A longitudinal study on the relationship between duration of untreated psychosis and executive function in early-onset first-episode psychosis

David Fraguas a,⁎, Jessica Merchán-Naranjo a, Ángel del Rey-Mejías a, Josefina Castro-Fornieles b, Ana González-Pinto c, Marta Rapado-Castro a,d,e, Laura Pina-Camacho b,f, Covadonga M. Díaz-Caneja a, Montserrat Graell g, Soraya Otero h, Inmaculada Baeza b, Carmen Moreno a, Mónica Martínez-Cengotitabengoa c,j, Elisa Rodríguez-Toscanoa, Celso Arango a, Mara Parellada a

⁎ Corresponding author at: Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón, CIBERSAM, ISGIM, School of Medicine, Universidad Complutense, Madrid, Spain

A total of 66 subjects were included in the study (19 females [28.8%], mean age 16.2 ± 1.6 years). The influence of DUP on changes in EF over the 2-year follow-up (expressed as a composite score of 5 cognitive abilities: attention, working memory, cognitive flexibility, response inhibition, and problem solving) was estimated using a multivariate linear regression model after removing the effect of intelligence quotient and control-ling for age, gender, diagnosis, premorbid adjustment, severity of positive and negative symptoms at baseline, global functioning at baseline, and mean daily antipsychotic dosage during follow-up.

Results: Mean DUP was 65.0 ± 6.9 days (95% confidence interval [CI], 51.2, 78.8). Median DUP was 47.5 days (range 2-180 days). Negative symptoms at baseline was the only variable signifi-cantly associated with EF at baseline (10.9% of explained variance [e.v. 10.9%], p = 0.007). Only shorter DUP (e.v. 8.7%, p = 0.013) and greater severity of baseline negative symptoms (e.v. 10.0%, p = 0.008) were significantly associated with greater improvement in EF.

Conclusions: In early-onset FEP, shorter DUP was associated with greater improvement in EF over a 2-year follow-up period.

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1. Introduction

Increasing evidence suggests that cognitive impairment is a core feature of schizophrenia (Heinrichs and Zalaknis, 1998; Kravariti et al., 2009; Mesholam-Gately et al., 2009; Reichenberg et al., 2009; Lewandowski et al., 2011; Carrion et al., 2013; Rund, 2013), and that it is already present at the first episode of early-onset psychosis (first psychotic symptom before age 18) (Mayoral et al., 2008; Zabala et al., 2010; Bombin et al., 2013) and even in individuals at ultra-high risk for psychosis (Ucok et al., 2013). Moreover, neuropsychological performance, especially executive function (EF), is a strong predictor of functional outcomes in patients with first-episode psychosis (FEP) (Rund et al., 2007; Bodnar et al., 2008; Tabares-Seisdedos et al., 2008; Nuechterlein et al., 2011; Shamsi et al., 2011; Vesterager et al., 2012; Carrion et al., 2013; Gonzalez-Ortega et al., 2013).

EF, defined as a set of cognitive abilities that enables subjects to plan and achieve goals (Elliott, 2003; Diamond, 2013; Koziol and Lutz, 2013),
comprises a set of cognitive processes such as planning, working memory, attention, problem solving, verbal reasoning, inhibition, mental flexibility, multi-tasking, and initiation and monitoring of actions (Chan et al., 2008).

Several studies have assessed the relationship between duration of untreated psychosis (DUP) and neuropsychological performance in adult FEP patients. The results are controversial. Some cross-sectional studies (Lappin et al., 2007; Barnes et al., 2008; Melle et al., 2008) and longitudinal studies (6–12 month follow-up) (Yamazawa et al., 2008; Cuesta et al., 2012; Dominguez et al., 2013) have found a significant relationship between shorter DUP and better overall cognitive function, while others, also cross-sectional (Norman et al., 2001; Barnett et al., 2005; Austin et al., 2013; Lutgens et al., 2014; Rapp et al., 2013) and longitudinal (Townsend et al., 2002; Rund et al., 2007; Melle et al., 2008; Goldberg et al., 2009), failed to find such a relationship. These controversial results may be in part attributable to sample size, study design, neuropsychological tests used, and mean/median DUP.

