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ORIGINAL ARTICLE

Predictive capacity of prodromal symptoms in first-episode psychosis of recent onset

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Background: Both the nature and number of a wide range of prodromal symptoms have been related to the severity and type of psychopathology in the psychotic phase. However, at present there is an incomplete picture focused mainly on the positive pre-psychotic dimension.

Aim: To characterize the prodromal phase retrospectively, examining the number and nature of prodromal symptoms as well as their relationship with psychopathology at the onset of first-episode psychosis.

Methods: Retrospective study of 79 patients experiencing a first-episode psychosis of less than 1 year from the onset of full-blown psychosis. All patients were evaluated with a comprehensive battery of instruments including socio-demographic and clinical questionnaire, IRAOS interview, PANSS, stressful life events scale (PERI) and WAIS/WISC (vocabulary subtest). Bivariate associations and multiple regression analysis were performed.

Results: Regression models revealed that several prodromal dimensions of IRAOS (delusions, affect, language, behaviour and non-hallucinatory disturbances of perception) predicted the onset of psychosis, with positive (22.4% of the variance) and disorganized (25.6% of the variance) dimensions being the most widely explained.

Conclusion: In addition to attenuated positive symptoms, other symptoms such as affective, behavioural and language disturbances should also be considered in the definitions criteria of at-high-risk people.

KEYWORDS

first-episode, phenomenology, prodrome, psychosis, recent-onset

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1 | INTRODUCTION

The early course of psychosis has traditionally consisted of 3 phases: premorbid phase, prodromal phase and initial psychotic phase (Tully & McGlashan, 2006). The prodromal phase of psychosis refers to the period before the onset of frank psychotic symptoms in which the first manifestations of illness or prodromal symptoms appear. There is great variability between patients regarding how their prodromes manifest; however, certain signs and symptoms are commonly described, most of them being non-specific (Yung & McGorry, 1996): reduced concentration and attention, reduced drive and motivation, depressed mood, sleep disturbances, anxiety, social withdrawal, suspiciousness, deterioration of role functioning and irritability.

Although not all patient report prodromal symptoms, approximately 80% to 90% of patients with psychotic spectrum disorder have described a variety of subacute symptoms in the months and years preceding psychosis. For this reason, in the last 2 decades, great research efforts have been made to develop and test operational criteria based mainly on subthreshold levels of psychotic symptoms (Cornblatt et al., 2003; Klosterkötter, Hellmich, Steinmeyer, & Schultze-Lutter, 2001; Yung et al., 1998). In a recent meta-analysis (Fusar-Poli et al., 2013), it was shown that there was a mean transition risk of 22% (17%-28%) at 1-year follow-up, independent of the different high-risk definitions used. Nonetheless, a majority of participants, also known as false positives, consistently do not develop psychosis over time. However, as the annual incidence for all forms of psychosis in the general population is only about 0.034% (Kirkbride et al., 2006), even the lowest conversion rates found still indicates a dramatic increase in the relative risk of illness. In this sense, having an effective mechanism to detect risk of psychosis could contribute to the development of more appropriate indicated prevention tasks. However, to date, there is a lack of consensus on the specific symptoms to include in the definition of the population at risk of psychosis, which focuses almost exclusively on subsyndromal positive psychotic symptoms such as abnormal thought content, perceptual abnormalities and speech disorders (Fusar-Poli, Carpenter, Woods, & McGlashan, 2014). As a consequence, high-risk subjects who develop severe negative symptoms or functional impairments (but no severe positive symptoms) are not considered to have transitioned to psychosis (Fusar-Poli & Van Os, 2013). In thin sense, we still need to learn the predictive capacity of different kinds of prodromal dimensions involved in the diverse incipient psychopathological manifestations of the illness in order to find more accurate detection methods. Besides, Addington et al. (2011) concluded that attenuated positive symptoms may predict a more severe condition in some, but by no means all, cases (approximately 35% developed a psychotic illness). Accordingly, positive symptoms per se do not make good predictors of psychosis. In this same line, Debbané et al. (2015), in a review study to assess the value of the schizotypy construct for the prediction of psychosis, indicated the importance of the multidimensionality of the schizotypy construct, and the value of assessing at least both the positive (cognitive-perceptual) and negative (affective-interpersonal) dimensions of schizotypy. Also, recent findings suggest that negative symptoms, cognitive impairment and a decline in functioning at baseline (Demjaha, Valmaggia, Stahl, Byrne, & McGuiere, 2012; Seidman et al., 2010; Valmaggia et al., 2013) are strongly associated with higher risk of transition to psychosis at follow-up. Moreover, Klosterkötter et al. (2001) who followed up high-risk people for 9.6 years demonstrated that the presence/absence of at least 1 basic symptom correctly predicted the presence/absence of a subsequent transition to schizophrenia in 78.1% of cases. Then, although conversion to full-blown psychosis is one possible outcome of current definitions of high-risk for psychosis, this occurs in a minority of persons. In this sense, due to limited predictive capacity and lack of consensus on the definition of the algorithms used in scientific literature to detect high-risk patients for psychosis, it is necessary to deepen into the characterization of the prodromal symptoms nearest at the onset of the psychotic episode from a retrospective approach. Thus, it will be possible to refine the definition of the population at high-risk for psychosis to be used in prospective studies, to improve their predictive capacity and to reduce the rate of false positives.

