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Symptomatic and functional outcome in youth at ultra-high risk for psychosis: A longitudinal study

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ABSTRACT

The current report assesses the clinical, functioning and demographic data of a cohort enrolled in the P3 prevention program for psychosis; a Spanish National Health System and Ministry of Science funded program. Comparisons are made between those individuals who had converted to psychosis and those who had not at 3 years after an average of 24 treatment sessions. Subjects included 61 participants meeting Structured Interview for Prodromal Syndromes criteria, with ages ranging from 17 to 31, and all meeting criteria for ultra-high risk of psychosis. Prospective follow-up data are reported for patients re-evaluated at 1 and 3 years. At 1-year follow-up, the conversion rate to psychosis was 18%, but increased to 23% at 3-year follow-up. The converted sample was older than the non-converted sample and more likely to have higher ratings on subsyndromal psychotic (positive and disorganized), negative and general symptoms, and lower levels of functioning at baseline assessment. Analyses of change over time indicated a clear clinical improvement in both clinically stable patients and in those who showed a transient psychotic state over time. No gender differences in symptom or functioning levels at the three follow-up time points were found; however, the interactions among conversion × gender × SOPS total score × time points significantly reflect that the growth profiles of the four groups (no conversion males, no conversion females, conversion males and conversion females) in the SOPS total score are not parallel and that, consequently, the four groups involved different patterns of change over time, males experiencing faster and longer deterioration when psychotic symptoms arise.

1. Introduction

The scientific interest and activity in the prodrome of psychosis is worldwide, and literature regarding this realm is expanding rapidly (Addington et al., 2007) since the early detection and treatment of psychotic disorders represents one of the most stimulating and significant challenges of the last few years in all areas of mental health care (McGlashan et al., 2007; McGorry et al., 2008).

While research is trying to elucidate the etiopathogenesis of psychotic disorders as a possible clue to the universal or selective primary prevention strategies for these severe and disrupting illnesses, clinical intervention programs have tried to enhance indicated primary prevention through early detection of at ultra-high risk (UHR) individuals.

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The prospective studies carried out in the last decade regarding the efficacy of the early intervention programs for psychosis have shown that treatments, regardless of being psychological or pharmacological, are more effective than placebo or simple supervision in the attainment of delaying transition to psychosis; combined interventions (psychological and pharmacological) obtain the best results; and early detection and intervention services present better results than traditional services. In addition, it has been observed that these results are especially important during the first year of active intervention and that, if said treatment is interrupted in the following three years, the intergroup differences disappear. Nevertheless, the psychosis-transition rates with combined treatments (psychosocial and antipsychotics) or only with Cognitive Behavior Therapy (CBT), fall between 6% and 26% for the first year and around 26% after three years (Broome et al., 2005; Cornblatt et al., 2004; McGorry et al., 2002; Morrison et al., 2007; Nordentoft et al., 2006; Phillips et al., 2007).

Many variables have been found to be associated with risk of conversion to psychosis in previous studies, including genetic risk with recent deterioration of functioning, severity of prodromal symptoms, greater social impairment, and substance abuse (Cannon et al., 2008; Haroun et al., 2006; Yung et al., 2004, 2006).

Gender differences have also been found in clinical presentation in UHR patients (Willhite et al., 2008) and, among young adults with a diagnosis of schizotypal personality disorder, it has been found that male individuals have a four-fold risk for conversion to schizophrenia one year after enrollment in a prevention program when compared to female patients (Nordentoft et al., 2006). Accordingly, it is likely that negative symptoms mediate differences in functioning between male and female patients that may predate conversion to psychosis (Willhite et al., 2008); although substance dependence could also explain a higher risk for conversion to psychosis in men (Chen and Murray, 2004).

To our knowledge, no studies have examined gender recovery profiles in UHR individuals when comparing patients with and without conversion to psychosis in the follow-up and particularly when the interaction of conversion to psychosis, gender and time points is considered.

The primary goal of this study was to explore several fundamental questions related to prodromal psychosis: 1) the impact of an early treatment on the course of prodromal symptoms in UHR youths, and particularly on conversion rates; 2) the risk of progression to psychosis with predictor variables; and 3) differential gender recovery profiles in the follow-up.

2. Method

2.1. Participants

The research was conducted with UHR participants enrolled in a prevention program for psychosis (P3) (www.p3-info.es), implemented in a public mental health service of the Sierrallana Hospital in northern Spain, and modelled after the program in Australia (Yung et al., 1996).

A total of 103 individuals were recruited and screened primarily by clinical referral in a catchment area of about 170,000 inhabitants. Referral sources were family physicians and other mental health and allied professionals, after recruitment campaigns, or family referrals in response to the P3 website; no participants were help seeking.

