Chapter 6

The limited predictive value of cognition for outcome in schizophrenia

Submitted:
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Abstract

Objective: This study examined the predictive value of cognitive functioning in a first episode group for course of illness and functional outcome in schizophrenia. ***Method***: One hundred and eighteen first episode patients were tested on a cognitive battery. One hundred and three patients participated in the follow-up two years after inclusion. Data were gathered to predict course of illness, social role functioning, competitive employment, and need for care. Differences in outcome between cognitively normal and cognitively impaired patients were also analyzed. ***Results***: Cognitive measures at inclusion did not predict relapse rate, social functioning or competitive employment. Time in psychosis or in full remission, as well as need for care were partly predicted by specific cognitive measures. Although statistically significant, the predictive value of cognition was very limited, explaining a maximum of six percent of the variance in these measures. There was a significant difference between patients with and without cognitive deficits in general on competitive employment status and the work role. ***Conclusions***: Although cognitive deficits in a global sense may affect work performance, the predictive value of specific cognitive measures for outcome in schizophrenia is quite limited. This challenges the idea that cognitive impairment should be considered as the core of the disease and suggests that the relation between cognition and outcome is not that straightforward, and might be affected by other mechanisms, such as mental effort and compensation.

1. Introduction

There is no doubt that cognitive deficits are often found in schizophrenia. As for the nature of the cognitive deficits in schizophrenia, most authors agree that there are specific deficits against a background of generalized cognitive dysfunctioning (Saykin et al., 1994). In an extensive meta-analyses the largest differences between schizophrenia patients and healthy controls were found for verbal memory, performance IQ and vigilance (Heinrichs and Zakzanis, 1998).
Schizophrenia often runs a chronic course, which is difficult to predict. One of the most important course specifiers is relapse rate. Relapse rate in the first year is relatively low but rises substantially in the following years. Five years after first contact it varies around 70 – 80% (Robinson et al., 1999; Wiersma et al., 1998). Common sense suggests that cognitive competence is likely to be a predictor of course of illness. One reliable study so far has investigated the predictive value of cognitive measures on course of illness. No significant effect was found (Robinson et al., 1999).
Functional outcome is multidimensional, consisting of several domains such as interpersonal functioning, functioning in community settings, performance of basic daily activities, occupational functioning. Although only a modest percentage of patients end up staying in a psychiatric hospital or living in sheltered accommodation (14% in a six-site European study; Wiersma et al., 2000), a large percentage of the patients living in the community experience problems with independent functioning, performance of basic daily activities or leisure activities. The onset of schizophrenia is also associated with a pronounced decline in employment (Mueser et al., 2001).
Although an increasing number of studies investigate the association between cognitive functioning and functional outcome in schizophrenia (see Green et al., 2000 for a review), only a few have investigated the longitudinal predictive value of cognition on functional outcome (Goldman et al., 1993; Johnstone et al., 1990, Addington and Addington, 2000; Fujii and Wylie, 2002; Velligan et al., 2000). The results are rather inconsistent. Two of these studies find no association (Johnstone et al., 1990, Addington and Addington, 2000). The other three found some significant cognitive predictors for several outcome domains (Goldman et al., 1993; Fujii and Wylie, 2002; Velligan et al., 2000). However, only one of these studies used a first episode group, while prediction is most

relevant early in the disease. No association was found, but in this study only two cognitive measures were used as a predictor.
Because of the lack of cognitive prediction studies in first episode groups, the aim of this study was to investigate the predictive value of cognitive functioning in recent onset group for course of illness, social role functioning, occupational functioning and need for care two years after inclusion.

2. Method

2.1. Subjects

The study included 118 patients who had recently experienced a first or a second psychotic episode according to DSM-IV and were diagnosed within the schizophrenia spectrum (schizophrenia, schizoaffective disorder, schizophreniform disorder). All patients participated in a Dutch multicenter study of the university hospitals of Amsterdam, Groningen and Utrecht. This study focused on the predictive value of neuropsychological and neurobiological factors for functional outcome at two year follow-up in all first or second episode patients who were referred to the departments of psychiatry for in- or outpatient treatment over a period of 1.5 years (1997-1998). After complete description of the study to the subjects, written informed consent was obtained. Diagnosis was based on a structured interview (SCAN; Wing et al., 1990 or CASH; Andreasen et al., 1992). Exclusion criteria were severe mental retardation and a known systemic or neurological illness. Hundred and three patients participated in the follow-up after two years (87%). There were no significant differences in age, sex, cognitive measures, and psychopathology at illness onset between these 103 patients and the 15 lost to follow-up. There was a significant difference in level of education ($F = 6.82$, $df = 1, 116$, $p = .010$) and mean abbreviated WAIS score ($F = 6.05$, $df = 1, 116$, $p = .015$) in favor of the patients who completed the follow-up assessment. At follow-up seventy-seven males and twenty-six females were included. Mean age at inclusion was 23.6 years (sd 5.5).
Forty-five healthy controls, thirty-eight males and seven females, were included in order to establish standard scores on cognitive tests. Exclusion criteria for

