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Declaration of Interest

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Abstract

Objective: Schizophrenia is associated with a large cognitive impairment that is widely believed to remain stable after illness onset. Yet, even to date, 10-year prospective studies of cognitive functioning following the first episode with good methodology are rare. We examined whether schizophrenia patients experience cognitive decline following the first episode, whether this decline is generalized or confined to individual neuropsychological functions, and whether decline is specific to schizophrenia.

Method: Participants were from a population-based, case-control study of patients with first-episode psychosis that were followed prospectively up to 10 years post first admission. A neuropsychological battery was administered at index presentation and at follow-up to patients with a diagnosis of schizophrenia (n=65), or other psychoses (n=41), as well as to healthy comparison subjects (n=103).

Results: The schizophrenia group exhibited declines in IQ and in measures of verbal knowledge, and memory, but not processing speed or executive functions. Processing speed and executive function impairments were already present at the first episode and remained stable thereafter. Magnitude of declines ranged between 0.28 and 0.66 standard deviations. Decline in measures of memory was not specific to schizophrenia and was also apparent in the group of patients with other psychoses. Healthy individuals with low IQ, on the other hand, showed no evidence of decline, suggesting that a decline is specific to psychosis.

Conclusions: Patients with schizophrenia and other psychoses experience cognitive decline after illness onset, but the magnitude of decline varies across cognitive functions. Distinct mechanisms consequent upon the illness and/or psychosocial factors may underlie impairments across different cognitive functions.

Introduction

Cognitive impairment is a core feature of schizophrenia(1, 2). Understanding the nature and course of this impairment may have important implications for our understanding of the pathophysiology of the disorder.

Research has shown that individuals diagnosed with schizophrenia experience cognitive decline from the premorbid to post-onset period. There is clear evidence for moderate cognitive deficits in children and adolescents who later develop schizophrenia, with meta-analyses showing an average premorbid deficit equal to 8 IQ points (0.5 Standard Deviation (SD))(3, 4). Cognitive deficits in adults diagnosed with schizophrenia are more pronounced, with meta-analyses reporting a 14-point IQ deficit (0.90 SD) in first-episode schizophrenia patients (5) and 15- to 21-point IQ deficits (1.0 to 1.5 SD) in chronic schizophrenia patients (1, 6, 7). In line with cross-sectional evidence, longitudinal studies of cognitive change in schizophrenia from before to after illness onset have shown evidence for cognitive decline (8). Three population-based studies have reported cognitive declines ranging from 6 to 12 IQ points (0.4 – 0.8 SD) between childhood and adulthood in individuals later diagnosed with schizophrenia (8-10).

Despite evidence for cognitive decline from before to after illness onset, the course of cognitive decline in schizophrenia remains unclear. While it is widely believed that cognitive impairments stabilize after illness onset (11-13), at least until older adult life (12, 14), few longitudinal studies have examined cognitive change from illness onset through to a decade later (**sTable 1**), and findings across studies and cognitive domains are mixed. Studies have reported a stabilization of the cognitive deficits, cognitive decline, as well as amelioration of cognitive functioning (**sTable 1** and ref # (15)).

Previous studies have been unable to comprehensively chart the course of cognitive deficits for several reasons. First, the majority of studies have used clinical samples, which may not be fully representative of the population of individuals with schizophrenia (8). Second, most studies followed participants for only 1 to 3 years from illness onset (**sTable 1**). We previously reported a slow, gradual increase in premorbid cognitive deficits, with losses equal to between 0.5 and 1 IQ point per year (16). Studies with short follow-ups, therefore, may be underpowered to capture decline. Third, few studies have included comparison groups, and therefore have not considered the potential impact of normative age-associated changes in cognitive functioning, which is necessary to rigorously test for cognitive change. Since, brain maturation continues into the third decade of life (17), previous estimates of the magnitude of cognitive decline may be biased. Finally, few studies have examined the effect

of medication on cognitive functioning, and yet recent findings suggest that antipsychotic medications may contribute to the severity of cognitive decline (18).