With the aim of improving primary care practitioners' skills for the detection, recruitment and referral of first-episode psychosis patients, three types of interventions were designed: an educational workshop, the delivery of information materials and the improvement of the assistential itinerary.

Any subject with valid SIPS/SOPS diagnosis (McGlashan et al., 2001a,b) at initial assessment was admitted into the baseline data. Forty-two did not meet UHR criteria for any of the prodromal syndromes, and 61 did as assessed by the SIPS/SOPS, and were included in the current study. Eligible UHR individuals were between the ages of 15 and 31 years, and were comparable in socioeconomic background, measured by level of parental education and employment at baseline. Exclusion criteria were the presence of neurological disorder and IQ below 70. All individuals who did not participate in the program were given referrals to other treatment facilities if desired. Informed consent was obtained from all subjects to enter the prevention program. For those under 18, parental informed consent was also required. No incentive was offered to patients for their participation in the study, but they were clearly informed that they had been referred to the study because they had had changes in their thoughts, behavior, or emotions, and that the program was specifically interested in problems experienced by young people.

2.2. Measures

At intake, all potential at-risk subjects received a comprehensive clinical assessment. The Structured Interview for Prodromal Syndromes (SIPS) was used as part of an extensive assessment protocol comprising a review of clinical symptoms, personality traits, neurocognitive measures, medical and medication history, social and family functioning. The SIPS is a semi-structured diagnostic interview designed by McGlashan and colleagues to specifically assess attenuated schizophrenia-like symptomatology for identifying prodromal states (Lemos et al., 2006; McGlashan et al., 2001a,b; Miller et al., 1999), which includes five components: a 19-item Scale of Prodromal Symptoms (SOPS), the Global Assessment of Functioning (GAF) scale (Hall, 1995) with well-defined anchor points, a DSM-IV schizotypal personality disorder checklist, a family history of mental illness, and a checklist for the Criteria of Prodromal Syndromes (Yung et al., 1998).

The SOPS contains five items to measure Positive symptoms, six items measuring Negative symptoms, and four items measuring Disorganization. There are also four items measuring General (non-specific) symptoms. In all cases, symptoms are rated from 0 ('absent') to 6 ('severe and psychotic', in the positive symptoms scale, and 'extreme' in the three other scales), with detailed, specific probes and anchors provided to determine level of severity.

All interviews were conducted by O.V. (Ph.D.) and other psychologists who have undergone specific training by Tandy Miller, one of the developers of the SIPS, in using the interviews and have commensurate clinical experience. Although the interview can, of course, be administered and scored in a single

session, a "dynamic" method was used in our study. According to this method, the interview was administered on three occasions in the first 4 weeks. Diagnoses of the converted patients to psychosis were obtained by expert psychiatrists using DSM-IV-RT criteria.

2.3. Procedure

The following clinical groups and operational criteria for psychosis proneness by Yung et al. (1998) were used at the time of index evaluation to enter the prevention program: 1) Attenuated Positive Prodromal Syndrome (APS); 2) Brief, limited, and intermittent psychotic syndrome (BLIPS); and 3) Genetic risk or Schizotypal Personality Disorder, and deterioration in functioning (GR or SPD + DF). Of the 61 participants, 52 (85.2%) met the APS criteria, 3 (4.9%) met the criteria for BLIPS, and 6 (9.8%) met the criteria for GR or SPD + DF.

Since psychological processes, such as meta-cognitions and self-schemas, play an important role in the transition from prodromal state to psychosis ('thought–emotion–behavior cycles'), all participants entering the study were offered a formulation-driven CBT intervention as described by French and Morrison (2004), consisting of an average of 24 planned sessions over 12 months (1 weekly session over the first term, 1 session every two weeks over the second term, and 1 monthly session over the second semester). During the follow-up period, one booster session every two or three months was also scheduled. Individual family therapy sessions were also scheduled with the same frequency.

Therapy targets with patients were attenuated positive symptoms (suspiciousness, ideas of reference, and thought broadcasting), suicide ideation and suicide prevention, self-concept (blame, uselessness and failure as a person), common emotional disorders present in high-risk individuals, and vocational guidance or reformulation of school and work aims.

Family therapy targets were psychoeducation, relationships at home, stress management, problem solving, secondary family anxiety and uncertainty of psychosis risk (Barrowclough and Tarrier, 1992).

Antipsychotic medication was also offered (Olanzapine 2.5–5 mg/day or Risperidone 1–2 mg/day) during the first semester of the treatment program to those patients who scored 5 on whichever P1–P5 items of the SOPS and who also showed acute clinical or functional impairment; however, each patient chose the treatment modality they preferred to undertake. Thirteen people (21.3%) exclusively received CBT, 37 (60.7%) a combined treatment of CBT and medication, and 11 (18 %) only accepted medication but not CBT.

