Entire duration of active psychosis and neurocognitive performance in first-episode non-affective psychosis

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Funding information
Instituto de Investigación Sanitaria Valdecilla y Universidad de Cantabria, Grant/Award Number: Predoctoral contract BOC49; REF. IDI-13; Nancy Mur; Instituto de Salud Carlos III, Grant/Award Number: Miguel Servet contract CP18/00003; Dr. Rosa Ayesa-

Abstract

Aim: To explore if the entire duration of active psychosis (DAP) is related to neurocognitive performance at baseline and at 3-year follow-up in patients with first episode psychosis (FEP).

Methods: DAP was estimated for 481 FEP patients. A neuropsychological battery was administered to measure neurocognitive specific domains, and a global indicator of neurocognitive impairment (global deficits score, GDS) was calculated. According to the DAP quartiles, four subgroups were formed, and these were compared. In addition, a logistic regression analysis was carried out to predict neurocognitive impairment at 3-year follow-up. Results: FEP patients with the longest DAP (more than 18.36 months) presented a more severe global neurocognitive impairment evidenced in their GDS, both at base- line ($F = 5.53$; $p < .01$) and at 3-year follow-up ($F = 4.16$; $p < .01$). Moreover, a sub- group of participants with DAP between 7.40 and 18.36 months showed a specific attentional decline over the 3-year follow-up ($F = 3.089$; $p < .05$).The logistic regression model showed that sex (Wald = 7.29, $p < .010$), premorbid adjustment (Wald = 7.24, $p < .010$), attention (Wald = 12.10, $p < .001$), verbal memory (Wald = 16.29, $p < .001$) and visual memory (Wald = 9.41, $p < .010$) were significant predictors of neurocognitive impairment 3 years after the FEP. The variables com- posing the DAP were not significant predictors in this model.

Conclusions: DAP seems to be related to global neurocognitive impairment in FEP patients. These findings contribute in several ways to our understanding of the effects of active psychosis on the brain, and provide the basis for future research.

KE YWOR DS

cognition, cognitive impairment, neuropsychology, psychosis, psychotic disorders

1 | INTRODUCTION

Neurocognitive impairment in first episode psychosis (FEP) has been demonstrated, showing associations with clinical and functional outcomes (Treen-Calvo et al., 2018; Wegener et al., 2005). Similarly, the persistence of active positive symptoms has been related to poorer clinical and functional outcomes (Pardo-de-Santayana et al., 2020; Watson et al., 2018). In this regard, the duration of untreated psychosis (DUP) has been extensively explored, evidencing significant links to response to treatment(Perkins et al., 2005)and social dysfunction

(Bratlien et al., 2013) in FEP patients. The neurotoxicity hypothesis proposes a possible explanation to this relationship, assuming that active psychosis is dangerous to the brain (Wyatt, 1991); therefore, indicating an early intervention in FEP. Recently, the duration of active psychotic symptoms after treatment (DAT) has been introduced to the study of FEP, evidencing relationships with recovery (Rund et al., 2016) and negative symptoms (Lyne et al., 2017). Unlike DUP, DAT takes into account the effects of relapses, so it could be useful to study the patients' long-term outcomes.

In order to obtain comprehensive information, the estimation of the entire duration of active psychosis (DAP) has been proposed. DAP refers to the complete period of time in which the psychotic symptoms remain present, from the onset of psychosis to the time after starting antipsychotic treatment (Pelayo-Terán et al., 2018).Previous studies observed that a longer DAP is related to poorer long-term functionality and it is a relevant predictor of negative symptomatology(Lyne et al., 2017; Pardo-de-Santayana et al., 2020).

However, current evidence regarding duration of psychosis and neurocognition is controversial. Rund et al. (2016) found in a FEP sample no significant relationship between DUP and neurocognition at 10-year follow-up. Conversely, Cuesta et al. (2012) evidenced that FEP patients with short DUP outperformed patients with long DUP on memory tasks and a pre-attentional visual task. Likewise, Chang et al. (2013) evidenced in a prospective study the influence of DUP over visual and verbal memory at 24 and 36 months of follow-up, even when controlling for covariates as negative symptoms. Regarding DAT, it has been found that a longer period is related to a weaker working memory performance in long-term (Barder et al., 2015). To our knowledge, no study has been conducted to explore the relationship between DAP and neurocognition. Furthermore, the measurement of neurocognitive functioning via neuropsychological testing is a significant component of assessment to detect cognitive impairment in FEP, offering a reasonable proxy measure to examine the neurotoxicity hypothesis.