In a previous report on this population-based, case-control study, we provided evidence for an IQ deficit, as well as varying degrees of impairment across individual cognitive domains following the first psychiatric diagnosis of schizophrenia (19). Study participants have since been followed-up and underwent neuropsychological testing a second time. Using identical neuropsychological measures at first assessment and follow-up, we were able to directly examine change in IQ and in individual cognitive functions after the first episode. To provide an accurate estimate of cognitive change over time, we compared patients to the healthy comparison subjects in the study followed during the same period. We tested three hypotheses. First, we examined the "IQ decline" hypothesis to establish whether schizophrenia patients exhibit a static IQ deficit or IQ decline. Second, we tested the "generalized decline" hypothesis to determine whether decline occurs across multiple cognitive domains, namely verbal knowledge, memory, language, processing speed, executive function/working memory and visuospatial ability. Finally, we tested the "specificity" hypothesis to establish whether any cognitive decline is specific to schizophrenia or common to other psychoses by examining cognitive change in individuals with psychotic disorders other than schizophrenia.

Methods

AESOP Study

Data were derived from the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study, a population-based, case-control study of first-episode psychosis. AESOP was approved by local research ethics committees and each participant gave written informed consent after receiving a complete description of the study. The study identified all first-episode psychosis cases (ICD-10: F10–F29 and F30–F33) aged 16 to 65 years presenting to specialist mental health services in tightly defined catchment areas of the United Kingdom (southeast London, Nottingham and Bristol) between September 1997 and August 2000. All potential cases making contact with psychiatric services (including adult community mental health teams, inpatient units, forensic services, learning disability services, adolescent mental health services, and drug and alcohol units) for the first time were screened. Exclusion criteria were previous contact with health services for psychosis, organic causes of psychotic symptoms, transient psychotic symptoms as the result of acute

intoxication (as defined by ICD-10), and IQ<50. A random sample of control subjects with no past or present psychotic disorder were recruited using a sampling method that matched cases and controls by area of residence. Hereafter, data collected at this phase of the AESOP study is referred to as 'baseline'.

At baseline, detailed information was collected to enable patients to be traced, re-contacted and re-interviewed approximately 10 years later ('follow-up'). At follow-up, patients currently in contact with mental health services were invited to participate through their clinical teams. Letters of invitation were sent to last known addresses of those not in contact with services. Non-responders were sent a second letter two to three weeks later. If patients were thought to have moved, contact was sought through their GP. Control subjects also provided contact details at baseline. Letters of invitation were sent and were followed-up with phone calls if no reply had been received within 2 weeks. If no reply had been received after 4 weeks, or where telephone numbers could not be obtained, in-person visits were made to the subject's address. A detailed overview of the AESOP study design and methods, as well as the follow-up has been published elsewhere (20, 21).

Analytic Cohort

Derivation of the sample included in the present analysis is illustrated in **Figure 1**. The analytic cohort consisted of healthy comparison subjects and subjects who had a consensus ICD-10 diagnosis at last follow-up of schizophrenia (F20), bipolar disorder or mania (F30.2, F31.2, F31.5), depressive psychoses (F32.3, F33.3) or other psychotic disorders including persistent delusional disorders and psychosis NOS (F22, F23, F28, F29). Both case and comparison subjects were required to be native English speakers or to have migrated to the UK by age 11. The latter ensured that all participants had a good command of English, even as a non-native language, by verifying that participants had completed at least their secondary education in the UK. Thus, this minimized the effect of linguistic or cultural biases on cognitive performance in a multiethnic sample.

Figure 1. Derivation of first-episode psychosis patients and healthy comparison subjects from the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) Project Baseline and 10-Year Follow Up.

Neuropsychological assessment

At baseline and follow-up, participants underwent cognitive testing with a neuropsychological battery, which assessed general intellectual ability (IQ), as well as specific cognitive

functions. Administration and scoring followed standard procedures. Full-scale IQ was estimated using the vocabulary, comprehension, digit symbol coding and block design subtests of the WAIS-R (22). Short forms of the WAIS-R have been shown to produce accurate estimates of full-scale IQ (23, 24). Specific functions were assessed using the following neuropsychological tests: *Memory* using the Rey Auditory-Verbal-Learning Test (RAVLT) trials 1 to 7 (learning, immediate and delayed verbal recall) (25), and the Visual Reproduction subtest of the Wechsler Memory Scale - Revised (WMS-R) (26); *Verbal knowledge* using the Vocabulary and Comprehension subtests of the WAIS-R (22); *Processing speed* using the WAIS-R digit symbol coding and the Trails-Making-Test Part A (27); *Executive function/working memory* using Trails-Making-Test - Part B (27), and Letter-Number Span (28); *Language* using Category (semantic) and Letter Fluency (categories: 'body parts'; 'fruits'; 'animals', letters: F; A; S) (29), and *Visuospatial ability* using the WAIS-R Block Design subtest.

