Dynamic and Static Cognitive Deficits in Schizophrenia and Bipolar Disorder After the First Episode

Jolanta Zanelli*,1,2, Abraham Reichenberg1,3,4, Sven Sandin3,6, Craig Morgan7, Paola Dazzan1,8, Izabela Pilecka1, Tiago Reis Marques1, Kevin Morgan9, Allan H. Young7, and Josephine Mollon2,

1Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK; 2Department of Psychiatry, Boston Children’s Hospital, Harvard Medical School, Boston, MA, USA; 3Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA; 4Department of Preventive Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA; 5Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; 6Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden; 7Centre for Public Mental Health, Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK; 8Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK; 9Department of Psychology, University of Westminster, London, UK

*To whom correspondence should be addressed; Department of Psychiatry, Boston Children’s Hospital, Harvard Medical School, 1 Autumn Street, Boston, MA 02115, USA; tel: +19173864864, e-mail: jolanta.w.zanelli@kcl.ac.uk

Few studies have comprehensively examined the profile of cognitive functioning in first episode psychosis patients throughout the lifespan, and from first episode to chronic stage. We assessed functioning in general and specific cognitive functions, comparing both schizophrenia (N = 64) and bipolar I (N = 19) patients to controls (N = 103). Participants were from a population-based, case-control study of first episode psychosis patients, who were followed prospectively up to 10 years post first admission. A cognitive battery was administered at baseline and follow-up. By combining longitudinal and cross-sectional data, we were able to examine the cognitive profile of patients and controls throughout the entire age range of our sample (16–65). Schizophrenia patients exhibited widespread declines in IQ, executive function, visual memory, language ability, and verbal knowledge. However, the ages at which these declines occurred differed between functions. Deficits in verbal memory, working memory, processing speed, and visuospatial ability, on the other hand, were present at the first episode, and remained relatively static thereafter. Bipolar I patients also showed declines in IQ, verbal knowledge, and language ability, albeit at different ages to schizophrenia patients and only in verbal functions. Deficits on measures of verbal memory, processing speed, and executive function remained relatively static. Thus, both schizophrenia and bipolar I patients experienced cognitive decline in general and specific functions after the first episode, but the age at which these declines occurred differed between disorder and function. Cognitive remediation efforts may be most fruitful when targeting individual functions during specific time periods throughout adulthood.

Key words: cognition/lifespan/longitudinal/psychotic disorders/schizophrenia/bipolar disorder

Introduction

Individuals with schizophrenia experience cognitive decline before illness onset.1 Cross-sectional data suggest moderate deficits in children who later develop schizophrenia (equal to 8 IQ points below controls2,3), and large deficits in both first episode (14 IQ points4) and chronic schizophrenia patients (15–21 IQ points5–7). Longitudinal studies of cognitive change from before to after illness onset have also shown evidence for cognitive decline (ranging from 6 to 12 IQ points8–10) between childhood and adulthood.

Whether schizophrenia patients also experience cognitive decline after the first episode is less clear. Findings across studies and cognitive domains are mixed, with evidence for decline, as well as amelioration.11 In a previous report on a population-based, case-control study of first episode psychosis patients followed up to 10 years after first admission, we provided evidence for cognitive decline.12 Specifically, schizophrenia patients showed declines on IQ, verbal knowledge, and memory. Patients with other psychoses also showed declines on measures of memory, suggesting that cognitive decline is not...
specific to schizophrenia, but occurs across the psychosis spectrum.

Nevertheless, important questions remain regarding the course of cognitive impairment in psychosis patients, particularly after the first episode and throughout the period between adolescence and late adulthood. First, the timing of cognitive decline remains unclear. In a previous study using cross-sectional data from a case-control study of adults with psychotic disorders, we found evidence for cognitive decline between early and middle adulthood, but not between middle and late adulthood.13 Second is the question of whether cognitive decline is specific to psychotic disorders. For example, bipolar I disorder has generally been associated with milder deficits than schizophrenia14 and even with above-average school performance.15 We previously reported age-associated differences between affective and nonaffective psychotic disorders,13 as well as between schizophrenia and other psychotic disorders.12 However, the cognitive course of patients with psychotic bipolar I disorder remains unexamined.

