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ORIGINAL ARTICLE

Intellectual functioning and the long-term course of schizophrenia-spectrum illness

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Background. Recent neurodevelopmental models of schizophrenia, together with substantial evidence of neurocognitive dysfunction among people with schizophrenia, have led to a widespread view that general cognitive deficits are a central aspect of schizophrenic pathology. However, the temporal relationships between intellectual functioning and schizophrenia-spectrum illness remain unclear.

Method. Longitudinal data from the Copenhagen High-Risk Project (CHRP) were used to evaluate the importance of intellectual functioning in the prediction of diagnostic and functional outcomes associated with the schizophrenia spectrum. The effect of spectrum illness on intellectual and educational performance was also evaluated. The sample consisted of 311 Danish participants: 99 at low risk, 155 at high risk, and 57 at super-high risk for schizophrenia. Participants were given intellectual [Weschler's Intelligence Scale for Children (WISC)/Weschler's Adult Intelligence Scale (WAIS)] assessments at mean ages of 15 and 24 years, and diagnostic and functional assessments at mean ages 24 and 42 years.

Results. Intellectual functioning was found to have no predictive relationship to later psychosis or spectrum personality, and minimal to no direct relationship to later measures of work/independent living, psychiatric treatment, and overall severity. No decline in intellectual functioning was associated with either psychosis or spectrum personality.

Conclusions. These largely negative findings are discussed in the light of strong predictive relationships existing between genetic risk, diagnosis and functional outcomes. The pattern of predictive relationships suggests that overall cognitive functioning may play less of a role in schizophrenia-spectrum pathology than is widely believed, at least among populations with an evident family history of schizophrenia.

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Introduction

It is well documented that a substantial proportion of patients suffering from the schizophrenia-spectrum disorders exhibit a variety of neurocognitive dysfunctions (Heinrichs & Zakzanis, 1998; Lenzenweger, 1998; Egan *et al*. 2001; Seaton *et al*. 2001; Fioravanti *et al*. 2005), which may also be observed (to a lesser extent) in their clinically unaffected biological first-degree relatives (Steinhauer *et al*. 1991; Cornblatt *et al*. 1992; Faraone *et al*. 1995; Mirsky *et al*. 1995; Cornblatt & Obuchowski, 1998; Egan *et al*. 2001). In addition to findings of specific deficits in attention, working memory and executive function (Shallice *et al*. 1991; McGrath *et al*. 1997; Seaton *et al*. 2001), many studies highlight a general impairment in intellectual functioning (Pollack *et al*. 1968; Dieci *et al*. 1997; Bilder *et al*. 2006; Woodberry *et al*. 2008; Urfer-Parnas *et al*. 2010*b*). The extent of this impairment was originally thought to be a powerful predictor of subsequent functioning, even more so than current symptom levels (Velligan *et al*. 1997, 2000; Harvey *et al*. 1998; Green *et al*. 2000). More recently, these findings have been challenged by studies showing that baseline neurocognitive dysfunction only accounts for 0–10% of the variance in both 1-year and 7-year outcomes (Milev *et al*. 2005; Perlick *et al*. 2008).

The general notion that schizophrenia is associated with impaired cognitive functioning has been

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conceived in terms of neurodevelopmental models (O'Donnell, 2007), in which cognitive impairment is already present in childhood and implicated in the developing disease process prior to onset, and decline models (Keefe & Fenton, 2007), in which a marked deterioration from pre-morbid levels of cognitive functioning is associated with onset and/or the disease progression after onset. A combination of both models is also possible. Note that the question of the temporality of cognitive deficit, raised by these models, is separable from the question of the nature of the cognitive deficit involved. As noted earlier, both specific neurocognitive functions and general intellectual functioning have been implicated. Owing to methodological constraints, this paper principally examines the evidence for a general intellectual deficit.

Evidence for neurodevelopmental models is provided by several studies that identify a relationship between lower pre-morbid IQ and later schizophrenia (Lane & Albee, 1964; Offord, 1974; Crawford *et al*. 1992; Jones *et al*. 1994; Cannon *et al*. 1999); however, other studies do not find this relationship (Lane & Albee, 1968; Isohanni *et al*. 1998*b*). Five large epidemiogical studies of male draftees (David *et al*. 1997; Davidson *et al*. 1999; Tiihonen *et al*. 2005; Reichenberg *et al*. 2006; Urfer-Parnas *et al*. 2010*b*) have demonstrated a clear relationship between low IQ as measured at the military draft evaluation and a subsequent risk for hospitalization for schizophrenia and other psychoses.

Evidence for decline models is offered by reports finding a significant fall between pre-morbid and post-onset intellectual assessments of schizophrenia patients (Frith *et al*. 1991; David, 1998; Gold, 1998; Sheitman *et al*. 2000). Although the traditional assumption is that cognitive performance continues to deteriorate after onset (Lubin *et al*. 1962; Schwartzman & Douglas, 1962; Frith, 1992; Green, 1996; Caspi *et al*. 2003; Hoff *et al*. 2005; Seidman *et al*. 2006), and cross-sectional comparisons of chronic *versus* first-episode patients have been offered to support this notion (Bilder *et al*. 1992), several cross-sectional and longitudinal reports have instead found a deficit at the time of onset that remains stable over the course of illness (Hyde *et al*. 1994; Mockler *et al*. 1997; Rund, 1998; Gold *et al*. 1999; Heaton *et al*. 2001; van Winkel *et al*. 2006).