Therefore, this study aimed to explore if the entire DAP is related to neurocognitive performance at baseline and at 3-year follow-up assessment in first episode non-affective psychosis patients. Based on previous evidence, it was hypothesized that those with longer DAP (a) would show worse performance in both cognitive assessments, and (b) would present more severe cognitive decline at the 3-year follow-up.

2 | MATERIAL AND METHODS

2.1 | Study design and population

In order to analyse the effects of DAP on clinical and neurocognitive variables in subjects with first-episode non-affective psychosis (according to DSM-IV criteria), an observational retrospective study was performed. Data were obtained from a cohort of patients enrolled in an epidemiological and longitudinal program at the Marqués de Valdecilla University Hospital in Cantabria, Spain, denominated 'Programa de Atención a FasesIniciales de Psicosis' (PAFIP) (Pelayo-Terán et al., 2008). This program was approved by the hospital's review board, and informed consent was given by all participants, according to international standards for research ethics (Clinical Trial identifier NCT02526030).

Four hundred and eighty-one patients (51.9% males) of PAFIP were recruited from 2001 to 2014, who had sufficient clinical information to estimate DAP. All participants met the following inclusion criteria: 15–60 years of age, living in the catchment area, experiencing their first episode of psychosis, no prior treatment with antipsychotic medication (if previously treated, a total of antipsychotic treatment ≤6 weeks), DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia or schizoaffective disorder. Exclusion criteria were: to meet DSM-IV criteria for drug dependence or mental retardation and to have a history of neurological disease or head injury, at baseline or 6 months psychiatric evaluation.

2.2 | MEASURES

2.2.1 | Sociodemographic and clinical variables

Demographic information such as gender, age, age of psychosis onset, years of education and medical records were collected from patients and relatives at admission. Social premorbid adjustment was estimated using the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982), with ratings from 0 (indicating the 'better') to 6 (denoting the 'worse').

Clinical assessment was performed at baseline and after 6 weeks, 3, 12, 24 and 36-month-follow-up by a trained psychiatrist (B.C.F.). At the 6-month follow-up, the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 2001) was carried out to confirm diagnosis. To measure clinical symptoms of psychosis, the scale for the assessment of negative symptoms (SANS) (Andreasen, 1989) and the scale for the assessment of positive symptoms (SAPS) (Andreasen, 1984) were used. Also, the 24-item brief psychiatric rating scale (BPRS) (Overall & Gorham, 1962) and the clinical global impressions (CGI) (Guy, 1976) were administered to track changes in symptoms over time.

2.2.2 | Estimation of entire DAP

Entire DAP was estimated by adding the DUP and the DAP after treatment (DAT) for each patient, according to Pelayo-Terán et al. (2018).

To obtain the DUP, the time (months) from the first continuous positive psychotic symptom to the initiation of adequate antipsychotic drug treatment (when treatment in PAFIP was initiated) was calculated. The date of positive psychotic symptoms onset (when total SAPS score was ≥3) was established based on the information provided by relatives and the patient during the FEP (Pelayo-Terán et al., 2018).

DAT was defined as the time (days that later were converted into months) with a score ≥ 3 on any SAPS subscale during relapses and exacerbation over the 3 years of follow-up (Pelayo-Terán et al., 2018).

Relapse was established when the patient met any of the following criteria after clinical improvement was achieved: a rating ≥ 5 on any key BPRS symptom items for at least 1 week, CGI scores of >6 for at least 1 week, hospitalization due to psychotic psychopathology, suicide attempt. Exacerbation was considered as such when the patient increased two points in the key BPRS symptoms. The information on the severity of symptoms during relapses and exacerbationfor DAT estimation was obtained via medical record. These data were originally collected at consensus meetings by two senior psychiatrists and a clinical nurse, after regular interviews with the patient (at baseline, 6 weeks, 3 months, 1, 2 and 3 years), routine visits and hospitalizations during the follow-up period.