Using data from a population-based, case-control study of first episode psychosis patients aged between 16 and 65 and followed prospectively up to 10 years after first admission, we examined the cognitive profile of patients with schizophrenia and bipolar I disorder throughout the adult lifespan. By combining longitudinal and cross-sectional data from all available subjects, we were able to model the cognitive course of patients and controls throughout the whole age range of our sample (16–65 years) ie, throughout the 5 decades between adolescence and late adulthood. We examined the cognitive course of general cognitive ability (IQ), as well as specific measures of verbal knowledge, memory, language, processing speed, executive function/working memory, and visuospatial ability. To provide an accurate estimate of the profile of cognitive deficits across adulthood and after the first episode, we compared individuals with schizophrenia and bipolar I disorder to controls. Controls were also aged between 16 and 65 and followed prospectively up to 10 years after baseline assessment.

Methods

Sample

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.16 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 16–65 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. Inclusion criteria were: (a) age between 16 and 65 years old; (b) resident within tightly defined catchment areas in Nottingham, Bristol, or southeast London; (c) presence of a first episode of psychosis (F10–F29 and F30–F33 in ICD-10) within the time frame of the study; and (d) no previous contact with health services for psychosis. Exclusion criteria were: (a) evidence of psychotic symptoms precipitated by an organic cause; (b) transient psychotic symptoms resulting from acute intoxication as defined by ICD-10; and (c) IQ less than 50.16 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, this phase of the AESOP study is referred to as “baseline.”

At baseline, detailed information was collected so that patients could be recontacted 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. Nonresponders were sent a second letter 2–3 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.

The analytic cohort consisted of patients with a consensus ICD-10 diagnosis of schizophrenia (F20) or bipolar I disorder (F30.2, F31.2, or F31.5), and controls, all of whom had at least 1 cognitive assessment. Groups of subjects with other depressive psychoses (F32.3 or F33.3) or other psychotic disorders (F22, F23, F28, and F29) were too small for a reliable statistical analysis and were therefore excluded. Both case and comparison subjects were required to be native English speakers or to have migrated to the United Kingdom by age 11. The latter ensured that all participants had a good command of English, even as a nonnative language, by verifying that participants had completed at least their secondary education in the United Kingdom. Thus, also minimizing the effect of linguistic or cultural biases on performance in a multiethnic sample. A detailed overview of the AESOP study design and methods, as well as follow-up have been published elsewhere.12,17,18

Diagnostic Assessment

Clinical data were collected using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN).19 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 (eg, 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.

Cognitive Assessment
At baseline and follow-up, participants underwent assessment with a cognitive battery, to estimate general intellectual ability (IQ), as well as performance on specific cognitive functions. IQ was estimated using the vocabulary, comprehension, digit symbol coding and block design subtests of the WAIS-R. Short forms of the WAIS-R have been shown to produce accurate estimates of IQ. Specific functions were assessed using the following tests: Memory using the Rey Auditory Verbal Learning Test (RAVLT) trials 1–7 (learning, immediate and delayed verbal recall), and the Visual Reproduction subtest of the Wechsler Memory Scale—Revised (WMS-R); Verbal knowledge using the Vocabulary and Comprehension subtests of the WAIS-R; Processing speed using the WAIS-R Digit Symbol Coding test and the Trail Making Test, Part A; Executive functioning/working memory using the Trail Making Test, Part B; and Letter-Number Span; Language using Category (semantic) and Letter Fluency (categories: “body parts”; “fruits”; “animals”, letters: F; A; S); and Visuospatial ability using the WAIS-R Block Design test. Administration and scoring followed standard procedures.

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

Statistical Analysis
All analyses were conducted using SAS version 9.3. To examine the age-associated profile of cognitive functioning from adolescence to late adulthood we used Generalized Linear Mixed-Model (GLMM) regression:

\[ Y = u + G(i) + T(j) + G \ast \text{spline}(\text{age})(i \cdot j) + \varepsilon_{ijk} \]

where \( i = 1, 2, 3 \) for schizophrenia, bipolar disorder, control, \( j = 1, 2 \) for visit 1 (baseline) and 2 (follow-up), \( k, \text{ and } \varepsilon \) is the residual term assuming residuals following an approximate normal distribution.