One problem with drawing definite conclusions from this work is that most studies are conducted after the onset of psychosis; that is, there are few, if any, designs that prospectively select a group of individuals and follow them from adolescence through the period of psychotic onset and into adulthood. Longitudinal high-risk studies, which follow cohorts at elevated genetic risk for schizophrenia from adolescence into adulthood, may provide a partial answer to these questions. Thus far, support for a neurodevelopmental deficit model among high-risk studies is weak. We previously found that pre-morbid IQ does not predict adult schizophrenia in the Copenhagen High-Risk Project (CHRP; Watson, Cannon, Schulsinger, Parnas & Mednick, unpublished observations). Similar negative results for predicting schizophrenia-related psychosis from general intellectual measures have been reported by the New York High-Risk Project (Ott *et al*. 1998) and the Israeli Kibbutz High-Risk Study (Mirsky *et al*. 1995). To the best of our knowledge, the question of cognitive decline has not been addressed in a high-risk paradigm.

The longitudinal nature of the CHRP, with its two IQ assessments, multiple diagnostic evaluations, and repeated measures of severity of psychopathology and of the level of functioning until midlife, provides us with a unique opportunity to test the decline model more closely. Moreover, the study allows for charting the potential influences of adolescent IQ on early adult functioning, and of early adult IQ on midlife functioning; these effects that can be investigated in relation to genetic risk, gender, socio-economic status (SES), diagnostic status and severity of illness.

Methods

Participants

This study uses data drawn from the CHRP, a longitudinal study of over 40 years' duration. The selection procedures have been described in detail previously (Mednick & Schulsinger, 1965). Essentially, 207 children (aged 10–18 years) of schizophrenic mothers were matched to 104 children of parents without psychiatric history. No children showed any severe psychopathology at this time. These participants were then followed up prospectively at approximately 5, 10 and 25 years from first contact. Attrition has not been excessive, as 94% were contacted at either the 10-year or 25-year assessment (and 76% participated in both); this follow-up rate is substantially better than other comparable longitudinal high-risk studies (Parnas *et al*. 1993).

Procedures and measures

Genetic risk

Genetic risk was defined as the number of biological parents with a schizophrenia-spectrum disorder. At the outset of the study, mothers' schizophrenia diagnoses were drawn from hospital records; these criteria were fairly stringent and have been shown to have high agreement with DSM-III-R (and especially

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DSM-IV) criteria (Jorgensen *et al*. 1987). In 1980, mothers without a psychiatric history in 1962 were screened a second time through the Danish psychiatric register, and one mother was found to have been hospitalized for schizophrenia. Fathers' diagnoses were principally derived from a psychiatric interview conducted in 1980–1983 and supplemented with information from the psychiatric register and the mothers' hospital charts. In all, 67 participants had fathers who were diagnosed with a schizophrenia-spectrum condition. From this information, 63 participants were assigned a risk of 2, 149 received a risk of 1, and 99 received a risk of 0. We note that this risk classification differs from the 'high-risk'/'low-risk' distinction used in many reports of these data (Mednick & Schulsinger, 1965; Cannon & Mednick, 1993; Parnas *et al*. 1993).

Other demographic variables

Gender was dummy-coded with males = 1 and females = 0. SES was measured using a seven-point (0–6) classification of the father's occupation (Svalastoga, 1959). Both SES and age of assessment (in 1962–1964) were drawn from a Social Worker's Interview conducted as part of Assessment I (as follows).

Assessment I: 1962–1964

At first contact (1962–1964), all 311 participants (average age 15 years) completed a day-long assessment that included a standard administration of Weschler's Intelligence Scale for Children (WISC). Standard subtest scale scores, Verbal IQ, Performance IQ, and Full-Scale IQ were obtained; Full-Scale IQ was used for the present study. During the same period, each participant's primary teacher was asked to fill out a brief report that included the participant's grades in Reading, Writing, Arithmetic, and Oral Speaking. These grades were reported on a five-point scale, with high marks indicating excellent academic performance. An overall grade was calculated by summing the four subject grades. Students missing one or more grades were given pro-rated scores based on available grades. Although grades are presumed to be related to intellectual functioning, we note that previous reports have not found them to predict psychosis (Isohanni *et al*. 1998*a*; Cannon *et al*. 1999).

Assessment II: 1967–1968

At approximately 5 years from the first assessment, 94% ($n = 293$) of participants were interviewed by a social worker. The social worker also interviewed the parents or other collateral sources when possible. In addition, an 'alarm network' of area psychiatric hospitals notified the research team of all hospitalizations of any study participants. Twenty of the CHRP cohort evidenced signs of serious psychopathology by this point, and were labelled the 'sick' group. This 'sick' designation is considered to be a useful index of an early onset for individuals who were later formally diagnosed as psychotic.

Assessment III: 1972–1974

Of the original 311 participants, 86% ($n = 267$; average age 24 years) were included in a major follow-up approximately 10 years after the first assessment. Of the 44 participants left out of Assessment III, five had died, six had emigrated, three were untraceable, and 30 refused to participate (Parnas *et al*. 1993). Diagnostic assessments consisted of the Present State Examination (PSE), the Current and Past Psychopathology Scale (CAPPS), and additional items developed by the researchers. Consensus diagnoses were assigned at the time; these diagnoses were later re-evaluated in 1992 in light of DSM-III-R criteria. For the purposes of the present analyses, the 1992 diagnoses were converted into three dummy-coded variables: psychosis (mostly schizophrenia), spectrum (cluster A; mostly schizotypal) personality disorder, and other mental illness. No mental illness was indicated by a 0 on all three variables (for a description of this technique, see Pedhazur & Schmelkin, 1991). Two additional outcome variables were created from the psychiatric data. A measure of the extent of psychiatric treatment was constructed using three ordinal items from the CAPPS, and a measure of the overall severity of illness was derived from two items from the CAPPS and one item from the PSE (see Table 1 for a list of these items). To calculate each outcome variable, items were equally scaled and then summed.

