groups added as covariates. Within effect sizes (Cohen d) were determined by dividing the difference between the baseline (t1) mean and the endpoint (t2) mean by the baseline standard deviation. In consideration of the fact that our patient samples were relatively small, we limited the number of statistical tests by analyzing only the neuropsychological factor scores.

Data analyses were done with SPSS for windows, version 14.0. The levels of significance follow the usual convention: $p < 0.05$ (*), $p < 0.01$ (**).

3. Results

Fig. 1 shows the three neuropsychological factor scores and the total scores of the two patient groups (PAA and PCA) at t1 and t2. Data are presented as box plots to indicate the variability of the underlying cognitive functions.

The standardized factor scores memory and the total score show a significant increase between t1 and t2 for both the PAA (memory: $t(32) = -11.92$, $p < 0.01$; total score: $t(31) = -5.82$, $p < 0.01$) and the PCA group (memory: $t(15) = -5.41$, $p < 0.01$; total score: $t(13) = -2.99$, $p = 0.10$). The standardized factors scores attention and abstraction do not increase significantly for both the PAA and the PCA group.

Table 3 depicts the mean z-scores and standard deviations for the neuropsychological factor scores and the total score for the PAA and PCA groups for both t1 and t2 along with the within effect sizes (Cohen d) and the results of the repeated measurement ANOVAs. The ANOVAs resulted in significant main effects for the factor "time" with regard to the standardized factor score memory and the total score. No significant main effects for the factor "time" could be shown for the standardized factor scores attention and abstraction. For the factor "group" no significant main effects were found for all of the standardized factors scores and the total score. Further, no significant interactions between the two factors (time × group) resulted for all standardized neuropsychological factor scores and the total score. Within effect sizes (Cohen d) are the highest for the factor score memory and the lowest for abstraction in both the PAA and the PCA group.

Analysis of confounders: results for repeated measurement ANOVAs for all standardized factor scores and the total score remained unchanged with regard to interactions (time × group) when adding the differences at t1

Table 2
Neuropsychological tests and raw scores of patient groups (PAA, PCA) and controls (CON) at t1 and t2

Test	Variables analyzed	PAA, mean (S.D.)		PCA, mean (S.D.)		CON, mean (S.D.)	
		t1/PAA N (33)	t2/PAA N (33)	t1/PCA N (16)	t2/PCA N (16)	t1/CON N (40)	t2/CON N (27)
Memory factor							
AVLT	Trial (T)1, T5, ΣT1–5, T7 (delay)	5.1 (2.1), 9.4 (3.0), 37.6 (11.1), 6.8 (3.6)	6.3 (1.5), 12.0 (2.3), 49.2 (9.6), 9.8 (3.8)	5.1 (1.8), 10.2 (3.2), 39.8 (12.9), 7.8 (3.5)	7.1 (2.3), 12.4 (2.9), 51.6 (9.9), 10.1 (3.1)	8.23 (1.97), 14.3 (1.14), 60.4 (6.78), 13.5 (1.91)	7.93 (2.0), 14.0 (1.52), 59.6 (8.36), 13.3 (2.28)
RCFT	Delayed recall	15.4 (8.1)	20.1 (8.6)	14.2 (6.2)	18.7 (8.3)	22.8 (5.63)	25.0 (6.45)
Abstraction factor							
WCST	Trials administered, percentage of perseverative errors, categories completed, failure to maintain set	107.4 (22.4), 16.8 (11.9), 4.7 (1.9), 1.2 (1.3)	99.8 (23.3), 12.1 (9.0), 5.3 (1.4), 1.3 (1.4)	102.6 (25.4), 21.4 (22.5), 4.5 (2.2), 0.6 (0.8)	97.9 (22.7), 12.4 (10.3), 5.1 (1.7), 1.0 (1.2)	96.8 (20.2), 12.1 (5.58), 5.58 (1.17), 0.55 (0.99)	85.6 (16.5), 8.89 (3.63), 5.78 (0.80), 0.52 (0.70)
Attention factor							
Trail Making Test	Trail A (time in s), Trail B (time in s)	33.9 (9.9), 95.1 (57.3)	30.0 (10.5), 79.0 (44.8)	43.0 (21.4), 84.2 (37.8)	29.2 (11.0), 72.4 (28.7)	26.0 (6.33), 53.2 (11.4)	22.9 (4.5), 53.3 (14.2)
Digit-Symbol	Number correctly assigned symbols	42.2 (12.6)	51.4 (12.6)	49.9 (12.7)	56.5 (13.0)	62.5 (9.99)	68.5 (8.6)
Digit-Span	Forward, backward	7.9 (2.0), 5.6 (2.2)	8.3 (1.9), 7.0 (1.9)	8.6 (2.3), 7.3 (2.7)	8.8 (2.0), 7.3 (2.1)	8.10 (2.04), 8.30 (2.40)	9.5 (2.34), 8.81 (2.47)
dsCPT	Sensitivity d', reaction time hits (in ms)	2.3 (0.9), 573.1 (101.6)	2.9 (0.8), 503.6 (83.6)	2.7 (1.0), 545.2 (63.6)	2.9 (1.1), 537.9 (96.0)	3.35 (0.97), 463.6 (48.3)	3.33 (1.10), 462.7 (50.8)
Verbal Fluency	Number words	28.5 (10.0)	32.6 (9.2)	34.5 (11.6)	34.2 (11.6)	38.5 (8.00)	40.8 (8.52)