GLMM models longitudinal data by permitting multiple measurements per person, as well as irregular intervals between measurements, thereby increasing statistical power while controlling for within-individual variation. GLMM also allows combination of longitudinal and cross-sectional data, thereby enabling inclusion of all available subjects ie, individuals with data from multiple time points, but also a single time point. Thus, there is no lower or upper limit in terms of the number of time points that can be modeled in GLMM, but the combination of both multiple and single time points, as in our study, enables a detailed examination of cognitive profiles throughout a wide age span. Specifically, in this sample, we were able to combine longitudinal data from 2 time points: baseline (ie, at first episode) and follow-up (up to 10 years after first episode), as well as cross-sectional data (from age 16 to 65) to examine the course of cognitive functioning from adolescence through to late adulthood. GLMM was used to model group (schizophrenia and bipolar I vs controls) main effects and group-by-age interactions. A statistically significant group main effect indicates a difference in cognitive performance between schizophrenia or bipolar I patients, and controls. Since we have already reported statistically significant cognitive deficits in both schizophrenia and bipolar I patients in this sample, the focus herein was on group-by-age interactions. A statistically significant group-by-age interaction would indicate a difference in cognitive course between the schizophrenia or bipolar I groups, and controls. Natural cubic splines were used to model age effects on cognition. Splines estimate the response relation without assuming that the data follow a particular form, such as linear or cubic, thus permitting evaluation of the functional form of associations and characterization of age-associated patterns, including points of nonlinearity. Age, sex, ethnicity, and years of education at baseline were included as covariates in all models. Importantly, interval between baseline and follow-up was accounted for in all models through the specification of spatial covariance structures, with distance as continuous time between baseline and follow-up ie, follow-up duration. We examined goodness-of-fit of the GLMM using plots of residuals. All statistical tests were conducted using 2-sided 5% level of significance.

Results
Baseline cognitive assessments were available for 137 patients (98 schizophrenia patients, 39 bipolar I patients), and 230 controls. Follow-up cognitive assessments were available for 83 patients (64 schizophrenia patients, 19 bipolar I patients), and 103 controls. Mean follow-up duration was 102.9 months (SD = 34.1) for controls, 110.4 months (SD = 26.5) for schizophrenia patients, and
118.7 months (SD = 28.2) for bipolar I patients. No statistically significant group differences in follow-up duration were found ($F = 2.41$, $P > .05$). Demographic characteristics of the baseline and follow-up cohorts are presented in table 1. Overall, controls and patients assessed at follow-up were similar to controls and patients assessed at baseline on demographic variables and full-scale IQ, suggesting that the cohort at follow-up was representative of the original cohort (table 1).

We used GLMM regression to model cognitive data. Examination of model residuals showed that these data were normally distributed.

**Table 1.** Demographic Characteristics of Controls, Schizophrenia, and Bipolar I Patients at Baseline and Follow-up

|                   | Baseline          | Follow-up         |
|-------------------|-------------------|-------------------|
|                   | Controls ($N = 230$) | Schizophrenia ($N = 98$) | Bipolar I ($N = 39$) | Controls ($N = 103$) | Schizophrenia ($N = 64$) | Bipolar I ($N = 19$) |
| Age               | Mean | SD   | Mean | SD   | Mean | SD   | Mean | SD   | Mean | SD   | Mean | SD   |
|                   | 37.28 | 12.60 | 27.32 | 9.14 | 27.85 | 7.68 | 35.99 | 10.87 | 25.87 | 7.90 | 29.78 | 9.14 |
| Full-scale IQ     | 103.70 | 15.82 | 86.32 | 15.73 | 99.64 | 15.49 | 106.18 | 16.44 | 87.70 | 16.51 | 104.00 | 12.68 |
| Male              | N    | %    | N    | %    | N    | %    | N    | %    | N    | %    | N    | %    |
| White             | 131  | 61.8 | 48   | 51.1 | 24   | 61.5 | 41   | 39.8 | 33   | 51.6 | 12   | 66.7 |
| Years of education|       |       |       |       |       |       |       |       |       |       |       |       |
| 11 (compulsory)   | 94   | 43.5 | 67   | 72.0 | 14   | 35.9 | 38   | 36.9 | 45   | 72.6 | 4    | 21.1 |
| 12–13 (postcompulsory) | 53   | 24.5 | 18   | 19.4 | 12   | 30.8 | 21   | 20.4 | 11   | 17.7 | 4    | 21.1 |
| 14+ (college, graduate, postgraduate) | 69   | 31.9 | 8    | 8.6  | 13   | 33.3 | 44   | 42.7 | 6    | 9.7  | 11   | 57.8 |