A short version of Weschler's Adult Intelligence Scale (WAIS) was given in the course of the assessment. It consisted of two verbal subscales (Vocabulary and Similarities) and two performance subscales (Block Design, Object Assembly). This choice of subscales was perhaps not ideal (as neither attention nor working memory were assessed), but the correlation of the sum of these subscales with Full-Scale IQ is likely to be high. Therefore, an estimated IQ was created by assuming that, for the 99 participants without a family history of mental illness (i.e. genetic risk = 0), the average distribution of IQ scores in 1972 would be roughly the same as the distribution of IQ scores in 1962. The raw sums of the WAIS subscales for this group were first normed using the mean and standard deviation of the 1962 Full-Scale IQ for the same group. Then, the WAIS subscale sums for all other participants were converted to IQ equivalents using the zero-risk group's benchmarks. Although this method

Table 1. *Composition of adult functional outcome scales*

Scale and source	Item
Extent of psychiatric treatment (1972–1974)	
CAPPS	Extent of out-patient treatment
	Number of psychiatric hospitalizations
	Total time of psychiatric hospitalizations (rated)
Extent of psychiatric treatment (1986–1989)	
Hospital records	Received any form of psychiatric treatment (lifetime)
	Number of psychiatric hospitalizations[b]
	Total years of psychiatric hospitalization[b]
Overall severity of illness (1972–1974)	
CAPPS	Overall severity of illness during the past month
	Overall severity since age 12
PSE	Index of definition (caseness)
Overall functioning (1986–1989)	
Psychiatric interview	GAS score
Social worker's interview	GAS score
Occupational and independent living impairment (1972–1974)	
C1[a] Social worker's interview	Changes in residence or lack of own residence
	Poor organization of finances
	Mostly dependent on others' income or assistance
	Has received public welfare during the past year
CAPPS	Poor work stability and performance during the past 5 years
	Impairment in daily routine and leisure time activities during the past month
	Impairment in major role activities (employment, education and/or domestic duties) during the past month
C2[a] Social worker's interview	Status of present job [–]
	Status of best (lifetime) job [–]
CAPPS	Decline in occupational status or responsibility during the past 5 years
	Low status of highest occupational level ever attained
Occupational and independent living impairment (1986–1989)	
C1[a] Social worker's interview	Highest 1-year functioning level since 1972 [–]
	Poor organization of finances
	Mostly dependent on others' income or assistance
	Has received public welfare during the past year
	Changes in residence or lack of own residence
	Independence of residence type [–]
	Poor standard of residence quality
	Poor lay-out (interior design and furnishings) of residence
C3[a] Social worker's interview	Status of present job [–]
	Status of best (lifetime) job [–]
	Work stability and performance during the past 5 years [–]
	Work stability since 1972–1974 [–]
	Elevation in occupational status during the past 5 years [–]

CAPPS, Current and Past Psychopathology Scale; PSE, Present State Examination; GAS, Global Assessment Scale; [–], item is reverse scored.

[a] The components composing the overall variable. See text for details.

[b] Log-transformed.

has the disadvantage of not being able to establish any absolute increases or decreases in IQ for the zero-risk group as a whole, individual improvements and declines in performance can readily be assessed relative to this overall 'normal' reference point.

Additionally, the participants were interviewed by a social worker, who asked questions related to educational and occupational achievement and also housing and financial situation. Based on these items, educational level was scored on a six-point ordinal

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scale developed by the researchers to take into account Denmark's multi-tiered educational system. A measure of occupational and independent living functioning was derived from both the CAPPS and the social worker's interview. First, six items from the CAPPS and 11 items from the social worker's interview were rationally selected for their relevance to participants' work, role functioning, finances, and home environment. These items were subjected to principal components analysis (SPSS FACTOR command, principal components extraction and varimax rotation) and the first two components were retained. Component scales were computed by summing all items loading more than 0.40 on each component. The items composing each component are listed in Table 1. Because of the conceptual and empirical overlap between these two scales ($r = 0.46$), we decided to sum the two component scales (after equal weighting) into a single index of occupational and independent living impairment.

Assessment IV: 1986–1989

In 1986–1989, approximately 25 years after the participants' first contact with the CHRP, 86% ($n = 267$; average age 42 years) were located and consented to reassessment. Of the 44 participants with missing data, 14 had died, 15 had emigrated, four were untraceable, and 11 refused to participate. A psychiatrist conducted several semi-structured diagnostic interviews, including the PSE (both last month and lifetime psychosis versions), the Schedule for Affective Disorders and Schizophrenia (SADS) and the Personality Disorder Examination (PDE), and symptom scales such as the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS). Preliminary diagnoses were re-evaluated in 1992 and DSM-III-R diagnoses were assigned. Once again, these diagnoses were converted into three dummy-coded variables. A thorough review of all available hospital records was also conducted in 1986–1989, from which treatment data were coded. A measure of the extent of psychiatric treatment (similar to the 1972–1974 outcome measure) was formed from three of the hospital records items (see Table 1). The number and duration of hospitalizations were log-transformed to correct for excessive positive skew prior to all items being equally weighted and summed.

A social worker's interview was also conducted. Overall functioning was calculated by averaging the Global Assessment of Symptoms (GAS) score assigned by the psychiatrist and the GAS score given by the social worker (see Table 1). This overall measure is presumed to be substantially similar to the overall severity index used for the 1972–1974 follow-up, albeit in the opposite direction. Education level was again scored on the same six-point scale as used for 1972–1974. As the CAPPS was not used in 1986–1989 and the social worker's interview items concerning work and independent living were somewhat changed from before, a new measure of occupational and independent living functioning needed to be created. A principal components analysis was performed on relevant items from the social worker's interview. Three components were extracted. The second component was dropped because of excessive missing data and its low correlation with other measures of work functioning. Component scales for components 1 and 3 were computed by summing items loading more than 0.40 on each component. The items composing each component are shown in Table 1. The two component scales were found to be highly intercorrelated (0.67), so the two component scales were summed after equal weighting to create a new index of occupational and independent living impairment. Unfortunately, no standardized test of intellectual functioning was given in 1986–1989, so 25-year IQ must remain a lacuna.

