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Poor premorbid school performance, but not severity of illness, predicts cognitive decline in schizophrenia in midlife

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ABSTRACT

Neurocognitive dysfunction is common in schizophrenia but its course and determinants remain uncertain. Our aim was to analyse if premorbid school performance and the severity of illness and functioning predict change in cognition in schizophrenia in a general population sample.

The sample included cases with schizophrenia spectrum disorder from the Northern Finland Birth Cohort 1966. Data on school marks at the age of 16 years, educational level at the age of 34 years, severity of symptoms and occupational functioning around first episode and after years of illness were gained from national registers, hospital notes and interviews. Change of verbal and visual learning and memory and executive functioning were examined between ages 34 and 43 years. The number of cases varied in analyses from 29 to 41, depending on missing data in particular cognitive tests.

Lower school marks at age 16 years and lower education at age 34 years predicted more decline of cognition. Measures of severity of illness or functioning were not associated statistically significantly with change of cognition. Premorbid school performance, but not later course of schizophrenia, related to change of cognition in midlife. Poor premorbid scholastic performance and post-onset cognitive decline may represent related processes as part of an endophenotype of schizophrenia.

1. Introduction

Neurocognitive deficits in schizophrenia are associated with functional impairments (Ekerholm et al., 2012; Hedman et al., 2013, Mesholam-Gately et al., 2009, Touloupoulou and Murray, 2004). Understanding more about the predictors of neurocognitive function in schizophrenia is of theoretical and potential practical importance. However, the longitudinal course of cognitive functioning and its predictors in schizophrenia remain unclear (Bora and Murray, 2014; Bozikas and Andreou, 2011; Irani et al., 2010). Longitudinally, in one study, 10-years follow-up duration of untreated psychosis (DUP) and

change of IQ did not relate, but a subgroup with long duration of active psychosis after the start of treatment demonstrated a significant cognitive decline (Barder et al., 2014). Low education, instead, has been associated with decline in selective attention over 4.5 years follow-up (Ekerholm et al., 2012) and decline in other cognitive scores (e. g., immediate memory, language, delayed memory) (Han et al., 2012); these results, combined with prior studies suggesting that scholastic performance may predict schizophrenia risk (Jones et al., 1994; MacCabe et al., 2008) and illness severity (Lauronen et al., 2007; Mäkinen et al., 2010), encouraged us to further investigate whether premorbid scholastic performance is associated with subsequent course of cognition in schizophrenia within the population based setting of the Northern Finland Birth Cohort 1966. Given previous evidence that higher amount of relapses associated with poorer cognition measured repeatedly at 5-years follow-up (Barder et al., 2013),

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we also investigated whether illness severity predicts subsequent cognitive decline.

Here, our aim was to analyse premorbid school performance, educational level and severity of illness and occupational functioning as predictors of cognitive change in schizophrenia. We hypothesized that both poor school performance and lower educational level, and more severe illness during the first episode and later course of illness, would associate with more decline in cognition.

2. Methods

2.1. Participants

The Northern Finland Birth Cohort 1966 (NFBC 1966) is an unselected general population birth cohort ascertained during mid-pregnancy, consisting 12,058 live-born children in the provinces of Lapland and Oulu with an expected delivery date during 1966. There were 11,017 eligible individuals in Finland at the age of 16 years. Of them, 83 individuals did not consent to the use of their data and have been excluded. The Ethical Committee of the Northern Ostrobothnia Hospital District has approved the study design of the NFBC 1966. The current study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

A baseline study of this sample was conducted in 1999–2001 (around the age of 34 years), with follow-up in 2008–2010 (around the age of 43 years). Participants were given a complete description of the study and had an opportunity to refuse to participate. All participants provided written informed consent (Husa et al., 2014, Kobayashi et al., 2014, Rannikko et al., 2015, Veijola et al., 2014).

