**Cognitive Change in Schizophrenia and Other Psychoses in the Decade Following the First Episode**

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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

4

56  have examined the effect of medication on cognitive functioning, and yet recent findings suggest

57  that antipsychotic medications may contribute to the severity of cognitive decline (18).

58  In a previous report on this population-based, case-control study, we provided evidence for an IQ

59  deficit, as well as varying degrees of impairment across individual cognitive domains following the

60  first psychiatric diagnosis of schizophrenia (19). Study participants have since been followed-up and

61  underwent neuropsychological testing a second time. Using identical neuropsychological measures

62  at first assessment and follow-up, we were able to directly examine change in IQ and in individual

63  cognitive functions after the first episode. To provide an accurate estimate of cognitive change over

64  time, we compared patients to the healthy comparison subjects in the study followed during the

65  same period. We tested three hypotheses. First, we examined the "IQ decline" hypothesis to

66  establish whether schizophrenia patients exhibit a static IQ deficit or IQ decline. Second, we tested

67  the "generalized decline" hypothesis to determine whether decline occurs across multiple cognitive

68  domains, namely verbal knowledge, memory, language, processing speed, executive

69  function/working memory and visuospatial ability. Finally, we tested the "specificity" hypothesis to

70  establish whether any cognitive decline is specific to schizophrenia or common to other psychoses

71  by examining cognitive change in individuals with psychotic disorders other than schizophrenia.

72

73  **Methods**

74  *AESOP Study*

75  Data were derived from the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP)

76  study, a population-based, case-control study of first-episode psychosis. AESOP was approved by

77  local research ethics committees and each participant gave written informed consent after receiving

78  a complete description of the study. The study identified all first-episode psychosis cases (ICD-10:

79  F10–F29 and F30–F33) aged 16 to 65 years presenting to specialist mental health services in tightly

80  defined catchment areas of the United Kingdom (southeast London, Nottingham and Bristol)

81  between September 1997 and August 2000. All potential cases making contact with psychiatric

82  services (including adult community mental health teams, inpatient units, forensic services, learning

83  disability services, adolescent mental health services, and drug and alcohol units) for the first time

84  were screened. Exclusion criteria were previous contact with health services for psychosis, organic

85  causes of psychotic symptoms, transient psychotic symptoms as the result of acute intoxication (as

86  defined by ICD-10), and IQ<50. A random sample of control subjects with no past or present

87  psychotic disorder were recruited using a sampling method that matched cases and controls by area

88  of residence. Hereafter, data collected at this phase of the AESOP study is referred to as 'baseline'.

89  At baseline, detailed information was collected to enable patients to be traced, re-contacted and re-

90  interviewed approximately 10 years later ('follow-up'). At follow-up, patients currently in contact

91  with mental health services were invited to participate through their clinical teams. Letters of

92  invitation were sent to last known addresses of those not in contact with services. Non-responders

93  were sent a second letter two to three weeks later. If patients were thought to have moved, contact

94  was sought through their GP. Control subjects also provided contact details at baseline. Letters of

95  invitation were sent and were followed-up with phone calls if no reply had been received within 2

96  weeks. If no reply had been received after 4 weeks, or where telephone numbers could not be

97  obtained, in-person visits were made to the subject's address.  A detailed overview of the AESOP

98  study design and methods, as well as the follow-up has been published elsewhere (20, 21).

99  *Analytic Cohort*

100  Derivation of the sample included in the present analysis is illustrated in **Figure 1**. The analytic

101  cohort consisted of healthy comparison subjects and subjects who had a consensus ICD-10 diagnosis

102  at last follow-up of schizophrenia (F20), bipolar disorder or mania (F30.2, F31.2, F31.5), depressive

103  psychoses (F32.3, F33.3) or other psychotic disorders including persistent delusional disorders and

104  psychosis NOS (F22, F23, F28, F29). Both case and comparison subjects were required to be native

105  English speakers or to have migrated to the UK by age 11. The latter ensured that all participants had

106  a good command of English, even as a non-native language, by verifying that participants had

107  completed at least their secondary education in the UK. Thus, this minimized the effect of linguistic

108  or cultural biases on cognitive performance in a multiethnic sample.