Therefore, given such previous controversial results and considering that no studies to date have assessed the relationship between DUP and changes in cognition in early-onset psychosis (EOP), we assessed the influence of DUP on changes in EF over a 2-year period in subjects with early-onset FEP and less than 6 months of positive symptoms.

2. Methods

2.1. Sample

All the study subjects were participants in the Child and Adolescent First-Episode Psychosis Study (CAFEPS). The complete methods of CAFEPS, a multicenter, longitudinal, 2-year follow-up study of FEP in children and adolescents, have been comprehensively described elsewhere (Castro-Fornieles et al., 2007). CAFEPS comprised a total of 110 patients with FEP consecutively recruited in outpatient and inpatient units at 6 hospitals in Spain. Recruitment took place between March 1, 2003 and November 31, 2005. A group of 98 age- and sex-matched healthy controls was also recruited in the CAFEPS study. Healthy controls were selected from state-funded schools in the same geographic areas as those attended by patients and from among children who were seen for routine pediatric visits at the same hospitals where the patients were recruited. Inclusion and exclusion criteria for controls were the same as for patients, except for the diagnosis of psychosis (Castro-Fornieles et al., 2007). For the purposes of this study, a subgroup of 79 controls (who completed both the baseline and the 2-year follow-up assessment) was used to transform patients’ raw scores to z-scores at the neuropsychological assessments.

The inclusion criteria for patients were as follows: 1) age between 7 and 17 years, and 2) a first psychotic episode according to DSM-IV criteria (i.e., presence of positive symptoms such as delusions, hallucinations, and/or disorganization) of less than 6 months’ duration at the baseline assessment. The exclusion criteria were as follows: 1) concomitant Axis I disorder at baseline; 2) intellectual disability (according to DSM-IV criteria for mental retardation); 3) any neurologic or pervasive developmental disorder; 4) history of head trauma with loss of consciousness; 5) pregnancy; and 6) substance abuse or dependence but not used if psychotic symptoms persisted 14 days after a negative urine drug test result.

At baseline, the vocabulary and block design subtests of the Wechsler Intelligence Scale for Children-Revised and the Wechsler Adult Intelligence Scale (WAIS-III), whose validity and reliability are 0.82 and from 0.60 to 0.80, respectively (Weschler, 1997).

EF was assessed using a neuropsychological battery comprising the following tests: Stroop Color-Word Test (Stoop), whose reliability has proven very consistent (ranging from 0.73 to 0.86) (Golden, 1975, 1994); Trail Making Test (TMT) (Reltan, 1959), whose reliability in clinical groups ranges from 0.69 to 0.94 for part A and from 0.66 to 0.86 for part B (Goldstein and Watson, 1989); Wisconsin Card Sorting Test (WCST), the generalizability of whose different component variables ranges from 0.52 to 0.71 (Heaton et al., 2001); Continuous Performance Test II (CPT-II) (Conners, 2000), the internal consistency of whose different component variables ranges from 0.83 to 0.94; Digit Span and Letter–Number sequencing subtest of the Wechsler Adult Intelligence Scale (WAIS-III), whose validity and reliability are 0.82 and from 0.60 to 0.80, respectively (Weschler, 1997).

EF was calculated as a composite score of 5 cognitive components: attention, working memory, mental flexibility, inhibitory control, problem solving, and selected individual measures from the aforementioned tests (using, in turn, composite scores for each cognitive component) (Table 1). Decisions about grouping individual measurements into cognitive components were based on the psychometric characteristics of the tests (Lezak, 1995; Elliott, 2003; Strauss et al., 2006; Diamond, 2013; Koziol and Lutz, 2013).

For patients and controls, the neuropsychological tests were administered at baseline and after 2 years of follow-up. For patients, the baseline neuropsychological assessment was delayed until 4–8 weeks after admission to allow acute symptoms to stabilize. The follow-up neuropsychological assessment was performed 2 years after baseline. All cognitive tests were administered by experienced neuropsychologists trained in their use. Inter-rater reliability using the intraclass correlation coefficient ranged from 0.80 to 0.99 in all cases. A complete description of the neuropsychological assessments of the CAFEPS study and of the neuropsychological performance in patients and controls at baseline and 2-year follow-up has been provided elsewhere (Zabala et al., 2010; Bombin et al., 2013).

