

## The association between cognitive deficits and different outcomes of schizophrenia

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### Summary

**Aim.** Schizophrenia is a disorder with different outcomes. Besides the positive and negative symptoms, cognitive impairment is an important core feature of schizophrenia and often pre-dates the disorder. Cognition has consistently been related to outcome in schizophrenia. Given this finding and the fact that diagnosing and treating schizophrenia as early as possible has better outcome chances, the current study investigated the hypothesis that cognitive performance is associated with two seemingly opposite outcomes: clinical remission and forced hospitalization three years after first assessment.

**Method.** Subjects in the current study were schizophrenia patients not in an active psychosis during cognitive testing (N = 321). The results of the cognitive tests were used as predictor variables for the status of remission or the occurrence of a forced hospitalization in the three years following the cognitive testing. The cognitive tests included were WAIS-III subtests (Digit symbol, Information, Arithmetic, Block Design), Benton Facial Recognition task, Hinting task and the Rey Auditory Verbal Learning task. Besides these cognitive predictors, several relevant covariates (gender, age, education, number of psychotic episodes, duration of illness and amphetamine, cannabis or cocaine intoxication) were analyzed. Two multinomial logistic regression analyses were conducted with the cognitive tests as independent variables and remission and forced hospitalization as dependent variables in separate models.

**Results.** The results showed that better performance on the verbal tasks (WAIS-III arithmetic score (b=0.17) and the WAIS-III information score (b=0.22)) and less psychotic

episodes ( $b=-0.64$ ) was associated with remission status. Worse performance on the memory task ( $b=-0.20$ ) and more psychotic episodes ( $b=0.85$ ) was related to forced hospitalization.

**Conclusion.** This three-year longitudinal study showed that higher verbal IQ is a protective factor and poor memory and higher number of psychotic episodes are risk factors of the outcome of schizophrenia. This suggests that future research on prediction tools for the outcome of schizophrenia should include assessment of verbal IQ and verbal memory.

**Key words:** schizophrenia, remission, forced hospitalization, cognition

## Introduction

The course of schizophrenia shows considerable heterogeneity, and a great amount of variability exists in the etiology, symptomology and outcome of the illness. Within the defined prodromal, acute and the residual stage of schizophrenia [1], diversity in progression of the illness can be specified. One of the first and most influential longitudinal studies of Manfred [2] on the course of schizophrenia described eight course types, wherein were variation concerning onset (abrupt versus insidious), symptom presentation (continuous versus intermittent) and outcome (poor versus non-poor). Only approximately 20% had the stereotypical insidious onset, continuous symptoms, and poor outcome.

Other influential longitudinal studies on schizophrenia demonstrate that the course of schizophrenia is not uniform [3, 4]. The DSM-5 has specified several course components that can be used one year after the diagnosis for describing the longitudinal course; continuous symptoms, multiple episodes in full remission, multiple episodes in partial remission, multiple episodes- currently in an acute episode, first episode in partial remission, first episode in full remission and an unspecified pattern [5, 6].

Some patients experience only one psychotic episode. However, it is more common for patients with schizophrenia to experience multiple psychotic episodes with potential recurrent hospitalizations [7, 8]. The description of the different outcomes, as stated above, does not contain recovery; an ill-defined construct in schizophrenia. Several studies [9, 10] have concluded that recovery is rare and currently there are no accepted scales to measure recovery [11]. A more clinically useful concept may be remission of schizophrenia [12]. In remission, the individual has no or minimal symptoms that do not interfere with functioning for a period of six months [13]. The Worldwide Schizophrenia Outpatient Health Outcomes study [14], in which 1,078 patients from 37 different countries were analyzed, found a mean rate of 66,1 % (range: 60.1% in North Europe to 84.4% in East Asia) for schizophrenia patients to reach remission after three years follow-up.

Cognitive deficits have been related to disadvantageous functional outcomes of independent living, social functioning, and vocational functioning in schizophrenia [15], and to adverse symptomatic/clinical outcomes [16]. Traditionally, cognitive impairment was thought to be evident only in elderly patients with schizophrenia. However, over the past decades, accumulating evidence has challenged this view [17-19]. It has even been suggested that the diagnostic criteria of schizophrenia should include specific reference to cognitive impairments characterizing the disorder [20, 21]. People

with schizophrenia have been shown to have a wide range of cognitive deficits which is reflected by impairments in intelligence, memory, speed of processing, attention, and executive functioning [22-24]. Furthermore, cognitive deficits may predict non-remission status [25, 26], impede occupational rehabilitation [27], or deteriorate insight (i.e. unawareness of illness).