109  **Figure 1.** Derivation of first-episode psychosis patients and healthy comparison subjects from
110  the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) Project Baseline
111  and 10-Year Follow Up.
112

113  *Neuropsychological assessment*

114  At baseline and follow-up, participants underwent cognitive testing with a neuropsychological

115  battery, which assessed general intellectual ability (IQ), as well as specific cognitive functions.

116  Administration and scoring followed standard procedures. Full-scale IQ was estimated using the

117  vocabulary, comprehension, digit symbol coding and block design subtests of the WAIS-R (22). Short

118     forms of the WAIS-R have been shown to produce accurate estimates of full-scale IQ (23, 24).

119     Specific functions were assessed using the following neuropsychological tests: *Memory* using the Rey

120     Auditory-Verbal-Learning Test (RAVLT) trials 1 to 7  (learning, immediate and delayed verbal recall)

121     (25), and the Visual Reproduction subtest of the Wechsler Memory Scale - Revised (WMS-R) (26);

122     *Verbal knowledge* using the Vocabulary and Comprehension subtests of the WAIS-R (22); *Processing*

123     *speed* using the WAIS-R digit symbol coding and the Trails-Making-Test Part A (27); *Executive*

124     *function/working memory* using Trails-Making-Test - Part B (27), and Letter-Number Span (28);

125     *Language* using Category (semantic) and Letter Fluency (categories: 'body parts'; 'fruits'; 'animals',

126     letters: F; A; S) (29), and *Visuospatial ability* using the WAIS-R Block Design subtest.

127     ***Diagnostic Assessment***

128     Clinical data were collected using the Schedules for Clinical Assessment in Neuropsychiatry

129     (SCAN)(30). The SCAN incorporates the Present State Examination, Version 10, to elicit symptom-

130     related data at time of presentation. Ratings on the SCAN are based on clinical interview, case note

131     review, and information from informants (e.g. health professionals, close relatives). Researchers

132     were trained on the SCAN with a World Health Organization-approved course and reliability was

133     established prior to commencement of the study using independent ratings of videotaped

134     interviews. Rater agreement was evaluated using Kappa statistics, which ranged from 1.0 for

135     psychosis as a category to between 0.6 and 0.8 for individual diagnoses. ICD-10 diagnoses were

136     determined using SCAN data through consensus meetings with one of the PIs and other team

137     members. Symptom severity was classified based on the SCAN Symptom Severity Rating Scale 2 as: 0

138     = Absent, 1 = Mild, 2 = Moderate and 3 = Severe (21).

139     ***Covariates and medication information***

140     Age was collected at baseline and follow-up. Sex, ethnicity, and level of education were collected at

141     baseline. Treatment history with typical and/or atypical antipsychotic medication was ascertained

142     for all patients from interview data and record review at follow-up.

143     ***Creating Norms for Neuropsychological Tests***

144     A regression-based approach was used to create normative standards for the neuropsychological

145     tests. Age at assessment, sex, ethnicity, and education were regressed on each of the

146     neuropsychological measures in the healthy comparison sample at baseline and follow-up. Next,

147     scores were adjusted on the basis of the regression results, and standard scores (i.e., z-scores) were

148 created. The same adjustment and standardization procedure were applied to the patient groups,

149 using the normative standards from the healthy comparison group.

150 *Statistical analysis*

151 Demographic and clinical characteristics of the baseline and follow-up cohorts were compared using

152 summary statistics. For descriptive purposes, we compared patients with schizophrenia or other

153 psychoses (including bipolar disorder, mania, depressive psychoses and other psychotic disorders) to

154 the comparison group on normative-adjusted IQ and specific neuropsychological tests at baseline

155 and follow-up using analysis of variance (ANOVA) models.

156 To examine the "IQ decline" "generalized decline" and "specificity" hypotheses, we compared the

157 schizophrenia and other psychoses groups to the comparison group on change in normative-

158 adjusted IQ and specific neuropsychological tests from baseline to follow-up. Change scores were

159 calculated by subtracting follow-up test scores from baseline test scores, so that positive scores

160 indicate cognitive amelioration and negative scores indicate cognitive decline. ANCOVA models with

161 planned orthogonal comparisons of each psychosis group to the comparison group, adjusting for

162 time from baseline assessment and baseline test score were used. Adjustment for baseline

163 performance is common in studies on cognitive change (31, 32). For the "IQ decline" hypothesis, the

164 significance level was set at $p$=0.05 (two-sided). For the "generalized decline" hypothesis, the

165 significance level was set at a Bonferroni-corrected level of 0.0038 (0.05/13). All analyses were

166 conducted using IBM SPSS Statistics version 24.