PAA: Patients with continuous atypical antipsychotic medication from t1 to t2; PCA: Patients with continuous conventional antipsychotic medication from t1 to t2; WCST: Wisconsin Card Sorting Test, dsCPT: Degraded Stimulus Continuous Performance Test, AVLT: Rey Auditory-Verbal Learning Test, RCFT: Rey Complex Figure Test.

Table 3
Means and standard deviations (in brackets) of the neuropsychological factor scores at t1 and t2 (standardized by controls, controlled for repeated testing), within effect sizes (Cohen d), and repeated measurement ANOVAs' main effects

	PAA (n = 33)			PCA (n = 16)			Repeated measurement ANOVAs (main effects)					
	t1	t2	Cohen d	t1	t2	Cohen d	Group, F (d.f. = 1)	p	Time, F (d.f. = 1)	p	Time × group, F (d.f. = 1)	p
Factor scores (z)												
Attention, M (S.D.)	−1.4 (0.9)	−1.1 (1.0)	0.33	−1.1 (1.1)	−0.9 (1.0)	0.18	1.036	0.413	2.403	0.128	0.405	0.528
Memory, M (S.D.)	−2.7 (1.4)	−1.1 (1.1)	1.14[**]	−2.4 (1.3)	−0.9 (1.0)	1.15[**]	0.542	0.485	129.919	<0.001	0.270	0.606
Abstraction, M (S.D.)	−0.6 (1.0)	−0.7 (1.4)	−0.10	−0.5 (1.3)	−0.7 (1.5)	−0.15	0.047	0.829	1.023	0.317	0.027	0.870
Total score, M (S.D.)	−1.6 (0.9)	−1.0 (1.0)	0.67[**]	−1.3 (1.0)	−0.8 (1.0)	0.50[*]	0.584	0.449	33.666	<0.001	0.124	0.726