Sex data were missing for 11 participants (10 controls, 1 schizophrenia patient). Ethnicity data were missing for 19 participants (14 controls, 5 schizophrenia patients). Education data were missing for 22 participants (18 controls, 4 schizophrenia patients). General Linear Mixed-Model (GLMM) regression with splines was run (a) using all possible combinations of covariates and (b) including only participants without any missing covariate data to ensure no bias had been introduced due to missing covariate data: results showed no bias and little effect of covariates.
both of these measures during late adolescence and early adulthood, with deficits only becoming evident after age 30. Like schizophrenia patients, bipolar I patients showed static deficits on verbal learning and delayed recall in the memory domain, Trail Making A in the processing speed domain, Trail Making B in the executive function domain, and category fluency in the language domain (Figure 2).

However, deficits in the bipolar I group were generally of smaller magnitude than in the schizophrenia group.

**Sensitivity Analyses**

Similar results were obtained when including only participants with data from both assessment time points
Discussed in the domains of memory and verbal knowledge,12 12,12 by showing in psychosis in several important ways.

The current results expand on our previous finding of IQ decline after the first psychotic episode,12 by showing that this decline is age associated, and occurs monotonically throughout adolescence to late adulthood. This is the first study, to the best of our knowledge, to have examined the course of cognitive impairment in both schizophrenia and bipolar I first episode psychosis patients throughout the 5 decades encompassing adolescence to late adulthood. Compared to healthy controls, both the schizophrenia and bipolar I groups showed a steady decline in IQ between adolescence and mid adulthood, followed by stabilization through to late adulthood. However, while the timing of this decline was similar across both patient groups, the magnitude differed, with the bipolar I group showing a greater IQ decline than the schizophrenia group. This finding appears contrary to evidence that schizophrenia patients show greater cognitive impairment than bipolar I patients. However, the bipolar I group outperformed both controls and schizophrenia patients throughout early adulthood and continued to outperform the schizophrenia group throughout the lifespan. This finding supports the notion that while the antecedents and early developmental trajectories of schizophrenia and bipolar I disorder may differ, common factors influence the cognitive deterioration that occurs after illness onset.29

The current results also build on our previous finding of cognitive decline in specific cognitive functions, specifically in the domains of memory and verbal knowledge,12 by showing that the age at which these declines occur differs between functions. In the schizophrenia group, deficits on measures of verbal knowledge and executive function increased continuously throughout adult life, while deficits on measures of memory and language only began deteriorating around the age of 40. In the bipolar I group, most of the decline in measures of verbal knowledge and language occurred prior to age 40, with deficits showing relative stabilization thereafter. These findings are in line with previous evidence for cognitive declines in verbal and executive functions after the first episode in schizophrenia patients,30,31 as well as previous evidence for progressive brain abnormalities.12–34 Progression of brain abnormalities has also been reported in bipolar I disorder,35,36 but this finding is less consistent than in schizophrenia.37