This current longitudinal study investigates whether baseline cognitive deficits in schizophrenia are related to two seemingly opposite outcomes, clinical remission and forced hospitalizations, after three years.

## **Method**

### **Study population**

This trial was part of the Dutch longitudinal Genetic Risk and Outcome of Psychosis study (GROUP-project), a collaboration between academic institutions in Amsterdam, Groningen, Maastricht and Utrecht and a great amount of attached healthcare centres. The study focused on the interaction between various vulnerability and protective factors, as well as genetic variation associated with the development of psychosis [28]. Subjects were invited to several diagnostic interviews, neuropsychological tasks, blood and urine sampling, as well as MRI. After both three and six year time intervals, participants were invited for testing again. Measurement inclusion criteria for patients were as follows: 1) age range between 16 and 50 years old 2) diagnosis of non-affective psychotic disorder and 3) good command of the Dutch language. The study protocol was approved by the Ethical review Board of the University Medical Center of Utrecht and each participating centre. Before participating, all subjects obtained a written informed consent.

For our patient sample, two extra criteria were added in the current study (see Flow Chart Figure 1.). The first extra inclusion criterion is a diagnosis of schizophrenia (DSM-IV diagnosis of 295.xx) during the first assessment and the three years follow-up measurement as assessed by the Comprehensive Assessment of Symptoms and History (CASH) [29] or the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [30]. Not all schizophrenia patients in the GROUP project had a diagnosis of schizophrenic disorder during both measurements. This could be due to subtle diagnostic and/or symptomatology changes between initial and subsequent inclusion. The second extra criterion was an exclusion criterion; patients who were in an active psychosis according to the definition of Evensen et al. [31] during the cognitive tests, were excluded.

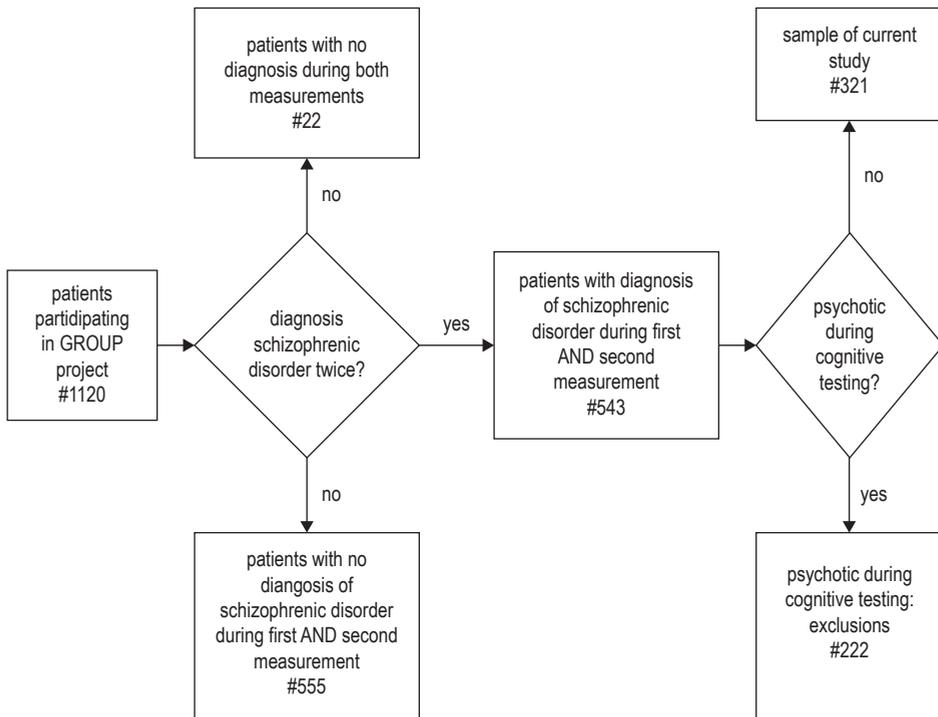


Figure 1. Flow Chart demonstrating the Formation of the Sample used in this Study

