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Neuropsychological Decline in Schizophrenia from the Premorbid to Post-Onset Period: Evidence from a Population-Representative Longitudinal Study

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Abstract

Objective—Despite widespread belief that neuropsychological decline is a cardinal feature of the progression from the premorbid to the chronic form of schizophrenia, few longitudinal studies have examined change in neuropsychological functioning from before to after the onset of schizophrenia. We addressed the following unresolved questions: Is neuropsychological decline generalized versus confined to particular mental functions? Is neuropsychological decline unique to schizophrenia? Do individuals with schizophrenia also have cognitive problems in everyday life?

Method—Participants were members of a representative cohort of 1,037 individuals born in Dunedin, New Zealand between 1972-73 and followed prospectively to age 38, with 95% retention. Assessment of IQ and other specific neuropsychological functions was conducted at ages 7-13, before the onset of schizophrenia, and again at age 38. Informants also reported on cognitive problems at age 38.

Results—Individuals with schizophrenia showed decline in IQ as well as a range of different mental functions, particularly those tapping processing speed, learning, executive functioning, and motor functioning. There was little evidence of decline in verbal abilities or delayed memory, however, and the developmental progression of deficits in schizophrenia differed across mental functions. Processing speed deficits increased gradually from childhood to beyond the early teen years, whereas verbal deficits emerged early but remained static through midlife. Neuropsychological decline was specific to schizophrenia, as no evidence of decline was apparent among individuals with persistent depression, children with mild cognitive impairment, individuals matched on childhood risk factors for schizophrenia, and psychiatrically healthy

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individuals. Informants also reported cognitive problems for individuals diagnosed with schizophrenia.

Conclusion—There is substantial neuropsychological decline in schizophrenia from the premorbid to post-onset period, but the extent and developmental progression of decline varies across mental functions. Findings suggest that different pathophysiological mechanisms might underlie deficits in different mental functions.

Neuropsychological Decline in Schizophrenia from the Premorbid to Post-Onset Period: Evidence from a Population-Representative Longitudinal Study Neuropsychological impairment is a core feature of schizophrenia (1), and understanding the nature and course of neuropsychological functioning in schizophrenia may have important pathophysiological implications. It is widely believed that individuals diagnosed with schizophrenia experience neuropsychological decline, relative to the general population, from pre- to post-illness onset, but relatively few published studies have examined change in neuropsychological functioning from before to after the onset of schizophrenia. The present study provides a rigorous test of neuropsychological changes in schizophrenia using a battery of neuropsychological tests administered in childhood (ages 7, 9, 11, and 13) and in adulthood (age 38) as part of an ongoing, population-representative longitudinal study.

There is clear evidence of mild neuropsychological deficits among children who later go on to develop schizophrenia (2). Neuropsychological deficits are even more pronounced among adults diagnosed with schizophrenia. For example, meta-analyses show an average premorbid 8-point IQ deficit (0.50 SD) among those who later develop schizophrenia (3) but a 14-21 point IQ deficit (0.90-1.40 SD) among first-episode and chronic schizophrenia patients (1, 4, 5). These findings suggest that individuals with schizophrenia experience a relative decline in neuropsychological functioning over time from pre- to post-illness onset, with stabilization in neuropsychological functioning thereafter (6, 7), or at least until older adulthood (8-10).

In line with cross-sectional evidence, the few longitudinal studies to address neuropsychological changes in schizophrenia from pre- to post-illness onset have consistently shown evidence of neuropsychological decline (Table 1). However, these studies are characterized by six limitations. First, the majority of these studies are based on clinical samples, which may not be representative of the full population of individuals with schizophrenia (22). Second, the baseline age-of-assessment varies considerably in these studies, with many studies assessing neuropsychological functioning for the first time in adolescence or adulthood, when prodromal symptoms (and altered neuropsychological functioning) tend to be present (23-25). Thus, these studies may underestimate the magnitude of the decline in functioning. Third, only five of these studies included a comparison group needed to provide a rigorous test of change in functioning. Fourth, many of these studies employed different neuropsychological tests across time, making it difficult to ascertain true change in functioning. Fifth, these studies focused exclusively on IQ (or IQ proxies). Since different neural systems underlie performance on different neuropsychological tests, other important mental functions, such as memory and executive functioning, should be examined as well. Sixth, none of the studies examined whether, in addition to poor IQ test performance, individuals with schizophrenia experience cognitive problems in their daily life.

In a previous report of our population-representative cohort followed prospectively from birth, we showed that children who later developed schizophrenia had IQ deficits, and we mapped changes in the specific mental functions that constitute the IQ across four measurement occasions from ages 7 to 13 years (26). Now that this cohort has been followed to age 38 and undergone additional neuropsychological testing, we examined

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change in IQ, as well as more specific neuropsychological functions, from before (ages 7-13) to after (age 38) the onset of schizophrenia using the same measures across time. In the present article, we tested four hypotheses. First, we tested the "IQ decline" hypothesis that individuals with schizophrenia experience IQ decline from before to after illness onset. We compared the group of individuals with schizophrenia to a psychiatrically healthy group in order to allow for an accurate interpretation of test-retest performance. Second, we tested the "generalized decline" hypothesis to determine whether decline is apparent broadly across different neuropsychological domains: verbal IQ, performance IQ, learning and memory, processing speed, executive, and motor functioning. Third, we tested the "specificity" hypothesis to address whether neuropsychological decline is specific to schizophrenia. We compared neuropsychological decline in schizophrenia to decline in three other groups: a persistent depression group, a mild cognitive impairment group, and a group at risk for schizophrenia. We evaluated neuropsychological decline in individuals with persistent depression to test if decline is common to other psychiatric disorders. Depression is characterized by neuropsychological impairment (27, 28), but it is not clear if there is neuropsychological decline from pre- to post-illness onset. We evaluated neuropsychological decline in children with mild cognitive impairment because, like children with schizophrenia, they exhibit cognitive difficulties early in life. However, unlike in schizophrenia, these children do not develop a psychotic condition. We also evaluated neuropsychological decline in "at-risk" individuals who did not develop schizophrenia but who matched those who did on key childhood risk factors (low IQ, family history of psychotic illness, low socioeconomic status). Fourth, we queried third-party informants to test the "everyday cognition" hypothesis that individuals with schizophrenia experience cognitive problems in daily life.

Methods

Participants

Participants are members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal investigation of the health and behavior of a complete birth cohort of consecutive births between April 1, 1972, and March 31, 1973, in Dunedin, New Zealand. The cohort of 1,037 children (91% of eligible births; 52% boys) was constituted at age 3 years. Cohort families represent the full range of socioeconomic status in the general population of New Zealand's South Island and are primarily of white European ancestry. Follow-up assessments were conducted with informed consent at 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and most recently at 38 years of age, when 95% of the 1,007 living study members underwent assessment in 2010-2012.