Diagnostic Assessment

Clinical data were collected using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)(30). The SCAN incorporates the Present State Examination, Version 10, to elicit symptom-related data at time of presentation. Ratings on the SCAN are based on clinical interview, case note review, and information from informants (e.g. health professionals, close relatives). Researchers were trained on the SCAN with a World Health Organization-approved course and reliability was established prior to commencement of the study using independent ratings of videotaped interviews. Rater agreement was evaluated using Kappa statistics, which ranged from 1.0 for psychosis as a category to between 0.6 and 0.8 for individual diagnoses. ICD-10 diagnoses were determined using SCAN data through consensus meetings with one of the PIs and other team members. Symptom severity was classified based on the SCAN Symptom Severity Rating Scale 2 as: 0 = Absent, 1 = Mild, 2 = Moderate and 3 = Severe (21).

Covariates and medication information

Age was collected at baseline and follow-up. Sex, ethnicity, and level of education were collected at baseline. Treatment history with typical and/or atypical antipsychotic medication was ascertained for all patients from interview data and record review at follow-up.

Creating Norms for Neuropsychological Tests

A regression-based approach was used to create normative standards for the neuropsychological tests. Age at assessment, sex, ethnicity, and education were regressed on each of the neuropsychological measures in the healthy comparison sample at baseline and follow-up. Next, scores were adjusted on the basis of the regression results, and standard scores (i.e., z-scores) were created. The same adjustment and standardization procedure were applied to the patient groups, using the normative standards from the healthy comparison group.

Statistical analysis

Demographic and clinical characteristics of the baseline and follow-up cohorts were compared using summary statistics. For descriptive purposes, we compared patients with schizophrenia or other psychoses (including bipolar disorder, mania, depressive psychoses and other psychotic disorders) to the comparison group on normative-adjusted IQ and specific neuropsychological tests at baseline and follow-up using analysis of variance (ANOVA) models.

To examine the “IQ decline” “generalized decline” and “specificity” hypotheses, we compared the schizophrenia and other psychoses groups to the comparison group on change in normative-adjusted IQ and specific neuropsychological tests from baseline to follow-up. Change scores were calculated by subtracting follow-up test scores from baseline test scores, so that positive scores indicate cognitive amelioration and negative scores indicate cognitive decline. ANCOVA models with planned orthogonal comparisons of each psychosis group to the comparison group, adjusting for time from baseline assessment and baseline test score were used. Adjustment for baseline performance is common in studies on cognitive change (31, 32). For the “IQ decline” hypothesis, the significance level was set at p=0.05 (two-sided). For the “generalized decline” hypothesis, the significance level was set at a Bonferroni-corrected level of 0.0038 (0.05/13). All analyses were conducted using IBM SPSS Statistics version 24.

Results

Demographic characteristics of the baseline cohort and the cohort assessed at follow-up are presented in **Table 1**. Follow-up neuropsychological assessments were completed on 106 patients (63 males), and 103 comparison subjects (40 males). Average follow-up duration was 109.3 months (SD=29.5) for patients and 102.9 (SD=34.1) for comparisons. Overall, the patients and comparisons assessed at follow-up were similar to the respective patients and

comparisons assessed at baseline in terms of demographic variables, suggesting that the cohort at follow-up was representative of the original cohort.

Cognitive impairment in schizophrenia and other psychoses at baseline and follow-up

As we have previously shown in the AESOP study cohort (19), patients with schizophrenia and patients with other psychoses showed deficits in IQ and individual neuropsychological tests at baseline. **Figure 2** illustrates that that schizophrenia patients exhibited widespread, persistent, cognitive impairment, performing significantly worse than comparison subjects at both baseline and follow-up on 11 out of the 14 measures. Patients with other psychoses also showed widespread impairments, but these were generally of smaller magnitude than schizophrenia patients (**Figure 2**). (**sTable2** presents the non-adjusted performance in IQ and specific neuropsychological tests at baseline and follow-up)

Figure 2. Neuropsychological Performance Among Patients with Schizophrenia and Other Psychoses at Baseline and Follow-Up[a].

[a] - Effect sizes (expressed in standardized [z] scores) and 95% Confidence Intervals (95%CI) of difference from comparison subjects at baseline and follow up. Comparison subjects set to zero (dotted line). Effect sizes are adjusted for age, sex, ethnicity, and level of education. 95% CI that do not include zero indicate statistical significance level p<0.05. Trailmaking A=Trail Making Test, Part A; Trailmaking B=Trail Making Test, Part B.