167

168 **Results**

169 Demographic characteristics of the baseline cohort and the cohort assessed at follow-up are

170 presented in **Table 1**. Follow-up neuropsychological assessments were completed on 106 patients

171 (63 males), and 103 comparison subjects (40 males). Average follow-up duration was 109.3 months

172 (SD=29.5) for patients and 102.9 (SD=34.1) for comparisons. Overall, the patients and comparisons

173 assessed at follow-up were similar to the respective patients and comparisons assessed at baseline

174 in terms of demographic variables, suggesting that the cohort at follow-up was representative of the

175 original cohort.

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

177 As we have previously shown in the AESOP study cohort (19), patients with schizophrenia and

8

178 patients with other psychoses showed deficits in IQ and individual neuropsychological tests at

179 baseline. **Figure 2** illustrates that that schizophrenia patients exhibited widespread, persistent,

180 cognitive impairment, performing significantly worse than comparison subjects at both baseline and

181 follow-up on 11 out of the 14 measures. Patients with other psychoses also showed widespread

182 impairments, but these were generally of smaller magnitude than schizophrenia patients (**Figure 2**).

183 (**sTable2** presents the non-adjusted performance in IQ and specific neuropsychological tests at

184 baseline and follow-up)

185 **Figure 2.** Neuropsychological Performance Among Patients with Schizophrenia and Other
186 Psychoses at Baseline and Follow-Up[a].
187

188 [a] - Effect sizes (expressed in standardized [z] scores) and 95% Confidence Intervals (95%CI) of
189 difference from comparison subjects at baseline and follow up. Comparison subjects set to zero
190 (dotted line). Effect sizes are adjusted for age, sex, ethnicity, and level of education. 95% CI that
191 do not include zero indicate statistical significance level p<0.05. Trailmaking A=Trail Making
192 Test, Part A; Trailmaking B=Trail Making Test, Part B.
193

194 ***Cognitive change in schizophrenia and other psychoses***

195 Next, we compared cognitive change over time in each of the psychoses groups (schizophrenia and

196 other psychoses) to cognitive change in controls to test the "IQ decline", "generalized decline" and

197 "specificity" hypotheses. **Figure 3** presents effect sizes of the difference in the within group change

198 from baseline to follow-up in IQ and individual neuropsychological tests between the psychoses

199 groups and controls. Effect sizes of 0.20, 0.50, and 0.80 reflect small, medium, and large effects,

200 respectively (33).

201 ***IQ decline hypothesis***: IQ decline in the schizophrenia group was significantly larger than in controls,

202 who showed no evidence of IQ decline. The IQ decline in the schizophrenia group compared to

203 controls was of small magnitude (ES=-0.28, 95% Confidence Intervals: -0.47 to -0.09, p=0.003), but

204 was not attenuated when adjusting for education, ethnicity, sex, age-at-baseline assessment, or

205 duration of follow-up, suggesting that IQ decline could not be attributed to these variables.

206 ***Generalized decline hypothesis***: Compared to controls, the schizophrenia group showed a larger

207 cognitive decline across tests in the memory and verbal knowledge domains (**Figure 3**). In the

208 memory domain, the schizophrenia group declines on verbal learning (p=0.001), immediate recall

209 (p<0.00006), and delayed recall (p<0.00001) reached the Bonferroni-corrected level of significance.

210 In the verbal knowledge domain, decline on vocabulary (p=0.003) reached the Bonferroni-corrected

211 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

245 with mild or moderate symptoms across multiple tests in the memory domain (Figure 4). However,

246 there was no association between change in symptom severity and change in cognitive functioning

247 (sTable 2 and sFigure 1), and no evidence for a dose-response relationship across levels of severity

248 (Figure 4). In the other psychoses group there was no evidence for an association between symptom

249 severity, or change in symptom severity, and change in cognitive functioning (Figure 4, sFigure1).