Schizophrenia

In the Dunedin study, schizophrenia was assessed at ages 21, 26, 32, and, most recently, 38. We previously described the schizophrenia cases up to age 32 (26, 29, 30). The current report updates this information with data from age 38. Full diagnostic criteria for schizophrenia were assessed with the Diagnostic Interview Schedule (DIS) (31, 32) at each age following the Diagnostic and Statistical Manual of Mental Disorders (DSM) (33, 34). To enhance the validity of our research diagnosis, we implemented special steps. First, we required hallucinations (which are not substance use-related) in addition to at least two other positive symptoms. This requirement is stricter than DSM-IV (34), which does not require hallucinations, although requiring them has been shown to reduce over-diagnosis. Second, because self-reports can be compromised by poor insight in schizophrenia, we required objective evidence of impairment resulting from psychosis, as reported by informants and as recorded in the study's life-history calendars, which document continuous histories of employment and relationships. Third, in our research, the DIS is administered by

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experienced clinicians, not lay interviewers. These clincians record detailed case notes. Our staff also rate observable symptoms manifested in affect, grooming, and speech during the full day participants spend at our research unit. Fourth, participants bring their medications, which are classified by a pharmacist. Fifth, informants report study members' positive and negative psychotic symptoms via postal questionnaires. Finally, study members' parents were interviewed about their adult child's psychotic symptoms and treatment as part of the Dunedin Family Health History Study (2003-2005). These data, accumulated in the Dunedin study at ages 21, 26, 32, and 38, were compiled into dossiers reviewed by 4 clinicians to achieve best-estimate diagnoses with 100% consensus. By age 38, 2% of the cohort (n=20/1007) met criteria for schizophrenia and had, according to the multi-source information collected in the dossiers, been hospitalized for schizophrenia (totaling 1,396 days of psychiatric hospitalization according to official New Zealand administrative record searches) and/or prescribed antipsychotic medications. An additional 1.7% (n=17) met all criteria for schizophrenia, had hallucinations, and suffered significant life impairment but had not, to our knowledge, been treated specifically for psychotic illness. Together, these two groups constituted a total of 37 cases of diagnosed schizophrenia in the cohort. Of these 37 schizophrenia cases, 4 died before the age-38 neuropsychological assessment and 2 refused to participate at 38, leaving an effective group size of n=31 for this article.

Of the 31 individuals diagnosed with schizophrenia that we report on here, the majority (55%, n=17) had received treatment specifically for psychotic illness. Of those who had not, to our knowledge, received treatment specifically for psychotic illness, nearly all reported receiving treatment for another mental health problem **(**Table 2). The two groups appeared similar on a variety of correlates, including adult IQ, personality functioning, substance dependence, and even receipt of government benefits, suggesting that the groups are comparably impaired. The notable exception was that those who had not received treatment for psychotic illness were from lower SES families.

The cohort's 3.7% prevalence rate of schizophrenia is high and should be understood in the context of the following 3 methodological aspects of our study. First, our birth cohort, with a 95% participation rate, lets us count psychotic individuals overlooked by prior surveys because individuals with psychotic disorders often refuse to participate in surveys and/or die prematurely (35), and surveys often exclude homeless or institutionalized individuals with psychosis. Second, our cohort members are all from one city in the South Island of New Zealand. It is possible, given geographical variation in rates of schizophrenia (36-38), that the prevalence of schizophrenia is somewhat elevated there. No data exist to compare prevalence rates of schizophrenia in New Zealand to other countries, but the very high prevalence of suicide in NZ could be consistent with an elevated prevalence of severe mental health conditions (39). Third, our research diagnoses did not make fine-grained distinctions among psychotic disorders (e.g., schizophrenia vs. schizoaffective disorder). Thus, those diagnosed with schizophrenia here might not be considered by all clinicians to have schizophrenia. We note, however, that over half of those we diagnosed were confirmed by treatment. Moreover, etiological mechanisms appear to be similar across the continuum of psychosis (40).

Persistent Depression

Depression was diagnosed at ages 18, 21, 26, 32, and 38 using the DIS (31, 32) following diagnostic criteria for the DSM (33, 34). Cohort members who diagnosed with depression on two or more occasions between ages 18-38 were classified in the persistent-depression group. We chose to focus on persistent depression in an effort to make this group more comparable to the schizophrenia group in terms of chronicity and severity of illness. Of the

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191 cohort members classified in the persistent-depression group, 6 did not have complete neuropsychological data, leaving an effective group size of n=185.

Mild Cognitive Impairment

Individuals with a childhood IQ (averaged across ages 7-13) of 80-89 were considered to have mild cognitive impairment (n=120).

Neuropsychological Functioning

We assessed neuropsychological functioning using tests of IQ, learning and memory, processing speed, executive, and motor functioning. Full-scale IQ can be thought of as an omnibus measure of general intellectual ability, because it captures overall ability across differentiable components of intellectual functioning (i.e., verbal IQ and performance IQ). Verbal and performance IQ can be further 'unpacked' to make finer-grained distinctions in ability. Learning and memory, processing speed, executive, and motor functions represent even more basic mental functions.

IQ was assessed in childhood at ages 7, 9, 11 and 13, before the onset of schizophrenia, and again in adulthood at age 38. We report comparison of the Wechsler Intelligence Scale for Children-Revised (WISC-R) (41) and the Wechsler Adult Intelligence Scale-IV (WAIS-IV) (42). Full-scale, verbal, and performance IQ were standardized to population norms with M=100 and SD=15; subtest scaled scores were standardized to population norms with M=10, SD=3. Learning and memory, processing speed, executive, and motor functioning were each assessed at ages 13 and 38 using, respectively, the Rey Auditory Verbal Learning Test (43), the Trail Making Test (44), and the Grooved Pegboard Test (43). Supplemental Table 1 provides details about each test.

Informant-Reported Cognitive Problems

Informant reports of study members' cognitive functioning were obtained at age 38. Study members nominated people "who knew them well." These informants were mailed questionnaires and asked to complete a checklist, including whether the study member had problems with their attention and memory over the past year. The *informant-reported attention problems* scale consisted of four items: "is easily distracted, gets sidetracked easily", "can't concentrate, mind wanders", "tunes out instead of focusing", and "has difficulty organizing tasks that have many steps" (internal consistency reliability=0.79). The *informant-reported memory problems* scale consisted of three items: "has problems with memory", "misplaces wallet, keys, eyeglasses, paperwork", and "forgets to do errands, return calls, pay bills" (internal consistency reliability=0.64). Informant-reported cognitive problems (attention and memory problems combined) were correlated with adult full-scale IQ ($r=-0.22$, $p<.0001$).

Control Variables

DSM (33, 34) cannabis and alcohol dependence were assessed at ages 18, 21, 26, 32 and 38, and DSM hard-drug (e.g., heroin, cocaine, amphetamines) dependence was assessed at ages 26, 32, and 38. Study members who diagnosed at 2 or more assessments were considered persistently dependent on these substances.