2.2.3 | Neurocognitive variables

A neuropsychological battery was administered to patients at baseline (~10.5 weeks after entering the PAFIP program) and 3-year follow-up. This evaluation included tests of (a) verbal memory (Rey Auditory Verbal Learning Test, RAVT) (Rey, 1964), (b) visual memory (Rey Complex Figure, RFC)(Osterrieth, 1944), (c) processing speed (WAIS-III Digit Symbol subtest) (Wechsler, 1997), (d) working memory (WAIS-III Digits Backward Subtest) (Wechsler, 1997), (e) executive function (Trail Making Test part B, TMTB) (Lezak, 1995), (f) motor dexterity (The Gooved Pegboard Test) (Lezak, 1995), and (g) attention (Continuous Performance Test, CPT) (Cegalis, 1991). Raw scores were transformed into Z scores, using a sample of 187 healthy volunteers described in previous studies (Ayesa-Arriola et al., 2016; Setién-Suero et al., 2019). The premorbid intelligence quotient (IQ) was estimated by the performance on the WAIS-III vocabulary subtest at baseline (Wechsler, 1997). Also, the global deficits score (GDS) was used as a global indicator of neurocognitive impairment. It was estimated by converting T scores of the neuropsychological tests to deficit scores, providing a general score between 0 (absence of impairment) and 5 (severe impairment) that indicates the presence and severity of cognitive impairment (Reichenberg et al., 2009). Previous publications have shown the usefulness of the GDS to detect cognitive decline (Burton et al., 2016; Carey et al., 2004).

2.3 | Statistic analysis

The Statistical Package for Social Science (IBM SPSS) version 21.0 was used for statistical analysis (SPSS Inc., 2016). Initially, descriptive statistics were estimated to form independent groups based on DAP quartiles. Univariate analysis of variance (ANOVA) and Bonferroni's post hoc test ($p< .05$) were used to compare clinical and sociodemographic variables for more than two independent groups. Group comparisons on categorical variables were performed using chi-square. Analysis of covariance (ANCOVAS) were ran to compare groups on neuropsychological measures controlling for bias of possible confounding variables (gender, age, premorbid IQ and years of education). For the longitudinal analysis of neurocognitive variables, repeated measures ANCOVAS were performed to compare main effect of DAP. Effects of time (longitudinal dimension), group (cross-sectional dimension), and time by group (interaction effect) were examined. All post hoc comparisons were Bonferroni corrected. All statistical tests were two-tailed, and considered significant if $p< .05$.

In addition, a multivariate logistic regression analysis was conducted for predicting general neurocognitive impairment at 3-year follow-up. The significant variables resulting from the primary analysis were introduced as predictorsin the model. The Nagelkerke's R^2 was examined, a measure of the proportion of explained variation in the logistic regression models.

3 | RESULTS

Of the 507 patients enrolled in the PAFIP program from 2001 to 2014, 481 had available information to estimate their DAP at 3-year follow-up. All participants met the inclusion criteria and gave their written consent. Demographic data of FEP patientsis shown in Table 1. The mean and median of DAP were 17.16 and 7.39 months; the mean and median of DUP were 12.32 and 2.50 months; and the mean and median of DAT were 4.83 and 2.65 months, respectively (Table 1). From this sample, 379 participants performed the neurocognitive battery at baseline, and 285carried it out at 3-year follow-up.FEP patients who underwent neuropsychological tests had significantly more years of education than those who did not ($T = -2.50$, $p < .05$), but no otherdifferences were found (Table S1).

3.1 | DAP subgroups: Their comparisons on sociodemographic and clinical variables

Four subgroups were made according the participants' DAP, by estimating the quartiles of this variable. According to the cut-off points for the 25th, 50th and 75th percentiles: subgroup 1 was made up of those with a DAP of less than 3.17 months, subgroup 2 of those with a DAP between 3.18 and 7.39 months, subgroup 3 of those with a DAP between 7.40 and 18.36 month, and subgroup 4 of those with a DAP greater than 18.36 months.

Individuals in subgroup 4 were significantly older than those in subgroup 3 ($F = 2.65$; $p<.05$). The differences in DAT, DUP, SANS, and premorbid adjustment between the four subgroups remained significant at $p< .01$ (see Table 1). No significant difference was found in the distribution by sex, although a trend of higher percentage of male was observed in subgroups with longer DAP. Also, there were no significant differences between subgroups regarding age of psychosis onset, years of education, SAPS initial scores or premorbid IQ.