250 **Figure 4.** Change in Neuropsychological Performance Among Patients With Schizophrenia and

251 Other Psychoses in Relation to Symptom Severity at Baseline[a]

252 [a] - Presented are effect sizes and 95% Confidence Intervals of difference in change from baseline
253 to follow up between the diagnostic group and comparison group as a function of symptom
254 severity at baseline. 95% Confidence Intervals that do not include zero indicate statistical
255 significance level $p<0.05$. Effect sizes are adjusted for age, sex, ethnicity, level of education, time
256 from baseline assessment and baseline test score. Trailmaking A=Trail Making Test, Part A;
257 Trailmaking B=Trail Making Test, Part B.
258

259 *Sensitivity analyses*

260 We also examined the potential impact of attrition by applying linear mixed models which permit

261 varying numbers of measurements per person and time point, while adjusting for within-individual

262 (i.e. between measures) variation. Similar results were obtained in models that included only cases

263 and controls with data from both assessment time points, and in models that also included cases

264 and controls with data from a single assessment, indicating results were not biased by attrition.

265 As a further comparison, we examined IQ change in controls with lower IQ (IQ<90 at baseline, equal

266 to 1SD below the control group mean, N=17, 16.5% of sample). These individuals are of interest

267 because, like schizophrenia patients, they also exhibit lower IQ, and yet they did not develop

268 psychosis. In contrast to patients with schizophrenia, individuals with lower IQ did not show

269 evidence of IQ decline, neither in absolute terms nor relative to controls without a cognitive

270 impairment since mean IQ at baseline was 84.9, and at follow up was 89.8 (F=0.97, p=0.35).

271

272 **Discussion**

273 Using a population-based, case-control sample followed prospectively from the first psychotic

274 episode we provide evidence for cognitive decline after illness onset in patients with schizophrenia.

275 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

309    similar, yet quantitatively smaller than the schizophrenia group. Thus, our findings suggest that

310    cognitive decline is not specific to schizophrenia, but also evident in other psychoses. However,

311    large, widespread, cognitive decline may still be specific to schizophrenia, since the other psychoses

312    group showed a smaller and less generalized cognitive decline.  Interestingly, there was no evidence

313    of decline in a key comparison group, namely individuals with lower IQ who did not develop

314    psychosis. This group may in fact experience a different process of regression-to-the-mean.

315    The current findings should be viewed in the context of certain limitations. First, although we found

316    evidence for cognitive decline after illness onset, we could not fully map the course of deficits and

317    cognitive functions may vary in the timing of decline following the first episode. Second, group sizes

318    did not allow for an analysis of the heterogeneity of cognitive course and also limited our ability to

319    investigate more specific diagnostic sub-groups, such as bipolar/mania. Third, we ruled out two

320    explanations for the observed cognitive decline, namely, type or duration of antipsychotic

321    treatment. Unfortunately, we did not have information to examine other potential moderators of

322    cognitive decline, such as social isolation, smoking and illicit drug abuse, victimization, or physical

323    health problems such as obesity, diabetes and hypertensions. Moreover, despite the fact that we

324    adjusted for education in all our analyses, poor education in the schizophrenia group after the first

325    psychotic episode could still partly explain some of the group differences.

326    There is conflicting evidence regarding the relationship between change in symptoms and cognitive

327    functioning (43, 44). In our study, change in severity of psychosis was only minimally associated with

328    cognitive change. These results are consistent with cross-sectional findings of only a weak

329    association between positive symptoms and cognitive impairment (45). Longitudinal evidence also

330    suggests a minimal association between change in positive as well as negative symptoms, and

331    change in cognition (43, 44, 46). Interestingly, in our study, schizophrenia patients with severe

332    symptoms at baseline showed greater cognitive decline than patients with mild or moderate

333    symptoms. While this group was small (21% of overall group), the magnitude of decline in the

334    memory domain was large. Thus, this finding points to a potential subgroup of schizophrenia

335    patients that may greatly benefit from being specifically targeted for cognitive remediation.

336    Our findings have important implications for understanding the nature and course of cognitive

337    impairment in schizophrenia, as well as other psychoses. Integrating the current findings with those

338    of previous studies (16) suggests that cognitive dysfunction in schizophrenia may result from a

339    complex interplay between an early, static neuropathology (47, 48) and dynamic age-related

340    processes (49, 50). As such, cognitive functions that develop and peak relatively early in life, such as

341    processing speed and visuospatial abilities (39) may show aberrant development, resulting in slowed

342    growth prior to the onset of schizophrenia (16), but relative stabilization throughout the illness

343    course. On the other hand, cognitive functions that continue to evolve through adult life, such as

344    language (39), may show further deterioration throughout the course of schizophrenia. Finally,

345    functions sensitive to age-related cognitive decline, such as memory, may begin to decline in middle

346    adulthood before normative aging becomes apparent (40).

