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SCIENCE DIRECT®
European Psychiatry 20 (2005) 70–73
EUROPEAN PSYCHIATRY
http://france.elsevier.com/direct/EURPSY/

Short communication

Prefrontal cognitive deficits in patients with schizophrenia treated with atypical or conventional antipsychotics

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Received 10 May 2004; accepted 24 August 2004

Available online 13 December 2004

Abstract

Forty-three patients with schizophrenia were investigated with a short neurocognitive screening battery focussing on working memory and executive functions. As compared to healthy controls, patients showed impairments in the modified card sorting test, in verbal fluency and all span tasks with exception of digit span forward. Patients who were treated with atypicals showed better performance in the digit ordering test (manipulation task) when compared to a group of patients who received conventional antipsychotics; this difference was not due to disease severity, age or education. Manipulation tasks might be useful for neurocognitive follow-up and intervention studies.

Keywords: Antipsychotic agents; Executive functions; Digit ordering test; Schizophrenia; Working memory

1. Introduction

Neurocognitive deficits are a core feature of schizophrenia and a good predictor of functional outcome [1,4]. Comprehensive neuropsychological testing of all relevant cognitive domains requires several hours and is not feasible in clinical practice. Short bedside batteries have been proposed that focus on working memory and executive functions [4]. These functions are preferentially mediated by frontostriatal networks and modulated by major neurotransmitters like dopamine [11,12].

Antipsychotic drugs are well-established to reduce psychotic symptoms via blockade of dopamine D2 receptors [6]. When compared to conventional neuroleptics the newer atypical drugs have fewer side effects and a more favourable impact on negative symptoms, cognitive deficits and social outcome of patients with schizophrenia [4,9,13,14]. However, there is still there is still some debate as to whether atypical antipsychotics are more effective in treating cognitive symptoms when compared to lower doses of conventional neuroleptics [8]. And so far, it is also not clear which cognitive processes are influenced differentially by conventional and atypical antipsychotic medication.

The aim of this study was to evaluate a short prefrontal screening battery that detects relevant cognitive deficits in patients with schizophrenia and allows differentiating disease and treatment effects.

2. Methods

2.1. Participants and design

Forty-three patients (19 female; age 39.2 ± 12.2 years) with a diagnosis of schizophrenia according to ICD-10 diagnostic criteria for research [16] were recruited from consecutive admissions to the Department of Psychiatry, University Hospital Leipzig, and interviewed by two experienced psychiatrists (U.M., T.B.) to exclude major psychiatric or medical comorbidity and perform standardised psychopathological and diagnostic ratings. The mean duration of their disease

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doi:10.1016/j.eurpsy.2004.08.006

was 10.3 ± 10.7 (range 0–38) years and the overall PANSS score was 62.5 ± 14.6 (range 40–94). They were tested at the end of or shortly after inpatient treatment on stable medication. Twenty-two patients (51%) were treated with atypicals only (clozapine [n = 10; mean dose 285, range 150–550 mg/day], olanzapine [n = 8; 16.4, 10–20 mg/day], risperidone [n = 4; 4.3, 1–6 mg/day], amisulpride [n = 3; 450, 350–600 mg/day], or quetiapine [n = 2; 550, 500–600 mg/day], including combinations), whereas 21 patients (49%) were treated with conventional neuroleptics (flupenthixol [n = 14, mean 7.5, range 2–17 mg/day], haloperidol [n = 7; 10.2, 4–21 mg/day], pimozide [n = 1; 4 mg/day], or levomepromazine [n = 1, 50 mg/day], including combinations, e.g. medium dose flupenthixol or haloperidol plus clozapine or olanzapine). Treatment with anticholinergics or benzodiazepines was interrupted before cognitive testing, if possible. Psychiatric co-medication with antidepressants (no tricyclics) and hypnotics in the evening (antihistaminic drugs or benzodiazepines) was equally distributed between the two groups. At the time of testing, eight patients (seven on atypical vs. one on conventional antipsychotics) were employed, 12 (seven vs. five) were unemployed or in training and 23 (8 vs. 15) received a disability pension.