Furthermore, a combination of potential psychopathological predictors with other risk factors could help to create a new algorithm to identify who is at risk with accuracy. Among these widely studied factors are the following: genetic markers such as family history (Esterberg & Compton, 2012), gender (Willhite et al., 2008) and schizotypy (Debbané et al., 2015); environmental factors such as stressful life events (Hotzman, Shapiro, Trotman, & Walker, 2012) and cannabis exposure (Dragt et al., 2012) and clinical predictors such as age at onset (Yung, Phillips, Yuen, & McGorry, 2004) and duration of untreated illness (DUI) (Keshavan et al., 2003).

Follow-up studies of the general population with psychotic experiences consider psychosis to be a dimensional phenomenon lying on a continuum with normality. These studies have demonstrated that shifts from nonclinical to clinical outcomes of psychosis are associated with the number, severity (Hanssen, Bak, Bijl, Vollebergh, & van Os, 2005; Welham et al., 2008) and temporal continuity (persistence) of psychotic experience (Linscott & van Os, 2013). However, in a retrospective study of patients with schizophrenia, Moukas, Stathopoulou, Gourzis, Beratis, and Beratis (2010) concluded that both the nature and number of the prodromal symptoms were related to the severity as well as to the type of psychopathology in the psychotic phase. Therefore, both prospective and retrospective approaches point the clinical importance of the characterization of the early phases because they may lead to the development of quantitative (accumulation of subclinical/prodromal symptoms) and qualitative (type of subclinical/prodromal symptoms) criteria to identify full-blown psychosis. However, to our knowledge, there are no published studies linking prodromal dimensions with severity and type of psychopathological dimensions at onset of FEP, including non-affective and affective psychotic disorders.

1.1 | Aims of the study

A better understanding of the prodromal phase in patients with recent-onset FEP may help design more precise methods to early detection and so improve prognostic of these disorders. Our hypotheses were as follows: (1) there is a varied profile of prodromal

symptoms, not exclusively composed of attenuated positive psychotic symptoms that occur before the first psychotic episode and (2) there is a combination of psychopathological predictors with other risk factors (genetic markers and environmental factors) that are good predictors of the clinical onset of psychosis. Therefore, we set ourselves the following aims: (1) to study the frequency of the experienced prodromal symptoms; (2) to analyse the relationship between the number and nature of prodromal symptoms and the severity of psychopathology at the onset of FEP and (3) to assess the predictive capacity of the prodromal symptoms and certain risk factors, in the development of different psychopathological dimensions at the onset of psychosis: negative, positive, excited, disorganized and anxiety-depression dimensions (using positive and negative syndrome scale [PANSS]).

2 | METHODS

2.1 | Participants

The sample was composed of 79 consecutive patients with recent-onset FEP. The patients were recruited from adult mental health services (AMHS) at Parc Sanitari Sant Joan de Déu and from the child and adolescent mental health services (CAMHS) at the Hospital San Joan de Déu, either at a hospital or at community psychiatric services belonging to the metropolitan area and outskirts of Barcelona (Spain).

Patients were entered into the study if they: (1) had 2 or more psychotic symptoms (delusions, hallucinations, disorganized speech, catatonic or disorganized behaviour and negative symptoms); (2) were aged between 12 and 45; (3) had had an initial psychiatric visit at any centre participating in the study; (4) had had initial contact with the mental health services within the previous 6 months and (5) had less than a year since onset of psychotic symptoms. These last 2 inclusion criteria allow achieve greater homogeneity in the sample of patients with a recent-onset of psychosis, thereby avoiding the inclusion of patients with long evolution of the psychotic symptoms from the onset of the first episode. Patients were excluded if they (1) had been diagnosed with intellectual disability, head injury, dementia or any organic psychoses; (2) had a low verbal IQ (IQ < 85) or (3) had an inadequate command of Spanish or Catalan.