2.2. Case identification

All cohort members over 16 years appearing on the nationwide Finnish Hospital Discharge Register (FHDR) until the end of 1997 for any mental disorder (i.e. ICD-8 diagnoses 290–309, ICD-9 290–316, and ICD-10 F00–F69, F99) were identified. All case records were scrutinized and diagnoses were validated for the DSM-III-R criteria. The reliability of researchers assessing schizophrenia diagnoses was good (kappa = 0.85) (Moilanen et al., 2003).

2.2.1. Baseline study

During 1999–2001 around the age of 34 years all 146 living cases with diagnosis of psychosis (62 females, 42%) were invited to participate in the baseline study. Altogether 92 (63%) cases (72 (79%) with schizophrenia spectrum disorders) participated. The Structured Clinical Interview for DSM-III-R (SCID I; Spitzer et al., 1989) was used for diagnostic assessment, together with all available information on illness history including individual medical records. The examination also included cognitive tests described below. After diagnostic interviews a total of 61 cases with a lifetime diagnosis of schizophrenia and 12 cases with other schizophrenia spectrum disorder were detected. Mean duration of illness of all these cases was 10.2 years (standard deviation, SD 4.3) at the baseline. The baseline study in 1999–2001 is presented in detail in Haapea et al. (2007).

2.2.2. Follow-up study

The follow-up study took place in 2008–2010 when the participants were around age 43 years. All the participants of the baseline study were invited to participate in the follow-up, and 44 (61%) individuals with schizophrenia spectrum disorder participated. The follow-up study included diagnostic interview (SCID-I, First et al., 2002) and the same cognitive tests as done at baseline. The original diagnoses were validated at follow-up for all subjects based on the SCID interview and by review of medical records. The mean duration

of illness until the follow-up study was 20.0 (SD 4.1) (Husa et al., 2014, Kobayashi et al., 2014, Rannikko et al., 2015, Veijola et al., 2014).

2.2.3. Final sample

The present study is based on those 41 individuals with a schizophrenia spectrum disorder for whom data on cognition was available at both baseline and follow-up. The schizophrenia spectrum group included the following DSM-III-R diagnoses: schizophrenia 295.1 (n = 9); 295.3 (n = 8); 295.6 (n = 1); 295.9 (n = 16); schizophreniform psychosis 295.4 (n = 1), schizoaffective disorder 295.7 (n = 5) and delusional disorder 297.1 (n = 1). Hereafter in this paper the term "schizophrenia" is used for schizophrenia and other schizophrenia spectrum disorders. The mean follow-up time between baseline and follow-up study was 9.1 years (SD 0.6) years.

2.3. Analysis of attrition

The final sample (n = 41) did not differ from those who participated in the baseline study but not the follow-up in gender, in a summary measure of the CVLT (correct responses in trials 1–5) at baseline, in PANSS total symptoms, onset age or number of psychiatric hospital treatment days. Compared to non-participants, participants had statistically significantly lower educational level at age of 31 years (based on national register data) (p = 0.038). The only five cases with tertiary education did not participate in the follow-up study.

The final sample (n = 41) did not differ from all the other schizophrenia spectrum cases of the whole NFBC 1966 regarding educational level at the age of 31 years, being or not being on disability pension, or cumulative number of psychiatric hospital treatment days.

2.4. Outcomes – neuropsychological assessments and change of cognition

A neuropsychological battery included the CVLT (California Verbal Learning Test; Delis et al., 1987), the VOLT (Visual Object Learning Test; Glahn et al., 1997) and the AIM (Abstraction, Inhibition, Memory; Glahn et al., 2000). These tests were administered at both baseline and follow-up (Juola et al., under revision, Kobayashi et al., 2014, Rannikko et al., 2015).

2.4.1. Verbal learning and memory

The CVLT was administered and scored by trained examiners in a fixed order in exactly the same way at baseline and follow-up. The CVLT was the only word-list memory task administered in a given neuropsychological test session to minimize possible interference effects between tests. The CVLT provides a brief, individually administered assessment of multiple strategies, processes, and errors involved in learning and remembering verbal material (Delis et al., 1987).