Statistical Analysis

We compared the schizophrenia and persistent-depression groups to a healthy group (a group of individuals who had no other current psychiatric disorder, such as depression, anxiety, or substance-use disorders; n=518) on change in neuropsychological functioning from childhood to adulthood. Change scores were created by subtracting the childhood test

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score (averaged across ages 7-13 for the IQ tests and subtests) from the adulthood test score. Negative scores indicate neuropsychological decline. In Tables 3-5, childhood and adulthood test scores as well as change scores are presented in standard deviation units (M=0.00, SD=1.00). Standardized scores reflect effect sizes for how different each group is from the cohort norm. Differences between pairs of groups can also be interpreted as effect sizes. Effect sizes of 0.20, 0.50, and 0.80 reflect small, medium, and large effects (45). Statistical tests involved planned, orthogonal comparisons of each psychiatric group to the healthy group and were adjusted for sex, though results were unchanged when sex was excluded from the model.

Results

Do Individuals with Schizophrenia Show IQ Decline?

Figure 1, **Panel A** shows that, consistent with findings from meta-analyses, the schizophrenia group evidenced a 9-point IQ deficit in childhood relative to the healthy group, and a 15-point IQ deficit in adulthood. The greater relative deficit among the schizophrenia group in adulthood was due to an average 6-point IQ decline within the schizophrenia group from childhood to adulthood (from 93.63 in childhood to 87.92 in adulthood). There was no evidence of IQ decline for the healthy group (from 102.71 in childhood to 102.44 in adulthood), and IQ decline was significantly greater in the schizophrenia than in the healthy group (p=.0009). IQ decline in the schizophrenia group was not attributable to current antipsychotic medication use, as an almost 6-point IQ decline (from 95.29 in childhood to 89.88 in adulthood; paired t=2.83, p=.0094) was still apparent among the n=24 individuals who did not use antipsychotic medication in the year prior to adult neuropsychological testing.

Is IQ Decline Specific to Schizophrenia?

Relative to the healthy group, the persistent-depression group showed a statistically significant 3-point IQ deficit in both childhood and adulthood (Figure 1, **Panel A**). There was no evidence of IQ decline for the persistent-depression group (Figure 1, **Panel A:** from 99.30 in childhood to 99.05 in adulthood), and estimates of IQ change for the persistent-depression and healthy groups did not differ (p=.98).

Figure 1, **Panel B** expands the analysis to show that full-scale IQ was relatively stable for the schizophrenia, persistent-depression, and healthy groups from age 7 to 13 years but dropped substantially for the schizophrenia group between ages 13 and 38 years. As a further comparison, we also evaluated IQ decline from childhood to adulthood among children with mild cognitive impairment and children at risk for developing schizophrenia. Children with mild cognitive impairment are of interest because, like children with schizophrenia, they exhibit cognitive difficulties early in life, but, unlike those with schizophrenia, they do not develop a psychotic condition. Figure 1, Panel B shows that, in contrast to children who develop schizophrenia, children with mild cognitive impairment did not show evidence of IQ decline.

Next, we used data from our population-representative cohort to match schizophrenia cases to “at-risk” individuals who did not develop schizophrenia but who shared key childhood risk factors with schizophrenia cases. Low IQ, low socioeconomic status, and a family history of schizophrenia are well-established risk factors for developing schizophrenia (46-48). As such, we used propensity-score matching (49, 50) to identify individuals who matched our schizophrenia cases on these risk factors but who did not develop psychotic illness (Table 3). IQ decline was not apparent among individuals at risk for schizophrenia. The at-risk group, with a similar childhood liability to develop schizophrenia as members of

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the schizophrenia group, showed IQ decline of −0.01 SD, whereas the schizophrenia group showed IQ decline of −0.39 SD. Thus, at-risk children who did not develop schizophrenia showed less IQ decline than their matched counterparts who did ($F(1, 91) = 8.57$, $p=.0043$). In sum, IQ decline was unique to those diagnosed with schizophrenia.

Is Decline in Neuropsychological Functioning Apparent Across Different Mental Functions?

Table 4 shows test scores (in standard deviation units) in childhood and adulthood for the healthy, schizophrenia, and depression groups on a range of different mental functions: IQ (and the subtests of different cognitive abilities that constitute the IQ), learning (Rey Total Recall), delayed memory (Rey Delayed Recall), processing speed (Trails A), executive functioning (Trails B), and motor functioning (Grooved Pegboard). The shaded area of Table 4 shows the change in test performance (in standard deviation units) from childhood to adulthood.

Relative to the healthy group, the schizophrenia group showed statistically significantly greater decline on all mental functions, except verbal IQ and Rey Delayed Recall (delayed memory). Inspection of the means suggests that the greatest declines occurred for digit symbol coding (processing speed), Rey Total Recall (learning), Trails A (processing speed), Trails B (executive functioning), and Grooved Pegboard (motor functioning). By comparison, the persistent-depression group generally did not show neuropsychological decline on any mental function.

Figure 2 expands the analysis to show that the progression of neuropsychological deficits from age 7 to 38 years varies across mental functions. Given our earlier report that children who later develop schizophrenia show developmental lags from age 7 to 13 in processing speed, working memory, and attention but static deficits in verbal abilities (26), we elected to show results for the 2 IQ subtests most representative of these processes: the digit symbol coding subtest and the similarities subtest. Figure 2, **Panel A** shows that deficits on the digit symbol coding task were not apparent at age 7 but emerged gradually from age 7 to 38 years. Figure 2, **Panel B** shows that deficits on the similarities task emerged by age 7 but remained relatively stable from age 7 to 38 years (Figure 2, **Panel B**).

Are there Alternative Explanations for the Neuropsychological Decline?

We ruled out three alternative explanations for the observed association between schizophrenia and neuropsychological decline, namely that these effects could be explained by: (a) cannabis dependence, (b) alcohol dependence, and (c) hard-drug dependence. We re-calculated the mean change in full-scale IQ for the healthy, schizophrenia, and persistent-depression groups, excluding individuals with each form of substance dependence. We elected to show results just for full-scale IQ for this analysis because full-scale IQ captures overall intellectual functioning. Table 5 shows that excluding individuals with each form of substance dependence did not alter the initial finding; effect sizes, representing within-person IQ change, remained virtually the same and remained statistically significant. Moreover, even after statistically adjusting IQ change scores for cannabis, alcohol, and hard-drug dependence conjointly, members of the schizophrenia group still showed statistically significantly greater IQ decline (M=-0.34 SD) than members of the healthy group (M=−0.03 SD, $p=.0049$).

Is Everyday Cognition Impaired?

Table 6 shows age-38 informant-reported attention and memory problems (in standardized units) for each group. This table shows that members of the schizophrenia group were rated 1.00 and 0.95 SD above the cohort mean on attention and memory problems, respectively,

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whereas members of the healthy group were rated −0.18 and −0.16 SD below the mean. By comparison, informants observed less pronounced attention and memory problems for the persistent-depression group.

Discussion

The present study showed evidence of neuropsychological decline in schizophrenia from pre- to post-illness onset in a population-based birth cohort of individuals followed prospectively from birth to age 38. This finding is consistent with prior longitudinal studies showing evidence of neuropsychological decline in schizophrenia (11-16, 18-20).