### Clinical measures

All relevant demographic information including age, educational degree, age of onset of psychosis, duration of the illness, as well as number of psychotic episodes and medication use was obtained by diagnostic interview. The cumulative number of psychotic episodes was obtained through self-report at inclusion and at follow-up. As the number of episodes may be dependent on duration of illness, we separately added duration of illness and total number of episodes (per year) since illness onset as covariates. This did not change any of the results. Additionally, besides CASH and SCAN, basic clinical characteristics were assessed. The variety of positive and negative symptoms of schizophrenia, as well as the general psychopathology during the past week was obtained via the Positive and Negative Syndrome Scale [32]. Cognitive assessment was done using an extensive neuropsychological test battery which is summarized in Table 1.

**Table 1. Explanation of the Cognitive Tests used in the GROUP Project**

Task (reference)	Neurocognitive domain	Measurements	Reliability and validity of test
Word Learning Task (Brand and Jolles, 1985)□	Verbal learning and memory	<ul style="list-style-type: none"> <li>– Total (of 3 trials) correct immediate recall</li> <li>– Total (of 3 trials) incorrect immediate recall</li> <li>– Total (of 3 trials) preservations immediate recall</li> <li>– Total correct delayed recall (after 20 minutes)</li> <li>– Total incorrect delayed recall</li> <li>– Total preservations delayed recall</li> </ul>	Reported reliability: 0.70 for List A (Snow et al., 1988). Test-retest reliability for a one-year interval between test administration was reported moderate, 0.55 (Snow et al., 1988). Correlations ratings of 0.50 to 0.65 with other grouping factor and other learning tools (Macartney-Filgnate & Vriezen, 1988) supports RAVLT validity.
Digit symbol (WAIS-III; Wechsler, 1997)□	Processing speed	Number of correct items in 120 seconds. The four WAIS-III tasks are summed up; a total scaled score is calculated by (score *11/4). The IQ score is derived from this score	The test-retest reliability is for the different constructs (Niolon, 2005): Full Scale: 0.96 Verbal IQ: 0.96 Performance IQ: 0.91 Verbal Comprehension: 0.95 Perceptual Organization: 0.88 Working Memory: 0.89 Processing Speed: 0.89 Content Validity was established by expert judges who reviewed the items. Criterion Validity was established by correlating WAIS-R and WAIS-III. The numbers are good. Construct Validity was established using a factor analysis. g Was supported, and verbal subtests correlated better with each other than performance subtests. (Niolon, 2005).
Block design (WAIS-III; Wechsler, 1997)	Reasoning and problem solving	Score depends on solving speed. The four WAIS-III tasks are summed up; a total scaled score is calculated by (score *11/4). The IQ score is derived from this score	
Information (WAIS-III; Wechsler, 1997)	Acquired knowledge	Number of correct Items. The four WAIS-III tasks are summed up; a total scaled score is calculated by (score *11/4). The IQ score is derived from this score	
Arithmetic (WAIS-III; Wechsler, 1997)	Working memory	Score is dependent on solving speed. The four WAIS-III tasks are summed up; a total scaled score is calculated by (score *11/4). The IQ score is derived from this score	
Benton Facial Recognition Task (Benton et al., 1983)	Visuospatial discrimination of unfamiliar faces	Total correct score (maximum score = 27)	
Hinting Task (Corcoran et al., 1995)	Theory of mind (social cognition)	Total correct score (maximum score = 20)	Reliability for this test is 0.65 (Roberts & Penn, 2009)

- Computerized assessment using E-prime 1.3.
- WAIS-III: Wechsler Adult Intelligence Scale.

The tests were administered in a fixed order. A short version of the Wechsler Adult Intelligence Scale– Third Edition short form (WAIS-III SF) [33, 34] was used to assess patients Intelligence Quotient (IQ) as measured with the following subtasks: Arithmetic (which measures working memory), Information (which measures general knowledge and long-term memory), Digit-Symbol Coding (as a measure of processing speed), and Block Design (as a measure of problem solving). Together, Arithmetic and Information subtasks measure the verbal IQ. Symbol Coding and Block Design measure the performance IQ. This method proved to be a reliable method for calculating the total IQ score for patients diagnosed with schizophrenia [35].

Recent cannabis, amphetamine and cocaine use was established by urinalysis by the Jellinek Clinic Laboratory. Cut-off level was 50 ng/ml, 1000 ng/ml and 300 ng/ml respectively.