The following variables describing different domains of verbal learning and memory were analysed in this study: 1. *Immediate free recall* – performance (correct responses) on List A provides a sum of trials 1 through 5. 2. *Long delay free recall* – the number of correct responses on List A in any order and by category after 15–20 min interval, reflects the examinee´s ability to retain verbal information over time. 3. *All intrusions* – the type of recall errors, which are responses not on the target list on short and long delay.

2.4.2. Visual learning and memory

The VOLT, a measure of visual-spatial learning and memory, was developed to examine aspects of visual-spatial learning and memory in a manner analogous to available verbal tests (e.g., CVLT). Like the CVLT, the VOLT has multiple learning trials, although the VOLT consists of four rather than five, followed by an interference list, as well as short delay and long delay trials (Glahn et al., 1997).

2.4.3. Executive functions

The AIM task is a computerized rule-abstraction/category learning task that requires subjects to use information to group stimuli in a meaningful way on the basis of feedback received during the test. In this task, manipulation of information is operationalized as visual abstraction. This task yields 2 outcome measures: total score on the abstraction trials and total score on the trials involving abstraction with memory (Glahn et al., 2000). Participants who performing below chance, i.e. who had less than 50% of correct answers were excluded.

2.5. Predictors of change of cognition

2.5.1. School marks at 16 years of age

Information on *school marks at the age of 16 years* was acquired from registers of the national application system for secondary education after compulsory schooling (Isohanni et al., 1998). In Finland, school marks range from 4 to 10. Each set of marks is defined in the following way: 4 is rejected, 5–6 are poor, 7–8 are satisfactory and 9–10 are excellent. The mean scores of all subjects, and theoretical and practical subjects, separately, were calculated from the school reports. The theoretical subjects at the time when the participants were 16 years of age were: native language, reading; native language, literal; second, third, fourth and fifth language; mathematics; chemistry; physics; history; biology; geography; religion and civics. The practical subjects were: physical education, music, drawing, craft, domestic science, commercial subjects, typewriting, and agriculture.

2.5.2. Educational level at the age of 34 years

Level of basic education at the age of 34 years ('O' level, 9 years; or 'A' level, 12 years) and vocational education (none, course or school, currently studying, college, polytechnic, or university) was ascertained in the baseline questionnaire. These were combined as level of education: Basic = O level with low vocational education (none, course or school, or currently studying); secondary = O level with high vocational education (college, polytechnic, or university), or A level with low vocational education; and tertiary = A level with high vocational education.

2.5.3. Measures of severity of illness and occupational functioning around first episode

2.5.3.1. Severity of positive and negative symptoms around first episode.
The presence of symptoms at the first psychotic episode was assessed retrospectively from the medical records using the Operational Criteria Checklist for Psychotic Illness (OPCRIT) (McGuffin et al., 1991). The symptoms were categorized using the factors presented by Matsuura et al. (2004). The amount of positive (includes items 73, 67, 61, 68, 75, 55, and 66), and negative symptoms (items 24, 29, 32, 33, and 25) were analysed separately as continuous variables.

2.5.3.2. Occupational functioning around first episode.
Occupational functioning was defined as the person achieving his/her premorbid occupational level, and was split into three categories: 1. unemployed for all of the time, before and after illness onset 2. employment decreased or was less than 50% of the time after illness onset 3. employment did not decrease or accounted for more than 50% of the time after illness onset. Decreases and increases in employment were defined by using the proportion of employment two years after the illness onset divided by the proportion of employment two years before the illness onset (Penttilä et al., 2013). Data about employment was received from the nationwide register of the Finnish Centre for Pensions.

