Acta Psychiatr Scand 2001: 104 (Suppl. 408): 75–80
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ACTA PSYCHIATRICA SCANDINAVICA
ISSN 0001-690X

Neuropsychological impairment in patients treated with depot neuroleptics: a longitudinal study

Tuninger E, Levander S. Neuropsychological impairment in patients treated with depot neuroleptics: a longitudinal study.
Acta Psychiatr Scand 2001: 104 (Suppl. 408): 75–80. © Munksgaard 2001.

Objective: To assess neuropsychological impairments among chronic functional psychotic patients over time, and relations with symptoms, drug dose and side effects.
Method: Thirty-four patients, representative of the most ill one-third of all patients with chronic functional psychoses known to the psychiatric services in a city catchment area, were assessed for clinical symptoms, drug side effects and by neuropsychological tests at study entry. They were then assessed repeatedly over 2 years.
Results: All patients were seriously impaired in the tests. The impairment was stable over time, in spite of substantial changes in the clinical state. The impairment was unrelated to drug and drug dose. Patients with prominent negative symptoms were most impaired and most unable to rate their performance in the tests.
Conclusion: Patients with chronic functional psychoses do relapse often, also late in the course of the disease. Negative symptoms, marked impairments in simple neuropsychological tests and impaired self-monitoring went together.

E. Tuninger, S. Levander

Department of Psychiatry, Malmö, Lund University, Sweden

Key words: schizophrenia; neuropsychology; longitudinal; depot neuroleptic drugs; side effects

Professor Stan Levander, Department of Psychiatry, U-MAS, SE-205 02 Malmö, Sweden

Introduction

Cognitive deficits are a prominent feature of schizophrenia. Several studies indicate that the neuropsychological impairment is primary and seen early in the course of the disease, and that the impairment is global rather than the regional or patchy one which characterizes traumatic brain lesions and most other dementia disorders. The effect of neuroleptics on cognitive performance has been discussed extensively. Acute treatment in chronic schizophrenic patients seems to impair some functions (vigilance and attention), but chronic medication seems to have less impairing effects (1). There are no studies in which the cognitive deficit among schizophrenic patients has been followed intra-individually over time, using test batteries rather than single tests, with control over symptoms, drugs and drug doses and side effects (2).

The meta-analysis by Green (3) suggests that cognitive deficits are linked strongly to prognosis and social outcome. One of the best overall predictors in his overview was reaction-time. This measure was significantly and strongly associated with all three outcome indices. Verbal working memory was the best overall predictor. In an early study by Weaver and Brooks (4), poor finger tapping and slow reaction-time were good predictors of outcome. Thus, even simple and unsophisticated tasks can be used to study salient aspects of the cognitive deficit of schizophrenia. An advantage

This paper was presented in part at the symposium 'Cognitive Dysfunction in Schizophrenia' at the 9th Congress of the Association of European Psychiatrists, 20 September, 1998 in Copenhagen. The symposium as well as this publication were supported by a non-restricted grant from Janssen Cilag, Denmark.

with simple tasks is that patients who have extensive deficits can also be tested.

The aim of this longitudinal study was to analyse relations among a set of simple neuropsychological tests, clinical symptoms and side effects, with control over the medication factor (depot administration and plasma level checks). Since only depot out-patients were included, the group can be characterized as poorly functioning in many respects, and with a high symptom load.

Material and methods

Subjects and clinical data

Patients were recruited from a 3-year follow-up neuroleptic dose-reduction study of out-patients with chronic psychoses treated with depot neuroleptics (5).

Neuropsychological testing commenced approximately 1 year after study entry, to allow for a stable recruitment into the project. All were out-patients and had been depot-treated for several years, except two who had had depot during 1 year. All except one had either a disability or retirement pension. Of initially 51 patients in the parent study, 34 (21 men and 13 women) accepted to participate in a series of neuropsychological test sessions. Of the missing 17 patients, six did not want to participate after study entry, nine left the follow-up part for other reasons (e.g. moved, relapsed), and two patients did not manage to understand the very simple test instructions.

The 21 men joining the study had a median age of 48 years, range 29–67, and the 13 women 60 years, range 33–74.

DSM-III-R (APA, 1987) provided the diagnostic criteria. Schizophrenia was the most common single Axis 1 diagnosis (24/34 patients). Eight patients fulfilled criteria for schizoaffective psychosis. Two patients had other chronic psychoses. Three schizophrenic patients abused drugs (alcohol two, amphetamine and cannabis one). The patients had suffered from their chronic illness for a long time (median 21 years, range 3–42). For schizophrenic patients without abuse the duration was median 15 years (range 6–42), for the three schizophrenic patients with abuse 28 years (range 6–35), for the schizoaffective group 26 years (range 12–40), and for the two with other psychoses range 3 and 9 years.

