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Research Paper

Neurocognition as a predictor of outcome in schizophrenia in the Northern Finland Birth Cohort 1966

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ABSTRACT

The purpose of this study was to study neurocognitive performance as a predictor of outcomes in midlife schizophrenia. There is a lack of studies with unselected samples and a long follow-up. The study is based on the prospective, unselected population-based Northern Finland Birth Cohort 1966. The study includes 43 individuals with schizophrenia and 73 controls, whose neurocognitive performance was assessed twice, at 34 and 43 years. At both time points we used identical neurocognitive tests to assess verbal and visual memory and executive functions. Our main aim was to analyse neurocognitive performance at 34 years as a predictor of clinical, vocational and global outcomes at 43 years. Additionally, the analysis addressed cross-sectional associations between cognitive performance and clinical, vocational and global measures at 43 years. The assessment of outcomes was performed in the schizophrenia group only. In the longitudinal analysis poorer visual memory predicted poorer vocational outcome and poorer long-term verbal memory predicted poorer global outcome. In the cross-sectional analysis poorer visual memory and lower composite score of neurocognition were associated with poorer global outcome. No individual neurocognitive test or the composite score of these predicted remission. These data indicate that neurocognition, especially memory function, is an important determinant of long-term functional outcome in midlife schizophrenia.

1. Introduction

Cognitive deficits in schizophrenia are related to functional outcomes, as shown in both cross-sectional (Fett et al., 2011; Green et al., 2000; Ventura et al., 2009) and longitudinal studies (Allott et al., 2011; Green et al., 2004; Ventura et al., 2011). However, some studies have failed to confirm this relationship (e.g. Addington et al., 1998; Johnstone et al., 1990; Verdoux et al., 2002).

The association between neurocognition and clinical outcomes is not equally well documented. Patients with greater neurocognitive ability have a higher likelihood of achieving (Helldin et al., 2006; Kopelowicz et al., 2005) and remaining in remission (Holthausen et al., 2007), though other studies have failed to show an association between neurocognition and clinical outcomes (Buckley et al., 2007; Li et al., 2010; Robinson et al., 1999).

One limitation of the research thus far is that outcome assessments have generally been completed concurrently or within a year after neurocognitive testing (Fujii and Wylie, 2002). Also the neurocognitive data have often been collected during or soon after acute psychosis (Norman et al., 1999). Many studies are cross-sectional and do not allow causal conclusions (Smith et al., 2002). The extensive variability in the methodology of the studies, including the selection of cognitive and outcome measures and confounding variables, precludes any definite conclusions regarding the relationship between cognition and outcomes (Allott et al., 2011).

There is a lack of population-based longitudinal studies investigating the relationship between cognition and outcomes, and studies with a long follow-up, per se, are relatively scarce. Additionally, studies with a long follow-up have not adjusted for potential confounders (Fujii and Wylie, 2002; Stirling et al., 2003).

Our aim was, in a birth cohort sample with a long follow-up, to study: a) whether the neurocognitive performance assessed after on average 10 years of disease onset at age 34 predicts remission or vocational or global outcomes at follow-up 9 years later (longitudinal analysis), and b) whether neurocognitive performance at follow-up is associated with outcomes (cross-sectional analysis).

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We hypothesised that impairments in neurocognitive functioning particularly in the domains of verbal memory and executive functions would be associated with poor vocational and global outcomes in schizophrenia in both cross-sectional and longitudinal analysis.

2. Materials and methods

2.1. Subjects

The Northern Finland Birth Cohort 1966 (NFBC 1966) is a prospective birth cohort based on 12,058 children with an expected date of birth in 1966 in the provinces of Oulu and Lapland (Rantakallio, 1969).

The detection of cases and validation of diagnoses are described in detail elsewhere (Isohanni et al., 1997; Moilanen et al., 2003). Briefly, all cohort members appearing on the Care Register for Health Care for a lifetime psychotic episode (n = 145) were invited to participate in a baseline study conducted in 1999–2001 including interviews and neurocognitive testing, and 91 (63%) participated. Altogether 73 received a DSM-III-R (SCID-I; Spitzer et al., 1989) diagnosis of schizophrenia spectrum disorder (61 of schizophrenia). From now on we will address the disorder simply as schizophrenia. Compared to participants, non-participants were more often single and on disability pension, and they had more psychiatric hospitalisations and more often a diagnosis of (narrow) schizophrenia. No differences between the groups were detected in terms of gender, education, unemployment periods, substance abuse, or age of psychosis onset (Haapea et al., 2007). Control subjects were selected randomly from the NFBC 1966 members living in the Oulu area with no history of psychotic disorder. Of the invited 187 subjects, 104 (56%) participated. The control group is used in this study only to assess the normative neurocognitive performance of the Finnish population.