Participants were re-assessed with the SIPS measures 12 and 36 months after the baseline assessment. Among these individuals, any subject who had completed at least one subsequent clinical evaluation (12 or 36 months) was included in the follow-up analyses. Information at all three time points was available on 27 of the original 61 participants (63% males). Data recording for this study began in 2002 and was completed in 2008 for follow-up.

Sixteen people (26.2%) had not been in the study long enough to have completed all the follow-up assessments. Six participants (9.8%) dropped out of the treatment and were non-contactable due to mobility (change of residence), 5 (8.2%) decided to be treated by a private-practice professional, and 5 (8.2%) dropped out supposedly due to their lack of interest in the treatment program, leaving a sample of 45 cases available for the follow-up analysis.

The procedure of this study was fully explained to all subjects and/or their legal guardians. Treatment protocol and informed consent procedures were approved by the Sierrallana Hospital ethics board.

2.4. Data analyses

Comparisons were made between those participants who had converted to psychosis and those who had not at 3 years after the treatment program. Appropriate parametric analyses were performed to compare clinical and demographic variables between groups.

2.4.1. Follow-up analyses

Participants have been recruited into the three-year longitudinal assessment study with naturalistic design. In order to assess changes in clinical symptoms (SOPS Positive, Negative, Disorganized, General scales, and SOPS total score), and functioning over time (GAF score) and to compare pattern changes of patients enrolled in the P3 program who made a conversion from UHR to psychosis and of those who did not, as well as gender differences in all six dependent variables simultaneously, repeated measures were obtained at three follow-up points, consisting of a Time 1 baseline assessment of participants at intake; at the end of the intervention program (Time 2), 12 months later, and two years later (Time 3) (assessing the period between Time 2 and Time 3). Participants' general functioning one year before intake was also rated at the baseline assessment. No correction parameter was used in the administration of repeated measures assessment.

A multivariate mixed model procedure adjusted by the Kenward–Roger solution available in SAS Proc Mixed (SAS Institute, 2007, version 9.1) was used. Age was introduced as covariate. Codes and tricks to fit these analyses using Proc Mixed are provided by Vallejo et al. (2007). Subsequently, having decided a reasonable model for the data by assuming a direct product first-order autoregressive model, the analyses were performed for the dependent variables separately because global significant differences were found.

3. Results

3.1. Demographic variables

Information regarding demographic data can be found in Table 1. There were no differences between male and female participants enrolled in this study on any demographic factors at baseline and on drop-out rates in the follow-up period, except on substance use which was somewhat more likely among male subjects.

3.2. Baseline differences

No significant differences were found in SOPS symptom ratings and GAF scores at baseline assessment between individuals who completed all the follow-up assessments and those who did not.

Table 1
Sample characteristics at baseline assessment.

Variables	Males ($n=40$)	Females ($n=21$)	Total ($n=61$)
Age (years), mean (SD), range	22.25	20.67	21.70
$t(59)=1.55$, $p=0.126$	(3.64), 17–31	(4.05), 15–30	(3.83), 15–31
Education			
Primary school, % (n)	42.5 (17)	33.3 (7)	39.3 (24)
Higher school, % (n)	22.5 (9)	28.6 (6)	21.3 (15)
Professional studies, % (n)	22.5 (9)	19.0 (4)	24.6 (13)
University studies, % (n)	12.5 (5)	19.0 (4)	14.8 (9)
$\chi^2(3)=0.978$, $p=0.807$			
Years of education, mean (SD)	10.68	11.14	10.84
$t(59)=-0.661$, $p=0.511$	(2.61)	(2.68)	(2.61)
Premorbid			
DUI [a] (months), mean (SD)	20.63	26.19	22.54
$t(59)=-0.751$, $p=0.456$	(25.41)	(31.18)	(27.40)
Drugs use [b], % (n)	60.0 (24)	33.3 (7)	50.8 (31)
$\chi^2(1)=3.918$, $p=0.048$			
Family history of psychosis, % (n)	32.5 (13)	38.1 (8)	34.4 (21)
$\chi^2(1)=0.191$, $p=0.662$			
GAF [c] (last year), mean (SD), range	68.58	68.86	52.30
$t(59)=0.057$, $p=0.955$	(18.32), 31–100	(18.99), 37–100	(12.55), 31–100
Drop-outs in the follow-up, % (n)	22.5 (9)	33.3 (7)	26.2 (16)
$\chi^2(1)=0.835$, $p=0.361$)			

[a] Duration of untreated illness, estimated on the basis of time between onset of symptoms and entry into the service. DUI was calculated by means of multiple source interviews, with patients and families.
[b] Illegal drugs use, without substance dependence.
[c] Global Assessment of Functioning: scores range from 0 to 100, higher scores indicating better levels of functioning.

