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Original Article

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Change in IQ in schizophrenia patients and their siblings: a controlled longitudinal study

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Abstract

Background. Lower intelligence quotient (IQ) has frequently been reported in patients with schizophrenia. However, it is unclear whether IQ declines (further) after illness onset and what the familial contribution is to this change. Therefore, we investigate IQ changes during the course of illness in patients with non-affective psychosis, their siblings and controls.

Methods. Data are part of the longitudinal Genetic Risk and Outcome of Psychosis (GROUP) study in the Netherlands and Belgium. Participants underwent three measurements, each approximately 3 years apart. A total of 1022 patients with non-affective psychosis [illness duration: 4.34 (S.D. = 4.50) years], 977 of their siblings, and 565 controls had at least one measure of IQ (estimated from four subtests of the WAIS-III).

Results. At baseline, IQ was significantly lower in patients (IQ = 97.8) and siblings (IQ = 108.2; $p < 0.0001$) than in controls (IQ = 113.0; $p < 0.0001$), and in patients as compared with siblings ($p < 0.0001$). Over time, IQ increased in all groups. In siblings, improvement in IQ was significantly more pronounced (+0.7 points/year) than in patients (+0.5 points/year; $p < 0.0001$) and controls (+0.3 points/year; $p < 0.0001$). IQ increase was not significantly correlated with improvement in (sub)clinical outcome in any of the groups.

Conclusions. During the first 10 years of the illness, IQ increases to a similar (and subtle) extent in a relatively high-functioning group of schizophrenia patients and controls, despite the lower IQ in patients at baseline. In addition, the siblings' IQ was intermediate at baseline, but over time the increase in IQ was more pronounced.

Introduction

Since its first delineation by Kraepelin (1896), cognitive dysfunction has been considered a core aspect of schizophrenia (Kahn and Keefe, 2013). Although many studies have focused on distinctive cognitive domains, less attention has been paid to general intelligence, despite it being a robust measure that integrates a variety of cognitive functions (Colom *et al.*, 2010). Lower intelligence quotient (IQ) or general cognitive ability composite scores (*g*) have consistently been reported in schizophrenia patients (Aylward *et al.*, 1984; Heinrichs and Zakzanis, 1998; Keefe and Fenton, 2007; Dickerson *et al.*, 2011; Irani *et al.*, 2011), indicating that IQ is lower once the illness is present.

This begs the question whether lower IQ is a result of the illness or whether it is a risk marker for schizophrenia. The latter is suggested by findings that mean IQ-scores are below those of healthy subjects years before the onset of psychotic symptoms in individuals who later develop schizophrenia (Woodberry *et al.*, 2008; Khandaker *et al.*, 2011; Dickson *et al.*, 2012; Agnew-Blais and Seidman, 2013; Kendler *et al.*, 2015; Hochberger *et al.*, 2018). More specifically, it is not the level of IQ *per se* but rather a deviation from what is expected based on the level of IQ of biological relatives (Kendler *et al.*, 2016).

Not only is lower IQ associated with future development of schizophrenia, also a *decline* in global cognitive functioning precedes the onset of psychotic symptoms in children (Kremen *et al.*, 1998) and adolescents (Fuller *et al.*, 2002; Reichenberg *et al.*, 2005; Mollon and Reichenberg, 2018), and this decline seems specific for schizophrenia (van Oel *et al.*, 2002; Meier *et al.*, 2014; Ullman *et al.*, 2017). In contrast to the consistent – though limited – evidence of IQ decline *prior to* illness onset, it is less clear whether it declines *after* illness onset (Zipursky *et al.*, 2013). Reviews summarizing longitudinal studies on cognitive functioning (e.g. global cognition such as IQ and specific cognitive domains) in schizophrenia fail to find evidence of decline over time (Rund, 1998; Kurtz, 2005; Irani *et al.*, 2011). However, these results are hard to interpret, since less than a third of the included studies compared performance in patients with that of a control group. This is problematic, because stability or improvement in patients may still represent a deficit when compared with changes in healthy

individuals (Szoke *et al.*, 2008; Granholm *et al.*, 2010; Harvey *et al.*, 2010; Bozikas and Andreou, 2011).

In a meta-analysis on longitudinal IQ studies that restricted itself to studies which included patients and healthy controls, Hedman *et al.* (2013) reported a relative decline – or lack of improvement – in intelligence in schizophrenia patients, which was interpreted as the absence of a learning effect. However, these results must be considered preliminary due to the relatively small number of subjects (i.e. 280 patients and 306 healthy controls) that were included in the few controlled longitudinal studies ($n = 8$) conducted so far.

IQ is a highly heritable trait (Posthuma *et al.*, 2001; Bouchard, 2009) and deficits in intellectual function are present in first-degree relatives of schizophrenia patients (Groom *et al.*, 2008; Maziade *et al.*, 2009, 2011). That the level of intelligence is affected in co-twins of patients indicates that lower IQ in schizophrenia can partly be explained by common genes (Toulopoulou *et al.*, 2007). So far, it is unknown to what extent the association between IQ *change* and schizophrenia liability is either causal or a consequence of common environmental influences or pleiotropic influences of genetic variants that lead to both lowering of IQ and increased risk for psychosis (Walters and Owen, 2007). Using a twin design, Hedman *et al.* (2012) reported a lack of increase in IQ in patients, not in co-twins, indicating that in chronically ill patients environmental factors implicated in the disease are associated with a lack of IQ improvement over time.

Larger studies – including patients, their family members and healthy controls – are needed to adequately address IQ change during the course of illness and the genetic and environmental contributions to this change. Therefore, we examined whether IQ change (measured three times with 3-year intervals) differs between 1022 patients with non-affective psychosis, 977 of their non-psychotic siblings, and 565 controls.

Method

Study design Genetic Risk and Outcome of Psychosis (GROUP)

Data are part of the longitudinal GROUP study in the Netherlands and Belgium. At baseline, patients were identified through clinicians working in regional psychotic disorder services, whose caseloads were screened for inclusion criteria. Subsequently, patients presenting at these services as either out-patients or in-patients were recruited for the study. Siblings were recruited via the proband. Controls were selected through random mailings to addresses in the catchment areas of the cases.