Follow-up examinations were conducted in 2008–2010 and all those who had participated in the baseline study were invited for reassessment. Altogether 43 (59%) individuals with schizophrenia and 73 (70%) controls participated again, also attending neurocognitive testing. The number of individuals in each neuropsychological test varies somewhat, as a few participants did not take part in all three tests. The participants of this study did not differ statistically significantly from subjects who participated in the baseline study but did not return for the follow-up investigation. Factors studied included gender, education, onset age, disability pension, hospitalisations, and baseline scores in the neurocognitive tests and in PANSS, CGI, and SOFAS (data not shown). We also compared our final sample to all other potential participants (non-participants at age 34 years and non-participants at age 43 years who were alive at age 43 years, n = 70). No statistically significant differences ($p < 0.05$) between the groups were detected in any of the variables studied (gender, onset age, cumulative number of psychiatric hospital days until year 2000, and receiving disability pension due to psychosis; data not shown). All participants signed a written informed consent prior to participation after a complete description of the study. The Ethical Committee of the Northern Ostrobothnia Hospital District has approved and keeps the study design of the NFBC 1966 under review.

2.2. Neuropsychological assessments

The same three neurocognitive tests were administered at both baseline and follow-up.

2.2.1. Verbal learning and memory

The California Verbal Learning Test (CVLT) is an auditory verbal memory test using a 16-item shopping list that is read to the participants five times (Delis et al., 1983). After each trial participants must repeat back as many items as they remember. The two dependent variables used in this study were: 1) CVLT Trials 1–5 (summary score, reflects immediate verbal memory and learning) and 2) CVLT long delay (free recall, items remembered approximately 20 min later, reflects long-term memory). The psychometric properties of the CVLT have been shown to be very good (Spreen and Strauss, 1998).

2.2.2. Visual learning and memory

The Visual Object Learning Test (VOLT) is a computerised test of visual object learning and memory (Glahn et al., 1997). It is modelled after the CVLT. VOLT has shown excellent internal consistency, and convergent and divergent validity (Glahn et al., 1997). The dependent variable is the total number of correct responses in the four trials. We excluded participants who performed below chance – i.e. who had less than 50% of correct answers – assuming they had not understood the test assignment.

2.2.3. Executive functions

The Abstraction and Working Memory task (AIM) is a computerised rule-abstraction/category-learning task that allows abstraction and working memory to be analysed independently (Glahn et al., 2000). The two dependent variables are the total number of correct answers in the two subtests; abstraction and abstraction plus memory test. Subjects with schizophrenia have been shown to perform worse than healthy controls in both subtests (Glahn et al., 2000). We excluded participants who performed below chance.

2.2.4. Composite score of neurocognitive tests

The z-scores using means and standard deviations of the control group for neurocognitive test measures were averaged, unweighted, into a single composite score, as done in many earlier studies (e.g. Buckley et al., 2007; Emsley et al., 2007; Siegel et al., 2006). This measure provides an estimate of the total amount of variance in outcome that can be explained by neurocognition in general.

2.2.5. Cognitively impaired vs. cognitively normal

In order to assess whether having overall neurocognitive impairment would influence outcome, we analysed the differences in outcomes between cognitively normal and cognitively impaired individuals. A participant was considered cognitively impaired if he/she had a test score of 2 or more standard deviations (SDs) below control average in at least one of the tests. It should be noted, however, that the impairment of 2 SD is severe and means performing worse that over 95% of the control subjects. This criterion has been used previously (e.g. Holthausen et al., 2007).

2.3. Outcome measures

2.3.1. Remission

We used the remission criteria suggested by the Remission in Schizophrenia Working Group (Andreasen et al., 2005). PANSS (Kay et al., 1987) was conducted in the follow-up study in 2008–2010. We were able to assess only the severity criteria of remission and not the 6-month stability of symptoms. However, we additionally required that individuals in remission had not been hospitalised during the past 6 months (information derived from the Care Register for Health Care) and did not report current psychotic symptoms in the Strauss–Carpenter Outcome Scale or the SCID-interview.