#### Measurement of remission and forced hospitalization

The status of remission was determined by the Remission tool [13] which is based on the Positive and Negative Symptoms Scale (PANSS) [32]. This tool defines remission as a period of at least six months in which the main symptoms are maintained on a low level. This means they have to be scored on PANSS as mild (score 3) or lower. The main PANSS symptoms are delusions (P1), conceptual disorganisation (P2), hallucinatory behaviour (P3), blunted affect (N1), social withdrawal (N4) and lack of spontaneity (N6), mannerism and posturing (G5), and unusual thoughts (G9). During the interview the number of forced hospitalizations so far is enquired by self-report.

#### Selection of non-psychotic group

To determine whether a patient was psychotic during the cognitive assessment, the method of Evensen et al. [30] was applied. They state that a score of 4 or higher (out of 7) on one the following items defines a psychosis: Delusions, Hallucinations, Grandiosity, Suspiciousness/ Persecution or Unusual thought content.

#### Statistical analysis

The cognitive tests as shown in Table 1 [36-43] were administered to assess neurocognitive functioning of the participants during the first measurement. The scores on these tests were used as the independent variables. The outcome variables consisted of Remission tool scores and the self-report regarding the forced hospitalizations during the follow-up measurement approximately three years later.

Because the main focus of this study targets a potential association between cognitive predictors and two different outcomes of schizophrenia, while taking into account several covariates, multinomial logistic regressions were used. In separate analyses, the association between cognitive factors (the four subscale WAIS-III scores, the Benton Facial score, the Hinting score, and the number of correct items on the immediate

recall of the verbal learning task, and covariates) and the different outcomes (remission status and forced hospitalization) was tested.

All tests were two-tailed at a significance level of  $p = 0.05$ . Data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) version 20.0.0.

## Results

### Outcome at 3 years follow-up

Table 2 shows the demographic characteristics of the sample as well as the results on the cognitive tests.

Table 2. Characteristics of the Sample

	In remission three years later		
	Yes	No	Unknown
	N = 207	N = 100	N = 14
Forced hospitalization in 3 years to follow			
Yes	13	17	1
No	194	83	13
Demographic variables			
Sex, M/F	148/59	77/23	12/2
Age at first inclusion, mean, (SD)	27.6 (6.5)	29.2 (8.0)	23.4 (4.9)
Cognitive tests results			
IQ score	99.5 (15.2)	94.5 (17.6)	90.6 (14.8)
WAIS-III block score	10.2 (3.3)	9.5 (3.5)	10.3 (2.8)
WAIS-III arithmetic score	10.3 (3.2)	9.1 (3.2)	8.6 (3.8)
WAIS-III digit score	7.9 (2.9)	7.05 (2.8)	5.8 (3.0)
WAIS-III information score	11.4 (2.9)	10.7 (3.4)	9.7 (2.9)
Benton score	23.0 (2.1)	22.5 (2.4)	23.3 (1.6)
Hints score	17.6 (2.7)	17.3 (2.9)	16.9 (3.6)
RAVLT immediate correct	24.1 (5.7)	22.2 (6.9)	23.8 (7.7)

RAVLT: Rey Auditory Verbal Learning Test

### Remission

The first multinomial logistic regression analysis was conducted with the four sub-scale WAIS-III scores, the Benton score, the Hinting score and the number of correct items on the immediate recall of the RAVLT as predictors for the status of remission. The following covariates were also included in this analysis; gender, age, education,

number of psychotic episodes, duration of illness and amphetamine, cannabis or cocaine intoxication (during the cognitive assessment with the result of the urine sample analysis).

Additional to the number of psychotic episodes, higher scores on information and arithmetic subscales of the WAIS-III were significantly associated with remission (see Table 3). The p-values were as follows: number of psychotic episodes ( $p = 0.004$ ), information score ( $p = 0.017$ ), arithmetic score ( $p = 0.019$ ).