The comparison among the three clinical APS, BLIPS and GR or SPD + DF groups did not reveal significant differences either in baseline SOPS positive, negative, disorganized and general symptoms, or in the GAF (Wilks' $\lambda=0.909$, $p=0.866$); however, significant differences were obtained in the overall analysis of the variables when patients were compared according to the three treatment modalities (Wilks' $\lambda=0.718$, $p=0.047$). Thus, patients receiving combined treatment of CBT and medication showed the highest ratings at baseline in every SOPS subscale, but not in the GAF; there were no significant differences in ratings on any of the symptoms scales or in psychosocial functioning between participants exclusively receiving CBT or medication.

As depicted in Table 2, significant differences were also found at baseline in the symptom scales when participants who made a transition to psychosis in the follow-up period and those who did not were compared, as the first group had been consistently worse at intake into the intervention program; nevertheless, using the conservative $\alpha=0.008$ after Bonferroni correction, negative symptoms did not significantly separate the groups. Concerning the GAF score, no significant difference exists between both groups.

Finally, as expected, male patients enrolled in the P3 program were found to have higher negative symptom ratings at baseline, although group differences were marginally significant (Table 3).

3.3. Outcome measures: conversion rates from UHR to psychosis

The conversion rate to psychosis was 18.03% ($n=11$) in the first year, and 22.95% ($n=14$) in the three-year follow-up period without gender statistical differences (9 males and 5 females, 22.5% and 23.8%, respectively); however, the rates were quite different among the three treatment groups. Thus, the transition rate was 27% in patients that only received medication, 0% in patients treated with CBT, and 29% in patients receiving both CBT and medication. Nevertheless, overall differences in conversion rates to psychosis in the

Table 2
Symptoms rating at all time points, comparing patients who made a transition to psychosis in the follow-up period and those who did not.

	No transition to psychosis ($n=47$)			Transition to psychosis ($n=14$)		
	Baseline ($n=47$)	12 month ($n=31$)	36 month ($n=20$)	Baseline ($n=14$)	12 month ($n=11$)	36 month ($n=7$)
Symptom measures [a]						
Positive symptoms, mean (SD)	10.57 (4.61)	4.26 (4.00)	1.30 (2.56)	15.00 (3.72)	12.00 (5.55)	6.14 (4.95)
Baseline $t(59)=-3.284$, $p=0.002$						
Over all time points $F(1, 57)=16.98$, $p<0.0001$						
Negative symptoms, mean (SD)	17.53 (8.21)	8.58 (7.80)	3.05 (4.70)	22.21 (6.01)	18.73 (8.17)	10.00 (5.29)
Baseline $t(59)=-1.976$, $p=0.053$ [b]						
Over all time points $F(1, 57)=10.68$, $p=0.002$						
Disorganized symptoms, mean (SD)	9.19 (3.50)	4.06 (3.61)	1.85 (2.62)	13.64 (3.00)	10.18 (4.33)	3.43 (2.22)
Baseline $t(59)=-4.311$, $p<0.000$						
Over all time points $F(1, 57)=16.11$, $p<0.0001$						
General symptoms, mean (SD)	11.11 (3.01)	5.37 (4.14)	2.29 (3.15)	13.79 (2.58)	9.00 (2.21)	6.38 (3.02)
Baseline $t(59)=-3.014$, $p=0.004$						
Over all time points $F(1, 57)=19.74$, $p<0.0001$						
SOPS total score, mean (SD)	48.47 (15.29)	22.61 (17.86)	8.74 (11.94)	64.64 (10.08)	48.36 (16.03)	24.43 (13.26)
Baseline $t(59)=-3.714$, $p<0.000$						
Over all time points $F(1, 57)=19.01$, $p<0.0001$						
GAF [c]	53.66 (11.96)	71.35 (15.86)	80.60 (11.05)	47.71 (13.84)	54.18 (10.59)	69.14 (10.16)
Baseline $t(59)=1.575$, $p=0.121$						
Over all time points $F(1, 57)=7.09$, $p=0.010$						

[a] Scale of Prodromal Symptoms (SOPS).
[b] Bonferroni correction for baseline comparisons, $p<0.008$.
[c] Global Assessment of Functioning.

Table 3
Symptoms rating at all time points, for males and females.