Clinical symptoms were assessed by the Comprehensive Psychopathological Rating Scale (CPRS (6)) and the Clinical Global Impression Scale (CGI (7)). Three subscales were computed reflecting positive, negative and affective symptoms (5). Tardive dyskinesia was rated by the Abnormal Involuntary Movements Scale (AIMS; (7)), and akathisia by the Barnes scale (8). Extrapyramidal symptoms (EPS) were assessed by the Simpson and Angus scale (9).

Medication

All patients were treated with depot (decanoate) injections of either perphenazine ($N=15$), flupenthixol ($N=9$), zuclopenthixol ($N=4$) or haloperidol ($N=6$). Anticholinergic medication were prescribed to 19 patients. Additional neuroleptic medication (more than 100 mg CPZ equivalents of a high dose neuroleptic) was given to three patients. Four patients had lithium. Medication data are summarized in Table 1. The depot doses were converted to oral CPZ equivalents (mg/day), using established bioavailibility and equipotentiality data of the four drugs (10).

The 2-year follow-up patient group

The initial group of 34 patients were tested once, 25 were tested twice and 23 were tested three times over the 2 years. The results will be reported for a subgroup of 18 patients who completed at least four test sessions. Four of these were schizoaffective. The median age of the 11 men was 47 years, range 29–65, and of the seven women 63 years, range 39–69. The depot drugs (decanoate) given initially were perphenazine to 10, flupenthixol to five, and haloperidol to six patients. Mean dose, expressed in CPZ equivalents was 313 ± 231 mg/day. Eight patients had anticholinergic medication and three had lithium. Results based on 25 patients tested twice or 23 patients tested three times did not differ from the findings for the 18 four-session patients.

Neuropsychological tests

Three simple sets of tests were selected from the APT computerized neuropsychological test battery (11). The selection was limited by the problem of the poor testability of the patients. A larger battery was chosen and tried initially, but the drop-out rate would then have increased beyond what was

Table 1. Data of the four depot neuroleptics (decanoate): depot dose/week, median (range); total neuroleptic medication expressed in chlorpromazine (CPZ)-equivalents (mg/day), mean ± SD; and plasma concentration, mean ± SD

Medication	*N*	Depot dose (mg/week)	CPZ-equiv.	Plasma conc. (nmol/L)
Perphenazine	15	36 (17–72)	298 ± 105	4.5 ± 1.6
Flupenthixol	9	10 (2.5–30)	221 ± 151	1.5 ± 0.7
Zuclopenthixol	4	95 (20–200)	516 ± 336	19.8 ± 7.9
Haloperidol	6	17 (13–100)	361 ± 384	6.4 ± 5.7

acceptable. The following tests were included in the set, and presented in the following order:

Visual Analogue Scale (VAS) self-ratings of the current state (last 3 days) concerning concentration difficulties, alertness, sleep and social activities (10 items).

Reaction-time (RT) comprising two subtests: (1) simple auditory RT to nine stimuli responding with the dominant index finger; and (2) Two-choice visual RT: 17 light stimuli to the right or left of a central fixation point, responding with the index finger of the corresponding side.

Finger tapping with (1) the right, (2) the left index finger; (3) alternation between the right index and middle fingers; (4) the corresponding for the left hand; and (5) alternation between the right and left index fingers. The duration of each task was 12 s.

Digit span test: a process-controlled number of digits are presented one by one on the screen. The sequence should be reproduced forwards (13 items) and backwards (11 items).

VAS self-ratings of stress, concentration difficulties, and ambitions during the testing, and a subjective evaluation of performance (seven items). Response times to all VAS items were recorded.

Neuropsychological test data comparison groups

Comparison test data are presented from the following groups of subjects:

1) *Norm data* (11) based on healthy subjects of both sexes, age 17–45 ($N > 500$, collected over several studies).
2) *Healthy elderly subjects* of both sexes ($N = 480$, mean age 75, range 67–103), screened as normal and free from disease within a project on car driving and the elderly (Department of Geriatrics, Huddinge Hospital).
3) *Young schizophrenic out-patients* of both sexes ($N = 29$, mean age 28, range 20–40), collected by Gråwe and Levander (12).
4) Patients with various *brain lesions*: stroke, subarachnoid haemorrhage and head traumas ($N = 31$, mean age 44, range 21–62), collected within a project on car driving and brain lesions (Department of Rehabilitation, University Hospital, Linköping).

Statistics

The reaction-time measures were skewed. A log transformation yielded normal distributions. None of the self-rating scale variables were normally distributed. Correlations were calculated by the Pearson coefficient whenever a variable pair was normally distributed, or else by Kendall's tau. Means were compared by *t*-tests or one-way ANOVAs when normally distributed, or else by the Mann–Whitney test.