2.5.4. Measures of severity of illness and occupational functioning at later course of illness

Severity of positive and negative symptoms at the age of 34 years was assessed by the Positive and Negative Syndrome Scale (PANSS)

(Kay et al., 1987). At the baseline study positive and negative dimensions of the PANSS were used to measure the amount of psychopathological, especially psychotic, symptoms during the previous week. This variable was analysed as continuous.

2.5.4.1. Occupational status at the age of 34 years.
Occupational capacity was defined as follows: Good occupational capacity = not on disability pension and working at least 50% of time during the year 2000 (i.e. at around age 34-years) vs. poor occupational outcome = working less than 50% of time and/or on disability pension. The information was combined using data from the pension register of the Social Insurance Institution of Finland and from the register of work periods of the Finnish Center for Pensions.

2.6. Characteristics of the sample

2.6.1. Gender
Male vs. female.

2.6.2. Alcohol use disorder by the baseline
Information on an earlier or current diagnosis of both alcohol abuse and dependency was ascertained in the SCID I interview at baseline.

Cumulative number of hospital treatment days of the cases was derived from the Care Register for Health Care).

Age of illness onset was based on evaluation of medical records (Penttilä et al., 2010), and used also as confounding variable in all analyses. Age of illness onset in this sample indicates roughly also length of illness. Since this being a birth cohort sample, the cases had varying length of illness, hence adjusting with age of illness onset was considered important.

Current use of antipsychotic medication was obtained by interview at baseline study.

2.7. Statistical analyses

Statistical analyses were implemented using IBM SPSS Statistics (version 22). Characteristics of the data are presented with mean values, standard deviations (SDs), frequencies and percentages. Associations between change of cognitive test scores between 34- and 43-years and the predictors were analysed using linear regression models. All the analyses were adjusted for corresponding baseline cognitive score and age of illness onset. P-values <0.05 were considered as statistically significant.

3. Results

3.1. Characteristics of the sample

The mean age of illness onset in cases was 23.6 years (SD 4.4). A more detailed description of the sample is presented in Table 1.

3.2. School marks at the age of 16 years, educational level at the age of 34 years and change of cognition

Lower mean of all school marks at the age of 16 years predicted more decline in VOLT, and abstraction with memory. Lower school marks in both theoretical and practical school marks predicted decline in VOLT. Lower practical school marks were associated also with more decline in long delay free recall of CVLT, abstraction with memory, and cognitive composite score. Low educational level at the age of 34 years was associated with more decline in abstraction with memory (Table 2). When associations between the mean of all school marks and change of VOLT were adjusted additionally (to baseline

Table 1
Baseline characteristics of the sample (n = 41).

Characteristics	
Follow-up time, years (mean, SD)	9.1 (0.6)
Females (n, %)	19 (46%)
Education (n, %)	
Basic	22 (54%)
Secondary	12 (29%)
Tertiary	7 (17%)
SOFAS (mean, SD)	51.0 (16.5)
Current or earlier alcohol use disorder (n, %)	9 (22.0%)
Age of psychosis onset, years (mean, SD)	23.6 (4.4)
Positive and Negative Syndrome Scale (PANSS) (mean, SD)	
Total	52.4 (19.5)
Positive	20.0 (5.7)
Negative	14.8 (9.2)
Cumulative number of hospital treatment days (median, IQR)	161 (44 - 753)
Current use (last 3 months) of antipsychotic medication (n, %)	
No current medication	13 (31.7%)
Typical antipsychotic	15 (36.6%)
Atypical antipsychotic	9 (22.0%)
Both typical and atypical antipsychotic	4 (9.8%)

SD = standard deviation, IQR = inter quartile range.

Fig. 1. Association between mean of all school marks and later change of VOLT in schizophrenia. *Interpretation: Poorer school marks associate with more decline in visual learning and memory in schizophrenia.*

cognition and onset age) by educational level at the age of 34 years, the associations remained statistically significant. In this model, educational level at the age of 34 years did not remain statistically significant. When the same adjustments were made for abstraction with memory, none of the associations remained statistically significant. The crude association between school marks and change of VOLT is illustrated in Fig. 1.