2.3.2. Global outcome

We measured global outcome with the Strauss–Carpenter Outcome Scale (SCS), which evaluates the following four items: need for hospitalisation, frequency of social contacts and useful employment during the past year, and symptom load during the past month (Strauss

and Carpenter, 1972). Each item is scored on a 5-point scale from 0 (very poor) to 4 (very good). The sum score was used in the analysis.

2.3.3. Vocational outcome

Vocational outcome was assessed separately for its economic and humane importance. The information on vocational activity was derived from the SCS. It was analysed as a dichotomised variable; 1) no useful employment, and 2) employed at least 25% of the time during the past year.

2.4. Covariates

We first ran statistical analyses without covariates, and then adjusted for age of psychosis onset, which simultaneously adjusts for the duration of illness as the individuals were of same age. Whenever statistical significance remained, we used other covariates that were gender, current antipsychotic medication, education, and baseline symptoms and functioning (factors presented in more detail in Tables 1 and 4, and in Husa et al., 2014).

2.5. Statistical methods

For analysing the associations between neurocognitive tests and remission or vocational outcome, logistic regression was used, except for the unadjusted difference between cognitive impairment groups, where Pearson's $\chi 2$ test was used. For analysing the associations between Strauss–Carpenter global outcome and the neurocognitive tests, linear regression was employed, except for the unadjusted differences between cognitive impairment groups where Student's t-test was used. A p-value <0.05 was considered statistically significant. Data were analysed using the SPSS version 22.

Table 1
Demographic and clinical characteristics at baseline (at age 34) and at follow-up (at age 43) of 43 subjects with schizophrenia.

Characteristics	At age 34 years		At age 43 years	
	n	**%**	**n**	**%**
Gender				
Male	23	53.5		
Female	20	46.5		
Diagnosis[a]				
Schizophrenia	36	83.7	36	83.7
Schizoaffective disorder	5	11.6	5	11.6
Schizophreniform disorder	1	2.3	1	2.3
Delusional disorder	1	2.3	1	2.3
Education[b]				
Basic	23	53.5	21	48.8
Secondary	12	27.9	9	20.9
Tertiary	8	18.6	12	27.9
At work[c]	16	37.2	13	30.2
	Mean	**Sd**	**Mean**	**Sd**
Onset age (years)[d]	23.6	4.4		
Age at the time of interview (years)	33.6	0.6	42.7	0.5
PANSS total score[e]	52.8	19.2	69.2	25.3
SOFAS score	50.7	16.2	52.5	17.9
	Md	**IQR**	**Md**	**IQR**
CGI	5	4 – 6	5	3 – 6
Dose of antipsychotics[f]	102	0 – 357	150	0 – 400

[a] Baseline diagnoses did not change during follow-up.
[b] Basic = 9 years of basic education with low vocational education; secondary = 9 years of basic education with high vocational education or 12 years of basic education with low vocational education; and tertiary = 12 years of basic education with high vocational education.
[c] Working status according to interviews (yes = working at least part-time, no = unemployed/on disability pension).
[d] Age of onset ranges between 16.7 and 31.0 years.
[e] PANSS (Positive and Negative Syndrome Scale) rating was based on psychiatric interview (mainly SCID I) at the baseline (at 34 years), whereas the specific PANSS interview was conducted at the follow-up study. The different assessment methods might explain the higher PANSS scores at follow-up.
[f] Dose of antipsychotic medication (chlorpromazine equivalent dose in milligrams) at the time of neurocognitive testing. CGI = Clinical Global Impression, SOFAS = Social and Occupational Functioning Assessment Scale, IQR = interquartile range.

3. Results

Sociodemographic information of the participants is presented in Table 1 and neurocognitive test scores in Table 2. Cases differed statistically significantly from controls in all of the neurocognitive tests. 12 (28%) cases were in remission at follow-up, 21 (49%) had been employed at least 25% during past year, and the mean SCS score was 10.5 (SD 3.7).

3.1. Results of the longitudinal analyses

In the unadjusted analyses better verbal memory (CVLT Trials 1–5) at age 34 predicted better global outcome at age 43, and better long-term verbal memory (CVLT long delay) predicted remission and better global outcome. Better performance on VOLT predicted better vocational and global outcomes. Higher composite score predicted better global outcome (Table 3).

