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ORIGINAL PAPER

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Premorbid IQ and schizophrenia

Increasing cognitive reduction by episodes

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Abstract In order to test the hypothesis that acute schizophrenia episodes have a negative impact on cognitive function, 35 consecutive non-abuse schizophrenia outpatients (age < 60) were enrolled in this study. All subjects for whom grades from the 9th year of the Swedish school system were available, had to complete a comprehensive computerized neuropsychological test session. Symptoms were rated by PANSS and GAF, previous episodes were tallied, and medication was logged. A premorbid cognitive score was calculated on the basis of school grades and validated by comparison with academic career and current cognitive performance (r = 0.56). Half had college level studies or higher, and the overall school grades for the group were above average. PANSS (sum = 59) and GAF [59] ratings as well as medication (M = 230 CPZ units) suggested a moderate symptom level. Two patients had no neuroleptic drugs, 16 had atypical and 17 had conventional neuroleptics. Vocabulary was intact. On average, patients had lost 1 standard deviation (SD) in most cognitive tests but response time slowing amounted to 3.5 SD. There were no differences in cognition between drug types and no correlation with CPZ dose. The number of previous episodes was positively correlated with reaction time prolongation and negatively correlated with short-term verbal memory, consistent with a previous study suggesting that acute episodes cause specific cognitive reduction.

Key words schizophrenia · school performance · premorbid IQ · cognitive reduction · episodes · atypical neuroleptics

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Introduction

There is now consensus that most core schizophrenic patients have some mild cognitive defects prior to diagnosis (Cantor-Graae, Ismail & McNeil 2000; Raedler, Knable & Weinberger 1998) that might potentially predict a predisposition for the disease (Davidsson, Reichenberg, Rabinowitz, Weiser, Kaplan & Mark). Furthermore there is a distinct deterioration in association with the first acute period of the disease (Bilder, Lipschutz-Broch, Reiter, Geisler, Mayerhoff & Lieberman 1992). The degree of deterioration predicts long-term outcome and response to treatment better than positive and negative symptoms (Green 1996, 1998, 2001). So far, indices of attention, working memory and executive functions (but also of reaction time) appear to be most affected by the disease process and carry most of the predictive power for outcome.

In this perspective, the study of the time course of cognitive reduction, from the prodromal phase and the acute phase of the first episode, during the intervals between new episodes, in exacerbations or new episodes, into an eventual defectuation phase or a phase of recovery, should be pursued. Several mainly cross-sectional studies have explored whether the development of cognitive deficits is progressive or essentially static by comparing first-episode patients with patients who have been ill for a long time. The findings are inconsistent, reflecting both the heterogeneity of the syndrome and the selection of patients as well as changes in treatment strategies over time. The focus of testing in those studies has been either complex functions assessed by conventional psychometric tests in the WAIS-tradition or key deficits studied by elaborate experimental designs. According to a relatively recent meta-analysis, there are only a handful of longitudinal studies in the literature that follow schizophrenic patients over at least two years, using a test battery (rather than single tests) to assess cognitive function (Rund 1999; Levander et al. 2001).

One longitudinal study from our group (Gråwe & Levander 2001), which followed first episode patients over three years, suggested that there was a deterioration of reaction time. Another longitudinal study focusing on chronic depot treated schizophrenic patients (Tuninger & Levander 2001) suggested stability of cognitive deficits over the time period but underlined the exceptional deficits in terms of motor speed and reaction time that characterized the patients. These deficits could not have existed premorbidly (they are never found in any "normal" material regardless of age) – consequently they must have appeared at some time during the course of the disease. A third study from our group, using a design in which consecutive schizophrenic patients were allocated to four groups based on the number of previous episodes (Levander et al. 2001), yielded an unexpected and highly significant finding – response preparedness decreased by almost one SD for each episode that was logged. It should be noted that the duration of untreated psychosis does not appear to be associated with worse cognitive functioning (Norman, Townsend & Malla 2001).