2.2 | Assessments

1. *Socio-demographic and clinical characteristics.* The socio-demographic characteristics (date of birth, age, gender, level of education, occupational status, socio-economic status using Hollingshead scale (Hollingshead & Redlich, 1958), current marital status and current living situation) and clinical features of the sample (age at first adequate treatment, family history, pharmacological treatment and cannabis use) were obtained with a questionnaire created specifically for this study.
2. *Diagnosis.* Principal diagnosis and comorbidities were established through the following instruments depending on patient age: The structured clinical interview for DSM-IV axis I (SCID-I) (First, Spitzer, Gibbon, & Williams, 1996) for adults and the Kiddie-schedule for affective disorders and schizophrenia (K-SADS-PL) (Kaufman et al., 1997; Ulloa et al., 2006) for adolescents. The K-SADS-PL was administered separately to parents and patients by trained researchers. Regarding psychometric properties, SCID-I has demonstrated a high level of reliability (eg, Kappas of at least 0.75 on symptoms, and 90% accuracy in diagnosis) and validity, with superior values of the SCID over standard clinical interviews (First et al., 1996). Likewise, the K-SADS-PL generates reliable and valid child psychiatric diagnoses (Kaufman et al., 1997). The Spanish version of the K-SADS-PL is a reliable instrument for the assessment of psychopathology in children and adolescents. Kappa coefficients were between the good and excellent range (kappa values range from 0.76 to 1) for present and lifetime disorders (Ulloa et al., 2006).
3. *Prodromal phase.* The interview for the retrospective assessment of the onset of schizophrenia (IRAOS) (Häfner et al., 1992) is a semi-structured interview designed to assess early signs and symptoms of psychosis, specifically for the assessment of individual social development, premorbid adjustment, onset of prodromal signs and symptoms, functional impairment and social disability. We used the indicators of the psychiatric illness section to assess prodromal symptoms in the last year before onset of FEP, in particular, the following dimensions: Non-hallucinatory disturbances of perception (IRAOS-NHDP), hallucinations (IRAOS-H), subjective disturbances of thinking and experiences (IRAOS-SDTE), delusions (IRAOS-D), cognitive impairment and/or decline (IRAOS-CI), behaviour (IRAOS-B), affect (IRAOS-A) and language (IRAOS-L). The information registered about these dimensions was completed using all available data, including clinical history data and interviews with patients and relatives. The presence of each prodromal symptom, experimented during the last year before the onset of psychotic episode, was considered taking into account the degree of conviction of patients about these symptoms. When at least 1 persistent symptom (in both duration and frequency) was held with full conviction, the onset of the psychotic episode was then considered. However, if the patient was able to cast doubt on the symptom or was able to give plausible explanation for the experience, the presence of a prodromal symptom was then considered. Age at first prodromal features, age at onset of psychotic episode, duration of initial prodrome (DPR) and DUI were assessed using the IRAOS scale. DPR was defined as the period from onset of the late prodromal symptoms until the onset of psychotic episode, and DUI was defined as the period from onset of the late prodromal symptoms until the first appropriate treatment was received. In these definitions the late prodromal symptoms refer to the symptoms experienced just prior to the onset of psychotic episode. The IRAOS interview has showed appropriate psychometric properties regarding validity measures (content validity is well founded, mainly due to its construction on the basis of expert assessments and the orientation of the research criteria across the ICD-10) and reliability measures (kappa reliability index range from 0.73 and 1.00 with regard to the determination of the exactness of the onset of symptoms) (Häfner, Löffler, Maurer, Riecher-Rössler, & Stein, 2003).

4. *Psychotic symptoms*. PANSS (Kay, Fizbein, & Opler, 1987; Peralta & Cuesta, 1994) is a scale used for measuring symptom severity, which includes 30 items scored on a Likert-type scale ranging from 1 (absent) to 7 (extreme), with higher scores indicating greater psychopathology. Internal consistency values of its subscales (positive, negative and general subscales) range between medium and high, and its convergent validity with other measures of psychiatric symptoms is high and ranges from 0.70 to 0.81. The intra-class correlation coefficient is high and rages from 0.71 to 0.80 for positive and negative subscales, respectively (Peralta & Cuesta, 1994). The evaluation was carried out assessing the maximum severity of symptoms from the onset of psychotic episode. For the purpose of this study, the 5-dimensional structure of PANSS determined by Emsley, Rabinowitz, and Torreman (2003) was used as dependent variable: negative factor, positive factor, excited factor, disorganized factor and anxiety and depression factor.
5. *Stressful life events*. Psychiatric epidemiology research interview-life events scale (PERI) (Dohrenwend, Krasnoff, Askenasy, & Dohrenwend, 1978; Vizcarro, 1987) collects information about the presence or absence of distinct stressful life events (positive and negative) during the previous year at onset of FEP. The internal consistency of the scale was good. Factorial analysis was held in which 4 areas were identified: functional discomfort, work-related stress, health problems and relationship problems, with Cronbach's alpha coefficients between 0.73 and 0.77 (Vizcarro, 1987). The Spanish version includes 102 items, which were grouped into 8 categories: academic, work, love and marriage, children, residence, legal affairs, finances and social activities. A global measure was used in this work, with higher scores indicating greater presence of stressful life events.
6. *Estimated premorbid IQ*. Wechsler adult intelligence scale (WAIS-III) Spanish version (Seisdedos et al., 1999) was used for people aged 16 or over and the Wechsler intelligence scale for children (WISC-IV) Spanish version (Corral, Arribas, Santamaría, Sueiro, & Pereña, 2005) was used for children and adolescents under 16. The estimated IQ was determined by vocabulary subtest, as several authors have previously suggested (Miralbell et al., 2010).

2.3 | Procedure

The fulfilment of the inclusion and exclusion criteria was reviewed by the clinicians, who referred the detected cases to the research team. The assessment was performed by 2 trained psychologists' experts in clinical psychology and neuropsychology. The evaluators scored over 0.70 in the intra-class correlation coefficient of all measure of the instruments before starting the study.