Cognitive change in schizophrenia and other psychoses

Next, we compared cognitive change over time in each of the psychoses groups (schizophrenia and other psychoses) to cognitive change in controls to test the “IQ decline”, “generalized decline” and “specificity” hypotheses. **Figure 3** presents effect sizes of the difference in the within group change from baseline to follow-up in IQ and individual neuropsychological tests between the psychoses groups and controls. Effect sizes of 0.20, 0.50, and 0.80 reflect small, medium, and large effects, respectively (33).

***IQ decline hypothesis*:** IQ decline in the schizophrenia group was significantly larger than in controls, who showed no evidence of IQ decline. The IQ decline in the schizophrenia group compared to controls was of small magnitude (ES=-0.28, 95% Confidence Intervals: -0.47 to -0.09, p=0.003), but was not attenuated when adjusting for education, ethnicity, sex, age-at-baseline assessment, or duration of follow-up, suggesting that IQ decline could not be attributed to these variables.

Generalized decline hypothesis: Compared to controls, the schizophrenia group showed a larger cognitive decline across tests in the memory and verbal knowledge domains (**Figure 3**). In the memory domain, the schizophrenia group declines on verbal learning (p=0.001), immediate recall (p<0.00006), and delayed recall (p<0.00001) reached the Bonferroni-corrected level of significance. In the verbal knowledge domain, decline on vocabulary (p=0.003) reached the Bonferroni-corrected level of significance. Compared to controls, the schizophrenia group showed no significant cognitive changes on Digit Symbol Coding and Trail-making-test Part A in the processing speed domain, Block Design in the visuospatial domain, and Trail-making-test Part B, Letter-Number Span, Letter Fluency and Category Fluency in the executive functions and working memory domain.

Specificity hypothesis: There was no evidence for IQ decline in the other psychoses group compared to controls (ES=-0.09, 95% Confidence Intervals: -0.30 to 0.11; p=0.37), (**Figure 3**). In terms of cognitive domains, like the schizophrenia group, the other psychoses group showed larger declines than controls across test in the memory domain, with verbal learning (p=0.001) reaching the Bonferroni-corrected level of significance. Like schizophrenia patients, the other psychoses group showed static deficits in tests of processing speed, executive functions and working memory, and visuospatial ability (**Figure 3**).

Figure 3. Change in Neuropsychological Performance Among Patients with Schizophrenia and Other Psychoses [a, *].

[a] - Presented are effect sizes and 95% Confidence Intervals of difference in change from baseline to follow up between the diagnostic group and comparison group. 95% Confidence Intervals that do not include zero indicate statistical significance level p<0.05. Effect sizes are adjusted for age, sex, ethnicity, level of education, time from baseline assessment and baseline test score. Trailmaking A=Trail Making Test, Part A; Trailmaking B=Trail Making Test, Part B.
* - Presents Bonferroni corrected level (p≤0.0038)

Medication

We examined the potential moderating effect of antipsychotic medication on IQ decline in the schizophrenia group. There was no statistically significant difference in IQ decline (*p*=0.23) between patients with a history of treatment with typical antipsychotics only (45% of sample) and those with a history of treatment with both typical and atypical antipsychotics (55% of sample). Duration of antipsychotic medication (mean = 323±192 weeks) did not attenuate IQ decline in schizophrenia (F=7.30, p=0.008 vs. F=7.20, p=0.009 for ANCOVA models with vs. without duration of treatment as a covariate).

Symptom severity

Since illness severity might influence cognition, we also examined the association between baseline symptom severity and change in cognitive functioning, as well as change in symptom severity between baseline and follow up and change in cognitive functioning. Schizophrenia patients with severe symptoms at baseline showed statistically significantly greater cognitive decline than patients with mild or moderate symptoms across multiple tests in the memory domain (Figure 4). However, there was no association between change in symptom severity and change in cognitive functioning (sTable 2 and sFigure 1), and no evidence for a dose-response relationship across levels of severity (Figure 4). In the other psychoses group there was no evidence for an association between symptom severity, or change in symptom severity, and change in cognitive functioning (Figure 4, sFigure1).

Figure 4. Change in Neuropsychological Performance Among Patients With Schizophrenia and Other Psychoses in Relation to Symptom Severity at Baseline[a]

[a] - Presented are effect sizes and 95% Confidence Intervals of difference in change from baseline to follow up between the diagnostic group and comparison group as a function of symptom severity at baseline. 95% Confidence Intervals that do not include zero indicate statistical significance level $p<0.05$. Effect sizes are adjusted for age, sex, ethnicity, level of education, time from baseline assessment and baseline test score. Trailmaking A=Trail Making Test, Part A; Trailmaking B=Trail Making Test, Part B.