Theoretically, the progressive deterioration of response preparedness that we found was thought to reflect increasing damage to a hypothesized functional unit denoted "action pattern generator", in analogy to a corresponding mechanism suggested to be the key problem in Parkinson's disease, "motor pattern generator" damage. The logistic link between an intention and the actual cognitive program that has to be executed is failing. This introduces time delays in the system and upsets the corollary discharge, which in turn can disconnect intentions and actions – leading to failure to recognize the inner workings of the mind as self-produced (Frith 1987). It should be noted that the next strongest association of episode-related deterioration in our study was verbal short-term memory – known to be strongly associated with the quality of the frontal lobe based central executive system.

There are several steps that must be taken before the model presented above can be accepted. The first step is a replication – that reaction time to simple stimuli and possibly verbal short-term memory are more deteriorated in schizophrenic patients who have had a higher number of acute episodes. If such a replication is associated with some control over premorbid cognitive functions, one main source of confounding error is eliminated. Swedish school grades of pupils are official data and available to anybody. The school system up to grade 9 has been uniform since the 1950s. Grades represent a Likert scale with five steps that are forced into a normal distribution with M = 3. These unique features can be used to assess general IQ at age 16, retrospectively. Grades of this kind have been demonstrated to be strongly correlated with IQ as assessed by the test battery used in the Levander et al. (2001) study of schizophrenic patients cited above (material described in Levander 1987; Jellhede 1999).

The main aim of the present study was to replicate the previous finding of episode-related deterioration of response preparedness, with control over premorbid IQ, in a group of DSM-IV-schizophrenia outpatients with a relatively late onset of illness. The patients came from a university town and were expected to have a higher level of premorbid functioning and therefore possibly less pronounced cognitive deficits than the average schizophrenic patient has.

Method

Subjects

Out of 72 outpatients (age < 60) with a registered diagnosis of schizophrenia (ICD-9; 295) consecutively seen by one physician (the main author) during 1996–98, 60 consented to participate in the study. Four patients were too ill to be tested and 7 patients were excluded because of concomitant alcohol or drug abuse. For 9 of the patients who were mostly immigrants it was not possible to obtain school records. Of the remaining 40 patients, one died before the study was completed. In four cases, the original diagnosis was changed after more clinical information accumulated (ADHD, Tourette syndrome, and Affective psychoses). The 35 patients with complete data sets (age 22–59) had a DSM-IV schizophrenia diagnosis. Patient characteristics are presented in Tables 1 and 2.

Patients were allocated to three subgroups on the basis of the number of previous acute episodes: those having had 1; 2 or 3; or more than 3 previous acute episodes. Such episodes were defined as a distinct increase in symptoms that required a substantial change in the treatment of the patients, either a change in status (from out- to

Table 1 DSM-IV-diagnosis categorized according to age and sex

	295.10		295.30		295.60		295.70		295.90	
	M	W	M	W	M	W	M	W	M	W
Age:										
20–30		1		1					1	2
30–40	1	2	1	6		1		2		3
40–50			2	2				2		2
50–60			1	1	2		1		1	

Table 2 Clinical data, including PANSS subscales, among three subgroups of schizophrenic patients defined according to the previous number of acute episodes

	Number of acute episodes			
	All subjects (N = 35)	1 (N = 11)	2–3 (N = 8)	> 3 (N = 16)
Women	29%	3	2	5
Men	71%	8	6	11
Age	39±10	36±7	40±13	40±10
CPZ (mg)	233±180	164±174	224±109	285±203
Onset age	29±8	32±8	30±10	27±8
Illness duration (years)	10±8	5±4	11±11	14±6
GAF	59±9	62±11	60±6	56±9
PANSS:				
Total	59±11	55±10	55±12	63±10
Positive	12±3	12±4	12±2	13±3
Negative	16±6	16±6	14±6	18±6
General	31±7	28±6	28±6	33±7

inpatient) or a non-trivial change of medication (cf. Tuninger 1997 and Levander et al. 2001). A new episode was not tallied unless 6 months had passed since the previous one. The distribution of the patients into these three subgroups was enough even to allow Analysis of Covariance as statistical method.