3.2 | Neurocognitive comparisons at baseline

No significant differences in neurocognition were found between DAP subgroups in any specific domain at baseline. Thus, the initial

TABLE 1 Demographic and clinical variables in FEP patients subgroups according to DAP

	Total sample		Subgroup 1 (≤ 3.17 months)		Subgroup 2 (3.18-7.39 months)		Subgroup 3 (7.40-18.36 months)		Subgroup 4 (> 18.36 months)		ANOVA	
	n	Mean (*SD*)	*n*	Mean (*SD*)	*n*	Mean (*SD*)	*n*	Mean (*SD*)	*n*	Mean (*SD*)	F	*p*
DAP (months)	481	17.16 (29.9)	120	1.89 (0.77)	121	4.88 (1.26)	121	12.35 (3.01)	119	49.93 (46.25)	110.77	< .001
DUP (months)	481	12.32 (28.81)	118	0.66 (0.48)	117	2.06 (1.57)	118	6.58 (4.65)	112	40.36 (47.74)	74.03	< .001
DAT (months)	481	4.83 (6.38)	120	1.23 (0.76)	121	2.81 (1.51)	121	5.76 (4.10)	119	9.57 (10.22)	52.17	< .001
Male sex (%)	269 (55.9%)		60 (50%)		66 (54.54%)		70 (57.85%)		73 (61.34%)		X^2 = 3.40	.334
Age[a]	481	29.87 (9.46)	120	29.45 (8.78)	121	29.81 (9.47)	121	28.46 (9.09)	119	31.80 (10.24)	2.65	.048
Age of onset	481	28.84 (9.10)	120	29.39 (8.78)	121	29.63 (9.49)	121	27.91 (9.03)	119	28.43 (9.11)	0.95	.414
Years of education	470	10.15 (3.18)	116	10.40 (3.08)	117	10.20 (3.35)	120	9.84 (3.05)	117	10.16 (3.26)	0.63	.595
Initial SANS[b]	478	6.47 (5.94)	119	4.60 (4.63)	119	6.42 (5.72)	121	7.31 (6.52)	119	7.54 (6.33)	6.22	< .001
Initial SAPS	479	13.64 (4.39)	120	13.77 (4.47)	119	13.24 (4.64)	121	13.29 (4.10)	119	14.29 (4.31)	1.48	.217
Premorbid adjustment[c]	416	3.10 (2.19)	98	2.23 (1.85)	102	2.66 (1.91)	108	3.43 (2.17)	108	3.97 (2.35)	14.350	< .001
Premorbid IQ	368	95.29 (13.32)	94	97.71 (11.88)	98	95.45 (13.50)	92	93.36 (13.32)	84	94.52 (14.38)	1.78	.150

Abbreviations: DAP, entire duration of active psychosis; DAT, duration of active psychotic symptoms after commencing treatment; DUP, duration of untreated psychosis; FEP, first episode psychosis; SANS, scale for the assessment of negative symptoms; SAPS, scale for the assessment of positive symptoms.

[a]Age difference was significant between subgroups 3 and 4 ($p < .05$).

[b]Initial SANS difference was significant between subgroups 1 and 3 ($p < .01$), 1 and 4 ($p < .01$).

[c]Premorbid adjustment difference was significant between subgroups 1 and 3 ($p < .01$), 1 and 4 ($p < .01$), 2 and 3 ($p < .05$), 2 and 4 ($p < .01$).

neurocognitive profile of all participants was similar: all FEP patients presented deficit in every domain compared with healthy controls, with attention and verbal memory being the most significantly impaired (see Figure 1). However, the ANOVAS showed a significant difference between subgroups in the GDS score ($F = 5.53$; $p < .01$) as a global indicator of neurocognitive impairment. Participants in subgroup 4 had higher deficit scores than the others; and this difference remained significant after potential confounders were adjusted ($F = 4.92$; $p < .01$).

3.3 | Neurocognitive comparisons at 3-year follow-up

Neurocognitive profiles of all subgroups at 3-year follow-up assessment are presented in Figure 1. After controlling for possible confounders (age, sex, years of education and premorbid IQ), ANCOVAS showed a significant group effect in GDS ($F = 4.16$, $p < .01$) (see Table 2). Specifically, participants in subgroup 4 had significant higher GDS scores than those in subgroup 1, suggesting that FEP patients with the longest DAP showed more severe global neurocognitive impairment at long term.

In addition, significant time effects were identified in three cognitive domains: verbal memory ($F = 6.54$; $p < .01$), visual memory ($F = 4.46$; $p < .05$) and working memory ($F = 4.32$; $p < .05$). For verbal memory, all subgroups improved their performance from baseline to the 3-year follow-up. However, for visual memory all participants decrease their performance at the 3-year re-assessment. Similarly, for working memory the subgroups 1, 2 and 3 scored lower at the follow-up; while subgroup 4 remained stable (see Table 2). No significant differences were found in other cognitive domains over time.