controls were a history of mental illness, mental retardation and a known systemic or neurological illness. Mean age was 23.8 years (sd 6.4). There were no significant differences between patients and controls for sex (χ^2 = 1.67, df = 1, 146, n.s.) or age (F = 0.63, df = 1, 146, n.s.). At inclusion twenty-four patients used typical antipsychotics, sixty-seven patients used atypical antipsychotics, eight patients did not use antipsychotic medication, and the medication data from four patients were missing. Ten patients also used anticholinergic medication.

2.2. Procedures and instruments

Cognitive measures

All patients completed an extensive neuropsychological battery after being stabilized for at least six weeks on medication. The cognitive measures in our study were chosen because of their widespread use in clinical practice, evidence for their discriminatory power in studies of schizophrenia patients and normal controls (Keefe et al., 1995; Saykin et al., 1994; van den Bosch et al., 1996) and some evidence for prediction of outcome according to former studies (Goldman et al., 1993; Fujii and Wylie, 2002; Velligan et al., 2000). Vigilance was assessed with the sensitivity index (d') of a double stimulus Continuous Performance Task. Processing speed was assessed with a compound scores of times in seconds on word reading and color naming on a computerized Stroop task and time on part A and part B of a modified version of the Trailmaking Test (Vink and Jolles, 1985). This version consists of three parts: part A with numbers 1 to 26, part B with letters A through Z and part C with 26 numbers and letters alternately. All speed measures showed high intercorrelations in the total group of subjects. Therefore they were averaged after a z-transformation based on the scores of the healthy controls, to create one score. Selective attention and inhibition was assessed with the Stroop interference score (Stroop color word minus Stroop color naming). General verbal learning performance (verbal encoding) was assessed with the total sum of words over the first five learning trials of the Dutch translation of the California Verbal Learning Test (Delis et al., 1987). Verbal Fluency was operationalized as the mean number of words over two categories in one minute (animals and professions). Intelligence

was assessed with four subtests of the Dutch translation of the Wechsler Adult Intelligence Scale (Stinissen et al., 1970): comprehension, vocabulary, block design and picture arrangement. The mean C-score of these four subtests was taken as a measure of intelligence. These C-scores go from 0 to 10 with a mean of 5 and an S.D. of 2. Because the Dutch translation of the WAIS is from 1970, we also give corrected mean C-scores in which we take into account an estimated IQ gain of 0.25 points a year from 1971 to 1997 (Flynn, 1998). The corrected mean C-score is 5.6 with an S.D. of 1.5, which is on an average level compared to the general population. Table 1 gives the scores on these cognitive predictors for patients and controls. Patients performed significantly below the level of controls on all cognitive measures, except for the WAIS score. To investigate whether having a cognitive impairment in a global sense at inclusion influenced outcome, we also analyzed the differences in outcome measures between "cognitively normal" (CN) and "cognitively impaired" (CI) patients. In order to assign patients to these groups, scores on a large neuropsychological battery were transformed into z-scores using means and SD's from the controls. A patient was considered cognitively impaired if he had at least one z-score of two or more below the control group (for more details: Holthausen et al., 2002).

Table 1. Means and standard deviations for cognitive predictors; patients compared with normal controls

	Patients N = 103	**Controls N = 45**	**Sign.**
Vigilance (CPT d')	3.53 (0.77)	4.29 (0.55)	.000
Speed of processing *	-1.9 (1.4)	0.0 (1.0)	.000
Selective attention (STROOP interference)	11.6 (11.4)	7.4 (5.2)	.037
Verbal encoding (CVLT trial 1-5)	45.7 (9.2)	56.4 (8.5)	.000
Verbal fluency (number of words)	18.0 (4.3)	22.7 (5.1)	.000
Intelligence (mean WAIS C-score 1-10)**	6.2 (1.5)		
Mean corrected WAIS C-score	5.6 (1.5)		

* Mean z-score on CPT reaction time, Trailmaking A, STROOP 1 and 2.
** Mean WAIS subtest score on Comprehension, Vocabulary, Block design, Picture arrangement.