**Table 3. Results of Multinomial Logistic Regression Analysis with cognitive predictors for Remission**

	95% CI for Odds Ratio			
	b (SE)	lower	Odds ratio	higher
Cut-off	1.38 (2.56)			
Age	- 0.04 (0.03)	0.90	0.96	1.03
Education	0.14 (0.10)	0.94	1.16	1.41
Duration of illness	0.08 (0.06)	0.97	1.09	1.22
Number of psychotic episodes	0.64 (0.22) *	0.34	0.53	0.82
Benton score	0.03 (0.08)	0.88	1.03	1.21
Hinting score	- 0.04 (0.07)	0.84	0.96	1.10
Correct immediate RAVLT	0.40 (0.04)	0.97	1.04	1.21
WAIS-III Block design score	- 0.04 (0.07)	0.84	0.96	1.09
WAIS-III Arithmetic score	0.17 (0.07) *	1.03	1.19	1.37
WAIS-III Digit symbol score	0.01 (0.07)	0.88	1.01	1.17
WAIS-III Information score	0.22 (0.09) *	0.67	0.81	0.97
Drug during tests	0.53 (1.67)	0.06	1.71	45.26
Gender	- 0.04 (1.70)	0.04	0.97	26.91
Drugs x Gender	- 0.09 (1.75)	0.03	0.92	28.07

Note:  $R^2 = 0.14$  (Cox & Snell);  $0.20$  (Nagelkerke); Model  $X^2(14) = 215.16$ ; \* $p < 0.05$ ; SE – statistical error; CI – confidence interval

Additional to the logistic regression analyses, ROC curves were made to show the cut-off points for the predictors for remission (see Figure 2, 3 and 4). The ROC curves show that 2 or less psychotic episodes in a lifetime so far predict the status of remission. A WAIS-III arithmetic score of 10 or more predicts remission, as well as a WAIS-III information score of 11 or more.

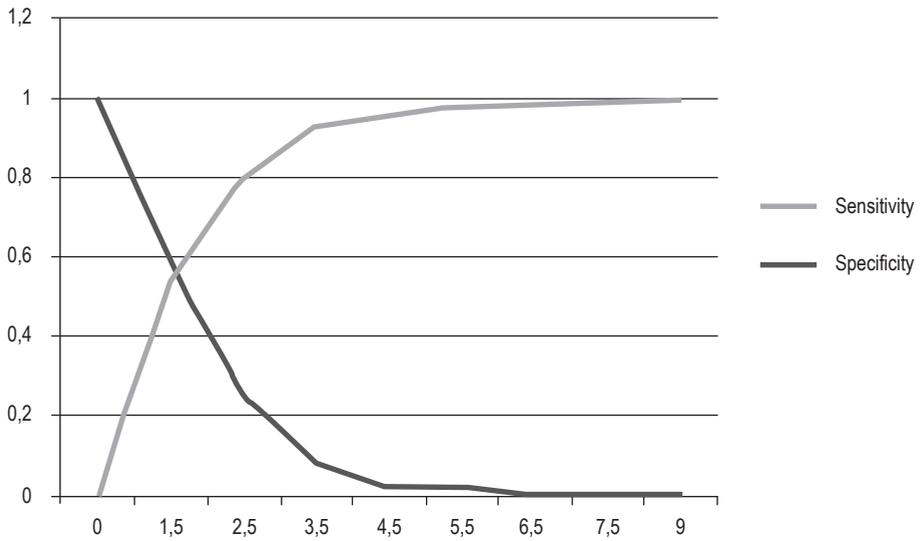


Figure 2. ROC Curve for cut-off point Number of Psychotic Episodes for the association with Remission

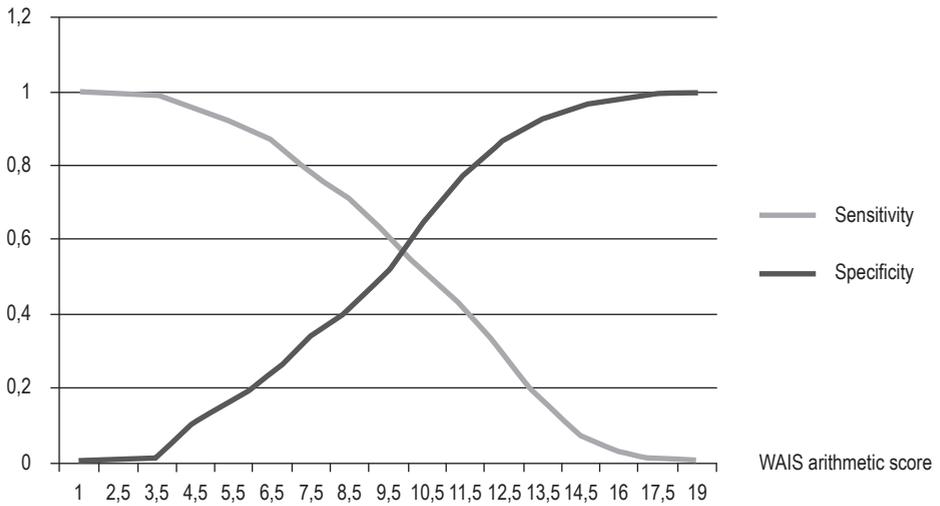


Figure 3. ROC Curve for cut-off point WAIS arithmetic score for the association with Remission