Sensitivity analyses

We also examined the potential impact of attrition by applying linear mixed models which permit varying numbers of measurements per person and time point, while adjusting for within-individual (i.e. between measures) variation. Similar results were obtained in models that included only cases and controls with data from both assessment time points, and in models that also included cases and controls with data from a single assessment, indicating results were not biased by attrition.

As a further comparison, we examined IQ change in controls with lower IQ (IQ<90 at baseline, equal to 1SD below the control group mean, N=17, 16.5% of sample). These individuals are of interest because, like schizophrenia patients, they also exhibit lower IQ, and yet they did not develop psychosis. In contrast to patients with schizophrenia, individuals with lower IQ did not show evidence of IQ decline, neither in absolute terms nor relative to controls without a cognitive impairment since mean IQ at baseline was 84.9, and at follow up was 89.8 ($F=0.97$, $p=0.35$).

Discussion

Using a population-based, case-control sample followed prospectively from the first psychotic episode we provide evidence for cognitive decline after illness onset in patients with schizophrenia.

These findings advance knowledge in three important ways. First, the results lend support to the “IQ decline” hypothesis. As a group, schizophrenia patients showed IQ decline between baseline and follow up assessments, with an effect size of small magnitude (ES=0.28). This finding is in contrast with earlier studies reporting stabilization of cognitive deficits after the onset of psychosis (15). However, previous studies had important methodological limitations, including a short follow-up period of patients, and lack of a comparison group that is similarly followed-up. The finding of IQ decline is in line with findings from neuroimaging studies of greater age-associated brain volume loss (34), as well as deviated gyrification trajectories in schizophrenia patients in adulthood (35). Moreover, reduction in cortical volume has been associated with IQ decline in schizophrenia patients (36).

Second, the current findings do not support the “generalized decline” hypothesis. Decline was not ubiquitous and varied across cognitive domains. The schizophrenia group exhibited declines in verbal knowledge and memory. In contrast, processing speed, executive functions and visuospatial ability did not decline. These contrasts can be generally viewed as reflecting differences between the impact of the illness on crystalized (verbal knowledge) vs. fluid (processing speed, executive functions, visuospatial) abilities. Our findings of decreasing crystalized abilities and memory scores between baseline and follow-up is in line with previous evidence (37) and suggest that increasing deficits in these domains may reflect actual loss of ability, rather than abnormal cognitive development (i.e. “lag”) (16). Alternatively, our findings may reflect difficulties with the maintenance and acquisition of new verbal knowledge due to substantial and increasing memory deficits. While most cognitive abilities in the general population start to show stabilization or even decline in early adulthood, crystalized abilities may peak much later (38-40). In our study, measures of fluid abilities showed a large deficit already at the first episode, which remained static thereafter. While previous longitudinal epidemiological studies have shown cognitive decline in schizophrenia from the premorbid period in childhood to the chronic stage in mid-adulthood (8-10), they were unable to determine when this decline occurred. Our findings suggest that most of the decline in fluid abilities occurs before the first episode, while crystalized abilities

may continue to decline after onset. Importantly, the decline in IQ after onset is likely to be due to the decline seen in crystallized abilities.

Third, the current findings do not support the “specificity” hypothesis since patients with schizophrenia, but also other psychoses, experienced cognitive decline. However, while patients with schizophrenia showed decline in IQ, memory and verbal knowledge, patients with other psychoses showed decline only in certain memory functions. Moreover, in line with previous reports (41, 42), the other psychoses group showed an overall impairment profile that was qualitatively similar, yet quantitatively smaller than the schizophrenia group. Thus, our findings suggest that cognitive decline is not specific to schizophrenia, but also evident in other psychoses. However, large, widespread, cognitive decline may still be specific to schizophrenia, since the other psychoses group showed a smaller and less generalized cognitive decline. Interestingly, there was no evidence of decline in a key comparison group, namely individuals with lower IQ who did not develop psychosis. This group may in fact experience a different process of regression-to-the-mean.