At baseline, patients met Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision [DSM-IV-TR (American Psychiatric Association, 2000)] criteria for a non-affective psychotic disorder. At follow-up measurements, after an average of approximately 3 and 6 years, the diagnostic interview was repeated. Exclusion criteria for healthy controls were a history of psychotic disorder or having a first-degree family member with a history of psychotic disorder.

The study protocol was approved centrally by the Ethical Review Board of the University Medical Center Utrecht and subsequently by the local review boards of each participating institute. All subjects gave written informed consent in accordance with the committee's guidelines.

Subjects

For all patients, diagnostic information from the available measurements was taken into account to decide what the most accurate diagnosis was. For patients with an illness duration at baseline of longer than 2 years the baseline diagnosis was chosen, while for patients with an illness duration at baseline, shorter than 2 years as well as for siblings and controls the last diagnosis was used. All individuals with at least one IQ measurement were included.

Measurements

Information on age, gender and highest educational level were assessed. Patients underwent the Positive and Negative Syndrome Scale [PANSS (Kay *et al.*, 1987)]; siblings and healthy controls were administered the Community Assessment of Psychic Experiences (CAPE; http://www.cape42.homestead.com) and the Structured Interview for Schizotypy-Revised [SIS-R (Vollema and Ormel, 2000)]. To assess substance abuse and dependence, the Composite International Diagnostic Interview [CIDI (Organization, 1997) section L (substance use)] was used. The WAIS-III short form was used to estimate IQ. For more detailed information, see online Supplement 1 and Korver *et al.* (2012).

Statistical analyses

GROUP database version 6.0 was used. Baseline differences between groups on demographic and clinical variables were investigated using analysis of variances for continuous variables and χ^2 statistics for categorical variables. Also, differences on baseline demographic and symptom severity variables between those who participated only once (either baseline, second or third measurement) and those who participated twice or three times were investigated.

Baseline IQ and change in IQ

We compared schizophrenia patients and their non-psychotic siblings with healthy controls on baseline IQ and change in IQ (and on the four individual subtests) applying multi-level mixed model analyses, using the lme function in the nlme package (Pinheiro *et al.*, 2012) in R (https://www.R-project.org/). The multi-level approach takes into account (1) the correlation between multiple measurements from the same person, (2) the correlation between individuals within a family and within a center, and (3) the presence of missing data. Consequently, individuals with only one or two IQ measurements can be included in the analyses, not just those with complete data. This reduces the uncertainty (e.g. noise) in the IQ estimates and the effect of attrition bias.

We applied a three-level model, i.e. measurements within subjects, within families, and within centers. Age was centered around the mean. IQ was modeled as a function of group membership (control, sibling, and patient), age (at each measurement), and the interaction between group and age. Consequently, *B*-values represent the mean IQ change per year in each group. We corrected for the potential confounding effect of gender. Random intercepts per subject, per family, and per center were applied. First, the control group served as a reference, resulting in the contrast between controls *v.* patients and controls *v.* siblings. Next, the patient group was defined as a reference to establish the contrast between patients *v.* siblings. The analyses were repeated for the scaled scores of the WAIS-III subtests.

To rule out that findings are explained by psychopathology in siblings or controls, analyses were repeated after excluding siblings and controls with a psychiatric diagnosis (hereafter referred to as

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being 'unaffected'). In addition, analyses were repeated including only schizophrenia patients and comparing them with unaffected siblings and controls.

Significance level was set at $p < 0.05/15 = 0.0033$ [five IQ-variables (IQ and four subtests) × three pair-wise comparisons].

(Subclinical) symptom severity

In patients, we investigated the effect of (change in) symptom severity on (change in) IQ. At each measurement, the five PANSS factor scores were highly correlated with the PANSS total score (all $r > 0.70$); we therefore used the total score as symptom severity measure to reduce the number of tests. We applied the same multi-level mixed model analysis, now modeling IQ as a function of symptom severity, age (at each measurement), and the interaction between symptom severity and age. Similar analyses were done in siblings using the SIS-R total score and CAPE total score. Again, the total scores were used because the correlation between the sum score of the positive and negative subscale of the SIS-R and the correlations between the sum score of the positive, negative and depression dimension of the CAPE were moderate to high in both groups (SIS-R: controls $r > 0.74$, siblings $r > 0.78$; CAPE: controls: all $r > 0.42$, siblings: all $r > 0.44$).

Results

Demographic and clinical characteristics

Age at baseline differed significantly between groups, with controls being almost 3 years older than patients and siblings. Males were significantly overrepresented in the patients relative to siblings and controls. Controls had significantly higher education levels than siblings, who in turn were higher educated than patients. No significant group differences were found for parental level of education.

Siblings had significantly more negative and depressive symptoms (CAPE), as well as higher scores on positive and negative schizotypy (SIS-R) than controls. See Table 1 for further demographic and clinical information.

For information on attrition, see online Supplement 2.

Baseline IQ and change in IQ

See Table 2 for results of the multilevel analysis. With the control group as a reference, the intercept gives the mean baseline (time = 0) IQ scores for a male (male = 1; reference group) aged 31.14 years (i.e. centered age). Estimates of deviation from the intercept are given for patients and siblings.

At baseline, the average IQ for a 31-year-old male control is 113.0. At baseline, both patients (IQ = 97.8) and siblings (IQ = 108.2) had a significantly lower IQ and lower subtest scores (except for Block Design) than controls. Siblings had significantly higher IQ and subtest scores than patients.

IQ increased significantly over time in all groups (controls: +0.3 points/year, siblings: +0.7 points/year, patients: +0.5 points/year) and the increase was significantly more pronounced in siblings as compared with controls and patients. Controls and patients did not differ significantly. See Fig. 1 and online Supplement 3.

Over time, controls improved significantly on Digit Symbol-coding (+0.05 points/year) and Block Design (+0.07 points/year), but not on Arithmetic and Information. On Digit Symbol-coding and Block Design, siblings showed a more pronounced increase in performance (+0.09 points/year and +0.13 points/year, respectively) as compared with controls and patients (+0.05 points/year and +0.09 points/year), which is a similar pattern as in IQ. No improvement was found in any of the groups on Arithmetic. Finally, siblings and patients (both +0.09) showed improvement over time on Information, which was significantly more pronounced than in controls (0.02 points/year) (see Fig. 2).