The present study advances knowledge in several ways. First, previous longitudinal studies focused almost exclusively on IQ. We showed that individuals with schizophrenia experienced decline in IQ as well as a range of different mental functions, particularly those tapping processing speed, learning, executive functioning, and motor functioning. Decline was greatest on the digit symbol coding task, which is consistent with prior research suggesting that this test, more so than other neuropsychological tests, taps a core impairment in schizophrenia and may reflect network integration problems (51). Decline was not ubiquitous across all mental functions, however. There was little evidence of decline in verbal IQ or delayed memory (Rey Delayed Recall). Impaired verbal IQ and delayed memory among cohort adults diagnosed with schizophrenia could be traced back to childhood deficits that remained relatively stable across development. These findings highlight the importance of ‘unpacking’ measures of generalized intellectual functioning, such as IQ, into more specific mental functions.

Second, we showed that neuropsychological decline was relatively specific to schizophrenia, as there was no evidence of decline among individuals in key comparison groups: children with mild cognitive impairment, at-risk children who did not develop schizophrenia, and individuals diagnosed with persistent depression. Prior research on the association between depression and neuropsychological decline has mainly focused on older adults and has yielded inconsistent findings, with some studies finding no association between depression and accelerated neuropsychological decline (52, 53) and others finding a positive association (54). Ours is the first study, to our knowledge, to examine depression-associated changes in neuropsychological functioning from pre- to post-illness onset in a relatively youthful cohort. Notably, in our study, individuals with persistent depression performed worse than healthy individuals on a handful of neuropsychological tests in adulthood and were rated by informants as having more cognitive problems as adults than healthy individuals. Neuropsychological test deficits, however, were apparent from childhood, consistent with the interpretation that lower IQ constitutes risk for depression (55, 56).

Third, our findings suggest that neuropsychological decline among individuals with schizophrenia is nontrivial. Estimates of decline ranged from 1/3 to 3/4 of a standard deviation unit more than average for the healthy group on tests tapping processing speed, learning, attention, working memory, and motor function. Moreover, cognitive impairment among individuals diagnosed with schizophrenia was apparent in everyday life, as third-party informants noticed substantially more attention and memory problems among adults diagnosed with schizophrenia.

The results of this study should be viewed in the context of its limitations. First, although we found evidence of neuropsychological decline in schizophrenia from pre- to post-illness onset, we could not fully map the developmental progression of neuropsychological deficits in schizophrenia from childhood to adulthood (funding agencies were unwilling to support repeated intellectual testing between ages 13 and 38). Nonetheless, we examined how

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deficits progressed from age 7 to 13 for different mental functions and linked these deficits to data obtained at age 38. Deficits on the digit symbol coding test were not apparent at age 7 but increased gradually from age 7 to 13, and by age 38, individuals with schizophrenia scored 1.08 SD below the healthy group on this test. Notably, in an earlier report of the age 7-13 neuropsychological test data (26), we showed that children who would later develop schizophrenia exhibited slowed growth in performance on the digit symbol coding test, and, based on this trajectory of slowed growth, we had predicted the >1SD adulthood deficit that we report here. This suggests that the "decline" in processing speed that we observed reflects a gradual, progressive process of slowed growth in this mental function that begins in childhood and continues beyond the early teen years. Exactly when in childhood the deficit in processing speed becomes evident is difficult to pinpoint, as at least two other studies have reported statistically significant deficits on the digit symbol coding task at approximately age 7 (12, 57). Conversely, we showed that deficits on the similarities test emerged early but remained relatively static from age 7 through midlife. These findings imply that different pathophysiological mechanisms underlie the various neuropsychological deficits observed in schizophrenia patients.

A second limitation is that our findings are based on a relatively small group of individuals diagnosed with schizophrenia. The small group size prevented us from conducting an in-depth exploration of heterogeneity in neuropsychological decline. However, given reports of schizophrenia patients with IQ's in the normal range (58, 59) and the presumption that these patients have escaped neuropsychological decline, we asked whether any of the individuals with schizophrenia in our cohort fit this profile. Of the 31 individuals diagnosed with schizophrenia, there were 3 individuals who both (a) had a childhood IQ of >100 and (b) showed IQ decline of < 3.19 IQ points (the standard error of measurement of the WISC-R). While 1 of these 3 people performed in the normal range on all adult neuropsychological tests, each showed decline on the digit symbol coding test (M=−0.88 SD), suggesting that decline in processing speed is a core feature of schizophrenia. These findings further suggest that average to above-average neuropsychological test performance among a subset of adults diagnosed with schizophrenia cannot be used to infer that neuropsychological decline has not occurred. Rather, prospective, baseline tests of neuropsychological functioning are necessary to document decline.

A third limitation concerns three unusual aspects of our sample that may limit the generalizability of our findings. First, the prevalence of schizophrenia is high. As we discussed earlier, this may be explained, in part, by a combination of our comprehensive repeated-measurement ascertainment strategy, high retention rates, and/or geographical variation. Second, a portion of individuals diagnosed with schizophrenia had not, to our knowledge, received treatment specifically for psychotic illness. These individuals had, however, come into contact with the mental health care system and were virtually indistinguishable from those who had been treated for psychotic illness on a variety of correlates. The one exception was that those who had not received treatment specifically for psychotic illness were from lower SES families, which might reflect that SES affects quality of care. Third, most individuals with schizophrenia were not taking antipsychotic medication in the year prior to adult testing. While this increases confidence that neuropsychological decline between ages 7-13 and 38 is not due to recent antipsychotic medication use, it raises the question of whether our results are generalizable to patients currently taking antipsychotic medication. We noted very little difference in IQ decline between those who were (n=7, IQ decline = ~7 IQ pts) and were not (n=24, IQ decline = ~6 pts) taking antipsychotic medication in the year prior to testing. Bolstering the generalizability of our findings is the fact that our estimates of the IQ deficit in both childhood (9 points) and adulthood (15 points) precisely match estimates from meta-analyses of the premorbid IQ deficit in schizophrenia (3) and the IQ deficit in first-episode schizophrenia (1, 4).