For patients, individual raw scores obtained in each test were transformed to z-scores based on the performance of the control group, both at baseline and at the 2-year neuropsychological assessment. To minimize the effect of age and education, the sample was divided at baseline into 3 age groups (9–14, 15–16, and 17 years). This classification was maintained at follow-up to obtain the 2-year z-scores. All z-scores were calculated such that higher scores always reflected better performance. For those tests where a higher raw score was indicative of poorer performance, the z-score sign was changed from plus to minus, and vice versa. In order to avoid the outlying value effect, z-scores were truncated at ±4.

To estimate changes in EF during the 2-year follow-up, we calculated relative change scores for each EF domain as a proportion of change (i.e., [score at 2 years minus score at baseline] / score at baseline).

2.4. Intelligence quotient (IQ) assessments

At baseline, the vocabulary and block design subtests of the Wechsler Intelligence Scale for Children-Revised and the Wechsler Adult Intelligence Scale (third edition) were used to estimate the IQ of participants younger than 16 years and 16 years and older, respectively (Satler, 2001).

2.2. DUP

DUP was calculated as the time elapsed between the first positive symptom recalled (delusions, hallucinations, or disorganization) and the baseline assessment. We used a clinical questionnaire to retrospectively determine the date of onset of positive symptoms. To be considered positive, a symptom did not have to be accompanied by functional decline. The threshold was set at a symptom score of 3 or more on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987; Peralta Martin and Cuesta Zorita, 1994). Sources of information included patient interview, clinical case notes, and questioning of relatives and caregivers.

2.3. Assessment of EF

Fig. 1 shows the participant flowchart. A subsample of 66 subjects (19, 28.8% females) completed the neuropsychological and clinical evaluations both at baseline and the 2-year follow-up. These patients composed this study sample.

The study was approved by the institutional review boards at all the participating clinical sites, and written informed consent was obtained from all participants and/or their parents or legal guardians.

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2.5. Clinical and functional assessments

Clinical assessments were performed at the corresponding clinical site by trained psychiatrists. Diagnosis was established according to DSM-IV criteria using the Spanish version of the Kiddie-Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version, a semi-structured diagnostic interview designed to assess current and past psychopathologic conditions (Kaufman et al., 1997; Soutullo, 1999).

The interview was administered both at baseline and at follow-up. Diagnostic consensus was achieved for those patients in whom the type of psychiatric disorder was in doubt. For data categorization, and in order to avoid the problem of diagnostic instability (Fraguas et al., 2008; Castro-Fornieles et al., 2011), we used the final diagnosis established at the 2-year clinical follow-up assessment. The 3 main diagnostic categories established were schizophrenia (including schizoaffective disorder), affective psychosis (including bipolar disorder and depression with psychotic symptoms), and other psychoses. According to the diagnosis at the 2-year assessment, our patient sample included 40 patients with schizophrenia (n = 32) or schizoaffective disorder (n = 8), 17 with affective psychosis (4 with depression with psychotic symptoms and 13 with bipolar disorder), and 9 with other psychoses (including psychosis not otherwise specified in 6 subjects and brief psychosis or schizophreniform disorder in 3 subjects).

Severity of positive and negative symptoms at baseline was measured using the Spanish validated version of the PANSS (Kay et al., 1987; Peralta Martín and Cuesta Zorita, 1994). Inter-rater reliability for the PANSS was determined using the intraclass correlation coefficient, which was higher than 0.80 for all subscales and for the total score.

Psychosocial functioning was assessed with the Children's Global Assessment of Functioning (C-GAS) scale (Shaffer et al., 1983), Spanish version (Ezpeleta et al., 1999). The scale was completed by the treating clinician after gathering all available clinical information.

Premorbid adjustment was assessed using the childhood subscale of the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982). The PAS data in our sample have been published elsewhere (Paya et al., 2013).

Chlorpromazine equivalents were used to derive the antipsychotic dosage and to calculate the cumulative doses taken during follow-up (Rijcken et al., 2003; Andreasen et al., 2010).