Including only patients with schizophrenia and/or excluding siblings and controls with a psychiatric diagnosis did not change this pattern of findings (see online Supplement 4).

(Sub)clinical symptom severity

In patients, lower IQ was significantly related to higher PANSS score, while IQ change was unrelated to symptom severity change. In siblings, higher SIS-R and CAPE scores were significantly related to lower IQ, while IQ change was unrelated to change in either measures. In controls, no significant associations were found between IQ (change) and (change in) SIS-R and CAPE scores (see Table 3).

Discussion

To our knowledge, this is the largest study to date – including 1022 patients with non-affective psychosis (72% schizophrenia), 977 of their siblings, and 565 controls – examining IQ at three measurements over a 6-year follow-up period. Our main finding is that patients, although displaying the expected lower IQ, did not differ from controls in terms of IQ change per year. That is, patients showed an average increase of 0.5 points/year, while controls increased with 0.3 points/year. IQ in siblings was higher than in patients but lower than in controls. Moreover, IQ increase in siblings (0.7 points/year) was significantly more pronounced than in patients and controls.

The finding in patients contrasts with our earlier meta-analysis in which we quantified studies comparing IQ change between patients and healthy subjects (Hedman *et al.*, 2013). The meta-analysis showed a smaller IQ increase in patients (effect size −0.48). IQ in both groups was quite similar between the current study and the meta-analysis (respectively, patients: IQ = 97.7 and 97.2; controls: IQ = 113.0 and 109.3), as was IQ increase in patients (respectively, +0.5 points/year and +0.3 points/year). However, there is a remarkable difference in IQ increase in controls between the meta-analysis (+2.1 points/year) and the current study (+0.3 points/year). The meta-analysis contained studies with major differences in sample characteristic (e.g. age, illness duration, and age at onset), methods to establish IQ (e.g. different versions of full scale or short versions of WAIS or WISC), and follow-up duration (ranging between 1 and 8 years), which might have played a role. As the current patient sample is more than three times larger than that included in the meta-analysis, we conclude that IQ does not (further) decrease during the first 10–15 years of the illness in schizophrenia. There is, however, suggestive evidence that IQ decline occurs in later stages of the illness (Harvey, 2001; Stirling *et al.*, 2003; McIntosh *et al.*, 2013). A meta-analysis of longitudinal cognition studies showed that the cognitive performances of first-episode patients, those at ultra-high-risk to develop psychosis, and healthy controls all significantly improved over time (Bora and Murray, 2014). Together, this supports the notion that cognitive abnormalities (including low IQ) in schizophrenia develop long before the onset of the

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Table 1. Demographic and clinical information of schizophrenia patients, siblings and controls at baseline

	Patients (pt)	Siblings (sib)	Controls (nc)	Between-group comparison	
N baseline	1022	977	565		
N after 3 years	590	587	284		
N after 6 years	602	657	364		
				Test statistic	*p*
Age at baseline (years, mean ± S.D.)	27.65 (7.82)	27.97 (8.24)	30.49 (10.56)	$F_{(2,2563)} = 21.62$	<0.001 nc > pt, nc > sib
Gender, M/F (% male)	782/240 (77%)	441/536 (45%)	257/308 (45%)	$\chi^2(df = 2) = 246.00$	<0.001
Interval between measurements 1 and 2 (years, mean ± S.D.)					
Interval between measurements 2 and 3 (years, mean ± S.D.)					
Illness duration at baseline (years, mean ± S.D.)	*N* = 1006, 4.34 (4.49)				
IQ at baseline (mean ± S.D.)	94.89 (16.07)	102.94 (15.56)	109.79 (15.13)		
IQ after 3 years (mean ± S.D.)	98.39 (16.59)	107.77 (16.93)	111.76 (16.60)		
IQ after 6 years (mean ± S.D.)	100.69 (17.79)	112.04 (17.76)	115.15 (17.44)		
Diagnosis					
No diagnosis	NA	724 (74%)	468 (83%)		
Schizophrenia	732 (72%)	NA	NA		
Schizoaffective disorder	154 (15%)	NA	NA		
Psychosis – other[a]	136 (13%)	NA	NA		
Mood disorder[b]	NA	217 (22%)	89 (16%)		
Other diagnosis[c]	NA	36 (4%)	8 (1%)		
Education in years, *N* mean ± S.D.	*N* = 998, 14.6 (2.4)	*N* = 970, 15.6 (2.2)	*N* = 562, 16.0 (1.9)	$F_{(2,2529)} = 84.55$	<0.001 nc > sib > pt
Mother: education in years, *N* mean ± S.D.	*N* = 923, 13.0 (3.9)	*N* = 913, 13.3 (3.5)	*N* = 546, 13.2 (3.0)	$F_{(2,2381)} = 0.91$	0.401
Father: education in years, *N* mean ± S.D.	*N* = 895, 14.0 (3.7)	*N* = 902, 14.2 (3.6)	*N* = 535, 13.8 (3.3)	$F_{(2,2331)} = 2.18$	0.114
PANSS Positive symptoms	*N* = 947, 13.9 (6.6)				
PANSS Negative symptoms	N = 937, 15.1 (6.6)				
PANSS Disorganization	*N* = 940, 16.7 (6.3)				
PANSS Excitement	*N* = 959, 12.0 (4.0)				
PANSS Emotional distress	*N* = 954, 15.8 (5.7)				
CAPE positive symptoms, frequency		*N* = 863, 0.21 (0.20)	*N* = 540, 0.19 (0.17)	$F_{(1,1526)} = 2.5$	0.114
CAPE positive symptoms, distress		*N* = 746, 0.46 (0.48)	*N* = 457, 0.42 (0.45)	$F_{(1,1202)} = 1.5$	0.221
CAPE negative symptoms, frequency		*N* = 863, 0.56 (0.38)	*N* = 540, 0.48 (0.31)	$F_{(1,1402)} = 15.9$	<0.001 sib > nc
CAPE negative symptoms, distress		*N* = 830, 0.70 (0.53)	*N* = 513, 0.66 (0.48)	$F_{(1,1342)} = 2.0$	0.158
CAPE depressive symptoms, frequency		*N* = 865, 0.63 (0.39)	*N* = 542, 0.57 (0.32)	$F_{(1,1406)} = 8.4$	0.004 sib > nc
CAPE depressive symptoms, distress		*N* = 831, 0.93 (0.61)	*N* = 522, 0.87 (0.57)	$F_{(1,1352)} = 3.0$	0.083
SIS-R positive		*N* = 970, 0.38 (0.42)	*N* = 557, 0.31 (0.34)	$F_{(1,1526)} = 13.2$	<0.001 sib > nc
SIS-R negative		*N* = 970, 0.27 (0.26)	*N* = 556, 0.23 (0.22)	$F_{(1,1525)} = 8.8$	0.003 sib > nc

Baseline information is presented here, unless only follow-up information was available.