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This study has a number of implications. First, results suggest that individuals diagnosed with schizophrenia experience neuropsychological decline from pre- to post-illness onset. Second, however, the extent of decline and the developmental progression of decline varies considerably across mental functions that can be generally organized as fluid and crystallized abilities. Fluid abilities (e.g., processing speed, learning, executive functioning) showed the most substantial decline, with deficits in processing speed, for example, increasing gradually from childhood to beyond the early teen years. In contrast, crystallized abilities (e.g., verbal IQ) did not decline. Rather, these deficits were apparent already in childhood and remained static through midlife. This suggests that different pathophysiological mechanisms underlie deficits in fluid and crystallized abilities seen in adult schizophrenia patients. Moreover, findings highlight that a substantial proportion of the neuropsychological deficits seen in adult schizophrenia patients is apparent before the onset of puberty, and future research on the emergence of neuropsychological deficits in schizophrenia should target early childhood to ascertain deficits in crystallized abilities and later childhood to ascertain deficits in fluid abilities. Finally, pharmacological and cognitive remediation therapies should target neuropsychological functioning as well as cognitive impairment in everyday life (60), as treatment strategies that target both outcomes may have the most chance of success (61).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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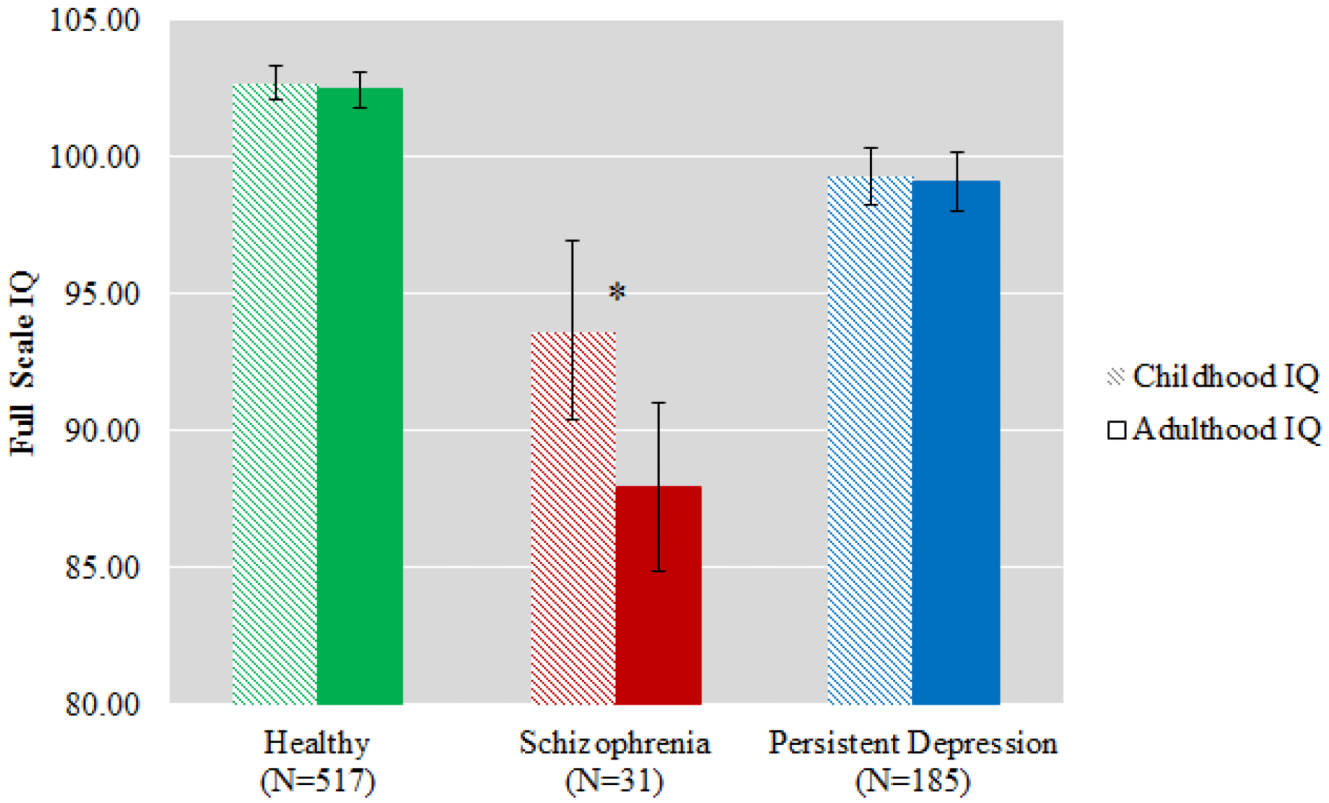

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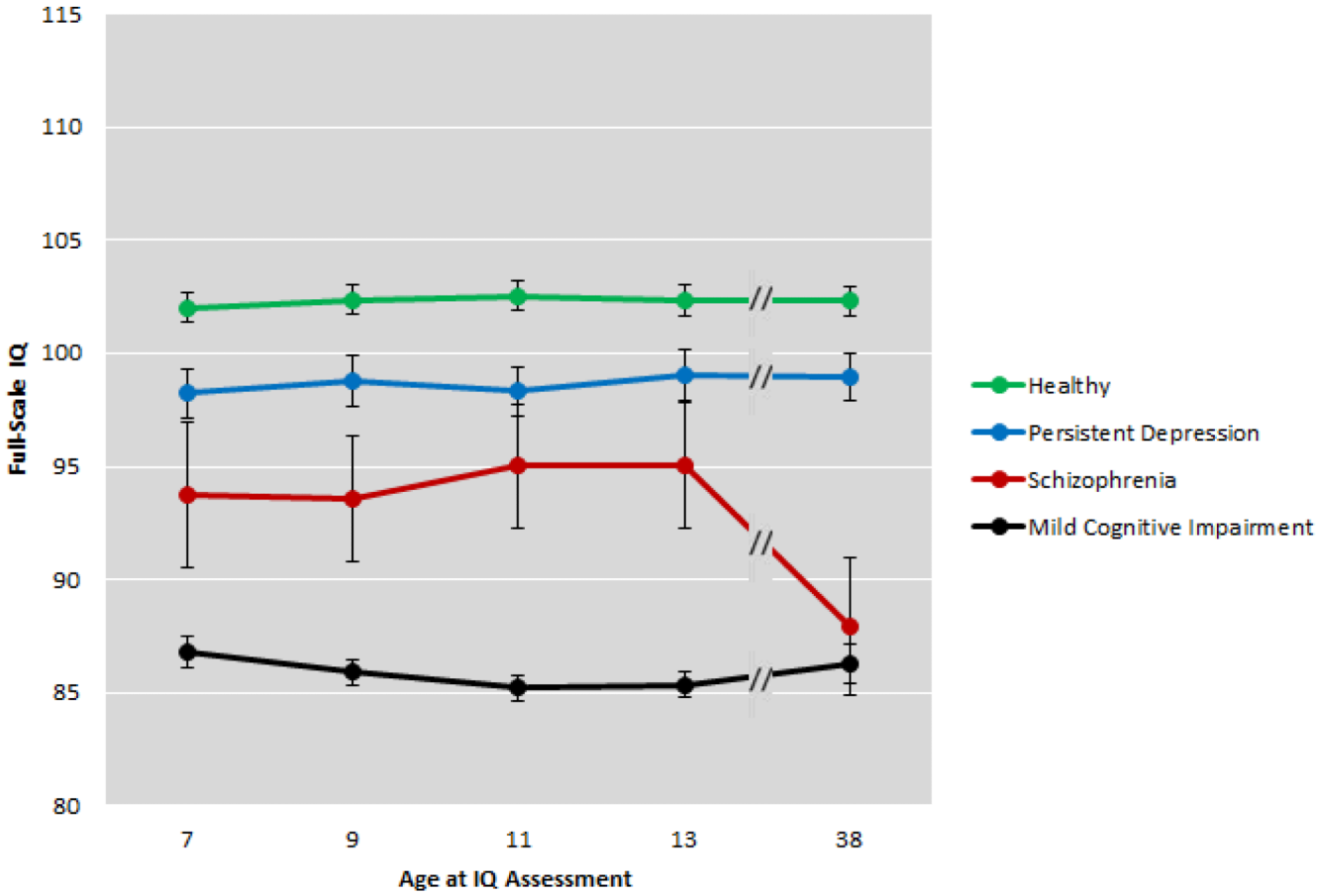

Figure 1.