All participants were informed of the study aims by their psychiatrist or researcher and provided written informed consent, including parental consent for those under 18 years of age. This study was approved by the Research and Ethics Committee of Sant Joan de Déu (Barcelona, Spain) and was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

2.4 | Statistical analyses

Median, range, mean and standard deviation were used to describe continuous variables. Frequencies and percentages were used to describe categorical variables. A Kolmogorov-Smirnov test was used to test for the normality of variables. To discover the predictive power of the prodromal symptoms, multiple regression analyses were performed. First of all, we assessed the bivariate associations between the independent factors (dimensions and total score of IRAOS) and risk factors (gender, family history, cannabis use, diagnosis, age, DPR, DUI, estimated premorbid IQ and stressful life events scale) with each of the 5 outcome variables (negative dimension, positive dimension, excited dimension, disorganized dimension and anxiety and depression dimension) by *t* test (or Mann-Whitney *U* test for variables without normal distribution) for categorical predictor variables and by Pearson's correlation coefficient (or Spearman's correlation coefficient for variables deviating from normality) for continuous predictor variables. One-way ANOVA was carried out when the independent variable had 3 categories (such as IRAOS-CI). The Cohen's *d* and correlation coefficient were used for effect size. Significant variables found in bivariate analysis were then entered into the regression models using the stepwise method. Before performing the regression analyses, we analysed influential cases through Cook's distance (values greater than 1 may be cause for concern; Cook & Weisberg, 1982) and studentized residuals (values greater than 3 may be cause for concern). We analysed the normality, independency and multicollinearity assumptions of each model through the Kolmogorov-Smirnov test, Durbin-Watson test (values around 2 indicate no autocorrelation; Doménech, 2007) and the variance inflation factor (VIF) (values greater than 10 may indicate a strong linear relationship with other predictors; Chatterjee & Price, 1991). There were no missing values in the dependent variables of the study (PANSS domains). Regarding the possible predictors, there were no missing values derived from the IRAOS interview, as well as in the variables age, gender and cannabis exposure. In contrast, there were missing values in the variables family history, DPR, DUI, estimated premorbid IQ and stressful life events scale. No values were imputed. We have analysed each variable using the size sample available.

All analyses used 2-tailed *P*-values and a .05 significance level. All statistical analyses were performed with 18th version of SPSS statistical software package (SPSS, Chicago, Illinois).

3 | RESULTS

3.1 | Socio-demographic and clinical characteristics

A total of 79 people aged 12 to 45 were assessed. Approximately 73.4% of the sample (n = 58) was composed of people experiencing a first non-affective psychotic episode. The median was a better indicator than the mean since DPR and DUI were heavily skewed, with 75% of the patients having the onset of a psychotic episode within 28.5 weeks after the onset of the late prodromal symptoms and having an appropriate treatment within 41.9 weeks from the onset of the late prodromal symptoms. Tables 1 and 2

describe socio-demographic and clinical characteristics of the sample.

3.2 | Characterization of the prodromal psychosis onset

In our study, we analysed the frequency of 58 different prodromal symptoms (Table 3). All the patients in the sample except one had experienced at least some specific and proximal prodromal symptom before full-threshold psychosis; however, the quantity and nature were different in each individual case. The average number of symptoms experienced during the prodromal phase was 18 (range 0 to 37), with 6 being the lowest number of accumulated prodromal symptoms among individuals of the study sample which experiencing an active prodromal phase.

3.3 | Associations regarding clinical, genetic and environmental predictors of the clinical onset of psychosis

In terms of distribution, PANSS subscales had a normal distribution in all categorical variables except for PANSS positive and disorganized in relation to family history and PANSS negative regarding diagnosis. In the continuous variables, all variables had a normal distribution except for age, DPR, DUI and 4 IRAOS dimensions (IRAOS-NHDP, IRAOS-H, IRAOS-B and IRAOS-L). In these instances, non-parametric statistics were used.

Association analysis revealed that the accumulation of prodromal symptoms during the last year before full-threshold psychosis (total IRAOS) was correlated with the severity of incipient disorganized symptoms only. In relation to the nature of prodromal symptoms, most IRAOS dimensions, except for IRAOS-SDTE and IRAOS-CI dimensions, showed significant correlations with psychopathology dimensions assessed after the onset of episode using PANSS scale (Table 4).

In addition, regarding risk factors considered in this study, a significant relationship between cannabis exposure and PANSS negative subscale was found, indicating that patients who used cannabis showed more severity of negative psychotic symptoms at the onset of the episode than those who did not. The effect size was medium (Cohen's $d = 0.58$). Also, PANSS disorganized and positive scores were related to family history, indicating that patients having first- or second-degree relatives with a history of a non-affective or affective psychotic disorder showed more severity of positive and disorganized symptoms at the onset of the psychotic episode. Effect sizes were medium (Cohen's $d = 0.70$) or large (Cohen's $d = 0.81$), respectively. No significant correlations were found between gender, diagnosis,

TABLE 1 Socio-demographic characteristics of the sample ($n = 79$)

Socio-demographic characteristics	
Age (mean, SD)	20.22 (6.71)
Gender, *n* (%)	
Female	35 (44.3)
Male	44 (55.7)
Level of education (*n*, %)	
Primary	46 (58.2)
Secondary	21 (26.6)
High school	7 (8.9)
University	5 (6.3)
Working currently (*n*, %)	
Yes	31 (39.2)
No	46 (58.2)
Missing	2 (2.5)
Current marital status (*n*, %)	
Single	72 (91.1)
Married/cohabiting	5 (6.3)
Separated/divorced	2 (2.5)
Current living situation (*n*, %)	
Lives with others	76 (96.2)
Lives alone	1 (1.3)
Other	2 (2.5)
Socio-economic status (Hollingshead scale)[a] (*n*, %)	
I	25 (32.1)
II	24 (30.8)
III	16 (20.5)
IV	9 (11.5)
V	4 (5.1)

[a] V is the highest socio-economic level in the Hollingshead scale.