After adjusting for onset age, the only statistically significant results remained between long-term verbal memory and global outcome, and between VOLT and vocational outcome (Table 3). For these associations, we also analysed several other potential confounders in addition to onset age. Gender and education had no great effect on the results, as opposed to negative symptoms, which significantly reduced the predictive power of neurocognition (Table 4).

3.2. Results of the cross-sectional analyses

In the unadjusted cross-sectional analysis, better long-term verbal memory was associated with remission, and better performance in AIM (abstraction subtest) with remission and better global outcome. Better performance on VOLT was associated with better vocational and global outcome. Higher composite score was associated with remission and better global outcome.

After adjusting for onset age, the only statistically significant findings remained between VOLT and composite score and global outcome (Table 5). For additional adjustments, please see Table 4.

4. Discussion

In this unselected general population sample in midlife, better visual memory predicted better vocational outcome whereas better long-term verbal memory predicted better global outcome in schizophrenia. In the cross-sectional analysis at 43 years, better visual memory and composite score were associated with better global outcome. Remission could not be predicted by neurocognition. Contrary to our hypothesis, executive functions did not correlate with functional outcome.

The comparison of different studies is challenging as studies have employed different assessment tools and methods and also the sample characteristics vary greatly. Of the previous studies, the work by Eberhard et al. (2009) is most comparable to ours in design. Both are longitudinal studies with participants of mean duration of illness at baseline about 11 years. Eberhard et al. (2009) had a larger sample size (n = 162) but a shorter follow-up period (five years) and they did not adjust for possible confounders. They concluded that cognitive deficits are predictive of social and vocational outcome but not of remission, which is in line with our results.

There is evidence to suggest that neurocognitive functioning is among the most important factors contributing to vocational outcome

Table 2
Cognitive performance of subjects with schizophrenia and controls at age 34 and 43.

	At age 34 years							At age 43 years						
	Cases			Controls				Cases			Controls			
Cognitive tests	n	Mean	Sd.	n	Mean	Sd.	Sig[g]	n	Mean	Sd.	n	Mean	Sd.	Sig[g]
CVLT trials 1–5[a]	42	47.98	13.59	74	59.81	7.31	<0.001	43	44.30	15.54	43	54.83	8.32	<0.001
CVLT long delay[b]	42	11.21	3.61	74	13.64	2.17	<0.001	43	10.12	3.87	43	12.47	2.48	<0.001
AIM (A+M)[c]	40	20.78	3.16	71	23.63	3.36	<0.001	32	20.81	3.49	32	23.92	2.94	<0.001
AIM (A)[d]	41	22.78	3.11	72	24.13	2.52	0.014	38	22.89	2.87	38	24.66	2.56	0.001
VOLT[e]	39	59.33	8.01	76	68.59	5.38	<0.001	36	60.92	8.24	36	68.79	5.24	<0.001
Composite score[f]	43	−1.23	1.21	77	−0.02	0.67	<0.001	43	−1.23	1.21	43	0.00	0.67	<0.001

[a] California Verbal Learning Test, immediate free recall, summary score.
[b] CVLT, long delay free recall.
[c] Abstraction and Working Memory task, abstraction and memory subtest.
[d] AIM, abstraction subtest.
[e] Visual Object Learning Test.
[f] Mean of z-scores standardised for control group.
[g] Difference between cases and controls.

(Christensen, 2007; Green et al., 2000). It has been suggested that the association between neurocognition and vocational or global functional outcome might be more marked in chronic psychosis than in first-episode subjects (González-Blanch et al., 2010; Stirling et al., 2003; Verdoux et al., 2002). In our sample consisting of participants who were in different phases of the illness, only visual memory predicted vocational outcome in the longitudinal analysis after adjusting for onset age. The cognitive domains investigated in this study have been associated with vocational outcome in prior studies (Dickerson et al., 2007; Hofer et al., 2005, 2011; Kern et al., 2011; Nuechterlein et al., 2011; Tsang et al., 2010).

It must be noted that vocational outcome is a rather difficult subject to study. For example in the Finnish social security system most individuals with schizophrenia will be granted disability pension and most of them will not be actively involved in the job market. Also, many other factors, besides disability payments, including demographics, cultural factors and insurance status (Harvey, 2007; Harvey et al., 2009) and psychosocial rehabilitation, motivation and vocational opportunities (Green et al., 2004), may exert a stronger influence on work outcome than cognition.