2.6. Statistical analyses

Normality of data distribution and homoscedasticity of variance were confirmed before all analyses using the Kolmogorov–Smirnov/Lilliefors and Levene tests, respectively. As DUP and EF data were not normally distributed, nonparametric tests were used. First, group differences in demographic data, cognitive variables (e.g., EF), and clinical variables (e.g., DUP) were tested. The comparison groups were patients included and not included in the analysis and diagnostic subgroups (i.e., patients with schizophrenia vs. affective psychoses and other psychoses). Differences in continuous variables were assessed using the Mann–Whitney or Kruskal-Wallis tests. Differences in qualitative variables were assessed using the χ² test or Fisher’s exact test when needed. Second, bivariate correlations between DUP and EF at baseline, DUP and

<table>
<thead>
<tr>
<th>Components of executive function</th>
<th>Neuropsychological tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>WAIS-III Digits Forward⁴</td>
</tr>
<tr>
<td></td>
<td>Number of Correct Responses CPT</td>
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<tr>
<td></td>
<td>Mean Hit Reaction Time CPT</td>
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<tr>
<td>Working memory</td>
<td>WAIS-III Digits Backward⁶</td>
</tr>
<tr>
<td>Mental flexibility</td>
<td>WAIS-III Number–Letter Sequencing⁴</td>
</tr>
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<td></td>
<td>Derived Score from TMT-B⁸</td>
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<tr>
<td></td>
<td>WCST Number of Perseverative Errors</td>
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<tr>
<td></td>
<td>WCST Number of Errors</td>
</tr>
<tr>
<td></td>
<td>WCST Number of Perseverative Responses</td>
</tr>
<tr>
<td>Response inhibition</td>
<td>Commissions CPT</td>
</tr>
<tr>
<td>Problem solving</td>
<td>Stroop Interference Score</td>
</tr>
<tr>
<td></td>
<td>WCST Conceptual Level Responses</td>
</tr>
<tr>
<td></td>
<td>WCST Number of Categories Completed</td>
</tr>
<tr>
<td></td>
<td>WCST Number of Correct Responses</td>
</tr>
<tr>
<td>WAIS-III: Wechsler Adult Intelligence Scale-III; TMT (A–B): Trail making Test (parts A and B); CPT: Continuous Performance Test-II; WCST: Wisconsin Card Sorting Test.</td>
<td></td>
</tr>
<tr>
<td>⁴ Number of longest series archived.</td>
<td></td>
</tr>
<tr>
<td>⁶ Score used in this study: [time to complete TMT (B) − time to complete TMT (A)] / time to complete TMT (A).</td>
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</table>
EF at 2-year follow-up, and DUP and change in EF score during the 2-year follow-up were determined using Spearman’s rank correlation coefficients. Third, the Wilcoxon rank-sum test was used to assess changes in EF scores from baseline to 2 years between diagnostic groups. Fourth, multivariate stepwise linear regression models were used to study the independent value of DUP at baseline and EF at 2 years, as well as the change in EF score from baseline to 2 years. This stage was completed after checking the model assumptions and studying the correctly adjusted model. Prior to performing the linear regression analyses, DUP and EF data were rank-transformed using an ANOVA-type statistical method (Ercog-Hurn and Mirosevich, 2008; Nimon, 2012). Moreover, since IQ correlates well with EF performance (Verdoux et al., 2001; Leeson et al., 2009), its effect was removed using the residuals from the regression models obtained for the patient group. Potential confounding factors associated with both DUP and EF—and which might thus obscure their relationship—were included in the multivariate stepwise linear regression model as follows: age (Huber, 1997; Verdoux et al., 2001; Amminger et al., 2011; Juola et al., 2013), sex (Verdoux et al., 2001; Wunderink et al., 2009), baseline to 2-year cumulative antipsychotic dosage (as chlorpromazine equivalents) (Emsley et al., 2007), global functioning at baseline (as C-GAF score) (Fraguas et al., 2014), premorbid adjustment (as PAS childhood score) (Larsen et al., 2000; Verdoux et al., 2001; Verbeek et al., 2013), and diagnosis (schizophrenia, affective psychosis, or other psychoses) (Schimmelmann et al., 2008; Wunderink et al., 2009; Schotte et al., 2012). No significant first-order interactions were found in the models. All statistical tests were 2-tailed and were performed using SPSS for Windows, Version 18.0.