Rationale of the analyses

Based on the existing findings and theoretical models in the literature, we created the hypothesized path model diagrammed in Fig. 1. It is useful to think of these proposed connections in terms of two separable systems: the basic disease model and the influence of intellectual variables. The basic disease model is represented by the paths and variables outlined in black; it shows a simple genetic-risk→severity-of-schizophrenia-spectrum-illness chain of events broadly consistent with polygenetic theory (Gottesman & Shields, 1982). This model specifies that genetic risk (perhaps in conjunction with demographic factors) predicts psychosis and spectrum personality at 10-year and 25-year follow-ups, and greater genetic risk (again, possibly in conjunction with demographic factors) presages increased severity of illness, as indicated by earlier age of onset (and thus more likely 'sick' by the 5-year follow-up) and decreased adult functioning in several domains: greater extent of psychiatric treatment, decreased occupational performance and independent living skills, and poorer overall functioning.

The influence of intellectual variables is represented by the variables and paths outlined in red. The key question is whether IQ and educational performance add appreciably to the prediction of spectrum illness and adult functioning and whether spectrum illness adds appreciably to the prediction of post-onset IQ.

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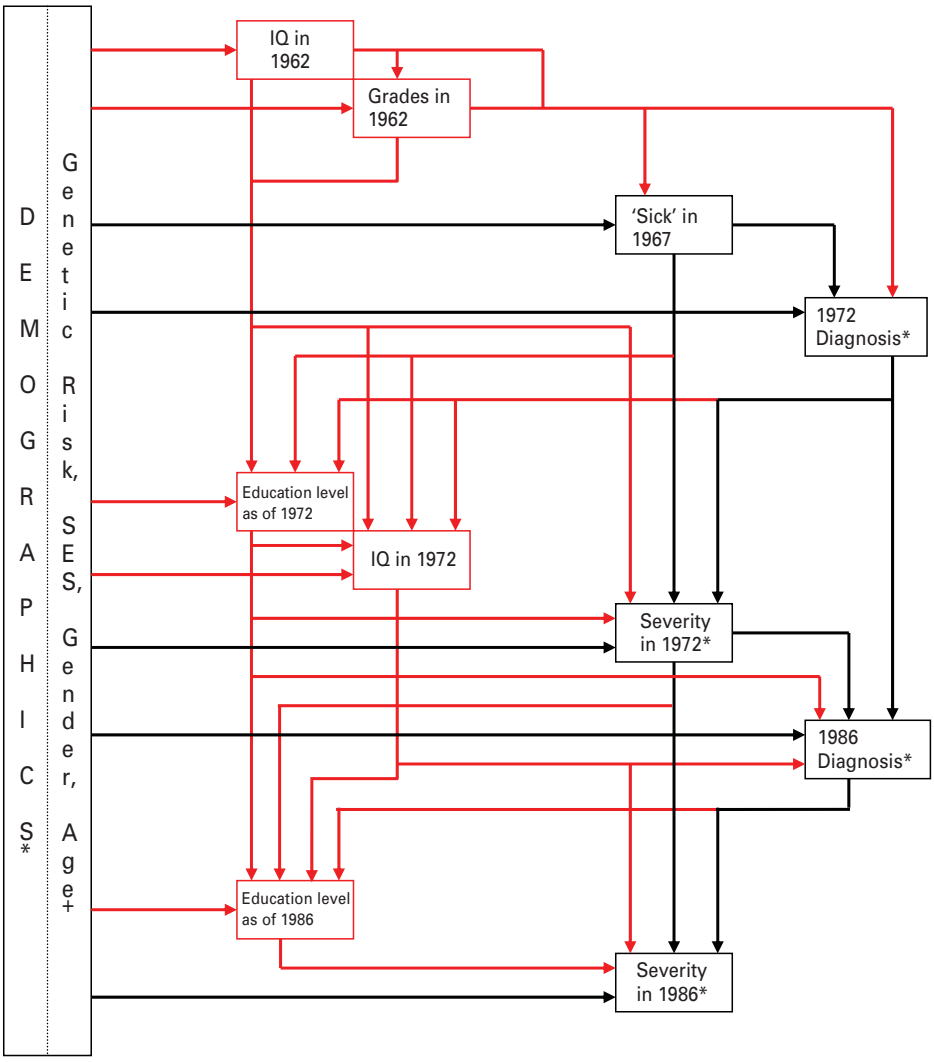

Fig. 1. The hypothesized path model. * General construct contains more than one variable. Diagnosis includes indicators of psychosis, spectrum personality, and other mental illness. Severity includes overall severity/functioning, extent of psychiatric treatment, and occupational and independent living impairment. Black paths and variables correspond to the basic disease model. Red paths and variables represent the role of intellectual functioning variables. + Age at assessment in 1962 is a hypothesized covariate for all analyses involving 1962 assessments (IQ in 1962 and Grades in 1962). SES, socio-economic status.

In this regard, our analyses will test three main hypotheses:

(1) Decreased intellectual functioning predicts schizophrenia-spectrum diagnoses, particularly schizophrenia and other psychoses. This is tested in two stages: (*i*) does pre-morbid IQ and/or school performance predict diagnosis at the 10-year follow-up and (*ii*) does adult IQ predict additional cases by the 25-year follow-up?

(2) Intellectual functioning predicts adult adjustment in three domains: occupational and independent living capabilities, use of psychiatric treatment services, and overall functioning. Again, this proposal is divided into two testable stages: (i) does pre-morbid IQ and/or school performance predict adjustment at the 10-year follow-up and (ii) does adult IQ predict sustained adjustment at the 25-year follow-up?

(3) Spectrum diagnosis, particularly psychosis, leads to a decline in adult IQ as compared to pre-morbid IQ. Furthermore, early-onset cases will show greater decline relative to later-onset cases.