Data on medication

Of the 34 patients who were medicated, 33 received neuroleptic drugs. Compounds were classified as conventional or atypical (risperidone, clozapine, olanzapine or remoxipride). Sixteen patients were treated with atypicals alone (in a few cases in combination with each other). The remaining patients were treated with conventional neuroleptics, in some cases in combination with atypicals. Doses of the drugs were converted to an equivalent dose of oral chlorpromazine (CPZ) as described by Tuninger & Levander (1997).

Neuropsychological assessment

The neuropsychological battery included tests selected from the computerized neuropsychological Automated Psychological Test system (APT; Levander, 1987; Jensen et al. 1999), which is considered "state of the art" in computerized testing by Kane (1999). Tasks and instructions are presented on a CRT screen in front of the subject, who responds to stimuli and tasks by pressing keys on a custom-designed ergonomic keyboard. In order to reduce the vast number of variables that can be output from the system, a standardized set of meta-analysis variables, expressed as T-scores for healthy male controls aged 20–50 years ($N > 1000$), were entered into the statistical calculations. The specific tests are listed below.

The *Associative Learning Test* modeled on the Digit Symbol Substitution Test uses letters instead of symbols. A translation table between 10 letters and digits is continuously present at the top of the screen. Letters are presented one by one in the center of the screen. The subject responds by entering the corresponding digit and at the same time tries to learn the link between the letters and digits. Test duration is 5 minutes.

The *Long-term Memory Test* is given 20 minutes after the Associative Learning Test. The task is the same but without access to the translation table between digits and letters. Test duration is 4 minutes.

In the *Digit Span Test*, digits are presented visually one after the other with process control of the length of the digit sequence. The task is to reproduce the presented sequence, first forwards for 13 sequences, and then in the reverse order for 11 sequences. Test duration varies according to the speed of the subject.

In the *Finger tapping Test* five subtasks are presented: Tapping with the index finger and alternation between the index and middle finger, for both hands, and alternation between the right and left index finger. Test duration is approximately 2 minutes.

In the K-test of *Selective Attention*, the task is to decide, as fast as possible, whether the letter k is present in a set of 10 characters presented in random positions on the screen. The test is administered in two versions, with either uniform squares or randomly selected letters as distracters. Rational subjects use a global strategy in the first and a sequential strategy in the second task. Test duration is 6 minutes for each subtest.

In Elithorn's *Perceptual Maze*, the task is to select a pathway through a triangular maze pattern from the bottom to the top. The maze is built up by neutral and target nodes. The pathway should be filled in so that it passes the maximum number of target nodes (there are always two separate correct pathways – one in the left half-field, one in the right). Again, two versions are presented, one version that encourages a sequential strategy (with target information) and one for which a global intuitive strategy is best suited (no target information). Test duration is 7 minutes for each subtest.

The *Reaction time* module comprises four versions (9 simple auditory stimuli, 9 simple visual, 17 two-choice visual, and 25 two-choice visual with auditory response inhibition stimuli (Go-NoGo). Test time is 8 minutes for the whole set.

The *Word Recognition Test* is a lexicon decision task in which subjects decide whether a combination of letters presented on the screen is a word or is nonsensical. After training on 32 three-letter stimuli, 80 4-letter stimuli are presented, of which 20 are commonly used words, 20 are less commonly used words, 20 are pronounceable non-words and 20 are non-pronounceable non-words. From the test an index of vocabulary and an index of word decoding speed is calculated. Test time is 5 minutes.

Meta-indices of Cognitive Strategies are extracted from several tests, e. g., the Speed-vs-Accuracy, the Impulsiveness-vs-Reflectivity, and the K-test Flexibility indices (Wirsén Meurling, 1999).