The current findings should be viewed in the context of certain limitations. First, although we found evidence for cognitive decline after illness onset, we could not fully map the course of deficits and cognitive functions may vary in the timing of decline following the first episode. Second, group sizes did not allow for an analysis of the heterogeneity of cognitive course and also limited our ability to investigate more specific diagnostic sub-groups, such as bipolar/mania. Third, we ruled out two explanations for the observed cognitive decline, namely, type or duration of antipsychotic treatment. Unfortunately, we did not have information to examine other potential moderators of cognitive decline, such as social isolation, smoking and illicit drug abuse, victimization, or physical health problems such as obesity, diabetes and hypertensions. Moreover, despite the fact that we adjusted for education in all our analyses, poor education in the schizophrenia group after the first psychotic episode could still partly explain some of the group differences.

There is conflicting evidence regarding the relationship between change in symptoms and cognitive functioning (43, 44). In our study, change in severity of psychosis was only minimally associated with cognitive change. These results are consistent with cross-sectional findings of only a weak association between positive symptoms and cognitive impairment (45). Longitudinal evidence also suggests a minimal association between change in positive as well as negative symptoms, and change in cognition (43, 44, 46). Interestingly, in our study, schizophrenia patients with severe symptoms at baseline showed greater cognitive decline than patients with mild or moderate symptoms. While this group was small (21% of overall group), the magnitude of decline in the memory domain was large.

Thus, this finding points to a potential subgroup of schizophrenia patients that may greatly benefit from being specifically targeted for cognitive remediation.

Our findings have important implications for understanding the nature and course of cognitive impairment in schizophrenia, as well as other psychoses. Integrating the current findings with those of previous studies (16) suggests that cognitive dysfunction in schizophrenia may result from a complex interplay between an early, static neuropathology (47, 48) and dynamic age-related processes (49, 50). As such, cognitive functions that develop and peak relatively early in life, such as processing speed and visuospatial abilities (39) may show aberrant development, resulting in slowed growth prior to the onset of schizophrenia (16), but relative stabilization throughout the illness course. On the other hand, cognitive functions that continue to evolve through adult life, such as language (39), may show further deterioration throughout the course of schizophrenia. Finally, functions sensitive to age-related cognitive decline, such as memory, may begin to decline in middle adulthood before normative aging becomes apparent (40).

In conclusion, the present study demonstrates that while a substantial proportion of the cognitive impairment seen in adult patients with schizophrenia, as well as other psychoses, is present already at the first episode, these patients continue to experience cognitive decline after illness onset. However, the nature of this decline varies across neuropsychological functions. While large deficits in processing speed are already apparent at the first episode, deficits in verbal knowledge and memory continue to increase. These findings suggest that different pathophysiological mechanisms may underlie individual neuropsychological deficits seen in adult psychosis patients. Future research should determine which of these are consequent upon the illness itself, and which on the psychosocial factors patients experience. Finally, these findings highlight the importance of targeting early developmental stages in future studies of the causes of cognitive deficits associated with psychosis, as well as in cognitive remediation efforts.