Panel A. IQ Decline. This figure shows full-scale IQ in childhood (averaged across ages 7-13 years) and adulthood (age 38 years) for the healthy, schizophrenia, and persistent-depression groups. Error bars=standard errors. The asterisk denotes a statistically significant difference (paired t=3.29, p=.0026) between childhood and adulthood IQ for members of the schizophrenia group.

Panel B. IQ Scores from Age 7 to Age 38 Years. This figure shows full-scale IQ in childhood (ages 7, 9, 11, and 13 years) and adulthood (age 38 years) for the healthy, schizophrenia, and persistent-depression groups as well as a group of children with mild cognitive impairment. Error bars=standard errors.

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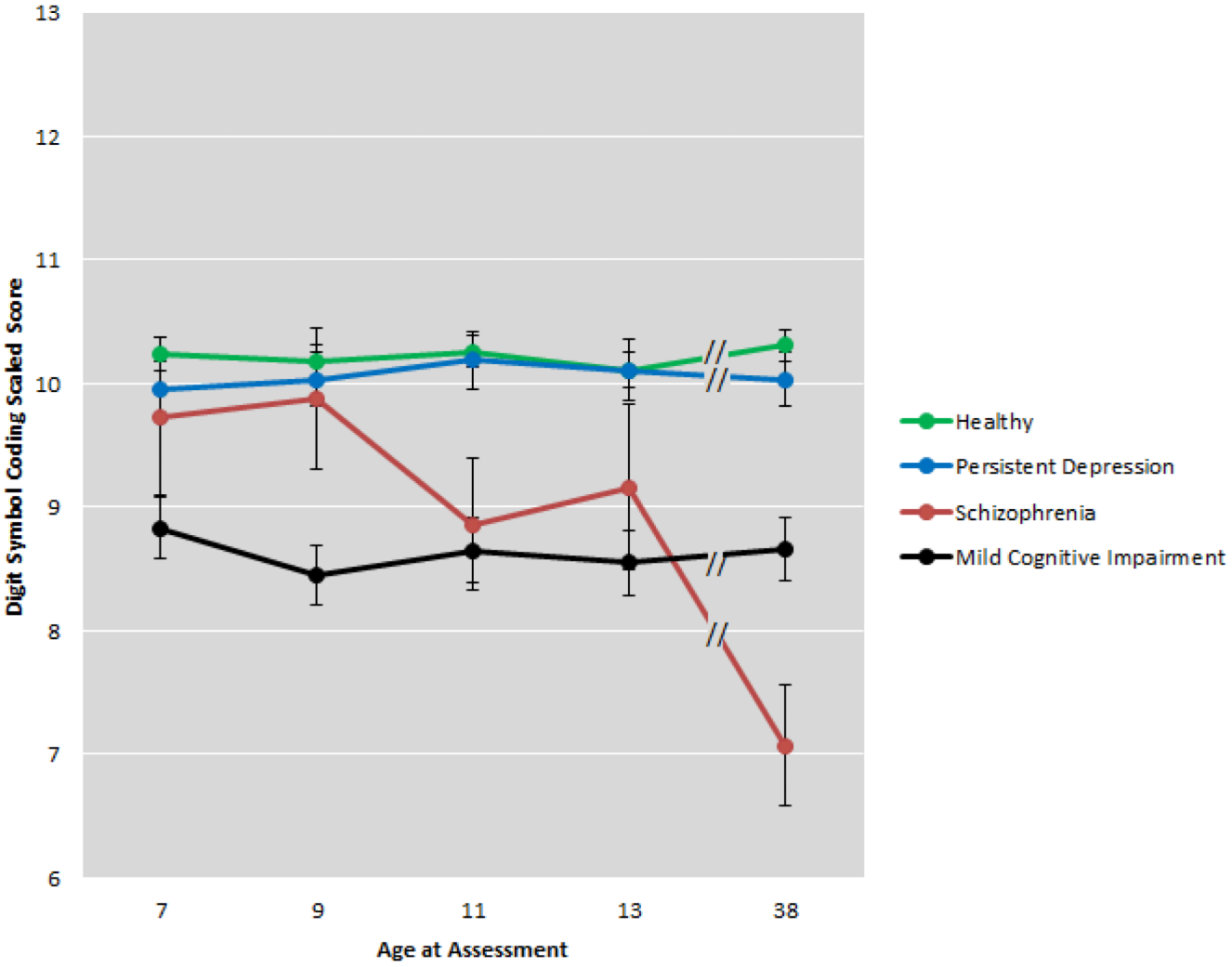

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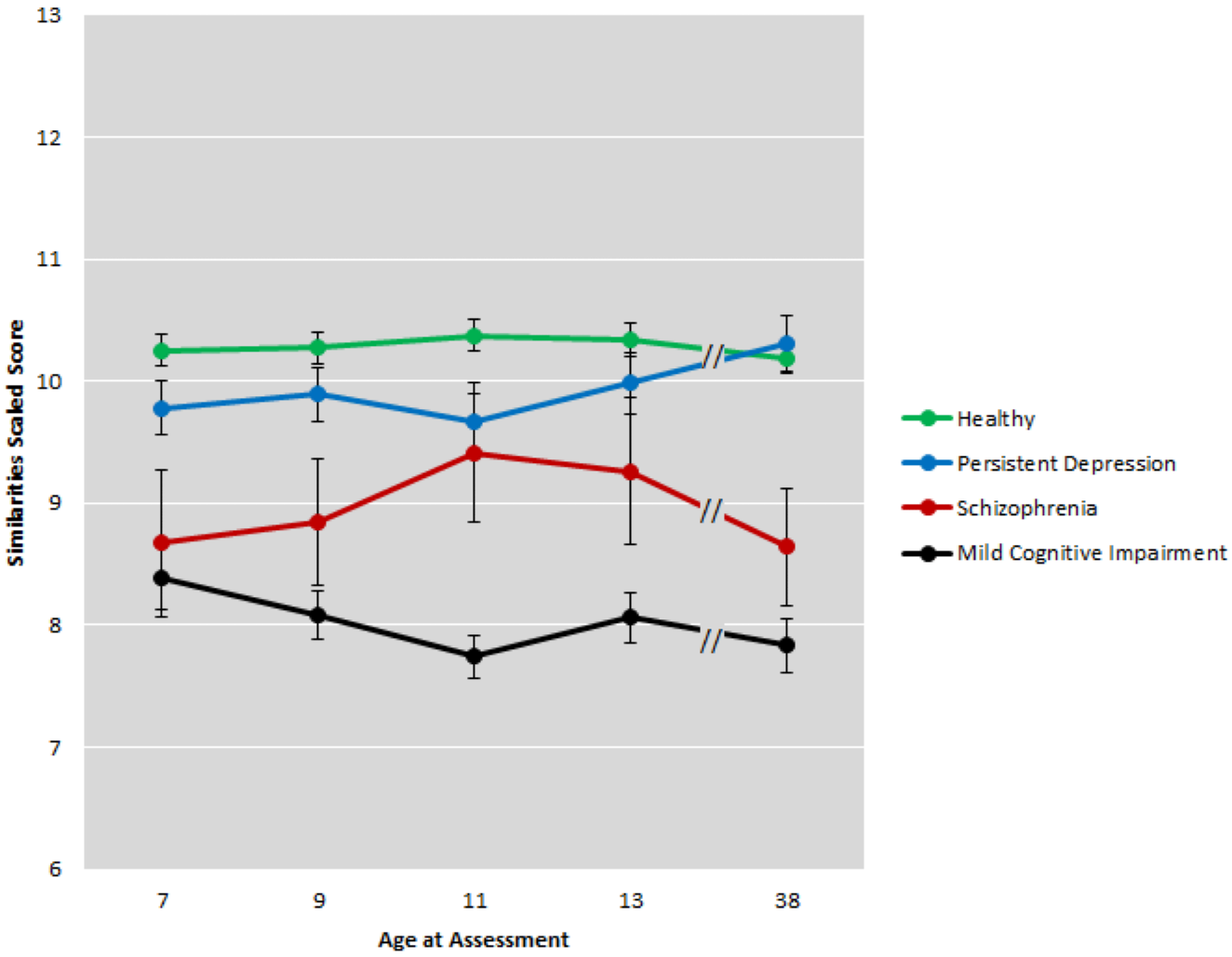