[a]Psychosis-other in patients: bipolar disorder *N* = 3, brief psychotic disorder *N* = 25, delusional disorder *N* = 11, drug induced psychotic disorder *N* = 8, psychotic disorder NOS *N* = 73, schizophreniform disorder *N* = 16.

[b]Mood disorder in siblings: bipolar disorder *N* = 21, cyclothymic disorder *N* = 1, depressive disorder NOS *N* = 5, dysthymic disorder *N* = 3, major depressive disorder *N* = 187. Mood disorder in controls: depressive disorder NOS *N* = 1, dysthymic disorder *N* = 1, major depressive disorder *N* = 87.

[c]Other diagnoses in siblings: ADHD *N* = 3, adjustment disorder *N* = 8, alcohol dependence/abuse *N* = 1, anorexia nervosa *N* = 2, Cannabis dependence/abuse *N* = 2, dyssomnia NOS *N* = 1s, panic disorder *N* = 5, PDD-NOS *N* = 4, sleeping disorder *N* = 4, PTSD N = 1, reading disorder *N* = 1, schizoid/schizotypal personality disorder *N* = 3, somatization disorder *N* = 1. Other diagnosis in controls: adjustment disorder *N* = 3, borderline personality disorder *N* = 1, sleeping disorder *N* = 2, PTSD *N* = 1, specific phobia *N* = 1.

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Table 2. Overview of multilevel analyses on differences between all patients, all siblings, and all healthy controls on IQ and change in IQ

	IQ		Digit Symbol Coding		Block Design		Arithmetic		Information	
	B (S.E.)	*p*	*B* (S.E.)	*p*	*B* (S.E.)	*p*	*B* (S.E.)	*p*	*B* (S.E.)	*p*
Baseline[a]										
Controls (reference)	113.0 (0.8)	**<0.0001**	11.0 (0.2)	**<0.0001**	11.8 (0.2)	**<0.0001**	12.2 (0.2)	**<0.0001**	12.6 (0.2)	**<0.0001**
Siblings	−4.8 (0.9)	**<0.0001**	−0.9 (0.2)	**<0.0001**	−0.3 (0.2)	0.0888	−0.8 (0.2)	**<0.0001**	−0.9 (0.2)	**<0.0001**
Patients	−15.2 (0.9)	**<0.0001**	−3.5 (0.2)	**<0.0001**	−1.6 (0.2)	**<0.0001**	−2.5 (0.2)	**<0.0001**	−1.2 (0.2)	**<0.0001**
Patients (reference)	97.7 (0.6)		7.5 (0.2)		10.2 (0.1)		9.7 (0.1)		11.3 (0.1)	
Siblings	+10.4 (0.6)	**<0.0001**	+2.7 (0.1)	**<0.0001**	+1.3 (0.1)	**<0.0001**	+1.7 (0.1)	**<0.0001**	+0.4 (0.1)	**0.0001**
Change[a]										
Controls (reference)	0.3 (0.05)	**<0.0001**	0.05 (0.009)	**<0.0001**	0.07 (0.01)	**<0.0001**	−0.02 (0.01)	0.1155	0.02 (0.01)	0.0902
Siblings	+0.4 (0.06)	**<0.0001**	+0.04 (0.01)	0.0033	+0.06 (0.01)	**<0.0001**	+0.04 (0.01)	0.0039	+0.07 (0.01)	**<0.0001**
Patients	+0.2 (0.06)	0.0076	+0.001 (0.01)	0.9274	+0.02 (0.01)	0.0730	+0.01 (0.01)	0.3412	+0.07 (0.01)	**<0.0001**
Patients (reference)	0.5 (0.04)		0.05 (0.01)		0.09 (0.01)		−0.002 (0.01)		0.09 (0.01)	
Siblings	+0.2 (0.05)	**<0.0001**	+0.04 (0.01)	**0.0015**	+0.04 (0.01)	**<0.0001**	+0.03 (0.01)	0.0289	−0.01 (0.01)	0.5938
Covariates										
Female gender	−4.2 (0.6)	**<0.0001**	1.1 (0.1)	**<0.0001**	0.09 (0.01)	**<0.0001**	−1.3 (0.1)	**<0.0001**	−1.4 (0.1)	**<0.0001**

p-values in bold represent group differences that reached significance after Bonferoni correction, $p < 0.0033$.
Removing gender or adding gender × group did not change results for IQ.
Removing affected controls, affected sibs, and/or non-schizophrenia patients did not change results for IQ.
[a]The control group was used as reference group. For controls the estimated scores and changes in scores per year during the interval are presented, while for patients and siblings the deviations from the scores in controls are provided.