Twenty-seven healthy subjects from the volunteers' panel of the Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, served as controls and were matched for sex (12 female), age (38.2 ± 13.9, range 22–58 years), and years of education.

Neurocognitive testing was performed in one session in a quiet wardroom. The protocol was approved by the Ethics Committee of the University of Leipzig and written informed consent was obtained from all participants.

2.2. Neurocognitive testing

A short neuropsychological testing battery of well-established paper and pencil tests was adapted from our previous studies in patients with Parkinson's disease and frontal lobe lesions [11,15]. A short description of all tasks is given in Table 1. Interestingly, our battery overlaps with the Brief Assessment of Cognition in Schizophrenia (BACS) battery in four of seven tests [4]. To assess manipulation processes in working memory we were using the digit ordering span task that has been developed by our group: similar to digit spans forward and backward, number sequences of increasing length are presented and have to be recalled in ascending order [15].

2.3. Data analysis and statistics

Neuropsychological and demographical data were compared by means of ANOVA or nonparametric Mann–Whitney U-tests, depending on normal distribution of the data. Spearman's rank sums were used to calculate correlations.

3. Results

As compared to controls, patients with schizophrenia showed significant deficits in all tests with the exception of digit span forward (Table 1). Patients treated with atypical antipsychotics only showed significant better performance in the digit ordering test when compared to those on conventional neuroleptics (5.0 ± 0.9 vs. 4.4 ± 1.3; U = 150.5, $P < 0.05$); this difference is not due to age (36.4 ± 12.5 vs. 42.2 ± 11.3 years) or disease severity as measured with the PANSS (61.3 ± 14.3 vs. 63.8 ± 15.1). There were no other significant differences between the two drug groups, with the exception of a trend for shorter disease duration (7.9 ± 10.7 vs. 12.8 ± 10.3 years) in the atypical group (Fig. 1).

In the patient group there were no significant correlations between cognitive and psychopathological parameters, with the exception of the PANSS disorganisation cluster. Higher disorganisation was correlated with lower performance on all manipulative spans (backward, ordering and reading) and categories in the modified card sorting test.

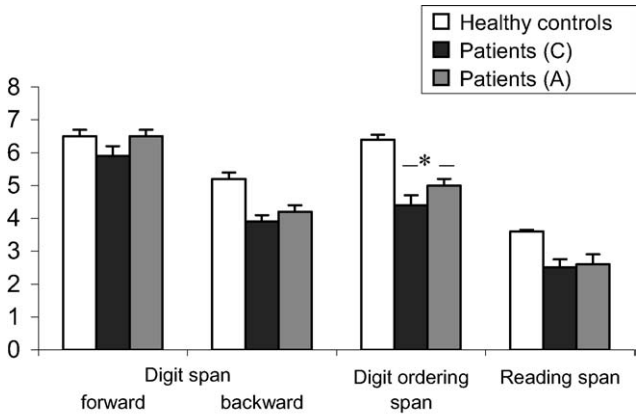
4. Discussion

We have shown that a short neurocognitive testing battery allows detecting deficits of working memory and executive

Table 1
Neurocognitive profile of patients with schizophrenia (n = 43) and healthy controls (n = 27) in the prefrontal battery (mean ± S.D.)

Task	Short description ([11,15] for details)	Patients	Healthy controls	U	P
Digit span	Recall digit sequences of increasing length forward and backward				
-Forward		6.2 ± 1.1	6.5 ± 1.1	490.0	>0.10
-Backward		4.0 ± 1.0	5.2 ± 1.0	208.5	<0.001
Digit ordering span	Recall digit sequences in ascending order	4.7 ± 1.1	6.4 ± 0.8	116.5	<0.001
Reading span	Recall last words of short sentences	2.5 ± 1.2	3.7 ± 0.3	150.0	<0.001
Verbal fluency	Name words that begin with F, P, R or animals in 60 s				
-Literal		23.7 ± 10.7	30.0 ± 10.8	372.5	<0.02
-Categorical		19.0 ± 5.7	26.2 ± 8.1	253.0	<0.001
MCST	Sort cards according to changing rules (with error feedback)				
-Categories		4.8 ± 2.0	6.4 ± 0.7	281.0	<0.001
-Perseverations		2.2 ± 3.0	0.4 ± 0.8	371.5	<0.01
MWT-A	Cancel words that do not exist in German	28.2 ± 5.5	31.8 ± 2.2	334.5	<0.01