3.3. Severity of illness around first episode and change of cognition

There were no statistically significant associations between severity of illness or occupational functioning at first episode and change of cognition, though more positive symptoms associated non-significantly with less decline, and more negative symptoms with more decline in cognition (Table 3).
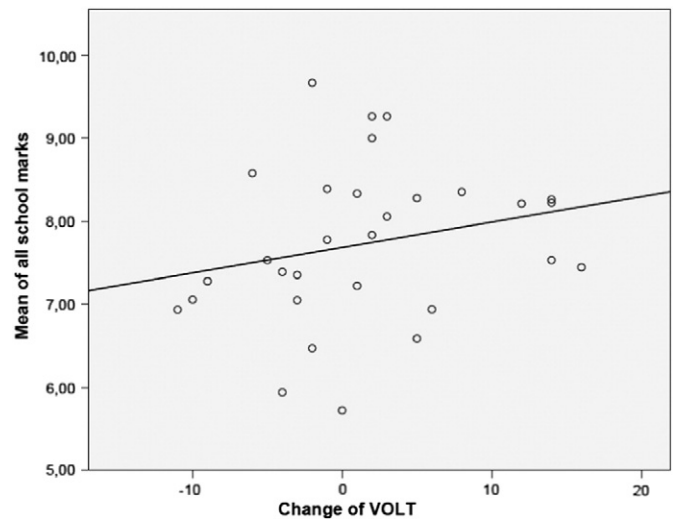
3.4. Later course of illness and change of cognition

Occupational functioning, positive and negative symptoms at later course of illness did not associate with change of cognition (Table 3).

4. Discussion

4.1. Main findings

Lower school marks at the age of 16 years and lower education at the age of 34 years predicted more decline of cognition in schizophrenia in

midlife. Somewhat surprisingly, and not supporting our hypothesis, the course of schizophrenia at first episode and later course of schizophrenia did not predict change of cognition.

4.2. Comparison to earlier studies

To our knowledge, there are no earlier studies on school performance as a predictor for longitudinal change of cognition in schizophrenia. Impairment in intellectual ability may exist from early in life, before the onset of illness, and it is not just a consequence of the pathological process of disease onset (Aylward et al., 1984; Bora and Murray, 2014; Fuller et al., 2002). In earlier studies, subjects who developed schizophrenia were more likely to have had impairments in childhood educational scores (Jones et al., 1994), and genetic factors have been proposed to account for poorer school performance in children of parents with schizophrenia (Jundong et al., 2012). In a schizophrenia study from Iowa, USA, poor scholastic test scores at grade 11 (age 16), but not grade 8, predicted poorer IQ, verbal fluency and auditory verbal learning at first episode; there was no association between scholastic measures and severity of symptoms in this study (Fuller et al., 2002). These studies and ours support the neurodevelopmental course of development of schizophrenia. In the previous study of this same NFBC 1966 sample later age of learning to stand at age about one year associated with more decline in cognition in schizophrenia, suggesting a putative link between developmental and

Table 2
School marks and later education as predictors of change of cognition from age 34-years to age 43-years in schizophrenia, adjusted for baseline cognition and age of illness onset. The background factors have been analysed separately in different analyses, not in same model.

	CVLT Immediate free recall		CVLT Long delay free recall		CVLT All intrusions		VOLT		AIM, abstraction without memory		AIM, abstraction with memory		Composite score	
	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value
School marks at age 16 years														
Mean of all school marks	0.19	0.25	0.20	0.18	−0.09	0.59	**0.36**	**0.031**	0.05	0.69	**0.32**	**0.038**	0.21	0.17
Mean of theoretical subjects marks	0.15	0.35	0.15	0.34	−0.04	0.83	**0.34**	**0.043**	0.06	0.66	0.28	0.071	0.15	0.33
Mean of practical subjects marks	0.25	0.13	**0.36**	**0.017**	−0.26	0.13	**0.38**	**0.028**	0.03	0.81	**0.40**	**0.008**	**0.38**	**0.015**
Low education at age 34 –years	−0.27	0.51	−0.19	0.60	0.13	0.70	−0.32	0.42	−0.44	0.15	**−0.71**	**0.038**	−0.25	0.38

Statistically significant results are in **bold**.
CVLT = California Verbal Learning Test, VOLT = Visual Object Learning Test, AIM = Abstraction, Inhibition and Memory.