Nevertheless, the most striking finding of ANCOVA was a significant group by time effect in the attention domain ($F = 3.089$; $p < .05$), thereby its longitudinal course differed between DAP subgroups. While subgroups 1, 2 and 4 incremented their scores in the attention task at the 3-year re-assessment, subgroup 3 decreased its mean rating. This indicates a specific attentional decline of a subgroup of FEP patients with DAP between 7.40-18.36 months. The longitudinal course in the other cognitive domains was similar in all subgroups, thus DAP did not modify them.

3.4 | Predictors of neurocognitive impairment 3 years after the FEP

The following variables were included in the logistic regression model to predict neurocognitive impairment at 3-year follow-up: DUP, DAT, sex, initial SANS score, age, premorbid adjustment, attention, verbal memory and visual memory. The regression models used data from 234 subjects, the best-fitting model ($X^2 = 88.03$, $p < .001$) accounted for the 42.1% of the variance (Nagelkerke $R^2 = .421$)and predicted correctly the 76.49% of the cases. Sex (Wald = 7.29, $p < .010$), premorbid adjustment (Wald = 7.24, $p < .010$), attention

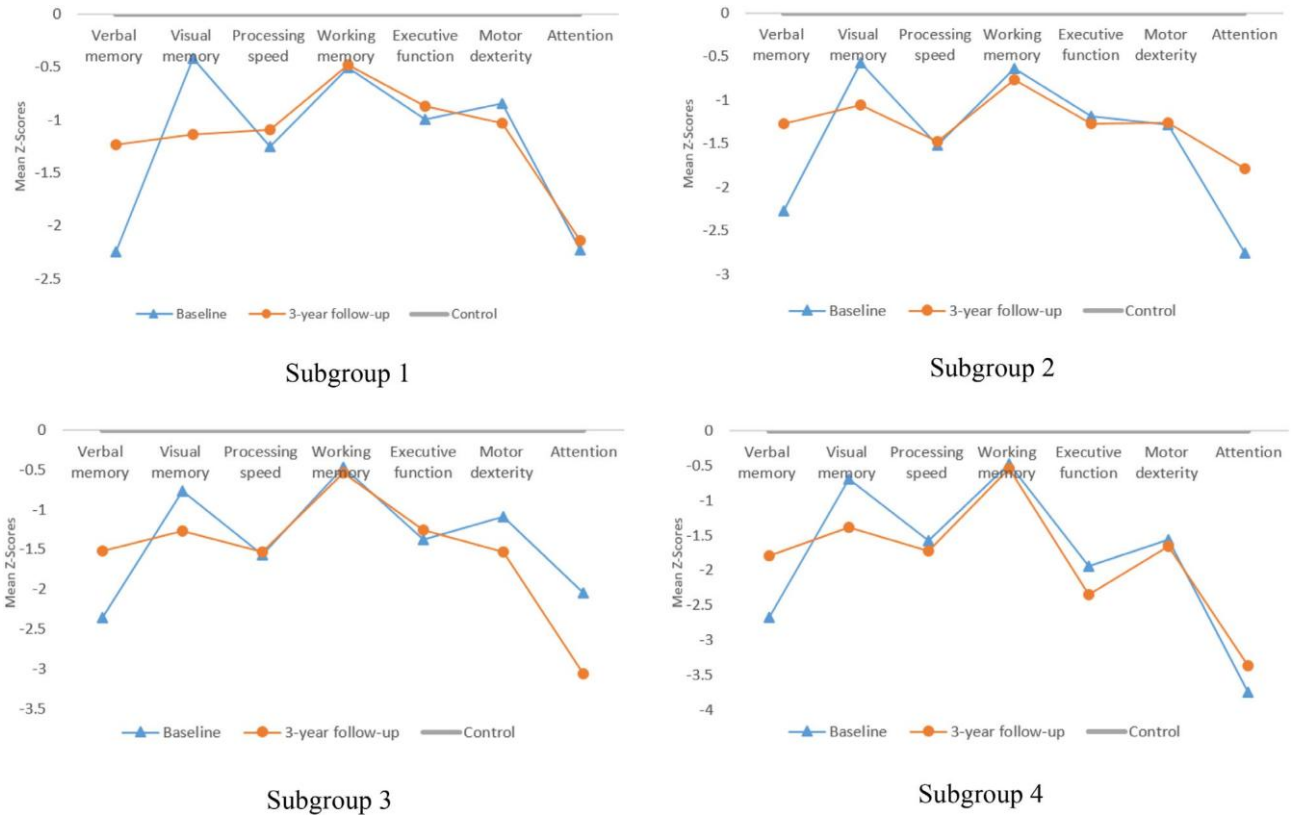

FIGURE 1 Neurocognitive performance of DAP subgroups at baseline and at 3-year follow-up