Procedure

Participants were asked about their school grades in association with visits to the outpatient mental health center. The actual grades were then collected from the schools (grades are official data in Sweden). The cognitive testing was part of the standardized clinical procedure, following recommendations from the Swedish Psychiatric Association. The test session takes approximately 90 minutes for a normal subject and typically a much longer time for patients with schizophrenia (instruction, motivation, resting after each test), even if the time on most of the tests is the same for all subjects. Therefore, all patients who completed all tests came at least twice for testing, to avoid exhaustion and keep motivation high. Symptom and GAF ratings were performed within one week of testing.

Statistics

The results of the psychometric tests are presented as T-scores ($M = 50$, $SD = 10$) of the APT meta-analysis variables. The statistical analyses are based on these scores. Various ANOVA and ANCOVA procedures were used when comparing clinical, educational, drug and neuropsychological test results in the different patient groups.

Results

Level 9 school grades

The primary school grades range from 1 to 5, five being the highest. A factor analysis suggested that all the grade ratings except physical education and handicraft belonged to one factor. It is reasonable to expect that the corresponding factor score has a high correlation with g-factor IQ (Jellhede 1999). In order to validate this index of premorbid IQ at age 16, we assigned a score ranging from 1 to 6 to reflect the attained education level. Score 1 was assigned to patients who did not complete secondary school, Score 2: less than 12 years formal education, Score 3: 12 years formal education but no academic level studies, Score 4: academic studies but no grade, Score 5: an academic degree, and Score 6, patients on post-doc level. One patient actually had two doctoral degrees. There was a linear increase in educational level with increasing grade scores (Table 3). A g-factor index based on the Current APT Performance (the average of all performance indices) correlated 0.56 with level 9 school grades. These three methodologically different indices were independently validating each other.

The average level 9 grade was higher than the Swedish national average – as expected the current group of patients can be assumed to have had a high average premorbid IQ.

Table 3 Primary school-ratings (factor scores = z scores) vs. achieved educational level (ANOVA, F (1.28) = 10.9**)

Education level	1	2	3	4	5	6
Factor scores ± SD	−0.84 –	−0.45 0.15	−0.46 1.05	0.29 0.75	0.33 0.98	1.04 0.78

Clinical data

As expected there were negative correlations between PANSS and GAF ratings. However, there were no correlations between CPZ and symptoms or GAF scores (Table 4). Patients with high premorbid IQ (high level 9 grades) had less pronounced negative and general symptoms.

Performance in relation to previous number of episodes for the three subgroups for clinical and drug data are given in Table 2 and data on the neuropsychological variables are found in Table 5. For the clinical data, the three subgroups of patients differed substantially with respect to age and time since onset of illness. It should be noted, however, that there was a large variation within each of the subgroups for all the clinical variables making it possible to compensate statistically for subgroup differences by analyses of covariance.

The subgroup differences for the neuropsychological variables displayed a pattern, whereby the degree and number of deficits increased gradually with a higher number of previous episodes for two neuropsychological variables: simple reaction time and verbal short-term memory. In contrast verbal and other complex skills related to the length of formal education remained largely intact. Thus, the widespread use of vocabulary as an index of premorbid intelligence gains support in our data, provided that the subjects are evaluated in their mother tongue. Neither symptoms nor drug dose (CPZ units) or drug type (conventional vs atypicals) differed statistically among the three subgroups.

Episode-related cognitive deterioration

A multiple stepwise regression equation was calculated, with number of previous episodes as the predicted measure and a subset of clinical and neuropsychological variables as predictors. The neuropsychological parameters that were chosen were the main performance meta-indices of the APT test battery (see Table 5). One of the two reaction time meta indices was replaced by the individual RT measure expressed in logarithmic form to compensate for the typical skewness in such reaction time data for schizophrenic patients (Levander et al. 2001). Of the twenty variables entered three were shown, by the regression algorithm, to be predictors of number of previous episodes: Short-term memory, Simple Reaction time and CPZ units (adjusted R = 0.66). Furthermore, regression analyses focusing on these three measures related to level 9 grades suggested that the development of the cognitive deficit was more pronounced for those with high premorbid IQ. However, high premorbid IQ patients still performed better on these three measures than low premorbid IQ patients.