	Baseline ($n=61$)		12 month ($n=42$)		36 month ($n=27$)	
	Males ($n=40$)	Females ($n=21$)	Males ($n=28$)	Females ($n=14$)	Males ($n=17$)	Females ($n=10$)
Symptom measures [a]						
Positive symptoms, mean (SD)	11.65 (4.32)	11.48 (5.65)	5.71 (5.68)	7.43 (5.39)	2.88 (4.33)	2.00 (3.13)
Baseline $t(59)=0.134$, $p=0.894$						
Over all time points $F(2,61)=0.19$, $p=0.826$						
Negative symptoms, mean (SD)	19.83 (7.22)	16.29 (8.96)	11.11 (9.07)	11.50 (9.22)	6.59 (6.19)	1.90 (3.07)
Baseline $t(59)=1.673$, $p=0.100$						
Over all time points $F(2,61)=0.07$, $p=0.930$						
Disorganized symptoms, mean (SD)	10.40 (3.51)	9.86 (4.52)	5.07 (4.96)	6.86 (3.82)	2.65 (2.67)	1.60 (2.41)
Baseline $t(59)=0.519$, $p=0.606$						
Over all time points $F(2,61)=0.13$, $p=0.880$						
General symptoms, mean (SD)	12.05 (2.96)	11.10 (3.36)	5.56 (4.05)	7.77 (3.77)	3.50 (3.45)	3.27 (3.95)
Baseline $t(59)=1.142$, $p=0.258$						
Over all time points $F(2,61)=0.85$, $p=0.432$						
SOPS total score, mean (SD)	54.00 (13.96)	48.71 (18.58)	27.11 (20.83)	33.86 (20.36)	16.00 (14.89)	8.10 (11.42)
Baseline $t(59)=1.251$, $p=0.216$						
Over all time points $F(2,61)=0.20$, $p=0.820$						
GAF [b]	52.23 (11.66)	52.43 (14.40)	69.07 (16.92)	62.43 (14.97)	75.65 (12.28)	81.00 (10.68)
Baseline $t(59)=0.060$, $p=0.953$						
Over all time points $F(2,61)=0.12$, $p=0.890$						

[a] Scale of Prodromal Symptoms (SOPS).
[b] Global Assessment of Functioning.

follow-up period among the three treatment modalities were marginally significant [$\chi^2(1,2)=4.950$, $p=0.084$].

The patients who converted to psychosis at follow-up were older at onset (Mean = 23.79; SD = 4.08) compared to those who remained stable (Mean = 21.09; SD = 3.56) [$t(59)=2.41$, $p=0.019$]; and no gender differences were found [$\chi^2(1)=0.013$, $p=0.908$.].

Conversion rate was higher in patients with previous history of illegal drug use (14.8%) than in those without such clinical record (8.2%); although the difference between both groups was not significant [$\chi^2(1)=1.318$, $p=0.251$]. However, a trend toward statistical significance was found when the conversion rates among the three clinical groups were compared: APS (19.7%), BLIPS (3.3%) and GR or SPD + DF (0%) [$\chi^2(1,2)=5.030$, $p=0.081$]. As can be observed in Fig. 1, schizophrenia diagnosis was more frequent among participants who converted to psychosis during the first three years of follow-up. Of the participants who remained stable, 46.81% still met criteria for ultra-high risk of psychosis, and 19.15% evolved toward diagnosis for some

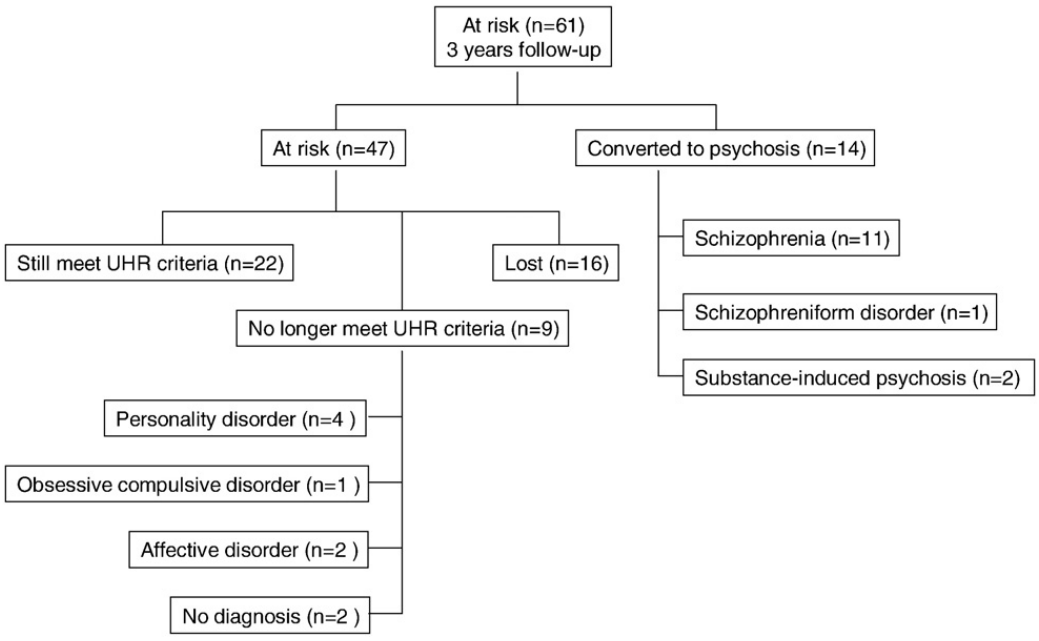

Fig. 1. Flow chart showing 3-year follow-up data of individuals identified as at risk for psychosis, and enrolled in the prevention program.

type of personality disorder, obsessive–compulsive disorder and affective disorder.