TABLE 2 Clinical characteristics of the sample ($n = 79$)

Clinical characteristics	
Age at first prodromal feature (mean, SD)	19.41 (5.99)
Age at onset of psychotic episode (mean, SD)	19.90 (6.01)
Age at first appropriate treatment (mean, SD)	20.54 (6.68)
Duration of initial prodrome (DPR), in weeks	
Median (range)	15.66 (0-226.37)
Mean (SD)	25.46 (35.58)
Duration of untreated illness (DUI), in weeks	
Median (range)	15.52 (0-226.51)
Mean (SD)	26.79 (36.24)
Daily antipsychotic medication (mg haloperidol equivalence)	
Mean (SD)	6.20 (4.90)
Principal diagnosis, *n* (%)	
Schizophrenia	7 (8.9)
Schizophreniform disorder	21 (26.6)
Schizoaffective disorder	1 (1.3)
Delusional disorder	2 (2.5)
Brief psychotic disorder	3 (3.8)
Substance-induced psychotic disorder	2 (2.5)
Bipolar disorder with psychotic features	12 (15.2)
Major depression with psychotic features	9 (11.4)
Psychotic disorder NOS	22 (27.9)
Diagnostic comorbidity, *n* (%)	
Attention-deficit/hyperactivity disorder	1 (1.3)
Adjustment disorders	1 (1.3)
Somatoform disorders	1 (1.3)
Mood disorders	2 (2.5)
Anxiety disorders	4 (5.1)
Substance-related disorders	11 (13.9)

TABLE 3 Prodromal symptoms in 79 patients with FEP

Prodromal symptoms (IRAOS)	
Non-hallucinatory disturbances of perception (IRAOS-NHDP), *N* (%)	
Derealization	28 (35.4)
Depersonalization	31 (39.2)
Unusual perception	30 (38.0)
Unusual illusions	18 (22.8)
Further perceptual disturbances (not hallucinations)	14 (17.7)
Others	5 (6.3)
Hallucinations (IRAOS-H), *N* (%)	
Auditory hallucinations	38 (48.1)
Visual hallucinations	15 (19.0)
Olfactory hallucinations	9 (11.4)
Gustatory hallucinations	4 (5.1)
Tactile hallucinations	12 (15.2)
Kinesthetic hallucinations	6 (7.6)
Cenesthetic hallucinations	18 (22.8)
Other hallucinations	33 (41.8)
Subjective disturbance of thinking and experiences (IRAOS-SDTE), *N* (%)	
Delusional mood	**61 (77.2)**
Thoughts being read	31 (39.2)
Thought insertion	7 (8.9)
Thought broadcasting	26 (32.9)
Thought echo or commentary	5 (6.3)
Thought blocking	**46 (58.2)**
Thought withdrawal	10 (12.7)
Passivity experiences	**79 (100)**
Weakness of focused thinking	**45 (57.0)**
Delusions (IRAOS-D), *N* (%)	
Overvalued idea	**60 (75.9)**
Delusions of control	25 (31.6)
Delusions of reference	**55 (69.6)**
Delusional perception, misperception	31 (39.2)
Delusions of persecution	**56 (70.9)**
Expansive delusions	27 (34.2)
Delusions of love	15 (19.0)
Delusions concerning appearance	9 (11.4)
Delusions of guilt	22 (27.8)
Nihilistic delusions	12 (15.2)
Hypochondriacal delusions	14 (17.7)
Bizarre delusions	21 (26.6)
Delusional ideas	13 (16.5)
Preoccupation with secret things/unusual thought contents	32 (40.5)
Other delusions	8 (10.1)
Cognitive impairment and/or decline (IRAOS-CI), *N* (%)	
Impairment of memory	44 (55.7)
Increased distractibility/disturbance of attention	**66 (83.5)**
Behaviour (IRAOS-B), *N* (%)	
Catatonic symptoms (hypokinesia or akinesia)	28 (35.4)
Catatonic symptoms (hyperkinesia)	18 (22.8)
Antisocial behaviour	18 (22.8)
Self-injury	22 (27.8)
Odd behaviour	4 (5.1)
Other behavioural abnormalities	5 (6.3)
Affect (IRAOS-A), *N* (%)	
Oversensitivity	**59 (74.7)**
Affective flattening	41 (51.9)
Loss of affective reactivity	36 (45.6)
Lability of affect	40 (50.6)
Incongruity of affect	15 (19.0)
Other changes in affect	6 (7.6)
Apathy	**50 (63.3)**
Language (IRAOS-L), *N* (%)	
Poverty of content of speech	26 (32.9)
Neologisms	9 (11.4)
Incoherence	33 (41.8)
Derailment	41 (51.9)
Non-verbal communication	31 (39.2)

The 10 prodromal symptoms more frequent are showed in italics.

age, DPR, DUI, estimated premorbid IQ and stressful life events scale with any PANSS subscales (Table 4).