REFERENCES

1. Reichenberg A, Harvey PD. Neuropsychological impairments in schizophrenia: Integration of performance-based and brain imaging findings. Psychological bulletin. 2007;133:833-858.
2. Kahn RS, Keefe RS. Schizophrenia is a cognitive illness: time for a change in focus. JAMA psychiatry. 2013;70:1107-1112.
3. Woodberry KA, Seidman LJ, Giuliano AJ, Verdi MB, Cook WL, McFarlane WR. Neuropsychological profiles in individuals at clinical high risk for psychosis: relationship to psychosis and intelligence. Schizophrenia research. 2010;123:188-198.
4. Khandaker GM, Barnett JH, White IR, Jones PB. A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. Schizophrenia research. 2011;132:220-227.
5. Mesholam-Gately RI, Giuliano AJ, Goff KP, Faraone SV, Seidman LJ. Neurocognition in first-episode schizophrenia: a meta-analytic review. Neuropsychology. 2009;23:315.
6. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology. 1998;12:426.
7. Fioravanti M, Carlone O, Vitale B, Cinti ME, Clare L. A meta-analysis of cognitive deficits in adults with a diagnosis of schizophrenia. Neuropsychology review. 2005;15:73-95.
8. Meier MH, Caspi A, Reichenberg A, Keefe RS, Fisher HL, Harrington H, Houts R, Poulton R, Moffitt TE. Neuropsychological decline in schizophrenia from the premorbid to the postonset period: evidence from a population-representative longitudinal study. American Journal of Psychiatry. 2013;171:91-101.
9. Seidman LJ, Buka SL, Goldstein JM, Tsuang MT. Intellectual decline in schizophrenia: evidence from a prospective birth cohort 28 year follow-up study. Journal of clinical and experimental neuropsychology. 2006;28:225-242.
10. Kremen WS, Vinogradov S, Poole JH, Schaefer CA, Deicken RF, Factor-Litvak P, Brown AS. Cognitive decline in schizophrenia from childhood to midlife: a 33-year longitudinal birth cohort study. Schizophrenia research. 2010;118:1-5.
11. Heaton RK, Gladsjo JA, Palmer BW, Kuck J, Marcotte TD, Jeste DV. Stability and course of neuropsychological deficits in schizophrenia. Archives of general psychiatry. 2001;58:24-32.
12. Kurtz MM. Neurocognitive impairment across the lifespan in schizophrenia: an update. Schizophrenia research. 2005;74:15-26.
13. Lewandowski KE, Cohen BM, Ongur D. Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. Psychological medicine. 2011;41:225-241.
14. Friedman JI, Harvey PD, Coleman T, Moriarty PJ, Bowie C, Parrella M, White L, Adler D, Davis KL. Six-year follow-up study of cognitive and functional status across the lifespan in schizophrenia: a comparison with Alzheimer's disease and normal aging. American Journal of Psychiatry. 2001;158:1441-1448.
15. Bozikas VP, Andreou C. Longitudinal studies of cognition in first episode psychosis: a systematic review of the literature. Aust N Z J Psychiatry. 2011;45:93-108.
16. Reichenberg A, Caspi A, Harrington H, Houts R, Keefe RS, Murray RM, Poulton R, Moffitt TE. Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. American Journal of Psychiatry. 2010;167:160-169.
17. Casey B, Tottenham N, Liston C, Durston S. Imaging the developing brain: what have we learned about cognitive development? Trends in cognitive sciences. 2005;9:104-110.
18. Seidman LJ, Shapiro DI, Stone WS, Woodberry KA, Ronzio A, Cornblatt BA, Addington J, Bearden CE, Cadenhead KS, Cannon TD. Association of neurocognition with transition to psychosis: baseline functioning in the second phase of the North American Prodrome Longitudinal Study. Jama psychiatry. 2016;73:1239-1248.
19. Zanelli J, Reichenberg A, Morgan K, Fearon P, Kravariti E, Dazzan P, Morgan C, Zanelli C, Demjaha A, Jones PB. Specific and generalized neuropsychological deficits: a