It deserves to be mentioned that only 7 participants (11.47%) were admitted to an inpatient unit in the follow-up period (6 belonging to the CBT + medication treatment group and 1 to the medication treatment alone), 5 during the first follow-up year and 2 in the second follow-up year. Even so, the average duration of hospitalisation was low, and the prescribed dose was half of that received by similar patients in routine care. None of them showed forensic complications (antisocial behaviors or delinquency), or suicide attempts/commission.

3.4. Longitudinal analyses

Significant statistical changes were observed in all clinical and functioning variables, when all variables were introduced in an overall analysis [$F(6, 99.6) = 232.89$, $p < .0001$].

Main effects of conversion to psychosis [$F(6, 102) = 3.99$, $p = .0012$], time points [$F(12, 162) = 13.57$, $p < .0001$], and the interaction of conversion × gender × time points [$F(12, 162) = 1.94$, $p = .033$] were found in the multivariate analysis, controlling the effect of age as covariate.

The effect of conversion to psychosis was statistically significant in all dependent variables, insofar as patients who made a transition to psychosis consistently showed higher ratings on positive, negative, disorganized, general symptom scales, and in the SOPS total score over time. However, a clear clinical improvement was found in both clinically stable patients and in those who showed a transient psychotic state over time. The comparison of both groups in the GAF score over time also showed significant differences, but again always demonstrating higher functioning in those patients without psychotic symptoms (Table 2).

A closer analysis of interaction effects among conversion conditions, gender of the participants and time points in every clinical and functional variable, showed that it was statistically significant in five of the six dependent variables. These included conversion × gender × SOPS positive symptoms [$F(2, 61) = 4.19$, $p = 0.019$], conversion × gender × SOPS negative symptoms [$F(2, 61) = 4.81$, $p = 0.011$], conversion × gender × SOPS disorganized symptoms [$F(2, 61) = 3.95$, $p = 0.024$], conversion × gender × SOPS total score [$F(2, 61) = 4.33$, $p = 0.017$], and conversion × gender × GAF total score [$F(2, 61) = 3.40$, $p = 0.038$]. The interaction effect of conversion × gender × SOPS general symptoms showed only a trend toward significance [$F(2, 61) = 2.81$, $p = 0.068$].

As is revealed in Fig. 2, the significant interactions reflect that the growth profiles of the four groups (no conversion males, no conversion females, conversion males and conversion females) in the SOPS total score are not parallel and that, consequently, the four groups involved different patterns of change over time.

3.5. Predictors of transition

An exploratory logistic regression analysis was also performed using progression to psychosis as the dependent variable, and baseline SOPS positive, negative, disorganized, and general subscale scores, baseline GAF score, age, gender, illegal drug use, years of education, family history of psychosis, and DUI as predictor variables. In this analysis, the main effect of SOPS and GAF scales and age was significant or marginally significant. This means that there is a significant increase in the odds of making transition when higher levels of disorganized, negative and positive symptoms, worse functioning, and higher age are present at baseline. All predictor variables accounted for 66% of the variance of transition. Summary statistics of predictor variables are shown in Table 4.

4. Discussion

The current paper reports on a 3-year follow-up of a cohort of young people who had been identified as being at UHR of developing a psychotic disorder enrolled in a prevention program for psychosis with the aim of reducing their risk of progression to first episode of psychosis. We consider that the integration of data across multiple sites and a longitudinal perspective on symptoms, functioning, and demographic variables could contribute to shed light on early intervention in psychosis, the

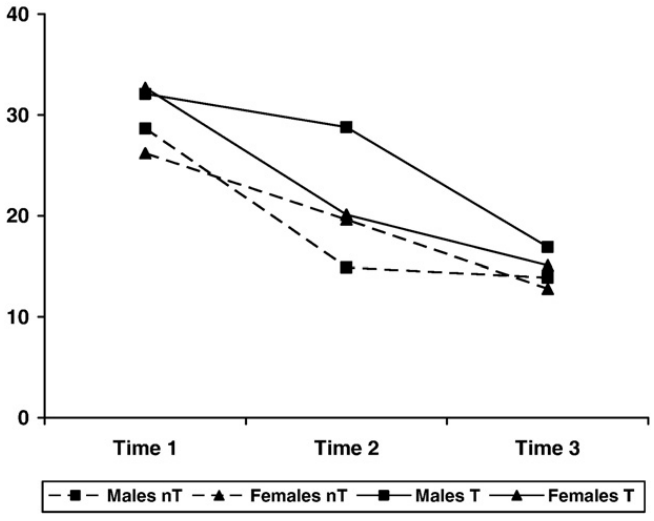

Fig. 2. SOPS total score over time in male and female patients, comparing those who made a transition (T) to psychosis in the follow-up period vs. those who did not (nT).