347    In conclusion, the present study demonstrates that while a substantial proportion of the cognitive

348    impairment seen in adult patients with schizophrenia, as well as other psychoses, is present already

349    at the first episode, these patients continue to experience cognitive decline after illness onset.

350    However, the nature of this decline varies across neuropsychological functions. While large deficits

351    in processing speed are already apparent at the first episode, deficits in verbal knowledge and

352    memory continue to increase. These findings suggest that different pathophysiological mechanisms

353    may underlie individual neuropsychological deficits seen in adult psychosis patients. Future research

354    should determine which of these are consequent upon the illness itself, and which on the

355    psychosocial factors patients experience. Finally, these findings highlight the importance of targeting

356    early developmental stages in future studies of the causes of cognitive deficits associated with

357    psychosis, as well as in cognitive remediation efforts.

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361 **REFERENCES**

362 1. Reichenberg A, Harvey PD. Neuropsychological impairments in schizophrenia: Integration of
363 performance-based and brain imaging findings. Psychological bulletin. 2007;133:833-858.
364 2. Kahn RS, Keefe RS. Schizophrenia is a cognitive illness: time for a change in focus. JAMA
365 psychiatry. 2013;70:1107-1112.
366 3. Woodberry KA, Seidman LJ, Giuliano AJ, Verdi MB, Cook WL, McFarlane WR. Neuropsychological
367 profiles in individuals at clinical high risk for psychosis: relationship to psychosis and intelligence.
368 Schizophrenia research. 2010;123:188-198.
369 4. Khandaker GM, Barnett JH, White IR, Jones PB. A quantitative meta-analysis of population-based
370 studies of premorbid intelligence and schizophrenia. Schizophrenia research. 2011;132:220-227.
371 5. Mesholam-Gately RI, Giuliano AJ, Goff KP, Faraone SV, Seidman LJ. Neurocognition in first-
372 episode schizophrenia: a meta-analytic review. Neuropsychology. 2009;23:315.
373 6. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the
374 evidence. Neuropsychology. 1998;12:426.
375 7. Fioravanti M, Carlone O, Vitale B, Cinti ME, Clare L. A meta-analysis of cognitive deficits in adults
376 with a diagnosis of schizophrenia. Neuropsychology review. 2005;15:73-95.
377 8. Meier MH, Caspi A, Reichenberg A, Keefe RS, Fisher HL, Harrington H, Houts R, Poulton R, Moffitt
378 TE. Neuropsychological decline in schizophrenia from the premorbid to the postonset period:
379 evidence from a population-representative longitudinal study. American Journal of Psychiatry.
380 2013;171:91-101.
381 9. Seidman LJ, Buka SL, Goldstein JM, Tsuang MT. Intellectual decline in schizophrenia: evidence
382 from a prospective birth cohort 28 year follow-up study. Journal of clinical and experimental
383 neuropsychology. 2006;28:225-242.
384 10. Kremen WS, Vinogradov S, Poole JH, Schaefer CA, Deicken RF, Factor-Litvak P, Brown AS.
385 Cognitive decline in schizophrenia from childhood to midlife: a 33-year longitudinal birth cohort
386 study. Schizophrenia research. 2010;118:1-5.
387 11. Heaton RK, Gladsjo JA, Palmer BW, Kuck J, Marcotte TD, Jeste DV. Stability and course of
388 neuropsychological deficits in schizophrenia. Archives of general psychiatry. 2001;58:24-32.
389 12. Kurtz MM. Neurocognitive impairment across the lifespan in schizophrenia: an update.
390 Schizophrenia research. 2005;74:15-26.
391 13. Lewandowski KE, Cohen BM, Ongur D. Evolution of neuropsychological dysfunction during the
392 course of schizophrenia and bipolar disorder. Psychological medicine. 2011;41:225-241.
393 14. Friedman JI, Harvey PD, Coleman T, Moriarty PJ, Bowie C, Parrella M, White L, Adler D, Davis KL.
394 Six-year follow-up study of cognitive and functional status across the lifespan in schizophrenia: a
395 comparison with Alzheimer's disease and normal aging. American Journal of Psychiatry.
396 2001;158:1441-1448.
397 15. Bozikas VP, Andreou C. Longitudinal studies of cognition in first episode psychosis: a systematic
398 review of the literature. Aust N Z J Psychiatry. 2011;45:93-108.
399 16. Reichenberg A, Caspi A, Harrington H, Houts R, Keefe RS, Murray RM, Poulton R, Moffitt TE.
400 Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study.
401 American Journal of Psychiatry. 2010;167:160-169.
402 17. Casey B, Tottenham N, Liston C, Durston S. Imaging the developing brain: what have we learned
403 about cognitive development? Trends in cognitive sciences. 2005;9:104-110.
404 18. Seidman LJ, Shapiro DI, Stone WS, Woodberry KA, Ronzio A, Cornblatt BA, Addington J, Bearden
405 CE, Cadenhead KS, Cannon TD. Association of neurocognition with transition to psychosis: baseline
406 functioning in the second phase of the North American Prodrome Longitudinal Study. Jama
407 psychiatry. 2016;73:1239-1248.
408 19. Zanelli J, Reichenberg A, Morgan K, Fearon P, Kravariti E, Dazzan P, Morgan C, Zanelli C, Demjaha
409 A, Jones PB. Specific and generalized neuropsychological deficits: a comparison of patients with
410 various first-episode psychosis presentations. American Journal of Psychiatry. 2010;167:78-85.