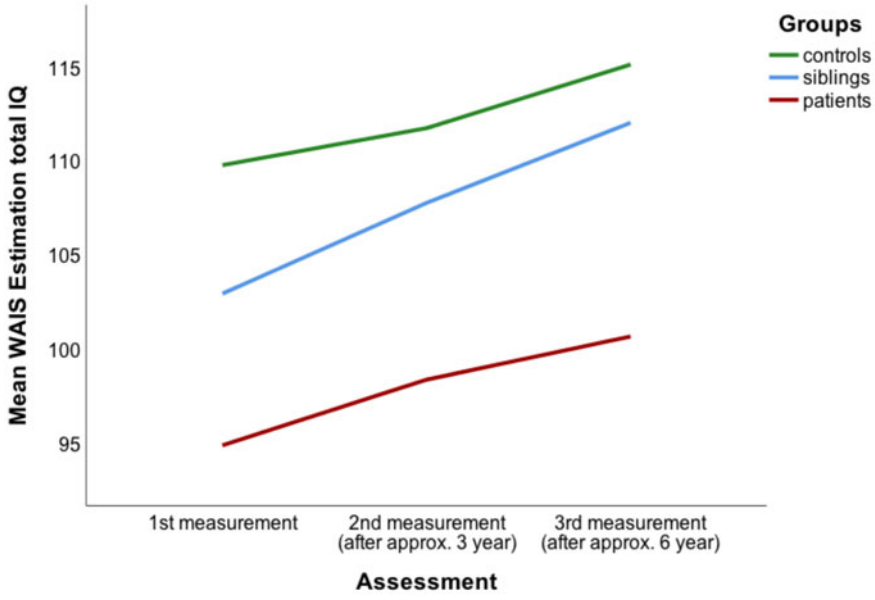

Fig. 1. Mean IQ at each measurement is plotted for patients, siblings, and healthy controls.

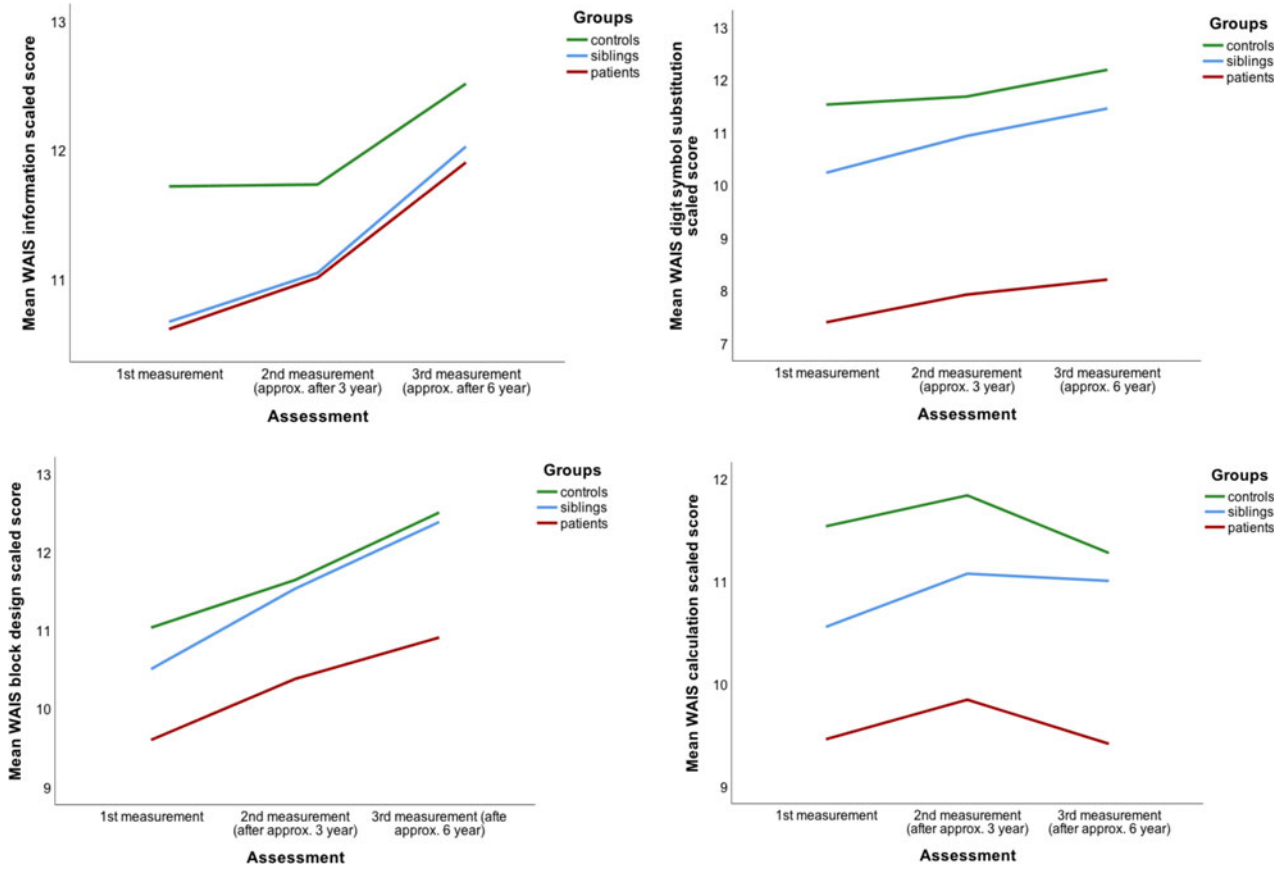

Fig. 2. Mean subtest score at each measurement is plotted for patients, siblings, and healthy controls.

first psychotic episode as a result of abnormalities in neurodevelopment.

Interestingly, siblings had a more pronounced IQ increase than controls and patients. This was explained by an improved performance on Digit-symbol Coding (relative to patients), Block Design, and Information (relative to patients and controls). Of particular interest is the improvement of the Information subtest score, as also patients showed a significantly greater increase in performance than controls. The WAIS Information subtest has been suggested to be an estimate of pre-morbid IQ (O'Connor *et al.*, 2012), despite overestimating IQ scores for both patients and controls. This may suggest that both patients and their siblings underperformed at baseline. Also, symptom severity does not offer a satisfactory explanation for the increased IQ in patients

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Table 3. The associations of IQ and IQ change with clinical or subclinical symptom measures in patients, siblings, and controls

	IQ				Change in IQ			
	B (S.E.)	df	*t*	*p*	*B* (S.E.)	df	*t*	*p*
Patients								
PANSS total	−1.83 (0.15)	1106	−11.80	<0.001	−0.02 (0.02)	1106	−1.24	0.216
Siblings								
CAPE total	−0.81 (0.32)	1091	−2.53	0.011	0.02 (0.04)	1091	0.43	0.667
Controls								
SIS-R total	−1.27 (0.49)	1204	−2.59	0.010	0.04 (0.05)	1204	0.73	0.465
CAPE total	0.69 (0.54)	602	−1.27	0.206	−0.04 (0.04)	602	−1.02	0.309
SIS-R total	−1.08 (0.80)	621	−1.36	0.175	0.04 (0.07)	621	0.52	0.603

and siblings, as improvement in (sub)clinical symptoms was unrelated to IQ increase in any of the groups.