Table 3

Severity of illness and functioning as predictors of change of cognition from age 34-years to age 43-years in schizophrenia, adjusted for baseline cognition and age of illness onset. The background factors have been analysed separately in different analyses, not in same model.

	CVLT Immediate free recall		CVLT Long delay free recall		CVLT All intrusions		VOLT		AIM, abstraction without memory		AIM, abstraction with memory		Composite score	
	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value
Severity of illness around first episode														
Good occupational functioning	0.26	0.50	0.36	0.39	0.34	0.37	0.07	0.88	0.31	0.35	0.46	0.25	0.11	0.70
Positive symptoms	0.29	0.053	0.26	0.086	0.10	0.53	0.17	0.32	0.02	0.91	0.25	0.10	0.27	0.064
Negative symptoms	−0.26	0.088	−0.04	0.81	0.27	0.11	−0.27	0.10	−0.06	0.65	−0.04	0.78	−0.28	0.060
Severity of illness at later course of illness, at age 34 years														
Good occupational functioning (i.e. not on disability pension)	−0.02	0.97	−0.09	0.86	−0.29	0.46	0.30	0.55	−0.01	0.99	0.31	0.48	0.14	0.70
Positive symptoms	0.05	0.76	0.12	0.49	0.17	0.38	0.05	0.79	−0.04	0.76	0.08	0.67	−0.02	0.93
Negative symptoms	−0.10	0.62	0.06	0.76	0.11	0.62	0.16	0.46	−0.16	0.26	0.01	0.96	0.09	0.67

Statistically significant results are in **bold**.
CVLT = California Verbal Learning Test, VOLT = Visual Object Learning Test, AIM = Abstraction, Inhibition and Memory.

degenerative aspects of the illness (Kobayashi et al., 2014). Here we extend our previous work to consider the time of adolescence, as we demonstrate that poorer school performance at age 16 years is associated with decline of cognition.

Regarding education and cognition (Ekerholm et al., 2012; Gould et al., 2012; Han et al., 2012), we have been able to extend earlier research, and shown that poorer adult educational level has an effect on longitudinal change of cognition after approximately 20 years of illness. However, in adjusted analyses only school marks remained significant (educational level non-significant). Poorer school achievements may contribute to poorer adult education that this way may be associated with change of cognition.

Regarding longitudinal associations between severity of illness and cognition, in earlier studies cognition has been used as predictor of later course of illness, where poorer cognition predicted worse subsequent functional (Allot et al., 2011, Green et al., 2004; Ventura et al., 2011) and clinical outcomes (Faber et al., 2011). In this same Northern Finland Birth Cohort 1966 sample poorer cognition at the age of 34 years predicted poorer vocational and global outcome at the age of 43 years in schizophrenia (Juola et al., in press). Now we have shown that symptoms or functioning around the first episode or later course of illness do not greatly predict the change of cognition at midlife. It may be that after illness onset several other factors may become more important (compared to severity of symptoms and functioning) regarding cognition, such as treatments (for example antipsychotic medication, Husa et al., 2014). However, there was some statistically non-significant association between presence of positive symptoms and less later decline in cognition, and presence of negative symptoms and more decline in cognition. Our modest sample size precludes drawing strong conclusions from negative findings.