Procedure

Patients were asked to participate in the neuropsychological testing after completing each symptom evaluation session of the main study. All assessments were obtained on the day of a regular depot injection. Plasma concentrations of the treatment drug were obtained the same day.

Results

The study entry patient group ($n = 34$)

Results of reaction-time, tapping, and digit span tests from the first test session for the 34 patients are shown in Tables 2–4, and compared to norm data and data from some other groups of subjects. The performance of the current group of patients was markedly inferior to all other groups.

Medication data and neuropsychology. No significant differences in clinical symptoms, side effects or drug load, expressed in CPZ units, were found among the four neuroleptic drug groups. Neuropsychological data did not differ among the four drugs or with drug dose, expressed in CPZ equivalents. Test results or side effects did not differ between patient groups with/without anticholinergic medication.

Patient data, clinical symptoms/side effects and neuropsychology. Reaction-time (RT) and finger tapping were significantly slowed by age: Kendall's tau ranged between 0.27 and 0.38 for RT measures, and between 0.20 and 0.30 for tapping measures (all $P < 0.05$). Short-term memory did not correlate with age. Extrapyramidal side effects (EPS) increased with age ($\text{tau} = 0.28$, $P < 0.05$). The strength of the association between motor test performance and age was weakened by partialling out EPS for some variables, but remained significant for simple auditory RT ($r = 0.45$, $P < 0.01$), and for tapping left ($r = -0.40$, $P < 0.05$) and alternation between right and left hands

Table 2. Results of the reaction time test time measures (msec) for the current group of schizophrenic patients ($N = 34$) and three comparison groups: norms, young schizophrenic patients and healthy old subjects

Group	Audi	VisuL	VisuR
Norms	203 ± 49	271 ± 64	263 ± 63
Young schiz.	236 ± 89	312 ± 82	314 ± 68
Age 67–91	349 ± 248	356 ± 118	351 ± 114
Current group	399 ± 241	516 ± 357	495 ± 300

Table 3. Results of the finger tapping test (taps/s) in mean ± SD for the current group of schizophrenic patients ($N=34$), norms and young schizophrenic patients

Group	TR	TL	AR	AL	ARL
Norms	6.8 ± 1.3	6.4 ± 1.0	4.0 ± 1.2	3.8 ± 1.2	4.5 ± 1.0
Young schiz.	5.5 ± 1.1	5.2 ± 1.4	3.2 ± 1.0	3.0 ± 1.1	3.5 ± 0.9
Current group	4.5 ± 1.8	4.0 ± 1.8	2.1 ± 1.5	1.9 ± 1.3	2.4 ± 1.5

Table 4. Results of the Digit Span test for the current group of schizophrenic patients ($N=34$), norms and a comparison group of brain lesion patients

Group	Forwards	Backwards
Norms	6.7 ± 1.0	6.3 ± 1.4
Brain lesions	5.1 ± 1.3	4.5 ± 1.1
Current group	4.6 ± 1.2	3.5 ± 1.1

($r=-0.38$, $P<0.05$). There were no differences between the sexes.

Twenty-one core schizophrenic patients were compared to eight patients with schizoaffective psychosis (excluding patients with abuse). Age, negative symptoms and CPRS sum scores did not differ significantly, nor did the results of the digit span, RT and alternating tapping tests. Schizophrenic patients were markedly slower at finger tapping right hand than the schizoaffective ones ($t=3.2$ $P<0.01$). The difference was non-significant for the left hand.

Symptom load, assessed by sum CPRS and CGI, was associated with a longer two-choice RT ($r=0.38$, $P<0.05$) and slower tapping ($r=-0.43$, $P<0.05$). The positive and affective subscales displayed no significant correlations, but negative symptoms were highly correlated with poor test results. The association was strongest for two-choice RT ($r=0.62$, $P<0.001$). Also tapping ($r=-0.59$, $P<0.001$) and alternation ($r=-0.46$, $P<0.01$) speed was markedly reduced for subjects with prominent negative symptoms. Short-term memory was not associated with any symptom variable. Negative symptoms correlated significantly with EPS ($r=0.43$, $P<0.05$). Partialling out EPS sum-scores did not change the association between negative symptoms and the neuropsychological variables except for the two intrahemispheric alternation tasks. Partialling out age did not change any of the correlations significantly.

Akathisia, tardive dyskinesia and tremor were not associated with test results. Total scores of EPS were significantly associated with fewer alternations ($r=0.43$; $r=0.49$) and fewer tappings ($r=0.46$; $r=0.30$).

Relapses or exacerbations during the follow-up time were not predicted by any of the neuropsychological or clinical parameters. Patients with early onset of psychoses (before age 25) did not differ from patients with later onset in respect of test results.