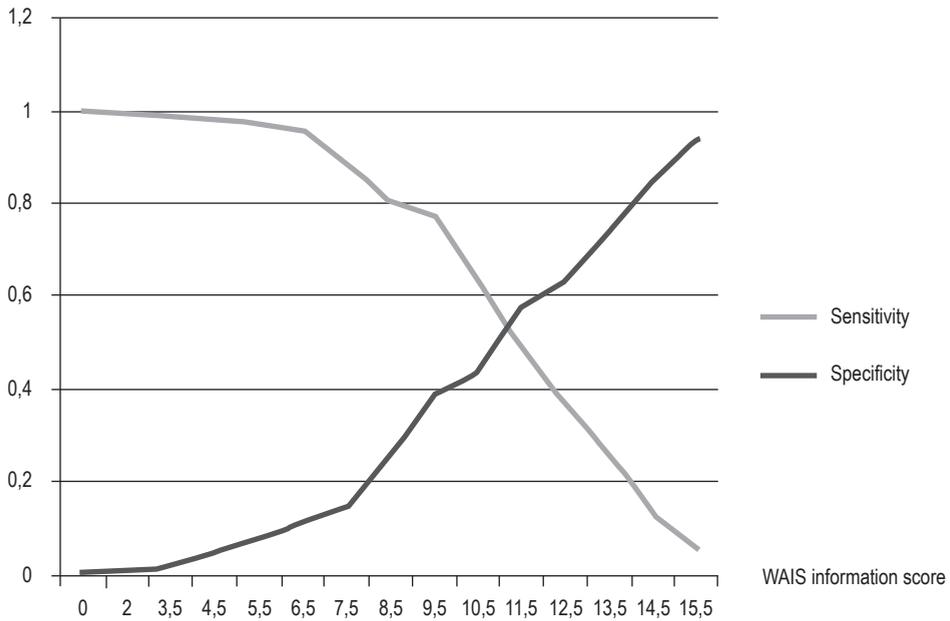


Figure 4. ROC Curve for cut-off point WAIS information score for the association with Remission

Forced hospitalization

The second multinomial logistic regression analysis was conducted with the four subscale WAIS-III scores, the Benton score, the Hinting score and the number of correct items on the immediate recall of the RAVLT as predictors for forced hospitalization. The following covariates were included in this analysis: gender, age, education, number of psychotic episodes, duration of illness, and amphetamine, cannabis or cocaine intoxication. Since negative symptoms predict poor outcome [44], the mean baseline score on the negative symptoms subscale of the PANNS was also added as a covariate.

The result of this multinomial logistic regression (see Table 4) shows that less correct items on the immediate recall of the RAVLT ( $p = 0.025$ ), and more psychotic episodes ( $p = 0.024$ ) was associated with a forced hospitalization.

Table 4. Results of Multinomial Logistic Regression Analysis with cognitive predictors for Forced Hospitalization

	95% CI for Odds Ratio			
	b (SE)	lower	Odds ratio	higher
Cut-off	- 0.39 (4.09)			
Age	- 0.05 (0.07)	0.83	0.95	1.10

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Education	- 0.25 (0.19)	0.53	0.78	1.13
Duration of illness	- 0.17 (0.15)	0.63	0.85	1.14
Number of psychotic episodes	0.85 (0.38)*	1.12	2.33	4.87
Negative symptoms PANSS	0.05 (0.07)	0.91	1.05	1.21
Benton score	0.26 (0.18)	0.92	1.30	1.83
Hinting score	- 0.05 (0.11)	0.76	0.96	1.19
Correct immediate RAVLT	- 0.20 (0.09)*	0.69	0.82	0.97
WAIS-III Block design score	- 0.09 (0.13)	0.71	0.92	1.19
WAIS-III Arithmetic score	0.21 (0.16)	0.91	1.23	1.68
WAIS-III Digit symbol score	- 0.13 (0.18)	0.62	0.88	1.24
WAIS-III Information score	0.15 (0.18)	0.81	1.16	1.65
Drug during tests	- 3.55 (2.03)	0.00	0.03	1.52
Gender	- 4.56 (2.14)	0.00	0.01	0.70
Drugs x Gender	4.18 (2.28)	0.74	65.08	5690.70