Our finding that neurocognitive performance did not predict remission is in accordance with prior studies using the same remission criteria (Brissos et al., 2011; Buckley et al., 2007; Eberhard et al., 2009; Emsley et al., 2007). However, marked neurocognitive differences have been shown between the remission groups in some cross-sectional (Helldin et al., 2006; Hofer et al., 2011) and in one longitudinal study with only a 6-month follow-up (Torgalsbøen et al., 2014). However, of these studies, only Hofer et al. (2011) controlled their results for confounders.

In our study, after adjusting for onset age, global outcome was associated with long-term verbal memory in the longitudinal analysis and visual memory and composite score in the cross-sectional analysis. Eberhard et al. (2009) found that most of their neurocognitive tests were associated with the 5-year global outcome. Siegel et al. (2006) studied both first-episode and previously treated subjects separately, and found, using only a composite score, no cognitive contribution to the 3-year global outcome after controlling for possible confounders. First-episode studies have shown associations between global outcome and verbal memory (Milev et al., 2005), global neurocognitive functioning (Robinson et al., 2004), and attention and memory (Keshavan et al., 2003). However, only the last two adjusted their results for confounders.

There is strong support for the association between executive functions and vocational and global outcomes (Green et al., 2000; Tsang et al., 2010). Our test of executive functions, the AIM task, differs from the more common card sorting/vigilance tests used in previous studies, which could have contributed to the lack of findings. In addition, AIM seemed to be a rather demanding task resulting in the exclusion of a substantial number (up to 20%) of subjects due to below chance performance.

Some inconsistencies in findings may relate to samples including either first episode or chronic schizophrenia patients, or a combination of both (Siegel et al., 2006). Another important issue affecting these partly contradictory findings is the role of confounding factors

Table 3
Standardised effect measures of neurocognitive tests predicting outcomes in schizophrenia: comparable effects between different cognitive tests.

	Remission				Vocational outcome				Global outcome			
	Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]	
Neurocognitive tests	OR_s	CI	OR_s	CI	OR_s	CI	OR_s	CI	β	Sig	β	Sig
CVLT trials 1–5 (n = 42)	1.44	0.69–3.02	1.13	0.49–2.60	1.94	0.97–3.88	1.58	0.73–3.39	**0.36**	**0.020**	0.26	0.102
CVLT long delay (n = 42)	**2.78**	**1.01–7.67**	2.49	0.81–7.62	1.87	0.94–3.73	1.45	0.67–3.13	**0.45**	**0.003**	**0.35**	**0.027**
AIM (A+M) (n = 40)[b]	1.30	0.65–2.58	1.16	0.39–2.06	1.37	0.72–2.62	1.17	0.57–2.42	0.02	0.925	−0.07	0.671
AIM (A) (n = 41)[c]	1.15	0.58–2.31	1.07	0.49–2.31	1.41	0.74–2.69	1.34	0.63–2.84	0.12	0.457	0.07	0.634
VOLT (n = 39)	1.50	0.72–3.13	1.28	0.56–2.89	**2.90**	**1.27–6.64**	**2.55**	**1.07–6.10**	**0.37**	**0.020**	0.29	0.069
Composite score	1.87	0.82–4.26	1.52	0.61–3.78	1.90	0.95–3.83	1.47	0.68–3.21	**0.34**	**0.026**	0.22	0.162

Unadjusted and adjusted longitudinal analyses; cognitive tests performed at 34 years, outcomes assessed at 43 years. OR_s = standardised odds ratio: odds ratio for outcome when predictor variable changes by one standard deviation, i.e. when the predictor variable increases by one SD, odds of having the outcome are multiplied by the amount indicated by the OR_s. Correspondingly if the predictor decreases by one SD, the odds are divided by the amount indicated by the OR_s. This way the statistic does not depend on the scale of the measure used and the different neurocognitive tests can be directly compared with one another. A similar method has been used previously with logistic regression (Nieminen et al., 2013). CI = confidence interval at 95% confidence level, β = standardised coefficient, Sig = p-value. In bold; p-value < 0.05.
[a] Adjusted for onset age
[b] AIM abstraction and memory subtest, 3 participants excluded due to below chance score.
[c] AIM abstraction subtest, 2 participants excluded due to below chance score.