Table 4
Logistic regression summary statistics of transition.

	Beta	SE	OR (95% CI)	*p* value
Baseline SOPS positive score	0.57	0.29	1.76 (1.00–3.13)	0.052
Baseline SOPS negative score	−0.23	0.12	0.80 (0.62–1.00)	0.051
Baseline SOPS disorganized score	0.93	0.38	2.54 (1.20–5.41)	0.015
Baseline SOPS general score	0.71	0.41	2.04 (0.91–4.57)	0.082
Baseline GAF score	0.22	0.11	1.25 (1.00–1.56)	0.049
Age	0.52	0.24	1.68 (1.06–2.66)	0.028
Illegal drugs use	−2.10	1.31	0.12 (0.01–1.60)	0.109
Years of education	0.30	0.28	1.36 (0.79–2.33)	0.271
Gender	1.23	1.22	3.41 (0.31–37.27)	0.315
Family history	−0.17	1.20	0.84 (0.08–8.74)	0.884
DUI	0.02	0.04	1.01 (0.94–1.10)	0.671

Note: OR = odds ratio; CI = confidence interval.

predictor variables of progression to psychosis, and gender differences in the follow-up.

During the first follow-up year of this study, 11 of the 61 participants developed a psychotic episode, and over the 3-year follow-up, 14 participants also did. The conversion rates vary across studies, but the 3-year rate of conversion from prodrome to psychosis in the present study was similar to that observed in other intervention programs (Broome et al., 2005; Cornblatt et al., 2004; McGorry et al., 2002; Morrison et al., 2007; Nordentoft et al., 2006; Phillips et al., 2007).

It is important to point out that 18% of the participants in the present study who converted to psychosis did it in the first year, and specifically in the first 9 months, with the number of cases who transited to psychosis in the 3-year follow-up being proportionally lower (the remaining 5%). These data seem to indicate that the treatment has the effect of aborting or delaying the transition to psychosis in individuals at high risk.

An important aspect that must also be highlighted is the occultation of symptoms by these patients at initial assessment or the existence in these samples of a group of patients with concealed first episodes of psychosis. In our study, of the 11 patients who transited to psychosis in the first year, in reality 3 were already psychotic at baseline and this information was obtained in posterior phases of treatment due to concealment or difficulties in describing the symptomatology which did not make detection possible. This means that, if this clinical situation had been appropriately detected at the beginning of the study, the real rates of transition to psychosis would have decreased to 13.11% ($n = 8$) in the first year and to 18.03% ($n = 11$) in the 3-year follow-up. This problem has already been pointed out by Nelson and Yung (2007), finding that almost 12% of clients who attended a first appointment at PACE clinic were psychotic, indicating that a substantial proportion of individuals thought to be prodromal are in fact suffering a first episode of psychosis.

Another important finding is that the rate of hospital admission in our study was 11% of the total sample, similar to the rates in the study by Phillips et al. (2007) and 50% of those who made a transition to psychosis; this result is particularly relevant as conventional services usually hospitalise 85% of first-episode psychosis and in specialized early intervention services the rates range from 65% reported in the LEO service in England to 73% in the EPICC centre in Australia (Power and McGorry, 2008). The absence of suicides is a relevant finding, which has been replicated in several studies of similar characteristics (Harris et al., 2008).

Our study indicates that an initial package of CBT for patients and their relatives is a promising method for intervening in the UHR (Morrison et al., 2007) since patients receiving CBT alone were successfully followed up; although it is also true that the CBT group showed the lowest baseline score level of symptoms as compared to the other treatment groups.

An important finding was the reduction in antipsychotic medication in patients who presented a first episode of psychosis and who were hospitalised during the follow-up period; this could also be attributed to the CBT treatment previously received. This phenomenon was also observed by Morrison et al. (2007) in their randomized controlled trial, suggesting an enduring benefit of psychological therapy over the long term.

In the comparison between those participants who transited to psychosis and those who did not in the clinical symptoms and the functioning level at the initial and subsequent assessments, it was observed that the first group consistently presented greater severity in all symptoms and worse functioning. These results were also evidenced when these variables were introduced as psychosis predictors in the logistic regression analysis, where our results reveal that UHR subjects who later make the progression to psychosis particularly have increased disorganized, positive and negative symptoms, and more deterioration in functioning, and are, to a great extent, similar results to those found in other recent studies (Addington et al., 2007; Cannon et al., 2008; Haroun et al., 2006; Velthorst et al., 2009; Yung et al., 2004).