3.4 | Prediction analysis of the clinical onset of psychosis

A multiple regression model was created for each psychopathology dimensions of PANSS (negative, positive, excited, disorganized and anxiety/depression). All models were stable across the sample and no strong correlation between 2 or more predictors existed in the regression models (Cook's distance <1; VIF >10). The regression model constructed to explore the predictors of positive psychotic symptoms at onset of illness revealed that both family history and IRAOS-D were significant predictors. They explained 22.4% of the overall severity of positive symptom variance. Furthermore, in relation to the regression model used to study the predictors of negative psychotic dimensions, IRAOS-A was the only significant predictor, explaining 8.5% of the overall severity of negative symptom variance. In relation to the severity of disorganized symptoms at the onset of illness, all predictors included in the model, family history, IRAOS-D and IRAOS-L were significant predictors. This model explained 25.6% of the overall severity of disorganized symptom variance. In the regression model constructed to predict incipient excited psychotic symptoms, IRAOS-B was the only significant predictor, explaining 7.0% of the overall excited symptom variance. Lastly, we examined the predictors of anxiety/depression symptoms at the onset of illness. The regression model revealed that IRAOS-NHDP was the only significant predictor, explaining 7.9% of the overall severity of anxiety/depression symptom variance (Table 5).

4 | DISCUSSION

4.1 | Main findings: Qualitative approach

From a qualitative point of view, the results of this study revealed that the 10 most frequent prodromal symptoms were the following:

TABLE 4 Associations between possible predictors and outcome variables

	PANSS positive		PANSS negative		PANSS disorganized		PANSS excited		PANSS anxiety and depression	
	Static	*P*	Static	*P*	Static	*P*	Static	*P*	Static	*P*
Possible predictors										
Qualitative variables										
Gender	.643[b]	.522	−.600[b]	.550	.100[b]	.921	.302[b]	.763	.076[b]	.244
Family history	383.500[a]	**.002**	−.584[b]	.561	387.000[a]	**.006**	.614[b]	.541	−.092[b]	.927
Cannabis exposure	1.135[b]	.261	478.000[a]	**.008**	−.759[b]	.450	1.213[b]	.229	−.297[b]	.767
Diagnosis	−.370[b]	.712	−.004[b]	.997	−.728[b]	.469	−1.509[b]	.136	−1.194[b]	.237
Quantitative variables										
Age (years)	−.209[d]	.064	−.263[d]	−.187	−.187[d]	.106	−.095[d]	.407	−.192[d]	.089
DPR (weeks)	−.088[d]	.480	.123[d]	.323	−.196[d]	.120	.077[d]	.538	.039[d]	.756
DUI (weeks)	−.132[d]	.290	.108[d]	.387	−.111[d]	.387	−.024[d]	.847	−.032[d]	.800
IRAOS-NHDP	.119[d]	.296	.123[d]	.279	.235[d]	**.041**	.027[d]	.814	.226[d]	**.045**
IRAOS-H	.272[d]	**.015**	−.127[d]	.266	.186[d]	.108	.224[d]	**.047**	.035[d]	.762
IRAOS-SDTE	.092[c]	.422	.030[c]	.792	.098[c]	.402	−.019[c]	.870	.092[c]	.420
IRAOS-D	.366[c]	**.001**	.033[c]	.770	.310[c]	**.006**	.146[c]	.199	.056[c]	.622
IRAOS-CI	.855[e]	.429	.230[e]	.795	.949[e]	.392	.090[e]	.914	.354[e]	.703
IRAOS-B	.134[d]	.238	.143[d]	.208	.202[d]	.081	.269[d]	**.017**	.301[d]	**.007**
IRAOS-A	−.183[c]	.106	.291[c]	**.009**	.181[c]	.118	−.075[c]	.509	.058[c]	.610
IRAOS-L	−.122[d]	.285	−.263[d]	**.019**	.276[d]	**.016**	−.085[d]	.455	−.016[d]	.886
IRAOS total	.191[c]	.092	.183[c]	.107	.358[c]	**.002**	.057[c]	.615	.150[c]	.187
Estimated premorbid IQ	.187[c]	.113	−.025[c]	.832	−.027[c]	.823	.054[c]	.652	−.024[c]	.841
Stressful life events scale	.183[c]	.142	−.136[c]	.278	−.009[c]	.946	.140[c]	.262	.016[c]	.896