Course of illness

Data were gathered with a case record form, using all possible sources of information. Data were analyzed over a mean period of 25 months (range 20-32). A relapse was defined as a period in which the patient experienced

delusions, hallucinations or conceptual disorganization, which interfered with daily life. These symptoms had to be severe enough to obtain a score of 4 (moderate) or higher on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). In order to score a new relapse, there had to be a previous period of 30 days without these psychotic symptoms. Only relapses after inclusion were counted. Thirty-eight patients (37%) experienced a psychotic episode at inclusion. Therefore we also looked at the percentage of time in psychosis. Remission was defined as a period without psychotic symptoms that would justify
a score of four or higher on the PANSS. We made a distinction between full and partial remission. Full remission was defined as a period without any psychiatric symptoms (PANSS scores < 2). Partial remission was defined as a period without severe psychotic symptoms, but with other psychiatric symptoms or less severe psychotic symptoms (PANSS scores < 4). The percentage of time in full remission was used for analyses.

Social functioning, competitive employment and need for care

Social functioning was assessed with the Groningen Social Disabilities Schedule (GSDS; Wiersma et al., 1988), a semi-structured interview that measures social role functioning on seven roles for the month preceding the interview. Social functioning was assessed at inclusion and at the follow-up. Mean social role score and the percentage of subjects showing disability on individual social roles were taken as outcome measures. Data concerning competitive employment were also gathered using the case record form. Competitive employment was defined as having a job, which enabled the person to make a living, or studying with a scholarship, because these students are required to fulfill certain standards concerning their study performance.
Need for care during the month preceding the follow-up was rated with the Camberwell Assessment of Needs (CAN; Slade et al., 1996). This is a structured interview in which the interviewer rates the need for care according to the patient on 22 topics on a 3-point scale (no problem, no problem /moderate problem due to help given, serious problem). We grouped the needs into four domains: ADL, mental health care, rehabilitation, services (Wiersma and Buschbach, 2001). The total number of needs (score ≥ 1), and the mean score on each of the four domains were taken as outcome measures.

2.3. Statistical analyses

All cognitive predictor variables were inspected to see if they resembled the normal distribution. A log transformation was performed for Stroop interference. The outcome data that were measured on an interval scale were also checked for normality of distribution. Relapse rate, time in psychosis, time in full remission, ADL-, rehabilitation- and service needs all had a positive skew and could not be normalized with the appropriate transformations. The other outcome measures resembled the normal distribution. Because hierarchical multiple regression analysis is rather robust for violation of the assumption that the criterion variable has to resemble the normal distribution we still used this method for analysis. For relapse rate, we also used logistic regression because the distinction between having no relapses at all and having one or more relapses appears to be most important. The predictive value of cognition for separate social roles, improvement or deterioration of social functioning over two years and competitive employment was analyzed with logistic regression. In order to investigate whether a cognitive impairment in a general sense at inclusion influenced outcome, differences in outcome between CN and CI patients were analyzed with one-way ANOVA's and $\chi 2$ tests. All tests were two-tailed.

3. Results

3.1. Outcome two years after inclusion

Course of illness

Seven of the 103 patients were psychotic during the entire follow-up period. Forty-nine patients had one or more relapses after inclusion. The mean percentage of time in psychosis for the whole group was 32%; the mean percentage of time in full remission was 25%. Fifty-three patients never were in full remission. The mean percentage of time in psychosis for these patients was 40%.

Social functioning, competitive employment and need for care

Table 2 gives the differences in social functioning between inclusion and follow-up. There was a significant improvement of the mean role score. Overall 69 % of the patients showed an improvement in social functioning, 29 % showed a deterioration, 2% remained stable. There were no differences in sex, age or course of illness between both groups. There was also a significant increase in the number of patients without social disabilities, from 2 patients at inclusion to 12 patients at follow-up ($p = .013$). Both at inclusion and follow-up, most patients showed disabilities in the work role.

Only 21 patients (21 %) fulfilled the criteria for competitive employment at follow-up. Of the remaining 81 patients (79%), 19 had regular activities, but depended on social welfare or their family to make a living. Five patients reported no problems for which they experienced a need for care. Most patients (67%) did have a need for care on 1 to 4 areas. The mean number of needs was 3.5, mostly concerning mental health care.