3. Results

3.1. Demographic and general characteristics of the sample

No differences were found in any demographic or clinical characteristics (age, gender, positive PANSS at baseline, negative PANSS at baseline, C-GAS at baseline, or IQ) between the patient group who completed the follow-up (n = 66) and those who did not (n = 44). Demographic variables and clinical characteristics of the sample at baseline are shown in Table 2.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Schizophrenia (n = 40)</th>
<th>Affective psychosis (n = 17)</th>
<th>Other psychoses (n = 9)</th>
<th>Total sample (n = 66)</th>
<th>Comparison between diagnostic groups (Kruskal–Wallis or Chi-square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years [95% CI]</td>
<td>15.98 (1.84)</td>
<td>16.78 (1.00)</td>
<td>16.05 (1.56)</td>
<td>16.20 (1.64)</td>
<td>sig. = 0.22</td>
</tr>
<tr>
<td>Male sex, no. (%)</td>
<td>30 (75.0%)</td>
<td>13 (76.5%)</td>
<td>4 (44.4%)</td>
<td>47 (71.2%)</td>
<td>sig. = 0.16</td>
</tr>
<tr>
<td>Educational level, mean (SD), years [95% CI]</td>
<td>11.35 (4.29)</td>
<td>9.44 (4.19)</td>
<td>13.56 (3.13)</td>
<td>11.18 (4.26)</td>
<td>sig. = 0.04</td>
</tr>
<tr>
<td>Estimated IQ, mean (SD) [95% CI]</td>
<td>93.98 (12.72)</td>
<td>72.72 (11.67)</td>
<td>111.15 (15.96)</td>
<td>101.13 (12.24)</td>
<td>181.89 (12.26)</td>
</tr>
<tr>
<td>Psychiatric hospitalization days, mean (SD), [95% CI]</td>
<td>20.87 (16.23)</td>
<td>16.71 (17.5)</td>
<td>20 (22.42)</td>
<td>19.63 (17.19)</td>
<td>sig. = 0.76</td>
</tr>
<tr>
<td>Daily chlorpromazine equivalents, mean (SD) [95% CI]</td>
<td>236.74 (129.23)</td>
<td>272.88 (147.98)</td>
<td>259.89 (120.54)</td>
<td>249.20 (123.12)</td>
<td>249.20 (123.12)</td>
</tr>
<tr>
<td>PAS, mean (SD) [95% CI]</td>
<td>8.63 (5.15)</td>
<td>7.00 (4.51)</td>
<td>4.89 (2.85)</td>
<td>7.70 (4.87)</td>
<td>sig. = 0.14</td>
</tr>
<tr>
<td>PANSS total score at baseline, mean (SD) [95% CI]</td>
<td>88.45 (18.34)</td>
<td>92.65 (28.01)</td>
<td>88.89 (20.82)</td>
<td>89.60 (21.25)</td>
<td>sig. = 0.92</td>
</tr>
<tr>
<td>C-GAF score at baseline, mean (SD) [95% CI]</td>
<td>31.48 (14.38)</td>
<td>31.35 (16.87)</td>
<td>31.89 (9.61)</td>
<td>31.77 (14.36)</td>
<td>sig. = 0.83</td>
</tr>
<tr>
<td>DUP, mean (SD), days [95% CI]</td>
<td>78.08 (56.03)</td>
<td>48.76 (53.68)</td>
<td>37.56 (46.77)</td>
<td>65 (56.04)</td>
<td>sig. = 0.03</td>
</tr>
<tr>
<td>DUP, median, days</td>
<td>58</td>
<td>24</td>
<td>19</td>
<td>47.5</td>
<td></td>
</tr>
</tbody>
</table>

C-GAF, Children’s Global Assessment of Functioning scale; DUP, duration of untreated psychosis; IQ, intelligence quotient; PANSS, Positive and Negative Syndrome Scale; PAS, Premorbid Adjustment Scale.

During follow-up, all patients except one were on second-generation antipsychotic medication (mean daily dose in chlorpromazine equivalents: 249.2 ± 132.1). Results for EF (by tasks and as a composite score, at baseline, at 2 years, and as change during follow-up) were unrelated to diagnosis.

Mean DUP was 65.0 ± 6.9 days (95% confidence interval [CI] [51.2, 78.8]), range 2–180 days. Median DUP was 47.5 days.