(Wald = 12.10, $p < .001$), verbal memory(Wald = 16.29, $p < .001$) and visual memory (Wald = 9.41, $p < .010$) at baseline were significant predictors of neurocognitive impairment 3 years after the FEP(see Table 3).

4 | DISCUSSION

The current study explored the association between the entire DAP and the neurocognitive performance at baseline and at 3-year follow up in FEP, by taking into account both periods, before and after, commencing treatment. FEP patients with the longest DAP (more than 18.36 months) were older, more frequently male and had higher rates of negative symptoms at baseline. Furthermore, they presented more severe global neurocognitive impairment, evidenced in their GDS. The GDS punctuations of all participants ranged from 1 to 1.75, thus exceeding the cut-off of 1 that indicates mild impairment, as established by a previous study of our group (Ayesa-Arriola et al., 2013). However, the global impairment was worse for those with the longest DAP, confirming the first hypothesis of the study. On the contrary, the second hypothesis was not fulfilled, as the neurocognition of FEP patients with the longest DAP did not deteriorate over the 3-year reassessment. This finding suggests that regardless of the DAP, the neurocognitive course of FEP individuals is stable, as it has been demonstrated by other longitudinal studies (Ayesa-Arriola et al., 2017;Barder et al., 2015;Rodríguez-Sánchez et al, 2013").

The more severe global neurocognitive impairment of FEP patients with the longest DAP reported here is consistent with previous evidence about DUP and neurocognition. Wang et al. (2016) found that DUP was associated with worse general cognitive functioning, and this relationship was more pronounced in those with low premorbid IQ. These results contrast with others that suggest the absence of relationship between DUP and neurocognition (Ayres et al., 2007; Bora et al., 2018; Galin´ska et al., 2005; Goldberg et al., 2009; Khawar et al., 2014). However, this divergence could be explained by methodological differences.

First, most of the studies with negative results have exclusively estimated DUP. However, the current study includes also the duration of active psychotic symptoms after treatment (DAT) to calculate the entire period. Likewise, Barder et al. (2015) identified a subgroup of FEP patients with long DAT who demonstrated a significant intellectual decline over 10 years, indicating an association between accumulated duration of psychosis and long-term neurocognitive course. In consequence, the variable DAT might be more useful to distinguish different cognitive trajectories compared to DUP.

Second, usually the studies with negative results about the association between DUP and neurocognition did not provide a global deterioration index (Ayres et al., 2007; Bora et al., 2018; Galin´ska et al., 2005; Goldberg et al., 2009; Khawar et al., 2014). Our results suggest that DAP is potentially related to a global neurocognitive impairment, so the exclusive analysis of the specific domains may be insufficient itself to show this association. Attention and verbal