Statistical analyses

The variables used in the analysis are listed in Table 2, together with their means, standard deviations, and the number of missing values for each. Note that all

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Table 2. *Descriptive summary of variables used*

Assessment	Variable	Missing values	Mean	S.D.
I: 1962–1964	Genetic risk[a]	0	0.88	0.71
	Socio-economic status (SES) in 1962[b]	4	2.23	1.97
	Gender[c]	0	0.57[m]	0.49
	Age at assessment (years)	4	15.09	3.02
	Full-scale IQ (WISC) in 1962	0	101.9	13.7
	Total school grades in 1962[d]	22	12.06	3.10
II: 1967–1968	Identified as 'sick' in 1967[e]	18	0.07[m]	0.25
III: 1972–1974	Psychosis in 1972[e]	44	0.13[m]	0.34
	Spectrum personality in 1972[e]	44	0.13[m]	0.34
	Other mental illness in 1972[e]	44	0.19[m]	0.39
	Education level as of 1972[f]	47	3.27	1.26
	Estimated full-scale IQ (WAIS) in 1972	47	102.6	13.2
	Occupational and independent living impairment in 1972[g]	47	10.05	8.11
	Overall severity of illness in 1972 (scored negatively)[h]	47	1.62	1.03
	Extent of psychiatric treatment as of 1972[i]	48	0.16	0.41
IV: 1986–1989	Psychosis in 1986[e]	44	0.12[m]	0.33
	Spectrum personality in 1986[e]	44	0.11[m]	0.31
	Other mental illness in 1986[e]	44	0.20[m]	0.40
	Education level as of 1986[f]	83	3.66	1.39
	Occupational and independent living impairment in 1986[j]	83	10.11	9.07
	Overall functioning (GAS) in 1986 (scored positively)[k]	56	74.3	9.7
	Extent of psychiatric treatment as of 1986[l]	32	0.52	1.17

WISC, Weschler's Intelligence Scale for Children; WAIS, Weschler's Adult Intelligence Scale; GAS, Global Assessment Scale; S.D., standard deviation.

[a] Number of schizophrenia spectrum parents (0–2).

[b] Scaled from 0 (Low) to 6 (High).

[c] Dummy-coded with Male = 1 and Female = 0.

[d] Scores range from 4 (Low) to 20 (High).

[e] Dummy-coded (1 = Yes, 0 = No).

[f] Scaled from 1 (Low) to 6 (High).

[g] Scores ranged from −4.9 (Good functioning) to 37.7 (Impaired functioning).

[h] Scaled from 0 (No disturbance) to 4 (Severe disturbance).

[i] Scaled from 0 (No treatment) to 2 (Extensive treatment).

[j] Scores ranged from −1.0 (Good functioning) to 44.3 (Impaired functioning).

[k] GAS scores range from 1 (Extreme impairment) to 100 (Superior functioning).

[l] Scores ranged from 0 (No treatment) to 7.3 (Extensive treatment).

[m] Means for all dummy-coded variables can be read as the proportion of the sample in the scored category (i.e. 'Male' for Gender, 'Sick' for Sick in 1967, and receiving the corresponding diagnosis for all diagnostic variables).

participants completed Assessment I, but 44 were missing in both Assessment III and IV. Any additional missing values noted were due to specific data sources. Multiple regression was used for all analyses. Following the logic of the rationale (see Fig. 1), each intermediate outcome was regressed on all hypothesized predictors, and backwards selection was used to trim variables with non-significant paths ($p < 0.10$) from the analysis. As both 1972 and 1986 diagnoses were dummy-coded into three variables, these variables were handled together. The diagnostic indices were entered first into the equation. Then, after backwards selection had removed non-significant predictors, the p values for the three diagnostic codes were examined. Diagnosis was only removed from the model when all three p values were non-significant; otherwise, it was retained in full.

For each analysis, cases with missing values in the criterion were excluded. Missing values in the predictors were generally handled through mean substitution. Although this solution tends to produce middle-heavy distributions and underestimates total variance, it has the advantage of maintaining sample means and only minimally reducing intercorrelations between variables. Because of assumptions of high stability, missing data in intellectual predictors were

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Table 3. *Summary of regression results*

Analysis[a]	Criterion	Basic disease model[b]		Complete model[b]		
		R^2	p	R^2	p	R^2 change[c]
A	Full-scale IQ in 1962			0.169	<0.0005	
B	Total school grades in 1962			0.180	<0.0005	
C	Identified as 'sick' in 1967	0.055	<0.0005	0.055	<0.0005	0
D1	Other mental illness in 1972	0.013	0.061	0.027	0.028	0.014
D2	Spectrum personality in 1972	0.030	0.004	0.030	0.004	0
D3	Psychosis in 1972	0.183	<0.0005	0.183	<0.0005	0
E	Education level as of 1972			0.311	<0.0005	
F	Estimated full-scale IQ in 1972			0.497	<0.0005	
G	Occupational and independent living impairment in 1972	0.401[d]	<0.0005	0.436	<0.0005	0.035
H	Overall severity of illness in 1972	0.565	<0.0005	0.573	<0.0005	0.008
I	Extent of psychiatric treatment as of 1972	0.322[e]	<0.0005	0.319	<0.0005	−0.003
J1	Other mental illness in 1986	0.128	<0.0005	0.128	<0.0005	0
J2	Spectrum personality in 1986	0.173	<0.0005	0.173	<0.0005	0
J3	Psychosis in 1986	0.692	<0.0005	0.692	<0.0005	0
K	Education level as of 1986			0.770	<0.0005	
L	Occupational and independent living impairment in 1986	0.419	<0.0005	0.442	<0.0005	0.023
M	Overall functioning in 1986	0.546	<0.0005	0.546	<0.0005	0
N	Extent of psychiatric treatment as of 1986	0.562[f]	<0.0005	0.574	<0.0005	0.012

[a] Corresponding to letters designated on final path diagram (Fig. 2).