Note: R2 = 0.11 (Cox & Snell); 0.28 (Nagelkerke); Model X2 (14) = 86.90; \*p < 0.05; SE – statistical error; CI – confidence interval

ROC-curves (Figure 5 and 6) show that two or more psychotic episodes, and 22 or less correct items on the immediate recall were related with a forced hospitalization.

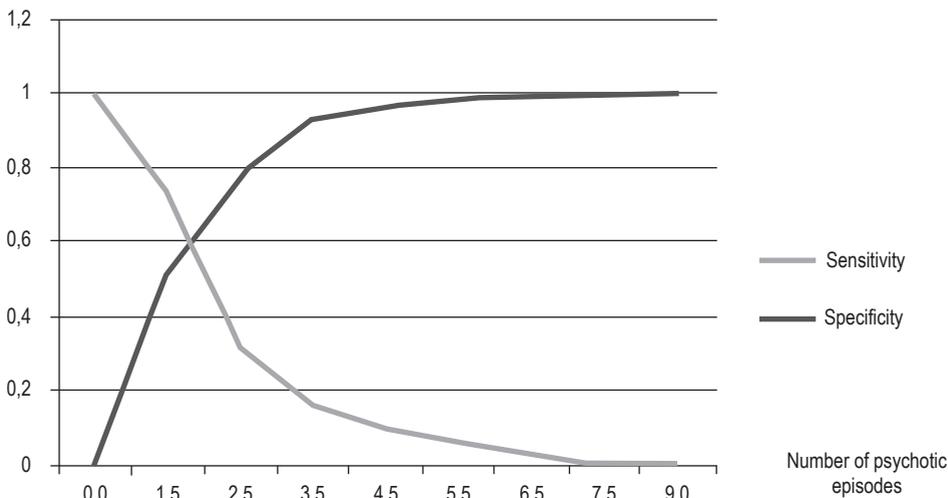


Figure 5. ROC Curve for cut-off point Number of Psychotic Episodes for the association with Forced Hospitalization

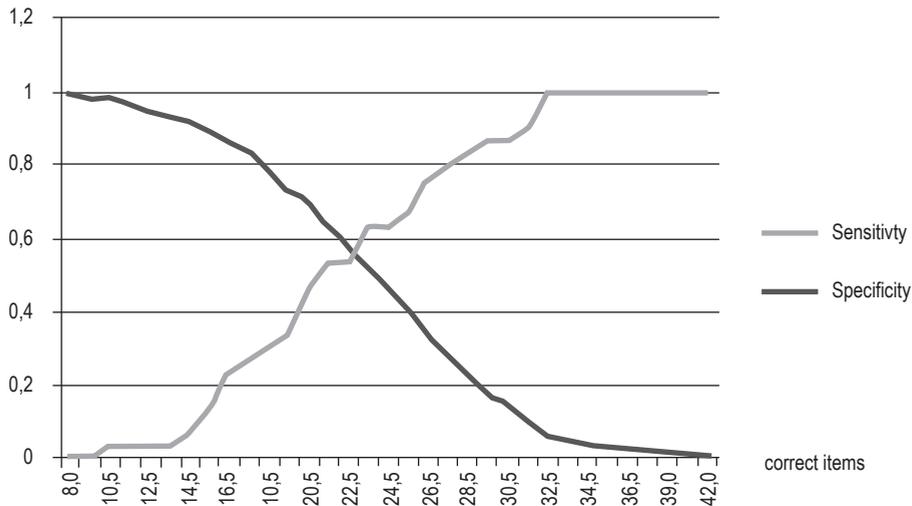


Figure 6. ROC Curve for cut-off point Number of Correct Items on Immediate Recall on the RAVLT for the association with Forced Hospitalization

## Discussion

The aim of this study was to investigate the association of cognitive deficits at baseline with two opposite outcomes in schizophrenia: clinical remission and forced hospitalization, which were measured after three years. A variety of cognitive tests were used to test this hypothesis.