Table 4 Intercorrelations among PANSS symptom ratings, GAF scores and medication (CPZ units)

	Neg	Gen	Sum	GAF	CPZ
Positive	−0.10	0.36	0.43	−0.39	0.11
Negative		0.39	0.65	−0.33	0.12
General			0.90	−0.44	0.06
Sum PANSS				−0.52	0.12
GAF					−0.31

Table 5 Neuropsychological test profile among schizophrenics expressed as T-scores (M = 50, SD = 10) for different numbers of previous episodes

	Number of episodes			
APT Index	1	2–3	> 3	p <
RT200	30.3	12.6	3.49	0.05
RT2000	45.2	43.8	44.5	NS
Selective attention	49.5	34.3	32.3	NS
Simult.capac. Background	41.5	34.0	37.8	NS
Foreground	44.5	48.3	39.6	NS
Vocabulary	55.1	53.2	53.0	NS
Verbal decode speed	45.6	36.8	44.5	NS
Grammatical reasoning	40.5	32.1	36.8	NS
Visuo-Spatial	44.7	40.6	38.7	NS
Verbal short-term memory	47.2	35.5	35.6	0.01
Verbal long-term memory	47.0	39.7	39.0	NS
Non-verbal scratch pad memory	53.5	41.0	45.4	NS
Tapping	43.4	34.8	36.0	NS
Alternation	44.5	34.6	41.1	NS

Discussion

The subjects who were scholastic high achievers deteriorated more in terms of z-scores. However, deteriorating from a higher level they were on the average less cognitively impaired at testing suggesting a "protective" effect of higher premorbid IQ (David et al. 1997). The main finding was that two neuropsychological indices, simple reaction time and verbal short-term memory deteriorated by new episodes. In contrast, performance in the other neuropsychological tests, except vocabulary, which appeared to be intact, dropped by at least one SD after the first episode, but then remained static. These findings cannot be explained with reference to premorbid cognitive deficits – the group of patients had Grade 9 school grades suggestive of above average IQ. Nor can it be explained by confounding with clinical symptoms or medication. Actually, medication contributed with a

separate effect to the episode-related deterioration in the two key neuropsychological indices (Reaction time and Short-term memory). Otherwise, medication (dose or atypical vs conventional) did not matter for symptoms, GAF scores or neuropsychological data.

The current findings represent the first cross-validation of the finding reported by Levander et al. (2001). It is noteworthy that the pattern of data is so similar. In contrast to the previous study, the current data involve control for premorbid IQ. Recently, reaction time data for 500 healthy subjects age 65–103 has been collected – only one of these subjects had reaction times slower than 3.5 SD. Thus, it is statistically impossible that the group mean deficit of reaction time of the schizophrenic patients is premorbid or age-related. Another recent study, of Wilson patients (Portala et al. 2001), suggests that these patients, with basal ganglia pathology, have a deficit pattern similar to schizophrenic patients with a pronounced reduction of response readiness. In contrast, abuse patients or forensic psychiatric patients display other types of deterioration profiles or are neuropsychologically intact.

A definite conclusion as to the existence of specific episode-related cognitive deterioration must be based on a longitudinal study with repeated measurements over time and the course of illness. In this way one would also get around the problem that we assumed that the school grade based z-score actually corresponds to the initial T-score for RT200 and short-term memory.

In order to validate the generative mechanisms that according to our hypothesis may be involved in the specific deteriorating process by episodes, other types of studies with repeated testing in an experimental setting would be necessary. Such investigations ought to involve the measurement of potentially stress-related important biochemical (for instance, glucocorticoid levels) and neurophysiological parameters such as brain blood flow, evoked responses and pre-pulse inhibition of the startle response. A more detailed comparison with Wilson patients might prove fruitful – the cognitive deficit pattern (of subcortical type with slowness as the main feature), its development over time and the probable location of pathology (the basal ganglia) appear to be similar.

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