3.2. EF at baseline and after 2 years of follow-up

Results for EF in patients, presented as z-scores (mean = 0 ± 1) based on the performance of the control group, showed that attention (−1.98 ± 1.77 to −0.88 ± 1.24, Wilcoxon rank-sum test, Z (Wilcoxon Z) = −4.679, p < 0.001), response inhibition (−0.72 ± 0.69 to −0.36 ± 0.63, Wilcoxon Z = −3.753, p < 0.001), problem solving (−0.65 ± 1.46 to 0.53 ± 1.15, Wilcoxon Z = −5.139, p < 0.001), and composite EF (−1.18 ± 0.81 to −0.57 ± 0.59, Wilcoxon Z = −5.408, p < 0.001) improved from baseline to the 2-year assessment. Conversely, changes over the follow-up period in working memory (−1.19 ± 0.96 to −1.22 ± 0.88, Wilcoxon Z = −0.629, p = 0.529) and mental flexibility (−1.35 ± 1.72 to −0.94 ± 1.11, Wilcoxon Z = −1.575, p = 0.115) were not significant.

3.3. Association between DUP and EF at baseline

Bivariate correlations between DUP and EF at baseline were not significant.

The linear regression model showed that negative symptoms at baseline was the only variable that significantly accounted for executive performance at baseline (beta: −4.811, 95% CI [−8.249, −1.374], p = 0.007, 10.9% of explained variance (e.g. 10.9%): the lower the severity of negative symptoms, the better the EF performance.

3.4. Association between DUP and EF after 2 years of follow-up

Bivariate correlations between DUP and EF at the 2-year assessment were not significant. There was a non-significant trend in the relationship between DUP and the 2-year composite EF score, Spearman's rho = −0.234 (p = 0.058); therefore, the longer the DUP, the lower the EF performance at 2 years.
Linear regression showed that none of the studied variables used in the multiple regression model were significantly related to EF at 2 years.

3.5. Association between DUP and change in EF over the 2-year follow-up

There was no non-significant trend in the relationship between DUP and change in EF over the 2-year period, Spearman’s rho = −0.241 (p = 0.051); the shorter DUP, the greater the improvement in EF.

Fig. 2 shows the bivariate relationship between DUP and change in EF.

There were no significant differences between correlation coefficients of schizophrenia and affective psychoses (Fisher r-to-z transformation, Z = −1.06; p = 0.289).

The linear regression model showed that the only significant predictors of change in EF during the 2-year follow-up were DUP (beta: −0.301, 95% CI [−0.536, −0.066], p = 0.013, e.v. 8.7%) and negative symptoms at baseline (beta: 4.688, 95% CI [1.260, 8.117], p = 0.008, e.v. 10.0%); therefore, the shorter the DUP and the greater the severity of baseline negative symptoms, the greater the improvement in EF.

4. Discussion

Our longitudinal study in children and adolescents with FEP shows that shorter DUP was associated with greater improvement in EF during follow-up.

To our knowledge, this is the first prospective evaluation of the relationship between DUP and EF outcome in patients with early-onset FEP. We previously reported that shorter DUP predicted greater functional improvement over a 2-year follow-up in early-onset FEP (Fraguas et al., 2014). In addition, previous studies have reported that DUP is an independent predictor of the likelihood of recovery in FEP patients (Marshall et al., 2005; Perkins et al., 2005). Thus, DUP might play a relevant role in the capacity for recovery of clinical and cognitive functions after a first episode of psychosis.

However, the nature of the association between DUP and EF remains unclear, with no conclusive explanation about whether there is a causal pathway between longer DUP and poorer outcome or, conversely, whether the relationship between DUP and outcome is a spurious finding, with no direct causal link between them (Rund, 2013; Fraguas et al., 2014). Three main hypotheses can be posed as follows: 1) longer DUP leads to poor EF outcome (Cuesta et al., 2012); 2) impaired EF at onset influences delay in seeking treatment and causes longer DUP (Cuesta et al., 2012); and 3) both longer DUP and poor EF outcome are manifestations of a third process (Rund et al., 2007).

Data on the cognitive performance of patients with first-episode EOP suggest that cognitive impairment is already present at the first episode, with a lack of (or minimal) further progression from then on (Bombin et al., 2013). We believe that early insults to the brain would produce dynamic rather than static impairments that manifest through deviant neurodevelopmental trajectories before the onset of psychotic symptoms (Arango et al., 2014). Early neurodevelopmental abnormalities may underlie both longer DUP and poorer improvement of EF in patients with first-episode EOP, thus potentially explaining the relationship between the two factors.