PAA: Patients with continuous atypical antipsychotic medication from t1 to t2; PCA: Patients with continuous conventional antipsychotic medication from t1 to t2. Within effect sizes (Cohen d) were determined by dividing the difference between the baseline (t1) mean and the endpoint (t2) mean by the baseline standard deviation.
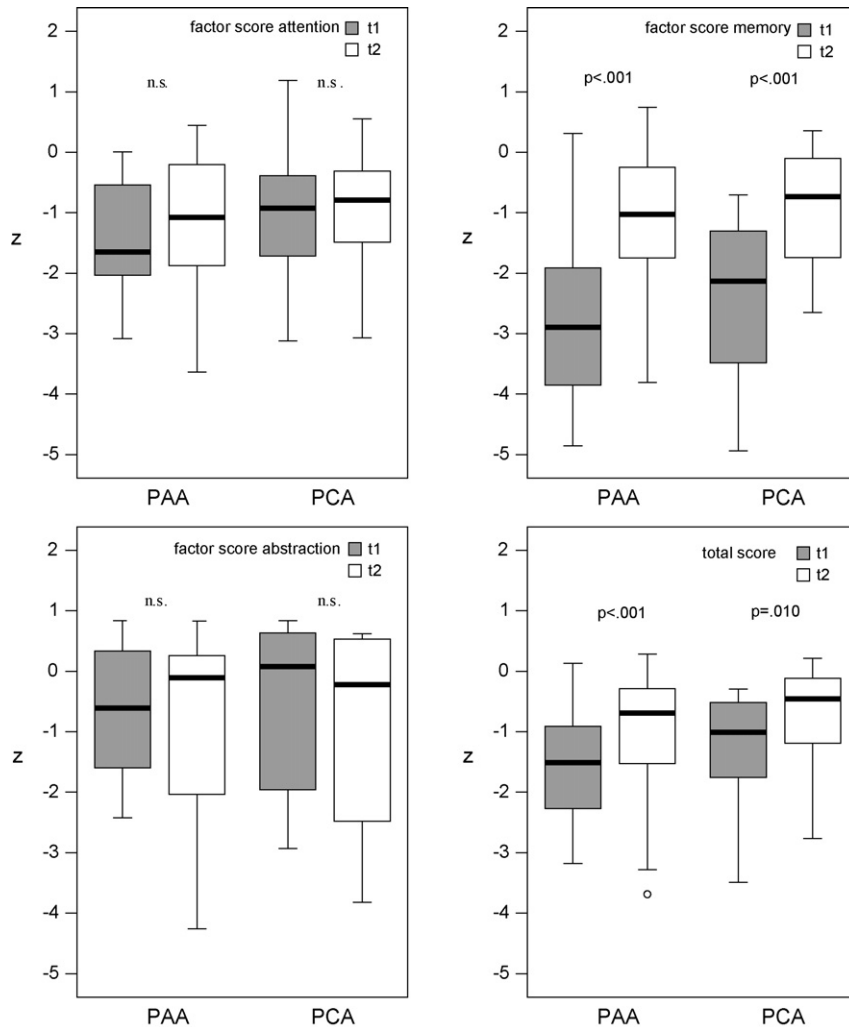
[*] $p < 0.5$.
[**] $p < 0.1$.

Fig. 1. Boxplots of neuropsychological factor scores at t1 and t2, standardized by controls, controlled for repeated testing: Patients with continuous atypical (PAA, $n = 33$) vs. continuous conventional (PCA, $n = 16$) antipsychotic medications. *Note*: Levels of significance refer to the *t*-tests for dependent samples; n.s.: not significant.

between the two patient groups (negative-syndrome of the PANSS, CPE, first versus multiple episode patients) as covariates.

4. Discussion

This longitudinal study aimed at examining the neurocognitive effects of atypical and conventional antipsychotic drugs in schizophrenia under naturalistic treatment conditions. The fact that patients were not randomly assigned to groups makes this study a good test of "real-world" efficacy.

The majority of published studies examining the effects of antipsychotic medication on cognitive functioning have substantial methodological weaknesses, which require careful consideration while interpreting these findings (Harvey et al., 2001). Many of these problems were addressed in this study, which included a longitudinal design, controlling for practice effects, a substantial follow-up period, comprehensive neuropsychological testing, and precise documentation and examination of potential confounders.

The selection analysis revealed that only 49 (60%) of the 82 longitudinally assessed patients had a continuous atypical or conventional antipsychotic medication. Obviously, the psychiatrists responsible for outpatient treatment