Table 2. Differences in social role functioning between inclusion and Follow-up

	Inclusion	Follow-up	Sign.
Mean role score*	1.2 (0.6)	0.9 (0.7)	.000
Self care**	44.7	22.5	.000
Family role	75.7	52.4	.000
Kinship role	60.2	50.0	ns.
Partner role	65.0	61.0	ns.
Citizen role	78.6	62.1	.012
Social role	62.1	58.3	ns.
Work role	86.4	68.0	.003

* Standardized GSDS ratings ranging from 0: no disability to 3: extreme disability.

** Percentage of subjects showing disability, differences between inclusion and follow-up were tested with the McNemar test, using the χ^2 distribution.

3.2. Prediction of course of illness, social functioning, competitive employment and need for care with cognitive variables

Cognition did not predict relapse rate. Even if the seven chronic psychotic patients were left out of the analysis, cognition still did not predict relapse rate. Selective attention and verbal fluency were significant predictors for time in psychosis. Verbal fluency was also a significant predictor for time in full

remission. Cognitive measures did not predict the mean social role score, disabilities on separate social roles, the distinction between improvement or deterioration in social functioning over two years or competitive employment. Vigilance did predict the number of needs and speed of processing predicted the need for care in the domain of rehabilitation (table 3).

Table 3. Hierarchical multiple regression on course of illness and need for care

	R	R^2	% explained variance	Beta	Sign.
Time in psychosis					
Selective attention	.23	.05	5	-.25	.010
Verbal Fluency				-.23	.020
Time in full remission					
Verbal Fluency	.20	.04	4	.20	.049
Number of needs					
Vigilance	.24	.06	6	.24	.018
Rehabilitation needs					
Speed of processing	.24	.06	6	-.24	.012

3.3. Differences between CN and CI patients

Table 4 gives an overview of the differences between CN and CI patients on all outcome measures. There were significant differences on the work role, competitive employment, the number of needs for care and the need for mental health care. We computed the odds ratios (OR) for the influence of cognitive impairment on the dichotomic outcome measures. The OR for CI patients showing impairment on the work role was 1.8. The OR for CI patients having no competitive employment was 1.4.

Table 4. Differences between CN and CI patients on all outcome measures

	CN patients (n = 20)	CI patients (n = 83)	Test	Significance (two-tailed)
Relapse rate (% patients)				
No relapse	65 %	52 %		
Relapse after inclusion	30 %	41 %	$\chi^2 = 1.133$	n.s.
Chronic psychotic	5 %	7 %		
Course of illness				
% of time psychotic	27 (36)	33 (33)	F = 0.575	n.s.
% of time full remission	27 (35)	24 (31)	F = 0.241	n.s.
Social functioning				
Total score[a]	0.79 (0.91)	0.83 (0.59)	F = 0.062	n.s.
Self-care[b]	26.3	20.0	$\chi^2 = 0.366$	n.s.
Family role	36.8	56.8	$\chi^2 = 2.458$	n.s.
Kinship role	52.6	48.8	$\chi^2 = 0.933$	n.s.
Partner role	47.4	64.6	$\chi^2 = 1.906$	n.s.
Citizen role	47.4	65.4	$\chi^2 = 2.131$	n.s.
Social role	52.6	58.0	$\chi^2 = 0.183$	n.s.
Work role	42.1	74.1	$\chi^2 = 7.228$	.007
Need for care				
Number of needs	2.5 (2.1)	3.8 (2.6)	F = 3.967	.049
Mental health care	0.17 (0.15)	0.28 (0.19)	F = 6.453	.013
ADL	0.05 (0.10)	0.11 (0.21)	F = 1.689	n.s.
Rehabilitation	0.20 (0.30)	0.26 (0.36)	F = 0.481	n.s.
Services	0.07 (0.12)	0.15 (0.23)	F = 1.991	n.s.
Competitive employment[c]	40	16	$\chi^2 = 5.734$	.017

[a]: Standardized GSDS ratings ranging from (0) no disability to (3) extreme disability
[b]: Percentage of subjects showing disability
[c]: Percentage of subjects with competitive employment

4. Discussion

In this longitudinal study the predictive value of cognitive functioning for course of illness and functional outcome in first onset schizophrenia was investigated.

As was expected, the patients as a group performed below healthy controls on all cognitive measures at inclusion. Both course of illness and functional outcome after two years in our sample illustrate the generally poor outcome of schizophrenia. Half of the patients had one or more relapses and a large part of the patients had psychiatric symptoms during most of the follow-up period. Only 21 percent of the patients were able to obtain competitive employment or to follow some kind of study. This is in accordance with the competitive employment rate mentioned in literature (Mueser et al., 2001). Although the majority of patients showed an improvement in social functioning at follow up

as compared to inclusion, most patients (82 %) still had social disabilities. Most patients experienced some need for care, especially in the area of mental health care.