TABLE 2 Change in neurocognition over the 3-year follow-up for DAP subgroups

	Subgroup 1			Subgroup 2			Subgroup 3			Subgroup 4			ANCOVAS		
	Baseline		3-year	Baseline		3-year	Baseline		3-year	Baseline		3-year			
	n	Mean (*SD*)	Mean (*SD*)	*n*	Mean (*SD*)	Mean (*SD*)	*n*	Mean (*SD*)	Mean (*SD*)	*n*	Mean (*SD*)	Mean (*SD*)	Group	Time	Time x group
Verbal memory	62	−2.28 (1.47)	−1.23 (1.43)	72	−2.21 (1.23)	−1.27 (1.20)	68	−2.23 (1.38)	−1.52 (1.50)	70	−2.68 (1.19)	−1.79 (1.19)	2.02	6.54[a]	0.917
Visual memory	62	−0.41 (0.99)	−1.00 (1.25)	72	−0.49 (1.05)	−1.06 (1.21)	68	−0.67 (0.82)	−1.27 (1.29)	70	−0.73 (1.11)	−1.38 (1.27)	1.14	4.46[b]	0.368
Processing speed	62	−1.24 (1.09)	−1.09 (1.27)	72	−1.60 (1.05)	−1.47 (1.21)	68	−1.42 (1.09)	−1.53 (1.40)	68	−1.60 (1.04)	−1.74 (1.04)	2.04	1.72	1.36
Working memory	62	−0.42 (0.75)	−0.48 (0.89)	72	−0.64 (0.74)	−0.76 (0.75)	68	−0.40 (0.96)	−0.54 (0.96)	69	−0.57 (0.79)	−0.54 (0.85)	2.15	4.32[b]	0.767
Executive function	59	−1.12 (2.04)	−0.90 (1.76)	69	−1.11 (1.92)	−1.23 (2.18)	66	−1.27 (2.38)	−1.25 (3.60)	66	−2.02 (2.65)	−2.16 (3.12)	2.49	0.26	0.113
Motor dexterity	57	−0.96 (1.77)	−1.07 (1.76)	68	−1.44 (3.76)	−1.27 (2.04)	65	−0.83 (1.20)	−1.46 (2.03)	70	−1.64 (2.46)	−1.65 (1.97)	0.875	0.52	2.23
Attention	56	−2.56 (4.96)	−1.69 (4.54)	63	−2.20 (3.56)	−1.89 (3.65)	62	−1.48 (2.67)	−2.92 (4.86)	64	−3.68 (5.17)	−3.38 (5.45)	1.53	1.11	3.089[b]
GDS[c]	52	1.18 (0.85)	1.04 (0.81)	59	1.43 (0.87)	1.23 (1.04)	59	1.25 (0.87)	1.45 (1.06)	58	1.75 (1.02)	1.71 (1.09)	4.16[a]	0.061	2.33

Note: Using sex, age (29.97), years of education (10.55) and premorbid IQ (95.88) as covariates.

Abbreviation: GDS, global deficits score.

[a]Group differences significant at $p < .01$.

[b]Group differences significant at $p < .05$.

[c]GDS difference was significant between subgroups 1 and 4 ($p < .01$).

TABLE 3 Predictors of general neurocognitive impairment in FEP at 3-year follow-up

Predictors (n = 234)	Wald	Significance	Exp (B)	95% CI forExp (B)	
				Inferior	Superior
DUP	0.087	0.767	0.997	0.979	1.016
DAT	1.010	0.315	1.029	0.973	1.088
Sex (male)	7.299	0.010	2.740	1.319	5.692
Age	1.598	0.206	1.028	0.985	1.074
Initial SANS	0.207	0.650	0.986	0.929	1.047
Premorbid adjustment	7.245	0.010	1.285	1.071	1.543
Attention	12.100	< 0.001	0.793	0.696	0.904
Verbal memory	16.295	< 0.001	0.557	0.419	0.740
Visual memory	9.411	0.010	0.573	0.401	0.818
Constant	14.905	< 0.001	0.024		

Note: Model summary: R^2 = 0.314 (Cox and Snell), 0.421 (Nagelkerke). X^2 = 88.030, p < .001. Method: Enter.

memory tasks were found to be more sensitive to detect neurocognitive impairment at baseline, in correspondence with other study (Lappin et al., 2007). In fact, the logistic regression model analysed here showed that performance in attention, verbal memory and visual memory at baseline were significant predictors of global neurocognitive impairment at 3 years of follow-up. Regarding verbal memory, its relevance for the identification of long-term neurocognitive impairment has already been evidenced (Barnes et al., 2008; Chang et al., 2016; Fraguas et al., 2014). However, the GDS was more sensitive to recognize the neurocognitive impairment of patients according to their DAP. This is because the GDS is obtained by averaging the deficit scores of all neuropsychological tests, allowing us to detect global cognitive impairment, although the specific domains do not express significant differences. Consistent with this, a recent meta-analysis showed that the longer the FEP patient remained without antipsychotic treatment, the greater the general cognitive decline (Allott et al., 2018). Therefore, we consider important to analyse both the specific cognitive domains and an index of global neurocognitive impairment, since together they could provide more complete information.

Third, possibly some studies evaluating DUP were unable to detect a relationship with poorer neurocognitive performance because this period was not long enough in their samples. As Rund (2014) proposed, perhaps there is a threshold value for a toxic effect of psychosis, rather than a linear relationship between the DAP and neurotoxicity.