VAS ratings. Almost all of the 10 subjective state VAS items were significantly associated with CPRS sum-scores, but not with the negative subscale. Approximately half of the correlations between subjective state and the two akathisia scales were significant, whereas symptoms of tardive dyskinesia did not seem to bother the patients (no significant correlation with any VAS item). Drug dose (expressed in CPZ units) was not related to any of the VAS items. No significant correlations were obtained between the seven test performance VAS items on one hand, and clinical assessments, neuroleptic dose level or objective test performance on the other hand.

The follow-up patient group

The 18 patients who participated in at least four test sessions during 2 years, were representative of the whole group of patients, i.e. they did not differ in respect of drug dose, clinical ratings or test results. Of the men 4/11 remained clinically stable during 5 years (from 1 year before the first test session until 2 years after the last session), two exacerbated, and five men relapsed (were admitted to hospital). Of the seven women, three remained stable, two exacerbated and two relapsed (13).

During the 2 years three patients changed medication from perphenazine depot to clozapine due to severe side effects and disturbing positive symptoms. One patient switched from perphenazine to haloperidol decanoate due to severe side effects (which did not reduce the side effects).

Medication dose, clinical symptoms, side effects and neuropsychology. The intraindividual *stability over time* for symptoms, side effects and neuropsychology was assessed as a reliability coefficient obtained from the within- and between-subject variance components in an ANOVA (14). The coefficient for clinical symptoms/side effects varied from 0.48 (akathisia) to 0.93 (tremor). The corresponding reliability coefficients for the neuropsychology parameters varied between 0.80 (digit span test backwards) to 0.95 (tapping right finger, two-choice RT and alternation between hands).

The overall *change over time* was assessed by ANOVAS as the linear trend of the main effect of time. Only one significant ($P<0.01$) analysis emerged: an increase for tapping with the right hand ($F(3/51)=5.81$).

Relations among measures over time were assessed by ANCOVAS. There were no marked deviations in the correlation pattern among data based on one measurement in 34 subjects, two in 25, three in 23 and four measurements in 18 subjects. There were no significant (with $P<0.01$ as criterion) intra-individual associations over time between any of the clinical, VAS and neuropsychological measures.

Neuropsychological data and clinical outcome. There were no significant relations between any of the neuropsychological measures and outcome (stable, exacerbation, relapse), nor any differences between test sessions preceding an exacerbation or relapse, and test sessions followed by a period of clinical stability.

Discussion

The current group of chronic psychotic patients treated with depot neuroleptics was markedly impaired on all neuropsychological indices compared to other groups of subjects. Impairments have been documented repeatedly during the current century, but the degree of impairment is often regarded as much less pronounced than in the present study. The current 34 patients comprise a less disturbed subgroup of all 89 depot treated out-patients of the catchment area, in which approximately 270 schizophrenic patients were known to the psychiatric services. The impairment was constant over four test sessions spread over 2 years, in contrast to the findings by Gråwe and Levander (this issue (15)) for a much younger and less ill sample of patients. The inter-individual variation was much more prominent than the intra-individual one. EPS scores and tapping speed, right hand, were significantly improved over the 2-year follow-up period. Medication, in terms of dose, specific neuroleptic drug, plasma concentration or anticholinergic medication did not affect test results.

Negative symptoms were strongly correlated to neuropsychological motor deficits. All motor test performance deteriorated somewhat by age. Extrapyramidal side effects seemed to affect more complex motor tests, such as alternation movements, more than simple motor tests.

Outcome after 5 years, expressed as hospitalizations or clinical exacerbations, was not predicted by any of the tests or clinical assessments. The poor predictive power cannot be due to a restriction of range in our poorly functioning sample of patients. The relapse rate during the 5-year follow-up was 50% for the main study patients. In spite of a large variation in clinical parameters, the neuropsychological deficit was highly stable over the 2 years. Thus, the illness seems to have come to a plateau in terms of cognitive functions, albeit on a very low level, after an average duration of 20–25 years.

The self-rating data suggest that patients under-report side effects, except akathisia. The subjective underestimation of side-effects has been reported earlier (16). For the clinician, it is important to use structured methods to assess side effects when evaluating patients. Overall, patients with prominent negative symptoms scored themselves as more symptom-free and well-functioning. Probably, this is a reflection of self-monitoring problems, which also showed up in their ratings of test performance. These ratings were characterized by a high frequency of either lop-sided or conventional 'in the middle' scores, and had no relation to their actual test performance.

The present study can be criticized for its small number of patients and a limited set of neuropsychological tests. However, there are no similar longitudinal studies published in the literature (2). The main conclusion is that a set of simple neuropsychological tests, similar to the ones used successfully to predict clinical outcome by Weaver and Brooks in the 1960s (4), can be used to test otherwise 'untestable' patients and be clinically useful.

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