4.3. Theoretical discussion

One potential explanation for association between premorbid school marks and later change of cognition might be the concept of cognitive reserve as a protective factor for later life cognitive impairments. Cognitive reserve, the ability of the mind to compensate in some way for brain changes, has been proposed in dementia and ageing research as a moderator between brain change and clinical outcome (Stern, 2012). In our study lower school marks at age 16-years and lower education at age 34-years predicted more decline of cognition in midlife schizophrenia. It may be that individuals with schizophrenia with better premorbid cognition and better educational attainment can somehow compensate for illness-related deficits,

perhaps by employing alternative cognitive and/or neural strategies to solve cognitive problems in unorthodox ways (Murray et al., 2010).

It is well established that low intelligence is a risk factor for schizophrenia, and in part this itself may relate to cognitive reserve, as altered cognitive functions such as attributional biases, or biases in data gathering, and self-monitoring, may predispose towards the development of delusions and hallucinations. The neurodevelopmental nature of schizophrenia complicates the issue of cognitive reserve, and the fact that better post-onset cognition predicts better functioning does not necessarily support the importance of cognitive reserve, because cognitive impairments in schizophrenia differ significantly at the time of diagnosis (Barnett et al., 2006). However, one reason to believe that cognitive reserve is an active process in schizophrenia is that the relationship between intelligence and schizophrenia is not restricted to the lower end of the intelligence spectrum: the risk appears to be linear over the IQ range (Jones et al., 1994), with individuals of average intelligence at significantly greater risk of schizophrenia than individuals with high IQ scores (Zammit et al., 2004). The protective effects of cognitive reserve would be expected to operate throughout the range of the intelligence spectrum in this manner.

Among individuals with schizophrenia higher premorbid and childhood intelligence has previously been associated with better social and functional outcome (Aylward et al., 1984; Munro et al., 2002). Hence, both education and participation in challenging activities may play a protective role and be potentially useful interventions to increase resilience in schizophrenia.

The distinctions between premorbid intelligence, post-onset cognitive ability, and magnitude of participation in the contemporary information society and in vocational life, may be artificial. Within the limits of modest sample size, the current study suggests that there are cognitive changes in schizophrenia that are systematically associated with premorbid cognitive functioning and that premorbid cognitive variables are more sensitive than clinical symptoms as factors for prediction of the course of cognition. If this suggestion is correct, then definition of illness onset becomes more complex. Therefore, further investigation in this specific area with larger sample size is needed.

4.4. Strengths and limitations

Compared to previous studies with usually short follow-ups, a long (nine-year) follow-up interval from ages 34 to 43 years was applied, which may contribute towards understanding the temporal correlations between predictive factors and change of cognition in early midlife. The study design made it possible to collect prospective data

from adolescent school marks and from midlife cognition in schizophrenia. An earlier study showed that the scholastic test scores at age 16 years, but not at younger age, predicted cognition after illness onset (Fuller et al., 2002), so the time frame of the school performance in our study may be optimal in terms of predicting later cognition. The general population design of this study decreases the potential sample selection bias. The birth cohort sample drawn from the same aged participants helps to minimize variance according to age variation. We maximised the re-test reliability by using identical measures of cognition – the CVLT, VOLT and AIM – at both time points.

Limitations of this study should be acknowledged. The lack on controls limits the ability to make illness specific conclusions, and the number of subjects is relatively small. Since cognition was not measured at early stages of illness, we do not know the time when the observed cognitive decline started. Additionally, we do not know how the cognitive abilities of the participants affected school achievement or adult education. We had a limited number of predictors and first episode symptoms were evaluated from hospital notes, not with questionnaires or interviews.

5. Conclusions

Premorbid school performance, but not so much later course of schizophrenia, seems to associate with change of cognition in midlife schizophrenia. These results suggest that the concept of cognitive reserve as a protective factor for later life cognitive impairment in the general population may be also relevant at midlife course in schizophrenia. We speculate that poor premorbid scholastic performance and post-onset cognitive decline may represent related processes as part of an endophenotype of schizophrenia.

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Conflict of interest

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