411    20.  Kirkbride JB, Fearon P, Morgan C, Dazzan P, Morgan K, Tarrant J, Lloyd T, Holloway J, Hutchinson
412    G, Leff JP. Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings
413    from the 3-center AeSOP study. Archives of general psychiatry. 2006;63:250-258.
414    21.  Morgan C, Lappin J, Heslin M, Donoghue K, Lomas B, Reininghaus U, Onyejiaka A, Croudace T,
415    Jones PB, Murray RM. Reappraising the long-term course and outcome of psychotic disorders: the
416    AESOP-10 study. Psychological medicine. 2014;44:2713-2726.
417    22.  Wechsler D: WAIS-R manual: Wechsler adult intelligence scale-revised, Psychological
418    Corporation; 1981.
419    23.  Silverstein A. Two-and four-subtest short forms of the Wechsler Adult Intelligence Scale-Revised.
420    Journal of Consulting and Clinical Psychology. 1982;50:415.
421    24.  Roth DL, Hughes CW, Monkowski PG, Crosson B. Investigation of validity of WAIS-R short forms
422    for patients suspected to have brain impairment. J Consult Clin Psychol. 1984;52:722-723.
423    25.  Schmidt M: Rey auditory verbal learning test: a handbook, Western Psychological Services Los
424    Angeles; 1996.
425    26.  Wechsler D. Instruction Manual for the Wechsler Memory Scale Revised. New York,
426    Psychological Corp. 1987.
427    27.  Reitan RM: Trail Making Test: Manual for administration and scoring, Reitan Neuropsychology
428    Laboratory; 1992.
429    28.  Gold JM, Carpenter C, Randolph C, Goldberg TE, Weinberger DR. Auditory working memory and
430    Wisconsin Card Sorting Test performance in schizophrenia. Arch Gen Psychiatry. 1997;54:159-165.
431    29.  Spreen O, Strauss E: A compendium of neuropsychological tests : administration, norms, and
432    commentary. New York, Oxford University Press; 1991.
433    30.  Wing JK, Babor T, Brugha T, Burke J, Cooper J, Giel R, Jablenski A, Regier D, Sartorius N. SCAN:
434    Schedules fonr Clinical Assessment in Neuropsychiatry. Archives of general psychiatry. 1990;47:589-
435    593.
436    31.  MM. G, J. W, LF. B, I. K, JM. R. When is baseline adjustment useful in analyses of change? An
437    example with education and cognitive change. American Journal of Epidemiology. 2005;162:267-
438    278.
439    32.  Overall J, Woodward J. Unreliability of difference scores: A paradox in the measurement of
440    change. Psychological bulletin. 1975;82:185-186.
441    33.  Cohen J. A power primer. Psychological bulletin. 1992;112:155.
442    34.  Kahn RS, Sommer IE, Murray RM, Meyer-Lindenberg A, Weinberger DR, Cannon TD, O'Donovan
443    M, Correll CU, Kane JM, van Os J, Insel TR. Schizophrenia. Nat Rev Dis Primers. 2015;1:15067.
444    35.  Cao B, Mwangi B, Passos IC, Wu MJ, Keser Z, Zunta-Soares GB, Xu D, Hasan KM, Soares JC.
445    Lifespan Gyrification Trajectories of Human Brain in Healthy Individuals and Patients with Major
446    Psychiatric Disorders. Sci Rep. 2017;7:511.
447    36.  Kubota M, van Haren NE, Haijma SV, Schnack HG, Cahn W, Hulshoff Pol HE, Kahn RS. Association
448    of IQ Changes and Progressive Brain Changes in Patients With Schizophrenia. JAMA Psychiatry.
449    2015;72:803-812.
450    37.  MacCabe JH, Wicks S, Lofving S, David AS, Berndtsson A, Gustafsson JE, Allebeck P, Dalman C.
451    Decline in cognitive performance between ages 13 and 18 years and the risk for psychosis in
452    adulthood: a Swedish longitudinal cohort study in males. JAMA Psychiatry. 2013;70:261-270.
453    38.  Czaja SJ, Charness N, Fisk AD, Hertzog C, Nair SN, Rogers WA, Sharit JJP, aging. Factors predicting
454    the use of technology: findings from the Center for Research and Education on Aging and
455    Technology Enhancement (CREATE). 2006;21:333.
456    39.  Hartshorne JK, Germine LT. When does cognitive functioning peak? The asynchronous rise and
457    fall of different cognitive abilities across the life span. Psychological science.
458    2015:0956797614567339.
459    40.  Salthouse TA. When does age-related cognitive decline begin? Neurobiology of aging.
460    2009;30:507-514.