Our data do not enable us to conclude whether there is a causal link between longer DUP and poorer outcome of EF. Actually, as occurs in the association between DUP and functional outcome, the relationship between DUP and EF may be confounded by factors such as insidious onset (Morgan et al., 2006), premorbid adjustment (Larsen et al., 2000, 2004; Lutgens et al., 2014; Fraguas et al., 2014), and severity of symptoms (Compton et al., 2011).

In any case, regardless of the underlying mechanisms involved in the relationship between DUP and outcome of EF, shorter DUP can be considered a marker of greater likelihood of improved EF.

Previous publications have reported a relationship between more severe negative symptoms and poor EF, especially in working memory (Vesterager et al., 2012; Bora and Murray, 2014; Gonzalez-Ortega et al., 2013), and between improved EF and reduced negative symptoms (Bora and Murray, 2014). In this context, our finding regarding the association between more severe negative symptoms at baseline and greater improvement in EF during follow-up may be seen as counterintuitive. However, it may have a simple and plausible explanation. In our sample, negative symptoms at baseline significantly correlated with EF at baseline, so the more severe the negative symptoms, the worse the EF. Additionally, EF changed positively during follow-up. Therefore, patients with poorer EF at baseline and, consequently, more severe negative symptoms at baseline, would have had more room to improve (Twamley et al., 2011).

Our study is subject to a series of limitations. First, DUP was calculated as the time elapsed between the first positive symptom recalled and the baseline assessment. Therefore, although baseline negative symptoms are associated with EF outcome, we are not considering the effect of duration of untreated negative symptoms. Furthermore, all patients in our sample had a positive DUP shorter than 6 months, which could reduce the applicability of our results to other early-onset FEP samples with more insidious onset. Even though there is variability in positive DUP in our sample (2–180 days; mean 65.0 ± 6.9 days; median 47.5 days), this may not reflect the range of variability in DUP in community samples of EOP and may limit our ability to detect relevant associations with cognitive functions. That being said, in the absence of standardized operational criteria for defining DUP (Compton et al., 2007), a sample with a shorter DUP may have allowed us to more accurately establish the time of onset and could provide a better scenario in which to study the independent influence of DUP on EF outcome, by reducing the potential confounding effect of insidious onset on cognitive outcome (Wiersma et al., 1998; Malla et al., 2011).

Second, there is no consensus on which cognitive functions are better included under the umbrella of EF. We decided to group individual measurements (factors) into an EF composite score based on previous literature and on the psychometric characteristics of the tests (Lecrubier et al., 1995; Elliott, 2003; Strauss et al., 2006; Jurado and Rosselli, 2007; Diamond, 2013; Koziol and Lutz, 2013).

Third, we did not include data on drug abuse during follow-up.

Finally, it is worthy of note that the design of this study does not allow for inference of a causal relationship between DUP and change in EF. We cannot confirm whether the association we found is causal.
in nature or whether it is mediated by another, as-yet unknown, under-lying variable.

Findings in previous longitudinal studies show that schizophrenia should not be considered an unavoidably deteriorating illness (Zipursky et al., 2013); therefore, early intervention based on pharmacological, psychotherapeutic, and psychosocial approaches could ensure a more favorable prognosis (Stafford et al., 2013; van Os and Murray, 2013). Considering DUP as one of the few feasibly modifiable factors, our results support its inclusion as a target for intervention, thus implying that reducing DUP can act as a protective factor, particularly in patients with early-onset FEP (Larsen et al., 2006), for whom prompt intervention has proven cost-effective (McCrone et al., 2013).

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Conflict of interest

Dr. David Fraguas has been a consultant and/or advisor to and has received honoraria from AstraZeneca, Bristol-Myers-Squibb, Janssen, Lundbeck, Otsuka, and Pfizer. Dr. Mara Parellada has been a consultant and/or advisor to and has received honoraria and/or grants from AstraZeneca, Bristol-Myers-Squibb, Janssen, Lundbeck, Otsuka, and Pfizer.

References


Connors, K., 2000. Connors’ Continuous Performance Test, CPT- II. MHS.