Our novel findings suggest, on the other hand, that patients with psychotic bipolar I disorder experience decline after illness onset across both general and specific cognitive functions. Interestingly, our findings also suggest both similarities and differences in the specificity, timing and magnitude of cognitive decline experienced by individuals with schizophrenia and those with bipolar I. This is in line with evidence for genetic overlap between the 2 disorders,38,39 and the notion of unique as well as common genetic and environmental factors interacting across the lifespan. Our finding of a large, static Digit Symbol Coding deficit in schizophrenia, but not bipolar I, provides evidence for the neurodevelopmental model of schizophrenia, whereby early pathologic processes interact with normal development, leading to progressive cognitive dysfunction in early life.40,41 On the other hand, our findings suggest normal and even superior cognitive functioning in bipolar I during late adolescence, at odds with a neurodevelopmental model. Moreover, cognitive decline in bipolar I patients was limited to verbal functions, while schizophrenia patients showed more widespread decline, including verbal functions, but also memory and executive function. Alternatively, our findings are also in line with evidence for elevated dementia risk in individuals with schizophrenia42,43 and bipolar disorder,44 as well as the theory of accelerated aging.45,46 However, evidence for accelerated aging remains mixed47,48 and future studies that extend beyond late adulthood are needed to fully examine possible neurodegenerative processes in psychotic disorders.

This study has certain limitations. First, the bipolar I group was small and did not allow analysis of heterogeneity of cognitive course. Moreover, since bipolar I patients in this sample exhibited psychotic symptoms, these findings may not generalize to all bipolar I patients. Nevertheless, this is the first study, to the best of our knowledge, to have examined the course of cognitive impairment in both schizophrenia and bipolar I patients throughout the adult lifespan. Second, while the integration of cross sectional and longitudinal data allowed us to examine the cognitive course across 5 decades between adolescence and late adulthood, there are pitfalls to cross sectional data. However, our findings are generally in line with previous meta analytic and longitudinal studies. Specifically, the schizophrenia group showed an IQ deficit of 6 IQ points (equal to 0.5 SD below controls) in late adolescence, in line with meta analytic findings of a moderate premorbid deficit in children and adolescents who later develop schizophrenia.19–21 Moreover, by mid adulthood, the schizophrenia group showed an impairment of 16 IQ points, more than 1 standard deviation below controls, in line with previous accounts.5,6 Finally, the 10 IQ point decline reported herein is consistent
with previous population-based longitudinal studies comparing childhood and adult IQ in schizophrenia patients.8–10 Nevertheless, future studies that prospectively follow schizophrenia and bipolar I patients more than 1 decade post first episode are needed to replicate our findings. Moreover, future longitudinal studies with 3 or more time points are needed to reliably replicate our finding of nonlinear cognitive profiles since these nonlinear profiles were estimated using 2 longitudinal time points, as well as by leveraging all available cross-sectional data. Third, while our sensitivity analyses showed that similar results were obtained when including only participants with data from both assessment time points (ie, longitudinal data only) compared to when including all participants (ie, combination of longitudinal and cross-sectional data), we cannot rule out residual confounding due to attrition. Similarly, future studies that examine the potentially confounding effects of follow-up duration are also needed. While we did not find significant group differences in follow-up duration, we cannot rule out residual confounding. Finally, while we were able to model cognitive profiles throughout the extensive period between adolescence and late adulthood, the majority of schizophrenia (84%) and bipolar I (81%) patients in our sample were below the age of 40. This decline in incidence with age is in line with the literature,50,51 and our results highlight the fact that the incidence of psychosis in later life, while attenuated, remains substantial. Future studies that are able to include more patients in late adulthood are needed to thoroughly examine late life cognitive profiles in psychosis, especially since these individuals are likely particular vulnerable to cognitive dysfunction.

In conclusion, the present findings demonstrate that both schizophrenia and bipolar I patients continued to experience cognitive decline throughout adulthood and after illness onset. However, the nature of this decline varied across disorders and cognitive functions. In schizophrenia patients, large deficits in processing speed and verbal memory were already apparent in early adulthood, whereas deficits in executive functions, verbal knowledge, language, and visual memory increased gradually through adulthood. In bipolar I patients, on the other hand, cognitive decline was limited to verbal functions and to the first half of adulthood. Thus, both common and unique pathophysiological mechanisms may underlie cognitive deficits in schizophrenia and bipolar I across the adult lifespan. Pharmacological and psychological remediation efforts that target individual cognitive functions during specific periods may therefore be most effective. This study provides an important first step in mapping out these potential functions and periods of intervention.

Supplementary Material
Supplementary material is available at Schizophrenia Bulletin.

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