Figure 2.

Panel A. Scaled Scores on the Digit Symbol Coding Subtest from Age 7 to Age 38 years. This figure shows scaled scores (population M=10.00, SD=3.00) on the Wechsler digit symbol coding subtest from age 7 to 38 years. The deficit among individuals with schizophrenia increased from age 7 to 38 years. Error bars=standard errors.

Panel B. Scaled Scores on the Similarities Subtest from Age 7 to Age 38 Years. This figure shows scaled scores (population M=10.00, SD = 3.00) on the Wechsler similarities subtest from age 7 to 38 years. The deficit among individuals with schizophrenia was apparent as early as age 7 and remained relatively stable from age 7 to 38 years. Error bars=standard errors.

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Table 1

Extant "re-Post" Illness Onset Studies. This table summarizes studies assessing neuropsychological decline from before to after the onset of schizophrenia. Studies are organized by methodology and date, with the most methodologically rigorous and recent studies appearing first.

Study	Sample	N(cases)	Baseline Age	Follow-up Age	Comparison Group?	Same Test Across Time?	Neuropsychological Tests	Finding
1. Kremen et al. 2010[11]	Epidemiological	10	5 or 9	Range: late 30's	Yes	Yes	Peabody Picture Vocabulary Test	Relative Decline
2. Seidman et al. 2006[12]	Epidemiological	26	7	35	Yes	Yes	Two IQ Subtests	Decline
3. Caspi et al. 2003[13]	Clinical	44	16-17	Range: 20's	Yes	Yes	Army Induction Tests	Decline
4. Schwartzman & Douglas 1962[14]	Clinical	50	Range: 20's	Range: 30's	Yes	Yes	Army Induction Tests	Decline
5. Bilder et al. 2006[15]	Clinical	39	17	Range: 20's	Yes	No	Scholastic Aptitude Test, IQ	Decline
7. Gochman et al. 2005[16]	Clinical	18	Range: childhood	Range: adolescence, adulthood	No	Yes	IQ	Decline
8. Russell et al. 1997[17]	Clinical	34	Range: 8-25	Range: 17-59	No	Yes	IQ	No Decline
6. Lubin et al. 1962[18]	Clinical	159	18	Range: 18-51	No	Yes	Army Induction Tests	Decline
9. Sheitman et al. 2000[19]	Clinical	27	Range: 9-17	Range: 18-60	No	No	Various IQ tests	Decline
10. Rappaport & Webb 1950[20]	Clinical	10	Range: adolescence	Range: 15-28	No	Yes (within participants), No (between participants)	Various IQ tests	Decline
11. Albee et al. 1963[21]	Clinical	112	Range: childhood	Range: adulthood	No	No	Various IQ tests	No Decline

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Table 2

Comparison of individuals diagnosed with schizophrenia who had versus had not received treatment for psychotic illness

Correlate (age at assessment)	Treated for Psychotic Illness (N=17)		Not Yet Treated for Psychotic Illness (N=14)		Cohort Norm (N[a]=942-1031)
	M/%[b]	95% CI	M/%[b]	95% CI	M/%[b]
Full-Scale IO (38)	87.16	78.03, 96.29	88.85	79.12, 98.57	100.00
Mental Health Treatment (20-38)			85.71%[d]		
Received Treatment for Mental Health Problem (20-38)	100%	100.00, 100.00		57.19, 98.22	46.29%
Hospitalized for a Mental Health Problem (20-38)	58.82%	32.92, 81.56	21.43%	4.66, 50.80	7.33%
Childhood SES[c] (birth-15)	−0.02	−0.54, 0.50	−0.57	−1.12, −0.01	0.00
Received Government Benefits (26-38)	88.24%	63.56, 98.54	92.86%	66.13, 99.82	42.01%
Persistent Substance Dependence (18-38)					
Persistent Tobacco Dependence	52.94%	27.81, 77.02	64.29%	35.14, 87.24	24.13%
Persistent Alcohol Dependence	29.41%	10.31, 55.96	28.57%	8.39, 58.10	14.96%
Persistent Cannabis Dependence	23.53%	6.81, 49.90	28.57%	8.39, 58.10	8.87%
Persistent Hard-Drug Dependence (26-38)	0%	0.00, 0.00	7.14%	0.18, 33.87	2.58%
Informant-Reported Personality[c] (26-38)					
Agreeableness	−0.78	−1.50, −0.06	−1.07	−1.51, −0.63	0.00
Constraint	−0.64	−1.08, −0.20	−1.00	−1.75, −0.26	0.00
Extraversion	−0.44	−1.04, 0.15	−0.49	−1.29, 0.32	0.00
Neuroticism	0.93	0.46, 1.41	0.96	0.39 , 1.52	0.00
Openness	0.06	−0.57, 0.68	−0.20	−0.96, 0.57	0.00

[a] Note. N's ranged from 942 to 1,031 due to different amounts of missing data across study measures.

[b] Means are shown for continuous variables; percentages are shown for dichotomous variables.

[c] Standardized to cohort M=0.00, SD = 1.00.

d. Based on self-report.

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Table 3

Mean scores on childhood risk factors for those who did (case) and did not (control) develop schizophrenia, before and after propensity score matching. This table shows that matching resulted in a high degree of similarity in the distributions of the childhood risk factors across cases and controls, as standardized bias after matching was below 10 for each risk factor.