[b] All significant predictors for the complete model are shown as paths in Fig. 2, together with their standardized regression (β) coefficients. In most cases, the significant predictors for the basic disease model are the same, excluding any intellectual variables. Exceptions are indicated here in the following notes.

[c] Due to the inclusion of intellectual variables.

[d] In addition to the predictors shown on the path diagram, the basic disease model for analysis G includes socio-economic status (SES) ($\beta = -0.11$).

[e] In addition to the predictors shown on the path diagram, the basic disease model for analysis I includes genetic risk ($\beta = 0.09$) and SES ($\beta = -0.10$).

[f] The basic disease model for analysis N includes other mental illness in 1986 ($\beta = 0.08$) but does not include SES.

imputed. Missing IQ values in 1972 were set to the existing values in 1962. The mean differential between 1972 and 1986 education levels was used to impute missing values on one variable from valid data on the other. If data were missing at both time points, mean substitution was used.

Results

For each regression analysis (labelled A–N) composing the path analyses, the overall proportion of variance explained (R^2) and the significance level (p) are reported in Table 3, and the final path diagram (reporting all significant predictors' β coefficients) is displayed in Fig. 2. Following our rationale above, we consider the results of the path analyses in two steps: first, considering only the relationships described by the basic disease model (i.e. the links between demographics, diagnoses and functional outcomes), and second, gauging the contributions of intellectual functioning variables to the prediction of diagnostic and functional outcomes.

Basic disease model

The final paths derived for the basic disease model are displayed in black in Fig. 2. To maximize visual clarity, the approximate size of each coefficient is shown by the line width for the respective path (see Fig. 2). All paths shown are significant at the $p < 0.10$ level, and the thicker paths ($\beta > 0.20$) are highly significant ($p < 0.001$). For each analysis, the R^2 and associated significance level for the basic disease model are listed in the middle columns of Table 3.

Although the inter-relationships among these variables are complex, the overall pattern clearly supports the hypothesized basic disease paths from Fig. 1. Genetic risk influences outcomes in 1967, 1972 and 1986 in the direction of schizophrenia-spectrum pathology. Diagnostic severity (i.e. psychosis and spectrum

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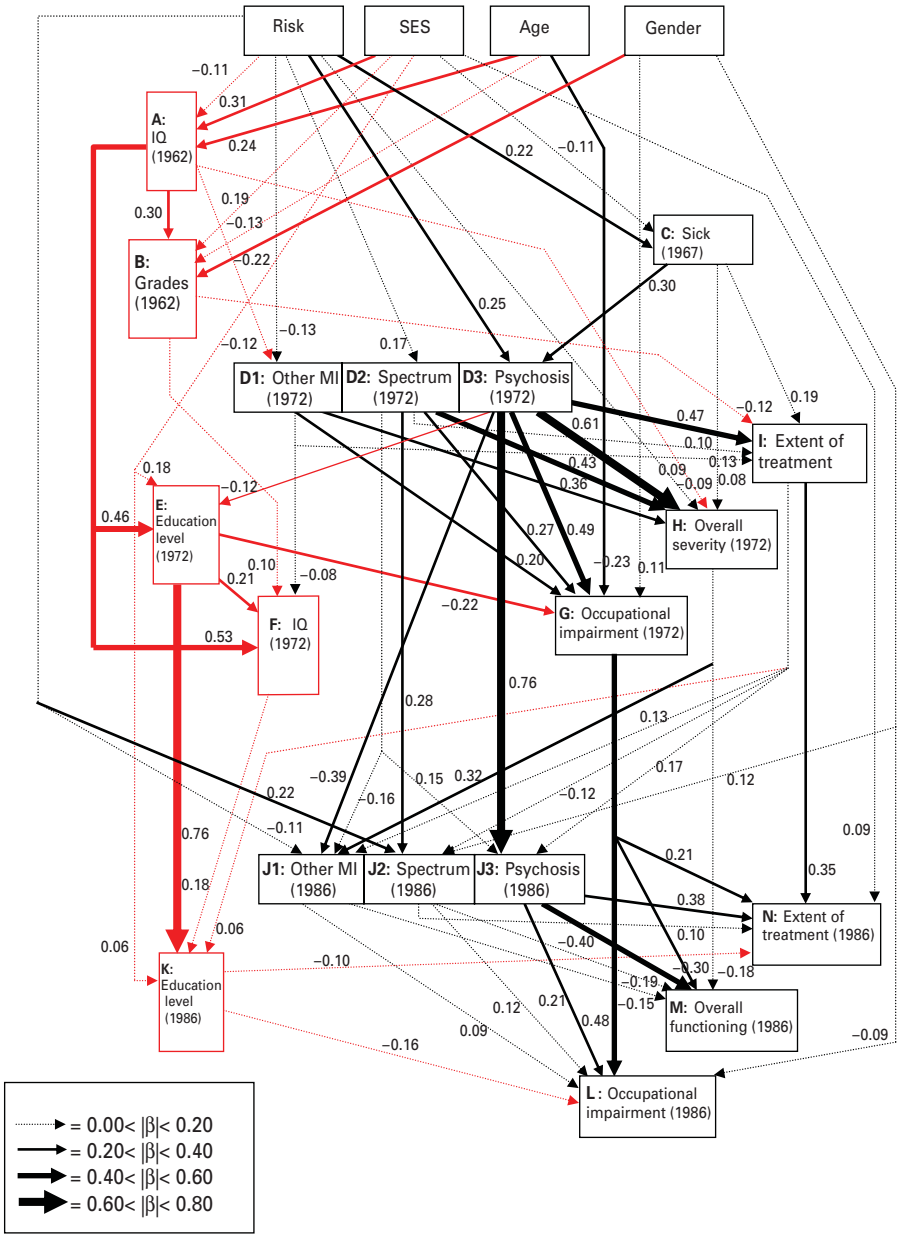

Fig. 2. The final path model. **A**, **B**, etc. designate the criterion variable for each regression analysis composing the path model. Black paths and variables correspond to the basic disease model. Red paths and variables represent the role of intellectual functioning variables. SES, socio-economic status.

personality, in that order) is consistently reflected in more severe functional outcomes. The only hypothesized relationships not supported by the results are (1) an effect of being 'sick' in 1967 on occupational and independent living impairment in 1972 and (2) most of the direct effects of risk on functional outcomes.