So, we can only speculate why siblings show a more pronounced IQ increase. One possibility is that familial risk for schizophrenia dampens intellectual development during adolescence and early adulthood. When the increased risk does not lead to full-blown psychosis, IQ normalizes to the level of those without familial risk. Alternatively, psychological factors may play a role. That is, at baseline, siblings may be more anxious than controls and patients, as they may be aware of being at increased risk to develop the same symptoms as their affected sibling. Over time this fear reduces, leading to better performance on the tasks. Except for the possible underperformance as indirectly suggested by the increase in the Information subtest score in siblings, we have no data to substantiate these arguments.

The subtle increase in IQ over time may also be a direct effect of repeated testing; repeated evaluation with the same test often leads to an improvement in performance, a so-called practice effect (Catron, 1978). If this is the case, patients show a similar practice effect as controls, while practice effects in siblings are more pronounced. However, whether these effects can solely be explained by practice effects is unclear. Practice effects are considered to be most pronounced with short interval durations (weeks), frequent retesting, and test coaching (Hausknecht *et al.*, 2007; Bartels *et al.*, 2010), all of which do not apply to the current study.

At baseline, the mean IQ in siblings was intermediate between that of patients and controls. This suggests that the association between IQ and schizophrenia is based on shared genetic and/or familial environmental influences. The sibling-design does not allow distinguishing between genetic and environmental contributions to variation in IQ. Previously, a multicenter twin-study reported that cognition (including IQ) shared a genetic influence with schizophrenia (Toulopoulou *et al.*, 2014), indicating that schizophrenia liability is in part caused by cognitive deficits. However, in a sample drawn from the Swedish national registries, Kendler *et al.* (2015) reported a similar association between IQ and schizophrenia risk among close relatives of patients and the general population, suggesting that genes that are shared among family members do not contribute to the association between IQ and schizophrenia. Thus, possibly environmental factors specific to those who eventually develop schizophrenia are causal to the schizophrenia–IQ association. An important difference between these two studies, which may explain the discrepancy in findings, is that Kendler *et al.* (2015) used IQ data acquired before illness onset, while Toulopoulou *et al.* (2014) obtained IQ after illness onset.

Despite the large sample size of this study, our findings must be considered in light of some limitations. First, baseline IQ in the controls was higher than the expected population mean of 100 (Wechsler, 1997). Importantly, and lending credence to our findings, patients had an IQ of approximately 1 S.D. below that of controls which is consistent with previous studies (Heinrichs and Zakzanis, 1998; Mesholam-Gately *et al.*, 2009). Nevertheless, IQ in patients was also relatively high. Thus, we may have included relatively high-functioning participants. Whether this may be caused by our ascertainment strategy, the norms that were used to create the Dutch version of the WAIS, or the ways that the IQ tests were implemented in this study remains unknown. Second, not all individuals participated at all three measurements. We applied statistical methods that allowed the inclusion of all individuals with at least one IQ measure, thereby reducing the bias and improving the accuracy of the IQ estimates. However, those patients who were lost for follow-up had more severe symptoms. The differences were subtle, though, with a difference in PANSS subscale-scores of approximately one point. More importantly, patients and siblings with only one IQ measure had significantly lower IQs (i.e. five–six points) than those who participated more than once. Possibly, had we included more severely ill patients or patients with a lower IQ multiple times, a decline (or a diminished increase) in IQ would have been found. There is also evidence that we lost the siblings with a lower IQ and it is unclear how this may have influenced our results. Finally, future work should investigate the influence of relevant confounders, such as medication use, illness course in terms of relapses and readmissions during the follow-up period, smoking and drug (ab)use on change in IQ during the course of illness, and might aim to identify the presence of subgroups of patients with a specific and well-defined cognitive and/or clinical profile [e.g. (Kubota *et al.*, 2015)].

In conclusion, during the first 10–15 years of the illness, IQ increases to a similar (and subtle) extent in relatively high-functioning schizophrenia patients and controls, despite the lower IQ in patients. Our findings implicate a nonlinear lifetime pattern of changes in intellectual performance. Previous reports showed a decline in the decade before the onset of psychosis (Kremen *et al.*, 1998; Reichenberg *et al.*, 2005) or even before the age of 18 months (Mollon *et al.*, 2018). We show here that this is followed by stability during early adulthood, and (at least

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in a subgroup of) patients in more advanced stages of schizophrenia again a more pronounced decline in some specific cognitive domains has been reported (Kirkpatrick *et al.*, 2008). This implies that most of the IQ decline may have occurred when psychosis is fully developed (or possibly shortly thereafter). Consequently, the underlying (brain) pathology of schizophrenia may be more developmental (Rapoport and Gogtay, 2011) and/or maturational (van Haren *et al.*, 2008) in nature rather than the result of a degenerative process. Furthermore, IQ of siblings was intermediate between that of patients and controls, implying the influence of familial factors. The steeper increase in IQ in siblings as compared with patients and controls needs further investigation and replication.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291718003537.

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References

Agnew-Blais J and Seidman LJ (2013) Neurocognition in youth and young adults under age 30 at familial risk for schizophrenia: a quantitative and qualitative review. *Cognitive Neuropsychiatry* **18**, 44–82.

American Psychiatric Association (2000) *Diagnostic and Statistical Manual of Mental Disorders*. 4th Edn. Text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association.

Aylward E, Walker E and Bettes B (1984) Intelligence in schizophrenia: meta-analysis of the research. *Schizophrenia Bulletin* **10**, 430–459.

Bartels C, Wegrzyn M, Wiedl A, Ackermann V and Ehrenreich H (2010) Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing. *BMC Neuroscience* **11**, 118.

Bora E and Murray RM (2014) Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: do the cognitive deficits progress over, or after, the onset of psychosis? *Schizophrenia Bulletin* **40**, 744–755.

Bouchard TJ (2009) Genetic influence on human intelligence (Spearman's *g*): how much? *Annals of Human Biology* **36**, 527–544.