MCST : Modified card sorting test; MWT-A : Mehrfachwortschatztest, version A (German NART equivalent).



* = p < 0.05 (difference between the two drug groups, see text)

Fig. 1. Working memory (span task) performance of healthy controls ($n = 27$) and patients with schizophrenia treated with conventional (C) ($n = 21$) or atypical (A) ($n = 22$) antipsychotic drugs (mean ± S.D.).

functions in patients with schizophrenia in a clinical routine setting. Most interestingly, patients treated with atypical antipsychotics performed better in the digit ordering test than patients treated with conventional antipsychotics.

Working memory performance correlates with other executive deficits and can be taken as an indicator of more general neurocognitive deficits in patients with schizophrenia [4,10]. Working memory involves not only the maintenance of information, but also a manipulative component, which may be more severely affected in schizophrenic patients [7]. In many everyday life situations (e.g. to participate in a discussion, to dial long telephone numbers, to operate machines or personal computers) it is necessary to manipulate bits of information in working memory. Correlations of performance in manipulation tasks and the PANSS disorganisation score reflect specific cognitive problems of patients with schizophrenia. Manipulation processes, as specifically captured by digit ordering, are improved by dopamine agonists [2], impaired by anticholinergic and glutamatergic drugs [2,5], correlate with degeneration of nigrostriatal neurons in Parkinson's disease [11] and may be a sensible parameter to detect neurotransmitter specific effects of cognitive enhancing treatment.

The following limitations of this study have to be considered: First, the cognitive results may be confounded by the use of several different antipsychotics in both the conventional and the atypical group. On the other hand the naturalistic design of our study reflects prescription habits in a typical European region. The increasing prescription of better-tolerated but more expensive atypicals in Germany and other European countries [3], will make it difficult to perform similar studies in the future. Second, the cross-sectional design of our study without follow-up investigations makes it difficult to distinguish an improvement of working memory processes by atypical medication from impairment by conventional drugs. Third, daily doses of haloperidol (and fluspenthixol) used in our clinic were relatively high at the time of the study. A recent meta-analysis showed that lower doses (2–5 mg/day) of haloperidol have beneficial effects on cognitive functioning when compared to placebo or no treatment in patients with schizophrenia [8]. It is unlikely that anticholinergic drugs or side effects confounded our findings, because none of the patients was treated with biperiden or amitriptyline at the time of neuropsychological testing. Fourth, there were more employed patients in the atypical group and more patients in the conventional group received a disability pension. It is not clear from these data, however, if better cognitive functioning favours employment or vice versa.

Although antipsychotic drugs have some benefit on cognitive function, further efforts to improve cognitive deficits in schizophrenia are required. There is a vital need for developing improved compounds for the treatment of cognitive deficits in schizophrenia. The combination of more specific cognitive enhancing drugs with cognitive remediation therapies might lead to better functional outcome in patients with schizophrenia [4].

This study contributes further evidence for a beneficial effect of atypical antipsychotics on prefrontal cognitive functions in schizophrenia. Further studies will investigate the predictive value of performance in the digit ordering and similar manipulation tasks for overall cognitive and social functioning.

Acknowledgements

This study was supported by the German Bundesministerium für Bildung und Forschung (BMBF)/Medical Faculty of the University of Leipzig (formel.1-13) and the Alexander von Humboldt-Foundation (Feodor Lynen-Fellowship awarded to U.M.).

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