	Before Matching			After Matching		
Childhood Risk Factors	**Case (n=31)**	**Control (n=875)**	**SB (%)**	**Case (n=31)**	**Control (n=62)**	**SB (%)**
Full-Scale IQ (ages 7-13)	93.63	101.05	46	93.63	93.89	0
Performance IQ (ages 7-13)	94.64	100.97	39	94.64	94.80	0
Verbal IQ (ages 7-13)	93.64	101.04	40	93.64	94.03	2
Family History of Psychotic Illness[a]	0.25	−.01	23	0.25	0.29	−3
SES[a] (ages 0-15)	−0.27	0.04	31	−0.27	−0.31	−5
Average Standardized Bias	-	-	36	-	-	−1

Note. We used propensity score matching to perform the match using SAS software (SAS, Inc., Cary, N.C.). First, we obtained propensity scores via a logistic regression predicting likelihood of developing schizophrenia based on the above childhood correlates. Next, we performed an optimal 2 (control) to 1 (case) match on these propensity scores, whereby matches were made based on the absolute difference in propensity score between cases and controls (49, 50). The maximum absolute difference was set to 0.10. Results were similar across models with different match parameters (i.e., varied number of cases matched to controls, varied maximum absolute difference).

[a]Standardized to cohort M=0.00, SD=1.00. SB = standardizedbias. Negative SB values indicate higher risk among the control group. A total of 906 study members (31 cases and 875 controls) were available for matching, as analyses required non-missing values for all childhood risk factors.

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Table 4

Neuropsychological Decline Across Different Mental Functions. This table shows mean childhood and adulthood neuropsychological test scores (in standard deviation units) for each group. The shaded column shows the change in test scores (in standard deviation units) from childhood to adulthood.

	Healthy (N=518)			Schizophrenia (N=31)			Persistent Depression (N=185)		
Neuropsychological Test	**Child**	**Adult**	**Δ**	**Child**	**Adult**	**Δ**	**Child**	**Adult**	**Δ**
Full-Scale IQ	0.18	0.16	−0.02	−0.42^{H}	−0.81^{H}	−0.39^{H}	−0.04^{H}	−0.06^{H}	−0.02
Performance IQ	0.15	0.15	0.00	−0.36^{H}	−0.90^{H}	−0.54^{H}	−0.02^{H}	−0.06^{H}	−0.04
Digit Symbol Coding Subtest	0.09	0.10	0.01	−0.22	−0.98^{H}	−0.76^{H}	0.09	0.02^{H}	−0.07
Block Design Subtest	0.14	0.09	−0.05	−0.25^{H}	−0.63^{H}	−0.38^{H}	−0.02	−0.01	0.01
Picture Completion Subtest	0.12	0.10	−0.02	−0.44^{H}	−0.63^{H}	−0.19	−0.04	−0.03	0.01
Verbal IQ	0.17	0.14	−0.03	−0.42^{H}	−0.67^{H}	−0.25	−0.05^{H}	−0.06	−0.01
Information Subtest	0.17	0.14	−0.03	−0.28^{H}	−0.33^{H}	−0.05	−0.05	−0.11	−0.06
Similarities Subtest	0.14	0.07	−0.07	−0.42^{H}	−0.45^{H}	−0.03	−0.01	0.12	0.13^{H}
Vocabulary Subtest	0.16	0.11	−0.05	−0.36^{H}	−0.48^{H}	−0.12	−0.04^{H}	0.01	0.05
Arithmetic Subtest	0.18	0.15	−0.03	−0.45^{H}	−0.66^{H}	−0.21	−0.08^{H}	−0.16^{H}	−0.08
Rey Total Recall	0.08	0.05	−0.03	−0.41^{H}	−0.88^{H}	−0.47^{H}	0.06	0.10	0.04
Rey Delayed Recall	0.08	0.06	−0.02	−0.37^{H}	−0.38^{H}	−0.01	0.06	0.10	0.04
Trails A (time in seconds)[a]	−0.01	−0.07	−0.06	0.24	0.73^{H}	0.49^{H}	0.06	0.01	−0.05
Trails B (time in seconds)[a]	−0.10	−0.11	−0.01	0.69^{H}	1.21^{H}	0.52^{H}	0.08^{H}	−0.05	−0.13
Grooved Pegboard (time in seconds)[a]	−0.07	−0.11	−0.04	0.37^{H}	1.04^{H}	0.67^{H}	0.01	−0.04^{H}	−0.05

Note. Superscript ‘a’ reflects tests for which higher scores in childhood and adulthood indicate worse performance. Positive change scores on these same tests reflect decline in performance from childhood to adulthood. Superscript ‘H’ reflects a statistically significant difference ($p<0.05$) as compared to the healthy group. Statistical tests are sex-adjusted. N's for the IQ subtests range from 514-518 for the healthy group, 30-31 for the schizophrenia group, and 184-185 for the persistent depression group. A subset of individuals completed IQ testing in childhood but did not complete the Rey Auditory Verbal Learning Test, Trail Making Tests, or Grooved Pegboard Test in childhood. Therefore, for the Rey, Trail-Making, and Grooved Pegboard tests, the n’s are: healthy =384-393, schizophrenia=21-22, and persistent depression=138-140. There were no differences in IQ decline between those who did and did not complete these tests, either for the cohort as a whole (F=.09, p=.76), the healthy (F=1.26, p=.26), the schizophrenia (F=0.12, p=.73), or the persistent depression (F=1.35, p=.25) group.

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Table 5

Ruling Out Alternative Explanations. This table shows mean change in IQ from childhood to adulthood (in standard deviation units) for the healthy, schizophrenia, and persistent-depression groups (in bold) and for each group excluding those with (a) persistent cannabis dependence, (b)persistent alcohol dependence, and (c) persistent hard-drug dependence.

	Healthy		**Schizophrenia**			**Persistent Depression**		
Test	**Δ IQ**	**N**	**Δ IQ**	**N**	**p**	**Δ IQ**	**N**	**p**
Full Scale IQ	−0.02	517	−0.39	31	.0009	−0.02	185	.98
Excluding Those With:								
Persistent Cannabis Dependence	−0.01	497	−0.41	23	.0015	0.01	162	.72
Persistent Alcohol Dependence	−0.01	476	−0.32	22	.0109	0.00	141	.86
Persistent Hard-Drug Dependence	−0.01	512	−0.37	30	.0011	−0.01	178	.89

Note. Statistical tests compare each psychiatric group to the healthy group and are sex-adjusted.

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Table 6

Cognitive Impairment in Everyday Life. This table shows mean age-38 informant-reported attention and memory problems (in standard deviation units) for the healthy, schizophrenia, and persistent-depression groups.

	Healthy (N=508)	Schizophrenia (N=30)		Persistent Depression (N=182)	
Informant-Reported Cognitive Problem	**M**	**M**	**p**	**M**	**P**
Informant-reported Attention Problems	−0.18	1.00	<.0001	0.11	<.0001
Informant-reported Memory Problems	−0.16	0.95	<.0001	0.09	<.0001

Note. Statistical tests compare each psychiatric group to the healthy group and are sex-adjusted.