Abbreviations: DPR, duration of initial prodrome; DUI, duration of untreated illness; IRAOS-NHDP, IRAOS-non-hallucinatory disturbances of perception; IRAOS-H, IRAOS-hallucinations; IRAOS-SDTE, IRAOS-subjective disturbance of thinking and experiences; IRAOS-D, IRAOS-delusions; IRAOS-CI, IRAOS-cognitive impairment; IRAOS-B, IRAOS-behaviour; IRAOS-A, IRAOS-affect; IRAOS-L, IRAOS-language. Family history: Refers to first and second-degree relative with a history of a non-affective or affective psychotic disorder. Cannabis exposure: Refers to use vs non-use of cannabis. Diagnosis: Refers to non-affective psychosis vs affective psychosis. Boldface indicates significant association.
[a] *t* test to parametric data (2-tailed).
[b] Mann-Whitney *U* test to non-parametric data.
[c] Spearman correlation to non-parametric data.
[d] Pearson's correlation to parametric data.
[e] One-way ANOVA to independent variables with only 3 values.

passivity experiences, increased distractibility/disturbance of attention, delusional mood, overvalued ideas, oversensitivity, delusions of persecution, delusions of reference, apathy, thought blocking and weakness of focused thinking. Therefore, this is an extremely variable symptom profile, including attenuated psychotic symptoms (APS; mainly disturbances of thinking), affective/negative and cognitive symptoms. In reference to the positive dimension, we found that prodromal symptoms, such as attenuated or subthreshold versions of psychotic symptoms (delusions or perceptual abnormalities), were good predictors of positive symptoms in the psychosis active phase. Similarly, Moukas et al. (2010) concluded that 3 of the 5 prodromal symptoms that carried a significantly greater risk for severe PANSS positive psychopathology were positive pre-psychotic symptoms. Our results support the inclusion of APS in the definitions of risk criteria for psychosis used in previous studies (Addington et al., 2007; Klosterkötter et al., 2005; Yung et al., 2003). However, in this study, attenuated positive psychotic symptoms are not the only predictor of onset of psychosis. Other types of prodromal symptoms such as language

TABLE 5 Multiple regression analyses for each of the 5 PANSS domains

	Baseline predictors	R^2	R^2_{change}	*F*	beta	*t* value	*P* value
PANSS positive	Family history	0.224	0.129	10.999***	0.305	2.979	.004**
	IRAOS-D		0.095		0.314	3.059	.003**
PANSS negative	IRAOS-A	0.085	0.085	7.133**	0.291	2.671	.009**
PANSS disorganized	Family history	0.256	0.103	8.257***	0.308	2.966	.004**
	IRAOS-D		0.067		0.242	2.339	.022*
	IRAOS-L		0.086		0.296	2.891	.005**
PANSS excited	IRAOS-B	0.070	0.070	5.839*	0.265	2.416	.018*
PANSS anxiety and depression	IRAOS-NHDP	0.079	0.079	6.585*	0.281	2.566	.012*

Abbreviations: IRAOS-NHDP, IRAOS-non-hallucinatory disturbances of perception; IRAOS-H, IRAOS-hallucinations; IRAOS-D, IRAOS-delusions; IRAOS-B, IRAOS-behaviour; IRAOS-A, IRAOS-affect; IRAOS-L, IRAOS-language. *$P < .05$; **$P < .01$; ***$P < .001$.

disturbances were related to disorganized active symptoms at the onset of illness. Similarly, Gourzis, Katrivanou, & Beratis (2002) showed that one of the prodromal symptoms with the greatest specificity for the disorganized subtype was poverty of content of speech. It seems that patients who experience delusions and language problems in the prodromal phase may develop more severe psychosis, similar to the disorganization dimension defined by Murray et al. (2005) which, among other symptoms, includes speech disturbances (ie, difficult to understand or incoherent). Furthermore, we observed that the presence of familial loading for the illness was a significant predictor of disorganized and positive dimensions at the onset of the FEP. This finding provides more evidence regarding the criteria selected to define people with ultra-high-risk for psychosis, adding a variable of genetic risk (family history) in order to enhance the predictive power.

In relation to the excited dimension, we found prodromal behavioural abnormalities to be the main and exclusive predictor. This finding supports the appropriateness of including "gross disorganized or catatonic behaviour" in the set of symptoms for the definition of the late initial prodromal stage (LIPS), which attempts to identify those at more immediate risk (Ruhrmann, Schultze-Lutter, & Klosterkötter, 2003) or "odd behaviour" to define the APS group (Yung et al., 2003). Disorganized behaviour is among the most replicated predictors of transition to psychosis and poor longitudinal functioning (Demjaha et al., 2012; Fusar-Poli et al., 2013).

Regarding the negative dimension, our results showed that the emotional disturbances in the prodromal phase were the only predictor. These affect impairments could be considered as the expressivity dimension of attenuated negative symptoms. Our results show that a profile characterized by these subclinical symptoms could predict the first presentation of broader negative symptoms, not only related to expressivity symptoms (ie, affective flattening) but also for an experiential dimension (ie, social withdrawal or active social avoidance). Previous studies have also found that attenuated negative symptoms may be a risk factor for transition to psychosis in a clinical high-risk population (Lencz, Smith, Auther, Correll, & Cornblatt, 2004; Piskulic et al., 2012) and have included emotional disturbances such as subjectively abnormal emotional experiences (Yung et al., 2005) and blunted affect (Mason et al., 2004; Yung et al., 2005) among negative-type subclinical psychotic symptoms. A recent study (Lyne et al., 2014) concluded that negative symptoms at prodrome onset predicted negative symptoms at first presentation with psychosis, specifically experiential symptoms.