Higher baseline verbal IQ (WAIS-III arithmetic scores and WAIS-III information scores), but not performance intelligence, was related to a greater chance of remission after three years. This suggests that patients with an average (or higher) verbal intelligence, in a non-active phase of the illness are more likely to reach the status of clinical remission in schizophrenia. Jones et al. showed already in 1994 that verbal skills are impaired in those children who later develop schizophrenia [45]. This study found that verbal intelligence, besides being associated with the development of schizophrenia, is also related to schizophrenia outcome. In addition, number of psychotic episodes was associated with remission status. This is in line with studies showing that relapse and greater severity of schizophrenia are associated with the number of psychotic episodes [46, 47].

Forced hospitalization was associated with worse memory, in particular the encoding and learning skills, as measured by the number of correct items on the immediate recall of the RAVLT. Others also found deficits in memory functioning to be associated with the outcome of schizophrenia [16], with moderate to high effect sizes ranging from Cohen's *d* value of 0.45 to 0.71. Despite this being a robust finding, some studies examining the relationship between verbal memory and illness outcome

did not find a better memory performance for remitted patients [48, 49]. Lepage et al. [16] stated, that these studies used a somewhat less pure memory task, which also tapped into executive functioning. Furthermore, Diaz et al. [50] and Buckley et al. [51] did not find an association between RAVLT memory task and remission status. The discrepancy with our results may be due to sample selection. These studies did not exclude schizophrenia patients who were in an active psychosis, which is known to influence cognitive functioning.

Impaired memory may impede outcome in schizophrenia in various ways. For example, it has been found that worse memory functioning is associated with poorer treatment decisions, such as medication adherence and therapy compliance, (i.e. forgetting to take medication or go to mental health service appointments) [52, 53]. Worse memory has also been associated with a deterioration of insight, or unawareness of illness [54, 55], which in turn may worsen outcome [56].

Moreover, forced hospitalization was also related to the number of psychotic episodes during the three year follow-up. This is consistent with Chabungbam et al. [46] who showed that patients in remission retrospectively experienced averagely 2.9 psychotic episodes as compared to relapsed patients, who experienced averagely 4.4 psychotic episodes. In our study we showed that two or more psychotic episodes are associated with (non)remission status and forced hospitalization during three years of follow up with a sensitivity rate of 57% and 60%, and a specificity rate of 40% and 43% respectively.

The results of this study might have some clinical implications. An important issue put forward by Kahn & Keefe (2013) is that in schizophrenia “the treatment of cognitive deficits should be central to any guidelines, which now is not.” [21] Our results are the evidence of this important role of cognition in outcome of schizophrenia. To predict outcome, neuropsychological functioning could be used. In particular the two WAIS-III verbal tasks and the RAVLT task. A score of 22 or less on the immediate recall of the RAVLT and two or more psychotic episodes were related to a forced hospitalization in the future. It might be useful to integrate (verbal) IQ measurements, verbal memory RAVLT and previous psychotic episodes into a prediction tool to measure schizophrenia outcomes. If a patient is at high risk for forced hospitalization one should monitor the patient more closely. Furthermore, to achieve remission status and to prevent forced hospitalization in schizophrenia cognitive remediation, aiming at improving verbal and memory skills, might be helpful. Cognitive remediation has shown moderate improvements on cognitive outcomes in schizophrenia [57].

Nevertheless, there are several limitations to this study. Firstly, although various cognitive domains have been examined, no information was gathered on executive functioning. Secondly, information on forced hospitalization was gathered through interviews with patients, which might not be as accurate as gathering the information through medical notes. Thirdly, the selection of patients in the non-active phase of the illness, which might have resulted in prediction to be more difficult for the entire group of patients with schizophrenia. Lastly, because of relatively small sensitivity and specificity rates, caution is needed for generalizability of the results. Before im-

plementing a valid outcome prediction tool in the clinical practice more research is recommended.

In conclusion, this three year longitudinal study in schizophrenia showed that higher verbal IQ is a protective factor and poor memory and higher number of psychotic episodes are risk factors in the outcome of schizophrenia. This suggests that future research on prediction tools for the outcome of schizophrenia should include assessment of (verbal) IQ and memory.

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