Our main finding was that the predictive value of cognition at illness onset on course of illness and functional outcome is very limited. One of the most important course specifiers, relapse rate, was not predicted by cognitive performance at inclusion. Selective attention and verbal fluency at inclusion predicted time in psychosis during the follow-up period and verbal fluency predicted time in full remission. Although significant, the predictive value of these cognitive measures was very limited, explaining five and four percent of the variance in these outcome measures respectively. These results are roughly in accordance with the only other study, which investigated the predictive value of cognition on course of outcome and found no significant effects (Robinson et al., 1999).

Cognitive measures at inclusion did not predict social functioning. This is not surprising, in view of the rather inconsistent results of other longitudinal prediction studies. However, there seems to be a sharp contrast with the conclusions of the meta-analysis of Green et al. (2000), which suggests that several cognitive functions have significant cross-sectional relationships with functional outcome. This could partly be due to inclusion of studies with laboratory assessment of social skills, in which similarities between neuropsychological test conditions and social skill assessment might have caused an overestimation of the real correlations between these constructs. A closer look at the results of the cross-sectional studies focusing on the association of cognition with social functioning in daily life, also shows that the results in this area are positive but not impressive (Goldman et al., 1993; Addington and Addington, 1999; Addington et al., 1998; Buchanan et al., 1994, Heslegrave et al., 1997; Jaeger and Douglas., 1992). Most studies find some significant correlations, but the p-values are all in the .01 - .05 range, which in view of the number of analyses in these studies, are not likely to survive a Bonferroni correction. The same holds for the association between cognition and work related variables (Addington and Addington, 1999; Addington et al., 1998; Bellack et al., 1999; Breier et al., 1991; Dickerson et al., 1996; Brekke et al., 1997; Lysaker et al., 1995).

Cognition seems to have some predictive value for need for care. Vigilance at inclusion did predict the number of needs for care a patient had at follow up. Speed of processing did predict the needs in the rehabilitation domain. The predictive value of these cognitive measures was also very limited, explaining 6 percent of the variance for both outcome measures. We cannot exclude the possibility that the subjective nature of the instrument used to assess need for care in this study has influenced this association. Most patients have told us during interviews that cognitive deficits, which were assessed at inclusion and subsequently explained to them, still played a role in their lives. It is conceivable that this affects their self-confidence in a negative way and therefore increases their subjective experience of need for care.

In a general sense, cognitive deficits appear to be associated with problems with the work role and with competitive employment at follow up. The risk of work-related impairments was almost twice as large for patients with cognitive impairments compared to patients without cognitive impairments at inclusion, and their chances on having competitive employment were reduced to a similar degree. It seems that having a cognitive deficit in general, regardless of the nature of the deficit, may affect work performance, and acts as a limiting factor for occupational functioning.

There are limitations to this study. First cognition was only measured at the beginning of the disease. It is possible that cognitive performance in our sample has deteriorated and that cognition at follow-up is associated with outcome. There is, however, evidence that cognitive deficits are relatively stable early in the disease (Rund, 1998). Secondly, the functional outcome measures are valid for the month preceding the follow-up, and might therefore be considered more or less a random indication. However, a closer look at the socio-demographic data gathered with case record forms shows that the social situation is rather stable for most patients after the initial months of the disease. Another limitation is that the effects of different kinds of anti-psychotic medication taken during follow-up are not known.

Our results suggest that the predictive value of cognition on course of illness and functional outcome is not that large and challenge the idea that cognitive impairment is the core of the disease. Nevertheless, most patients show obvious cognitive deficits and many of them indicate that they are bothered by these deficits in daily life. It is possible that the relation between cognitive test

performance and functional outcome is obscured by compensation-mechanisms, which enable some patients to partly conceal their cognitive problems by investing more effort during test performance. In daily life however, when there is a constant appeal to many different cognitive functions, this compensation is likely to fail. This is in accordance with results from functional imaging studies, suggesting that schizophrenia patients show neural inefficiency, which shows as elevated activity on performance-corrected tasks (Ramsey et al., 2002). We think that future studies on the relation between cognition and outcome in schizophrenia should include measures to assess this compensation during cognitive testing, such as subjective ratings of mental effort, psycho physiological parameters or brain imaging patterns of compensatory cortical activation.

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