Our results indicated that at 3-year follow-up, participants with DAP between 7.40 and 18.36 months (subgroup 3) present a specific attentional decline and an increase of thugs (see Table 2). This group of FEP patients had the lowest premorbid IQ (see Table 1), although this difference was not significant it could have relevant repercussions. Previous evidence suggested that DUP have a greater effect on neurocognition in cases of low IQ (Lappin et al., 2007; Wang et al., 2016) and low cognitive reserve (Amoretti et al., 2018). Therefore, it could be possible that a long DAP affects the neurocognitive course to a greater degree in those with low IQ.

It is interesting to note that although the participants with the longest DAP presented the highest global neurocognitive impairment index; neither DUP nor DAT were significant predictors of long-term neurocognitive impairment in the logistic regression model. On the contrary, the premorbid adjustment was a significant predictor, which confirms the relationship between worse premorbid adjustment and more severe neurocognitive impairment showed by Béchard-Evans et al. (2010).

Likewise, sex was a significant predictor of neurocognitive impairment at 3 years after the FEP, as males were more frequently affected. It has been proposed that neurocognitive differences by sex in schizophrenia are similar to those in the general population, where women outperform men in processing speed and verbal memory (Ayesa-Arriola et al., 2014; Ittig et al., 2015; Torniainen et al., 2011). Complementary explanations for these differences have been suggested, including neuroanatomical dysmorphisms (Womer et al., 2016) and hormonal differences (Gurvich et al., 2018). Furthermore, we found that the percentage of male was higher in the subgroups with longer DAP. This difference was not statistically significant, but agrees with the findings of Barder et al. (2015). The possible difference on DAP between males and females could be explained by differences of the help seeking process. Ferrari et al. (2018) found that woman were more active in asking for help, while men had more difficulties in talking about their symptoms. Therefore, the initiation of treatment for male patients could be delayed, incrementing their DAP period. Nevertheless, a meta-analysis determined that the specific sex differences in FEP are no associated with DUP length (Cascio et al., 2012), so further investigations must take sex differences into account when studying DAP.

Although our results informed that patients with longer DAP presented more severe negative symptoms at baseline, negative symptoms were not found significant predictors of neurocognitive impairment at 3-year follow-up. This relationship between DAP and negative symptoms corresponds with others (Chang et al., 2013, 2016; Rapp et al., 2013). Lyne et al. (2017)explained that positive symptoms could act as neurotoxic stressors that in long-term manifest as negative symptoms, but this hypothesis has not been proven.

Overall, the main implication of these findings relate to treatment. Early intervention of FEP patients could probably reduce their DAP, thus preventing a possible neurotoxic effect and improving their long-term outcomes. A previous research in our group by Pardo-de-Santayana et al.(2020) suggests that reducing this period should be an essential focus of intervention, as it is related to the functionality of patients even 10 years after the FEP. Among the actions to implement in early intervention are the selection of an adequate antipsychotic treatment (Pelayo-Terán et al., 2008), the improvement of treatment adherence (Stowkowy et al., 2012), the reduction of drug abuse (Alvarez-Jimenez et al., 2012) and the promotion of psychosocial support (Broussard et al., 2013). Also, the possible vulnerability of patients with low IQ or low cognitive reserve to the neurocognitive deterioration caused by a prolonged DAP, indicates the importance of neuropsychological evaluation of FEP patients.

5 | LIMITATIONS

The main strength of this study was the incorporation of the variables DUP, DAT and DAP to the analysis of neurocognition. Therefore, the data about DAP was more comprehensive. However, the main limitation was to determine the cut-off points of DAP for the formation of subgroups because the literature does not offer optimal values. Furthermore, when considering active psychosis as a score greater than three on the SAPS scale, patients with residual positive psychotic symptoms were not included. In addition, there is no consensus on the measurement unit. Finally, the estimation of DAT was performed retrospectively. The calculation of positive symptom scores was meticulous and involved three experts (one psychiatrist, nurse and social worker), but there could be measurement errors associated with the collection of information through interviews with family members and patients.

6 | CONCLUSION

The present study evidences a relationship between the entire DAP and a global indicator of neurocognitive impairment in FEP patients. However, other socio-demographic variables, such us sex and premorbid adjustment, and baseline cognitive performance on attention, verbal memory and visual memory domains, were better predictors of neurocognitive impairment 3 years after the FEP.

These findings contribute in several ways to our understanding of the effects of active psychosis on the brain, and provide the basis for future research.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the collaboration of all members of the PAFIP team, as well to thank all patients and family members who participated in the study.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data supporting this study is available by requesting it from the corresponding author NMG. The data is not public because it contains confidential information that could compromise the participants' privacy.

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