Intellectual variables

The complete model, displayed in Fig. 2 by both black and red paths, consists of the addition of the variables of IQ, school grades, and education level (red variables and paths) to the basic disease model. In Table 3, the R^2 for the complete model is listed to the far right for each analysis, together with its overall significance. In the last column of the table, the basic disease model R^2 is subtracted from the corresponding complete model R^2 to obtain a change in R^2 due to intellectual variables.

Among the intellectual variables, the most notable results are (1) the consistent time-lagged relationships between IQ and educational achievement and (2) the persistent benefit of higher SES on almost all intellectual outcomes.

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In the rationale, we proposed three hypotheses concerning the relationship between intellectual functioning and schizophrenia-spectrum illness. These hypotheses are now evaluated on the basis of their fit to the data.

(1) *Decreased intellectual functioning predicts schizophrenia-spectrum diagnoses, particularly psychosis.* This hypothesis fails to be supported on two counts. First, neither IQ nor grades in 1962 are significant predictors of schizophrenia-spectrum diagnoses in 1972. Second, IQ in 1972 is not predictive of additional spectrum cases by 1986. The only predictive relationship that holds is a small tendency for lower IQ to predict cases of other (non-spectrum) mental illness in 1972. For both psychosis and spectrum personality outcomes, the change in variance explained (R^2) due to intellectual variables is 0.

(2) *Intellectual functioning predicts adult adjustment in three domains: occupational and independent living capabilities, use of psychiatric treatment services, and overall functioning.* This is a bit of a mixed picture. IQ in 1962 does not predict occupation and independent living or extent of treatment in 1972. Decreased IQ does slightly predict overall severity in 1972 ($\beta = -0.09$); however, upon further (*post-hoc*) analysis, IQ does not predict severity for those with spectrum illnesses, only for those with other (non-spectrum) illnesses ($\beta = -0.28$ for this subsample). IQ in 1972 does not predict functioning in mid-adulthood. Although intellectual capability does not seem to be related to adult functioning, there is an important link between education level and concurrent occupational and independent living success ($\beta = -0.22$ in 1972, $\beta = -0.16$ in 1986, both in the expected direction). Changes in R^2 corresponding to this education–occupational functioning link are 0.035 in 1972 and 0.023 in 1986. Additionally, higher education level contributed to less psychiatric treatment by 1986. Upon further analysis, this protective effect is both pronounced among and restricted to those with psychotic disorders ($\beta = -0.41$ for this subsample).

(3) *Spectrum diagnosis, particularly psychosis, leads to a decline in adult IQ as compared to pre-morbid IQ.* The evidence from our sample is to the contrary; there is no significant decline in IQ (i.e. 1972 IQ controlled for 1962 IQ) associated with a concurrent psychotic or spectrum personality diagnosis. Second, early onset of spectrum disorder ('Sick' in 1967) does not seem to influence IQ in 1972.

Discussion

The longitudinal nature of the CHRP has allowed us to paint a thorough picture of the intellectual, symptomatic and functional development of those at risk for schizophrenia from adolescence into mid-adulthood. Our analyses point to the operation of two distinct systems: the first being intellectual ability and its manifestation in educational achievement; the second being a schizophrenia-spectrum disease process that, especially in instances of psychosis, dramatically impacts adult functioning. Contrary to models proposed in the literature, we find no evidence for any significant relationship between these two systems, excepting a pragmatic benefit of higher education evidenced in better occupational and independent living status at both age 24 and 42 and reduced reliance on treatment by age 42.

Similarly to the findings from other high-risk projects (Mirsky *et al*. 1995; Ott *et al*. 1998), we fail to find that decreased full-scale IQ predicts later schizophrenia-related psychosis. Although the New York High-Risk Project reports a trend for lower performance IQ (PIQ) among pre-psychotic individuals (Ott *et al*. 1998), and has had substantial success using an attentional measure that includes the Digit Span subtest (Erlenmeyer-Kimling *et al*. 2000), no subtest or index was found to be predictive in our own sample (Watson *et al*., unpublished observations). A recent reanalysis of the Copenhagen sample seems to show that coding deficits can predict schizophrenia-spectrum outcome (Sorensen *et al*. 2006); however, as these deficits are associated with genetic risk for schizophrenia, and genetic risk was not controlled for in the regression analyses, these results are inconclusive.

The lack of predictive power of intellectual functioning for later psychotic diagnosis is strongly at variance with the substantially lower IQ found among pre-schizophrenia patients in three recent draft studies (David *et al*. 1997; Davidson *et al*. 1999; Urfer-Parnas *et al*. 2010*b*). Rescaled mean IQ scores for pre-schizophrenic individuals are 95.3 for the Israeli cohort, 92.5 for the Swedish cohort, and 94.4 for the Danish cohort (*versus* mean = 100 and standard deviation = 15 for normal controls). Other population studies, such as the British 1946 birth cohort, have noted pre-morbid deficits as large as one standard deviation (Jones *et al*. 1994).