tended to switch between the two groups of antipsychotics or combined them. This high attrition rate might restrict the generalizability of our results. Although the baseline characteristics of the patients included in the present analyses were comparable to those who were dropped, this does not mean that the groups were not different in some variables not measured. Further, our selection analysis found twice as much patients with a continuous atypical antipsychotic medication than patients with a conventional one. Both patient groups did not differ with regard to most of the demographic and clinical psychopathologic characteristics. The only exceptions were the higher proportion of first-episode patients and the higher scores on the negative-syndrome scale of the PANSS in the PAA group. Further, the PCA group demonstrated significantly higher CPE at baseline. Since patients were not randomly assigned to the treatment conditions, these differences are in accordance with the clinical expectation. Atypical antipsychotics are thought to have beneficial effects on positive as well as negative symptoms, to reduce extrapyramidal side-effects, and to improve neurocognition and medication compliance. These considerations might explain the higher proportion of atypically medicated patients and why atypical antipsychotics have been preferably prescribed to the first-episode patients and those with predominantly negative symptoms. Furthermore, the higher chlorpromazine-equivalents in the PCA group might reflect the propensity to prescribe conventional antipsychotics at higher doses than atypical ones. Even though the known differences between the patient groups were controlled for, we cannot exclude that the groups were not somehow different in some dimension not assessed. This is a limitation of the non-randomized design of the present study.

The standardized factor score memory and the global cognitive functioning score showed a significant increase between t1 and t2 for both the PAA and the PCA group. The factor scores attention and abstraction did not increase significantly for both patient groups. A limitation of our study is the fact that the test-retest interval for the control group was significantly longer than for both patient groups. Since longer intervals might be accompanied by lessened practice effects, we cannot rule out the possibility that practice effects in the patient groups were not completely neutralized.

The repeated measurement ANOVAs resulted in no significant interactions between the factors time and group for all standardized neuropsychological factor scores and the total score. Adding the a priori differences (t1) between the two patient groups as covariates did not change the interaction results. Thus, our study could not demonstrate any differential treatment effects of atypical versus conventional antipsychotic drugs on neurocognition in schizophrenia under conditions of clinical routine treatment. Further, independent from the pharmacological regimen global cognitive impairment (total score) in both patient groups remained approximately one standard deviation below normative level.

Atypical and conventional antipsychotic medications resulted in high and nearly identical effect sizes for the factor score memory. These effect sizes are comparable to the effect size of our total follow-up sample of 82 patients (Klingberg et al., 2008). Concerning global cognitive functioning (total score), effect sizes of the present study were moderate (approximately half a standard deviation) and relatively similar between groups. This result supports the view that the difference in cognitive benefit seems to be small and clinically not significant. The randomized, double blind CATIE trial (Keefe, Bilder, et al., 2007) reported smaller effect sizes with regard to a composite score of neurocognition. Three main factors might have contributed to this difference. First, a sampling effect might be one factor. As the focus of the present study was on stabilization conditions, we tested the patients at the beginning stabilization phase and excluded those who relapsed within 3 months prior to the planned follow-up. Thus, our results might apply only to patients who have the ability to recover from their illness. Second, unlike Keefe, Bilder, et al. (2007) who included only patients with chronic schizophrenia, the present study also comprised first episode patients. In a further study, Keefe, Sweeney, et al. (2007) compared the effects of olanzapine, quetiapine, and risperidone on cognitive functioning in patients with early psychosis. In this sample cognitive improvements were modest and more comparable to the findings of our study. Third, an advantage to the non-random assignment of medications in the present study is that if a medication is clinically more effective for certain subgroups of patients who are recognizable by health care professionals, the neurocognitive effectiveness of this treatment might be enhanced.

Our study points to the methodological challenge of gathering samples like these under conditions of routine outpatient treatment. The heterogeneity of the medications in both patient groups might be viewed as a limiting factor of the study, since within each class (conventional versus atypical antipsychotics) the different medications could exert differing effects. Nevertheless, our findings are consistent with those of recent randomized trials (Green et al., 2002; Keefe, Bilder, et al., 2007; Keefe, Seidman, et al., 2004). Even with the higher dose of conventional antipsychotics at the time of baseline testing no smaller cognitive benefit of conventional antipsychotics was found. Although our study had small sample sizes, which calls for a replication of its results in a larger group of subjects, the practitioner can draw the following conclusion from the results: If there is an indication for a prolonged conventional antipsychotic

medication, we do not withhold the patient the chance of recovering from cognitive impairments. Administering antipsychotic medications in an individually optimized manner seems to have the potential of improving some aspects of neurocognition in schizophrenia, regardless of the kind of antipsychotic medication.

Declaration of interest

There are no conflicts of interest.

Acknowledgements

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