In relation to the dimension of anxiety and depression analysed in this study, non-hallucinatory disturbances of perception showed predictive capacity for psychotic episodes characterized by affective symptoms. Moukas et al. (2010) showed that patients experiencing hyperacusis during the prodromal phase scored significantly higher on the general PANSS at onset of frank psychosis. Both findings could be important for future retrospective studies geared to optimizing risk criteria for affective psychosis.

In summary, these results indicate that attenuated positive psychotic symptoms are good predictors of the clinical onset of the psychosis active phase, but they are not the only ones. In this sense, the definitions of risk criteria for psychosis should include a wider range of subclinical symptoms with good predictive capability for the onset of psychosis, such as language problems, disorganized behaviour, affective impairments and non-hallucinatory disturbances of perception. In addition, another factor that should be maintained in the definitions of risk for psychosis is the presence of psychotic familial loading in order to enhance the predictive power.

4.2 | Main findings: Quantitative approach

From a quantitative approach, it should be noted that the great majority of, although not all, first-episode patients show at least some prodromal symptom prior to onset of the psychotic disorder (Häfner et al., 2003; Yung & McGorry, 1996). In our sample, only 1 patient did not report the presence of prodromal symptoms. Regarding the number of prodromal symptoms accumulated until culmination of the FEP, this study shows that approximately a third of the prodromal symptoms analysed appeared in the last year before the onset of episode, and a greater presence of prodromal symptoms was associated with more disorganized psychosis. Similar results were found by Moukas et al. (2010) but in relation to positive and general PANSS. Häfner et al. (1995) in a follow-back study of first-episode schizophrenia observed that in the year prior to onset, symptoms were accelerated in number and intensity up to the psychosis threshold. In addition, the study revealed that this accumulation in the early course of illness occurs in a mixture of 3 clinical symptom categories (nonspecific, negative and positive symptoms). From the psychosis continuum model, a greater load of subclinical psychotic experiences is considered to be a predictor of greater probability of clinical outcome (Kaymaz & van Os, 2010).

Lastly, one limitation of our study is related to the characterization of prodromal phase of psychosis through a retrospective approach. This design entails a great limitation in the accuracy of assessment of predictors for psychosis when the illness has already appeared, which may lead to inaccurate reporting. However, this study investigates a broad spectrum of proximal prodromal symptoms, which have been experimented in the year before the debut of FEP, thus reducing memory biases. So, an advantage of this study is the fact that only patients who had recently developed the psychotic stage were investigated for their prodromal symptoms and they therefore had better recollection of events in the pre-psychotic period. Moreover, the clinical information analysed in this research has been collected and contrasted with a variety of information sources (personal interviews with patients, family information, professional information or/and chart histories) in an attempt to overcome this limitation.

On the other hand, we have taken into account the complexity of the phenomena under study, since there is a very narrow line between prodromal symptoms and full-psychotic symptoms, making it difficult to establish differences between them. The following criterion was determined to define a symptom as attenuated or prodromal and not fully psychotic: a lack of conviction about the "real" nature of symptoms.

5 | CONCLUSION

This study provides evidence of symptomatic heterogeneity in the proximal prodromal phase of transition to psychosis, not only

including sub-threshold positive psychotic symptoms. Second, the number of prodromal symptoms accumulated to full-threshold of psychosis is associated with the kind of psychopathology in the initial psychotic phase of the illness, specifically with disorganized dimension. Lastly, prodromal dimensions have differing capacities for predicting psychopathological dimensions at the onset of psychosis, with positive and disorganized dimensions being the most widely predicted.

These findings therefore indicate that the development of each dimension of full-blown psychosis is already differentially programmed from the prodromal phase. Future research should be directed at studying whether or not identified specific groups of FEP (Ochoa et al., 2013) are characterized by different prodromal symptoms.

Our findings may have clinical implications in relation to several issues: (1) prodromal characteristics identified in retrospective studies could be regarded as a new class of risk factors in prospective studies, especially those focused on indicated prevention; (2) the psychosis risk algorithms used to date should be modified, taking into account a broader approach with negative and less-specific subclinical symptoms (such as behavioural, language and emotional disturbances) and this might guide future research regarding the phenomenology of the "attenuated psychosis syndrome," currently considered to be a category in section III of DSM-5 under "conditions for further study." In addition, as indicated from the European Psychiatric Association (EPA) (Schultze-Lutter et al., 2015), other potential risk factors should be taken into account to increase the predictive capacity of these algorithms (eg, a positive family history of psychosis or neurocognitive abnormalities, among others); (3) new specific and stage-appropriate treatments should be developed, taking into account the heterogeneity of symptoms prior to the first manifestations of illness and aimed at ameliorating the distress caused by these symptoms (Carpenter, 2009). The focus of interventions in high-risk patients needs to be broadened with regard to outcomes and intervention approaches, as recommended by the EPA (Schmidt et al., 2015).

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Conflict of interest

The authors declare no potential conflict of interests.

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