Table 4
Neurocognitive performance as a predictor of outcomes in schizophrenia.

Predictor and outcome	OR	CI		Sig
VOLT at age 34 years and vocational outcome at age 43 years				
Antipsychotic medication[a]	1.11	1.00	1.24	0.061
Gender	**1.13**	**1.01**	**1.26**	**0.034**
Education[b]	1.14	1.00	1.31	0.051
Medication, gender and education combined	1.12	0.98	1.29	0.102
Corresponding outcome at baseline[c]	1.10	0.98	1.23	0.098
PANSS total score[d]	1.12	0.97	1.29	0.134
PANSS positive score[d]	**1.19**	**1.02**	**1.38**	**0.029**
PANSS negative score[d]	1.09	0.97	1.24	0.157
Predictor and outcome	**B**	**SE**	**β**	**Sig**
CVLT long delay at age 34 years and global outcome at age 43 years				
Antipsychotic medication[a]	0.32	0.17	0.31	0.074
Gender	**0.36**	**0.16**	**0.35**	**0.030**
Education[b]	**0.35**	**0.16**	**0.35**	**0.032**
Medication, gender and education combined	0.25	0.18	0.25	0.156
Corresponding outcome at baseline[c]	0.26	0.16	0.26	0.109
PANSS total score[d]	0.23	0.15	0.23	0.145
PANSS positive score[d]	**0.34**	**0.14**	**0.33**	**0.024**
PANSS negative score[d]	0.25	0.16	0.24	0.136
VOLT at age 43 years and global outcome at age 43 years				
Antipsychotic medication[a]	**0.16**	**0.07**	**0.36**	**0.040**
Gender	**0.16**	**0.08**	**0.36**	**0.040**
Education[b]	**0.15**	**0.07**	**0.35**	**0.048**
Medication, gender and education combined	0.15	0.08	0.34	0.058
Corresponding outcome at baseline[c]	0.13	0.07	0.29	0.090
PANSS total score[d]	0.04	0.06	0.09	0.502
PANSS positive score[d]	0.09	0.07	0.21	0.175
PANSS negative score[d]	0.02	0.06	0.04	0.772
Composite score at age 43 years and global outcome at age 43 years				
Antipsychotic medication[a]	0.92	0.46	0.31	0.054
Gender	**0.96**	**0.45**	**0.31**	**0.038**
Education[b]	0.90	0.47	0.30	0.064
Medication, gender and education combined	0.85	0.50	0.28	0.100
Corresponding outcome at baseline[c]	0.64	0.44	0.21	0.153
PANSS total score[d]	0.33	0.37	0.11	0.367
PANSS positive score[d]	0.61	0.40	0.20	0.138
PANSS negative score[d]	0.28	0.38	0.09	0.467

Additional adjustments for the associations that remained statistically significant after adjusting for onset age. All are adjusted for onset age and in addition with the variable presented in each row. OR = odds ratio, CI = confidence interval at 95% confidence level, B = unstandardised coefficient, β = standardised coefficient, SE = standard error, Sig = p-value. In bold; p-value < 0.05.

[a] Dose of antipsychotic medication (chlorpromazine equivalent dose in milligrams) at the time of neurocognitive testing

[b] Level of education at the time of neurocognitive testing (see Table 1 for details).

[c] Baseline functioning (vocational outcome adjusted for work status at 34 years, global outcome for CGI (Clinical Global Impression) at 34 years).

[d] PANSS (Positive and Negative Syndrome Scale) conducted at the time of neurocognitive testing.

that potentially include age of psychosis onset, duration of illness, gender, education and baseline functioning and symptoms (Allott et al., 2011). As antipsychotic medication may have an effect on neurocognition (Husa et al., 2014; Keefe et al., 1999; Mishara and Goldberg, 2004), we also considered current antipsychotic medication as a possible confounder. Due to our relatively small sample size we were unable to reliably adjust (and interpret) our results with multiple confounders simultaneously; however, we adjusted our results for the abovementioned factors separately in combination with onset age (Table 4). Adjusting for onset age and negative symptoms especially influenced our results rendering many associations nonsignificant.