Bozikas VP and Andreou C (2011) Longitudinal studies of cognition in first episode psychosis: a systematic review of the literature. *The Australian & New Zealand Journal of Psychiatry* **45**, 93–108.

Catron DW (1978) Immediate test-retest changes in WAIS scores among college males. *Psychological Report* **43**, 279–290.

Colom R, Karama S, Jung RE and Haier RJ (2010) Human intelligence and brain networks. *Dialogues of Clinical Neuroscience* **12**, 489–501.

Dickerson F, Stallings C, Vaughan C, Origoni A, Khushalani S, Dickinson D and Medoff D (2011) Cognitive functioning in recent onset psychosis. *The Journal of Nervous and Mental Disease* **199**, 367–371.

Dickson H, Laurens KR, Cullen AE and Hodgins S (2012) Meta-analyses of cognitive and motor function in youth aged 16 years and younger who subsequently develop schizophrenia. *Psychological Medicine* **42**, 743–755.

Fuller R, Nopoulos P, Arndt S, O'Leary D, Ho BC and Andreasen NC (2002) Longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia through examination of standardized scholastic test performance. *The American Journal of Psychiatry* **159**, 1183–1189.

Granholm E, Link P, Fish S, Kraemer H and Jeste D (2010) Age-related practice effects across longitudinal neuropsychological assessments in older people with schizophrenia. *Neuropsychology* **24**, 616–624.

Groom MJ, Jackson GM, Calton TG, Andrews HK, Bates AT, Liddle PF and Hollis C (2008) Cognitive deficits in early-onset schizophrenia spectrum patients and their non-psychotic siblings: a comparison with ADHD. *Schizophrenia Research* **99**, 85–95.

Harvey PD (2001) Cognitive impairment in elderly patients with schizophrenia: age related changes. *International Journal of Geriatric Psychiatry* **16** (suppl. 1), S78–S85.

Harvey PD, Reichenberg A, Bowie CR, Patterson TL and Heaton RK (2010) The course of neuropsychological performance and functional capacity in older patients with schizophrenia: influences of previous history of long-term institutional stay. *Biological Psychiatry* **67**, 933–939.

Hausknecht JP, Halpert JA, Di Paolo NT and Moriarty Gerrard MO (2007) Retesting in selection: a meta-analysis of coaching and practice effects for tests of cognitive ability. *The Journal of Applied Psychology* **92**, 73–85.

Hedman AM, van Haren NE, van Baal GC, Brans RG, Hijman R, Kahn RS and Hulshoff Pol HE (2012) Is there change in intelligence quotient in chronically ill schizophrenia patients? A longitudinal study in twins discordant for schizophrenia. *Psychological Medicine* **42**, 2535–2541.

Hedman AM, van Haren NE, van Baal CG, Kahn RS and Hulshoff Pol HE (2013) IQ change over time in schizophrenia and healthy individuals: a meta-analysis. *Schizophrenia Research* **146**, 201–208.

Heinrichs RW and Zakzanis KK (1998) Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology* **12**, 426–445.

Hochberger WC, Combs T, Reilly JL, Bishop JR, Keefe RSE, Clementz BA, Keshavan MS, Pearlson GD, Tamminga CA, Hill SK and Sweeney JA (2018) Deviation from expected cognitive ability across psychotic disorders. *Schizophrenia Research* **192**, 300–307.

Irani F, Kalkstein S, Moberg EA and Moberg PJ (2011) Neuropsychological performance in older patients with schizophrenia: a meta-analysis of cross-sectional and longitudinal studies. *Schizophrenia Bulletin* **37**, 1318–1326.

Kahn RS and Keefe RSE (2013) Schizophrenia is a cognitive illness: time for a change in focus. *JAMA Psychiatry* **70**, 1107–1112.

Kay SR, Fiszbein A and Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* **13**, 261–276.

Keefe RSE and Fenton WS (2007) How should DSM-V criteria for schizophrenia include cognitive impairment? *Schizophrenia Bulletin* **33**, 912–920.

Kendler KS, Ohlsson H, Sundquist J and Sundquist K (2015) IQ and schizophrenia in a Swedish national sample: their causal relationship and the interaction of IQ with genetic risk. *American Journal of Psychiatry* **172**, 1–7.

Kendler KS, Ohlsson H, Mezuk B, Sundquist JO and Sundquist K (2016) Observed cognitive performance and deviation from familial cognitive aptitude at age 16 years and ages 18 to 20 years and risk for schizophrenia and bipolar illness in a Swedish national sample. *JAMA Psychiatry* **73**, 465–471.

Khandaker GM, Barnett JH, White IR and Jones PB (2011) A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. *Schizophrenia Research* **132**, 220–227.

Kirkpatrick B, Messias E, Harvey PD, Fernandez-Egea E and Bowie CR (2008) Is schizophrenia a syndrome of accelerated aging? *Schizophrenia Bulletin* **34**, 1024–1032.

Korver N, Quee PJ, Boos HB, Simons CJ and de Haan L, GROUP investigators (2012) Genetic Risk and Outcome of Psychosis (GROUP), a multi-site longitudinal cohort study focused on gene-environment interaction: objectives, sample characteristics, recruitment and assessment methods. *International Journal of Methods in Psychiatric Research* **21**, 205–221.

Kraepelin E (1896) Psychiatrie (8th edn.). Reprinted (1971) in parts as Dementia Praecox and Paraphrenia (trans. R.M. Barclay).

Kremen WS, Buka SL, Seidman LJ, Goldstein JM, Koren D and Tsuang MT (1998) IQ decline during childhood and adult psychotic symptoms in a community sample: a 19-year longitudinal study. *The American Journal of Psychiatry* **155**, 672–677.

Kubota M, van Haren NE, Haijma SV, Schnack HG, Cahn W, Hulshoff Pol HE and Kahn RS (2015) Association of IQ changes and progressive brain changes in patients with schizophrenia. *JAMA Psychiatry* **72**, 803–812.

Kurtz MM (2005) Neurocognitive impairment across the lifespan in schizophrenia: an update. *Schizophrenia Research* **74**, 15–26.