461    41.  Koenen KC, Moffitt TE, Roberts AL, Martin LT, Kubzansky L, Harrington L, Poulton R, Caspi A.
462    Childhood IQ and Adult Mental Disorders: A Test of the Cognitive Reserve Hypothesis American
463    Journal of Psychiatry. 2009;166:50-57.
464    42.  Reichenberg A, Caspi A, Harrington H, Houts R, Keefe R, Murray RM, al. e. Static and Dynamic
465    Cognitive Deficits in Childhood Preceding Adult Schizophrenia: A 30-Year Study. American Journal of
466    Psychiatry. 2010;167:160-169.
467    43.  Hughes C, Kumari V, Soni W, Das M, Binneman B, Drozd S, O'Neil S, Mathew V, Sharma T.
468    Longitudinal study of symptoms and cognitive function in chronic schizophrenia. Schizophrenia
469    research. 2003;59:137-146.
470    44.  Bergh S, Hjorthoj C, Sorensen HJ, Fagerlund B, Austin S, Secher RG, Jepsen JR, Nordentoft M.
471    Predictors and longitudinal course of cognitive functioning in schizophrenia spectrum disorders,
472    10years after baseline: The OPUS study. Schizophrenia research. 2016;175:57-63.
473    45.  Ventura J, Hellemann GS, Thames AD, Koellner V, Nuechterlein KH. Symptoms as mediators of
474    the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis.
475    Schizophrenia research. 2009;113:189-199.
476    46.  Hoff AL, Svetina C, Shields G, Stewart J, DeLisi LE. Ten year longitudinal study of
477    neuropsychological functioning subsequent to a first episode of schizophrenia. Schizophrenia
478    research. 2005;78:27-34.
479    47.  Weinberger DR. Implications of normal brain development for the pathogenesis of
480    schizophrenia. Arch Gen Psychiatry. 1987;44:660-669.
481    48.  Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? British medical journal
482    (Clinical research ed). 1987;295:681.
483    49.  Kirkpatrick B, Messias E, Harvey PD, Fernandez-Egea E, Bowie CR. Is schizophrenia a syndrome of
484    accelerated aging? Schizophrenia bulletin. 2008;34:1024-1032.
485    50.  Koutsouleris N, Davatzikos C, Borgwardt S, Gaser C, Bottlender R, Frodl T, Falkai P, Riecher-
486    Rössler A, Möller H-J, Reiser M. Accelerated brain aging in schizophrenia and beyond: a
487    neuroanatomical marker of psychiatric disorders. Schizophrenia bulletin. 2013:sbt142.

488