Onset age represents a surrogate measure for the severity of neurocognitive deficits as early-onset patients express more severe impairment in many neurocognitive domains (Rajji et al., 2009). Thus, controlling our results for onset age might obscure true findings. However, in a birth cohort setting, where subjects have had their illness onset at different times, controlling for onset age also implies an adjustment for the duration of illness. Consequently, this adjustment was considered necessary. The adjustments notwithstanding, we believe there is a true and clinically relevant connection between neurocognition and functional outcomes, despite the fact that other underlying factors partly explain the association.

4.1. Strengths and limitations

This study is a longitudinal (and cross-sectional) assessment of neurocognition of individuals with schizophrenia and their controls based on an unselected population-based sample with a long follow-up. We employed identical neurocognitive tests at two time points (at 34 and 43 years) to maximise retest comparability. Unfortunately, neurocognition has not been assessed at an earlier age in this cohort.

There are limitations concerning this study. Our sample size is relatively small and the average power to detect large effect sizes (Beta ≥ 0.5) was 86% ($p < 0.05$), but only 45% for medium effect sizes. The fact that neurocognition was a rather weak predictor of outcomes may be explained by the limited power to find associations. Nevertheless, as we detected some significant associations between functional outcomes and neurocognition, we believe that these associations truly exist.

Our selection of neurocognitive tests was limited, and differences in overall neurocognition could not be evaluated. However, tests measuring verbal and visual memory and executive functions have in many previous studies been associated with outcome in schizophrenia (Fett et al., 2011; Green et al., 2000).

In conclusion, this population-based study with a long follow-up analysing neurocognition as a predictor of outcomes shows that visual learning and memory are associated with vocational and global outcomes.

Table 5
Standardised effect measures of the associations between cognitive tests and outcomes in schizophrenia at 43 years: comparable effects between different cognitive tests.

	Remission				Vocational outcome				Global outcome			
	Unadjusted		Adjusted [a]		Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]	
Neurocognitive tests	OR_s	CI	OR_s	CI	OR_s	CI	OR_s	CI	β	Sig.	β	Sig.
CVLT trials 1–5 (n = 43)	2.47	0.99–6.20	2.15	0.86–5.37	1.50	0.79–2.86	1.28	0.64–2.56	0.27	0.078	0.19	0.204
CVLT long delay (n = 43)	**2.55**	**1.01–6.45**	2.12	0.82–5.47	1.45	0.77–2.74	1.13	0.57–2.23	0.26	0.088	0.16	0.295
AIM (A+M) (n = 32)[b]	1.18	0.55–2.54	1.07	0.47–2.45	2.10	0.93–4.70	2.14	0.87–5.27	0.14	0.454	0.08	0.636
AIM (A) (n = 38)[c]	**2.37**	**1.00–5.62**	2.53	0.92–6.97	1.74	0.86–3.50	1.57	0.73–3.36	**0.36**	**0.025**	0.29	0.057
VOLT (n = 36[d])	1.25	0.59–2.66	0.83	0.34–2.00	**2.87**	**1.19–6.93**	2.24	0.90–5.58	**0.45**	**0.006**	**0.36**	**0.035**
Composite score	2.93	1.09–7.85	2.43	0.94–6.34	1.74	0.90–3.37	1.44	0.70–2.96	**0.40**	**0.008**	**0.31**	**0.036**

Unadjusted and adjusted cross-sectional analyses. OR_s = standardised odds ratio (for a more detailed description, see the footnotes of Table 3), CI = confidence interval at 95% confidence level, β = standardised coefficient, Sig = p-value. In bold; p-value < 0.05.

[a] Adjusted for onset age.

[b] AIM abstraction and memory subtest, 8 participants excluded due to below chance score.

[c] AIM abstraction subtest, 2 participants excluded due to below chance score.

[d] 2 participants excluded due to below change score.

Also long-term verbal memory predicted global outcome whereas remission could not be predicted by neurocognition. Adjusting for confounders, especially for age of onset/duration of illness, diminished the predictive value of neurocognition. However, this does not eliminate the clinical importance of neurocognitive functioning; functional outcomes can to some extent be predicted by neurocognitive performance, although other underlying factors explain, in part, the associations.

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Contributors

PJ, JM and EJ designed the study and wrote the first version of the manuscript. MI and JV were in charge of the data collection. PJ and HS did the statistical analyses. All authors participated in the critical revision of the manuscript and provided approval for the final version to be published.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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