comparison of patients with various first-episode psychosis presentations. American Journal of Psychiatry. 2010;167:78-85.
20. Kirkbride JB, Fearon P, Morgan C, Dazzan P, Morgan K, Tarrant J, Lloyd T, Holloway J, Hutchinson G, Leff JP. Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AeSOP study. Archives of general psychiatry. 2006;63:250-258.
21. Morgan C, Lappin J, Heslin M, Donoghue K, Lomas B, Reininghaus U, Onyejiaka A, Croudace T, Jones PB, Murray RM. Reappraising the long-term course and outcome of psychotic disorders: the AESOP-10 study. Psychological medicine. 2014;44:2713-2726.
22. Wechsler D: WAIS-R manual: Wechsler adult intelligence scale-revised, Psychological Corporation; 1981.
23. Silverstein A. Two-and four-subtest short forms of the Wechsler Adult Intelligence Scale-Revised. Journal of Consulting and Clinical Psychology. 1982;50:415.
24. Roth DL, Hughes CW, Monkowski PG, Crosson B. Investigation of validity of WAIS-R short forms for patients suspected to have brain impairment. J Consult Clin Psychol. 1984;52:722-723.
25. Schmidt M: Rey auditory verbal learning test: a handbook, Western Psychological Services Los Angeles; 1996.
26. Wechsler D. Instruction Manual for the Wechsler Memory Scale Revised. New York, Psychological Corp. 1987.
27. Reitan RM: Trail Making Test: Manual for administration and scoring, Reitan Neuropsychology Laboratory; 1992.
28. Gold JM, Carpenter C, Randolph C, Goldberg TE, Weinberger DR. Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. Arch Gen Psychiatry. 1997;54:159-165.
29. Spreen O, Strauss E: A compendium of neuropsychological tests : administration, norms, and commentary. New York, Oxford University Press; 1991.
30. Wing JK, Babor T, Brugha T, Burke J, Cooper J, Giel R, Jablenski A, Regier D, Sartorius N. SCAN: Schedules fonr Clinical Assessment in Neuropsychiatry. Archives of general psychiatry. 1990;47:589-593.
31. MM. G, J. W, LF. B, I. K, JM. R. When is baseline adjustment useful in analyses of change? An example with education and cognitive change. American Journal of Epidemiology. 2005;162:267-278.
32. Overall J, Woodward J. Unreliability of difference scores: A paradox in the measurement of change. Psychological bulletin. 1975;82:185-186.
33. Cohen J. A power primer. Psychological bulletin. 1992;112:155.
34. Kahn RS, Sommer IE, Murray RM, Meyer-Lindenberg A, Weinberger DR, Cannon TD, O'Donovan M, Correll CU, Kane JM, van Os J, Insel TR. Schizophrenia. Nat Rev Dis Primers. 2015;1:15067.
35. Cao B, Mwangi B, Passos IC, Wu MJ, Keser Z, Zunta-Soares GB, Xu D, Hasan KM, Soares JC. Lifespan Gyrification Trajectories of Human Brain in Healthy Individuals and Patients with Major Psychiatric Disorders. Sci Rep. 2017;7:511.
36. Kubota M, van Haren NE, Haijma SV, Schnack HG, Cahn W, Hulshoff Pol HE, Kahn RS. Association of IQ Changes and Progressive Brain Changes in Patients With Schizophrenia. JAMA Psychiatry. 2015;72:803-812.
37. MacCabe JH, Wicks S, Lofving S, David AS, Berndtsson A, Gustafsson JE, Allebeck P, Dalman C. Decline in cognitive performance between ages 13 and 18 years and the risk for psychosis in adulthood: a Swedish longitudinal cohort study in males. JAMA Psychiatry. 2013;70:261-270.
38. Czaja SJ, Charness N, Fisk AD, Hertzog C, Nair SN, Rogers WA, Sharit JJP, aging. Factors predicting the use of technology: findings from the Center for Research and Education on Aging and Technology Enhancement (CREATE). 2006;21:333.
39. Hartshorne JK, Germine LT. When does cognitive functioning peak? The asynchronous rise and fall of different cognitive abilities across the life span. Psychological science. 2015:0956797614567339.

40. Salthouse TA. When does age-related cognitive decline begin? Neurobiology of aging. 2009;30:507-514.
41. Koenen KC, Moffitt TE, Roberts AL, Martin LT, Kubzansky L, Harrington L, Poulton R, Caspi A. Childhood IQ and Adult Mental Disorders: A Test of the Cognitive Reserve Hypothesis American Journal of Psychiatry. 2009;166:50-57.
42. Reichenberg A, Caspi A, Harrington H, Houts R, Keefe R, Murray RM, al. e. Static and Dynamic Cognitive Deficits in Childhood Preceding Adult Schizophrenia: A 30-Year Study. American Journal of Psychiatry. 2010;167:160-169.
43. Hughes C, Kumari V, Soni W, Das M, Binneman B, Drozd S, O'Neil S, Mathew V, Sharma T. Longitudinal study of symptoms and cognitive function in chronic schizophrenia. Schizophrenia research. 2003;59:137-146.
44. Bergh S, Hjorthoj C, Sorensen HJ, Fagerlund B, Austin S, Secher RG, Jepsen JR, Nordentoft M. Predictors and longitudinal course of cognitive functioning in schizophrenia spectrum disorders, 10years after baseline: The OPUS study. Schizophrenia research. 2016;175:57-63.
45. Ventura J, Hellemann GS, Thames AD, Koellner V, Nuechterlein KH. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. Schizophrenia research. 2009;113:189-199.
46. Hoff AL, Svetina C, Shields G, Stewart J, DeLisi LE. Ten year longitudinal study of neuropsychological functioning subsequent to a first episode of schizophrenia. Schizophrenia research. 2005;78:27-34.
47. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry. 1987;44:660-669.
48. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? British medical journal (Clinical research ed). 1987;295:681.
49. Kirkpatrick B, Messias E, Harvey PD, Fernandez-Egea E, Bowie CR. Is schizophrenia a syndrome of accelerated aging? Schizophrenia bulletin. 2008;34:1024-1032.
50. Koutsouleris N, Davatzikos C, Borgwardt S, Gaser C, Bottlender R, Frodl T, Falkai P, Riecher-Rössler A, Möller H-J, Reiser M. Accelerated brain aging in schizophrenia and beyond: a neuroanatomical marker of psychiatric disorders. Schizophrenia bulletin. 2013:sbt142.