Maziade M, Rouleau N, Gingras N, Boutin P, Paradis ME, Jomphe V, Boutin J, Létourneau K, Gilbert E, Lefebvre AA, Doré MC, Marino C, Battaglia M, Mérette C and Roy MA (2009) Shared neurocognitive dysfunctions in young offspring at extreme risk for schizophrenia or bipolar disorder in eastern Quebec multigenerational families. *Schizophrenia Bulletin* **35**, 919–930.

Maziade M, Rouleau N, Mérette C, Cellard C, Battaglia M, Marino C, Jomphe V, Gilbert E, Achim A, Bouchard RH, Paccalet T, Paradis ME and Roy MA (2011) Verbal and visual memory impairments among young offspring and healthy adult relatives of patients with schizophrenia and bipolar disorder: selective generational patterns indicate different developmental trajectories. *Schizophrenia Bulletin* **37**, 1218–1228.

McIntosh AM, Gow A, Luciano M, Davies G, Liewald DC, Harris SE, Corley J, Hall J, Starr JM, Porteous DJ, Tenesa A, Visscher PM and Deary IJ (2013) Polygenic risk for schizophrenia is associated with cognitive change between childhood and old age. *Biological Psychiatry* **73**, 938–943.

Meier MH, Caspi A, Reichenberg A, Keefe RS, Fisher HL, Harrington H, Houts R, Poulton R and Moffitt TE (2014) Neuropsychological decline in schizophrenia from the premorbid to the postonset period: evidence from a population-representative longitudinal study. *The American Journal of Psychiatry* **171**, 91–101.

Mesholam-Gately RI, Giuliano AJ, Goff KP, Faraone SV and Seidman LJ (2009) Neurocognition in first-episode schizophrenia: a meta-analytic review. *Neuropsychology* **23**, 315–336.

Mollon J and Reichenberg A (2018) Cognitive development prior to onset of psychosis. *Psychological Medicine* **48**, 392–403.

Mollon J, David AS, Zammit S, Lewis G and Reichenberg A (2018) Course of cognitive development from infancy to early adulthood in the psychosis spectrum. *JAMA Psychiatry* **75**, 270.

O'Connor JA, Wiffen BD, Reichenberg A, Aas M, Falcone MA, Russo M, Sood PG, Taylor H and David AS (2012) Is deterioration of IQ a feature of first episode psychosis and how can we measure it? *Schizophrenia Research* **137**, 104–109.

Pinheiro JC, DebRoy SD, Bates DJ and Sakar D (2012) nlme: Linear and Nonlinear Mixed Effects Models. (R package version 3.1-105.).

Posthuma D, de Geus EJ and Boomsma DI (2001) Perceptual speed and IQ are associated through common genetic factors. *Behavior Genetics* **31**, 593–602.

Rapoport JL and Gogtay N (2011) Childhood onset schizophrenia: support for a progressive neurodevelopmental disorder. *International Journal of Developmental Neuroscience* **29**, 251–258.

Reichenberg A, Weiser M, Rapp MA, Rabinowitz J, Caspi A, Schmeidler J, Knobler HY, Lubin G, Nahon D, Harvey PD and Davidson M (2005) Elaboration on premorbid intellectual performance in schizophrenia: premorbid intellectual decline and risk for schizophrenia. *Archives of General Psychiatry* **62**, 1297–1304.

Rund BR (1998) A review of longitudinal studies of cognitive functions in schizophrenia patients. *Schizophrenia Bulletin* **24**, 425–435.

Stirling J, White C, Lewis S, Hopkins R, Tantam D, Huddy A and Montague L (2003) Neurocognitive function and outcome in first-episode schizophrenia: a 10-year follow-up of an epidemiological cohort. *Schizophrenia Research* **65**, 75–86.

Szoke A, Trandafir A, Dupont ME, Méary A, Schürhoff F and Leboyer M (2008) Longitudinal studies of cognition in schizophrenia: meta-analysis. *British Journal of Psychiatry* **192**, 248–257.

Toulopoulou T, Picchioni M, Rijsdijk F, Hua-Hall M, Ettinger U, Sham P and Murray R (2007) Substantial genetic overlap between neurocognition and schizophrenia. *Archives of General Psychiatry* **64**, 1348–1355.

Toulopoulou T, van Haren N, Zhang X, Sham PC, Cherny SS, Campbell DD, Picchioni M, Murray R, Boomsma DI, Hulshoff Pol HE, Brouwer R, Schnack H, Fañanás L, Sauer H, Nenadic I, Weisbrod M, Cannon TD and Kahn R (2014) Reciprocal causation models of cognitive vs volumetric cerebral intermediate phenotypes for schizophrenia in a pan-European twin cohort. *Molecular Psychiatry* **20**, 1–11.

Ullman VZ, Hornik-Lurie T and Reichenberg A (2017) A population-based study of premorbid scholastic achievement among patients with psychiatric disorders. *Psychiatry Research* **253**, 281–286.

van Haren NEM, Hulshoff Pol HE, Schnack HG, Cahn W, Brans R, Carati I, Rais M and Kahn R (2008) Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. *Biological Psychiatry* **63**, 106–113.

van Oel CJ, Sitskoorn MM, Cremer MP and Kahn RS (2002) School performance as a premorbid marker for schizophrenia: a twin study. *Schizophrenia Bulletin* **28**, 401–414.

Vollema MG and Ormel J (2000) The reliability of the structured interview for schizotypy-revised. *Schizophrenia Bulletin* **26**, 619–629.

Walters JTR and Owen MJ (2007) Endophenotypes in psychiatric genetics. *Molecular Psychiatry* **12**, 886–890.

Wechsler D (1997) *WAIS-III: Wechsler Adult Intelligence Scale* (3rd edn). Administration and Scoring Manual. San Antonio, TX: Psychological Corporation.

Woodberry KA, Giuliano AJ and Seidman LJ (2008) Premorbid IQ in schizophrenia: a meta-analytic review. *American Journal of Psychiatry* **165**, 579–587.

World Health Organization (1997) Composite International Diagnostic Interview (CIDI). Version 2.1.

Zipursky RB, Reilly TJ and Murray RM (2013) The myth of schizophrenia as a progressive brain disease. *Schizophrenia Bulletin* **39**, 1363–1372.