There are several possible explanations for this difference. First, these population studies are only able to identify hospitalized schizophrenic patients, whereas our study includes non-treated and non-hospitalized cases as well. If our sample is any indication, as much as 33% of schizophrenic individuals are never

hospitalized and 15% evade treatment of any sort. However, this difference in target samples cannot satisfactorily account for our findings. If treated cases were indicative of greater cognitive dysfunction, we would have expected a relationship between pre-morbid IQ and treatment severity, which was not present. In addition, when we reran the regression analyses for hospitalized patients only, the prediction was not improved.

Another difference lies in the diagnostic criteria. We used DSM-III-R criteria, and combined both schizophrenia ($n=33$) and other (mostly atypical) psychoses ($n=10$) into a single category; the population studies used the clinical ICD-8/9 criteria for schizophrenia, which were very conservative, reflecting a clearly deteriorating Kraepelinian prototype (Jorgensen *et al*. 1987). Three pieces of evidence argue against the salience of this difference for our results. First, we observed no relationship between IQ and illness severity (except for non-spectrum cases). Second, we found no increase in predictive efficacy when the analyses were rerun using a diagnostic outcome of schizophrenia instead of psychosis. Third, low pre-morbid IQ in the Swedish and Danish draft studies was also predictive of non-affective psychoses that did not meet ICD criteria for schizophrenia, a category possibly included in the DSM-III-R conception.

Another possible explanation for the discrepancy in findings is that population cohorts studies do not select for or assess genetic risk. As an effect of genetic risk on lower IQ has been documented (Mednick & Schulsinger, 1968; Landau *et al*. 1972; Ott *et al*. 1998; Watson *et al*., unpublished observations), population studies may be simply detecting low IQ as a spurious predictor, which, in reality, is indexing a genetic risk level.

Additionally, we did not detect any decline in IQ between pre-morbid and early adult assessments due to psychosis; nor did early onset of spectrum pathology affect later IQ. These negative findings are at odds with findings from many follow-back studies (Frith *et al*. 1991; David, 1998; Gold, 1998; Sheitman *et al*. 2000), although they have received some previous support (Albee *et al*. 1963; Russell *et al*. 1997). Most remarkably, when pre-morbid IQ was removed from the regression equation, no concurrent relationship between diagnostic status and IQ in 1972 was detected. This means that not only did CHRP psychotic individuals *not* experience a decline in their intelligence but also their post-onset intelligence was equivalent to that of other groups.

It is possible that the 'quest for decline' noted in the literature may be as much theory driven as evidence based, perhaps influenced by the Kraepelinian notion of 'Verblödung' (increasing 'feeble-mindedness') (Kraepelin, 1913), and Goldstein's influential notion of a 'loss of abstract attitude' (Goldstein, 1964). In some theoretical formulations, the obvious changes in thought processes and belief formation that occur in schizophrenia may be seen as sequelae of more general information-processing or language deficits (Landre & Taylor, 1995; Frith, 1996). Indeed, one article entertained a causal link between intellectual impairment and propensity to false beliefs (David *et al*. 1997). Countering this view, cognitive deficits are not detected in *all* patients with schizophrenia (Goldstein *et al*. 1996) and clinical experience teaches us daily that exceedingly bright persons suffer from typical and full-blown schizophrenic syndromes; therefore, it seems that general intellectual impairment cannot be a *necessary* component of the illness (Urfer-Parnas *et al*. 2010*a*).

Aside from the obvious limitations in drawing firm causal conclusions from naturalistic data, our study was limited by its relatively small sample and the likelihood that more severe individuals were over-represented in data missing from the adult assessments (Parnas *et al*. 1993). One major caveat to our findings is that they are restricted to measures of general intellectual functioning. Neither the WISC nor the WAIS is geared to assessing the discrete neurocognitive deficits which hold the most promise as indicators of psychosis. It is likely that more predictive results might have been obtained if measures of discrete cognitive functions (such as the Wisconsin Card Sort, Stroop, Continuous Performance Test, Attention Span Task, and Halstead–Reitan neuropsychological battery) had been used in the Copenhagen study. In this respect, recent multi-center longitudinal studies using standardized clinical and neurocognitive assessments hold promise for clarifying the precise relationship between schizophrenia-spectrum illness and neurocognition (Braff *et al*. 2007; Calkins *et al*. 2007; Carter & Barch, 2007; Nuechterlein *et al*. 2008; Woods *et al*. 2009).

Although we originally set out to analyze the effects of intellectual functioning, the most incisive findings from the current study highlight the robustness of the basic disease model. The overall result is a consistent pattern of linear associations between increased risk, decreased age of onset of psychopathology, and increased severity of spectrum condition. The level of genetic risk (measured over three values) predicts the earliest breakdowns, spectrum syndromes (especially psychosis) in early adulthood, and additional spectrum cases later in life. In turn, 1972 spectrum personality outcome predicts additional cases of psychosis later in life. In addition to these patterns, we verify that psychosis results in a severe and sustained impairment across diverse functional domains; this

impairment is also noted to a lesser degree with spectrum personality disorders. We note that although many previous studies have identified links between certain pairs of these variables, this is the first study we are aware of that shows time-lagged relationships among all of them in the same sample.

This pattern of results is consistent with a model positing a single, continuous dimension of disease severity operating through time. Earlier age of onset, decompensation into psychosis, and extent of functional impairment can all be seen as aspects of schizophrenia-spectrum severity associated with higher levels of genetic risk. Lower levels of genetic risk and/or spectrum severity may result in later age of onset, spectrum personality outcome, and only moderate functional deficits. This model supports continuous-threshold theories of schizophrenia etiology (Gottesman & Shields, 1982), and implies that dimensional spectrum severity is manifested through several distinct domains of functioning, such as symptomatology, societal functioning, chronicity, and the like (in agreement with Strauss & Carpenter, 1972). Although these conclusions are intriguing, further research using continuous multivariate models is needed to specify the mechanisms at work.

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Declaration of Interest

None.

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