Concerning age, we have found that older UHR subjects enrolled in the program were more psychosis-prone than younger participants, which could suggest a deteriorating effect of having the symptoms for a longer time, or that the identification of cases was inconveniently late. As Yung et al. (2007) point out, the decline in transition rates may be due not only to functioning and symptom levels, but to the treatment being more effective when implemented at the early stage of illness.

By contrast, we have not found that a family history of psychosis or substance use was a significant predictor of psychosis in the follow-up as in the Cannon et al. (2008) study. Occasional substance use, but not substance dependence, could explain such a difference in most of the cases of our sample; notwithstanding, the absence in predictive power of family history of psychosis may be attributed to the buffer effect provided by the therapeutic program received, although this is only a possibility which should be confirmed by other studies.

No gender differences were found in symptom or functioning levels at the three follow-up time points, which is not in keeping with expectations from studies in normal population or with the results found by Willhite et al. (2008) in a UHR sample where males were found to have significantly higher levels of negative symptoms and lower levels of functioning at baseline and follow-up time points; and that different combinations in symptoms may contribute to different functional outcomes.

Previous studies found that UHR subjects who develop psychosis over a follow-up period of 3 years show volume reductions in gray matter volume in frontal, temporal and parietal cortex (Borgwardt et al., 2008), and that antipsychotic treatment contributes to the brain changes observed in psychosis, acting regionally rather than globally on

the brain (Smieskova et al., 2009; Navari and Dazzan, in press); but intervention strategies may prevent, ameliorate or delay the structural and functional changes during or before the first episode of psychosis (Pantelis et al., 2003).

A longitudinal analysis of our data reveals that clinical and functional recovery in the follow-up period is excellent in patients that did not show the transition to psychosis, and even marked in those who did, which allows us to confirm the efficacy of the treatment program. However, a finding in our study that we consider relevant and novel is the analysis of the conversion × gender × SOPS total score × time points interactions which revealed that women follow a progressive and sustained course of clinical improvement regardless of having or not a first-episode psychosis during follow-up, whereas in men it was confirmed that the onset of a psychotic episode produces a more negative and deteriorating effect in the intermediate phases of follow-up although in the long-run clinical recovery is attained (i.e., males experience faster and longer deterioration when psychotic symptoms arise). Gender differences in the recovery pattern cannot be explained by a longer prodromal period (the duration of untreated illness) or higher symptom levels at intake.

Caution should be kept in mind when interpreting the present findings owing to the limitations of this study. A methodological limitation is that this was not a randomized study, but rather all subjects enrolled in the program were included according to order of arrival.

As is usually the case in longitudinal studies, a number of participants were lost to follow-up, mainly due to the mobility of this population; however, participants' involvement in this treatment modality was noteworthy, over 73% staying in the program three years later.

Finally, no hypotheses were developed as to why some participants met the prodromal criteria and did not convert to psychosis, and determine whether it is possible to identify the factors that protected them or delayed conversion.

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Contributors

Each of the coauthors made a substantial contribution to formulate the objectives, to conduct all analyses of this study and the drafting of the manuscript, and each approved the manuscript for submission.

Conflict of interest

None of the authors received any funding from sources that would provide a conflict of interest with regard to this research.

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References

Addington, J., Cadenhead, K.S., Cannon, T.D., Cornblatt, B., McGlashan, T.H., Perkins, D.O., Seidman, L.J., Tsuang, M., Walker, E.F., Woods, S.W., Heinssen, R., 2007. North American prodrome longitudinal study: a collaborative multisite approach to prodromal schizophrenia research. Schizophr. Bull. 33, 665–672.

Barrowclough, C., Tarrier, N., 1992. Families of Schizophrenic Patients: Cognitive Behavioural Intervention. Chapman & Hall, London.

Borgwardt, S.J., McGuire, P.K., Aston, J., Gschwandtner, U., Pflüger, M.O., Stieglitz, R.D., Radue, E.W., Riecher-Rössler, A., 2008. Reductions in frontal, temporal and parietal volume associated with the onset of psychosis. Schizophr. Res. 106, 108–114.

Broome, M.R., Woolley, J.B., Johns, L.C., Valmaggia, L.R., Tabraham, P., Gafoor, R., Bramon, E., McGuire, P.K., 2005. Outreach and support in South London (OASIS): implementation of a clinical service for prodromal psychosis and the at risk mental state. Eur. Psychiatr. 20, 372–378.

Cannon, T.D., Cadenhead, K., Cornblatt, B., Woods, S.W., Addington, J., Walker, E., Seidman, L.J., Perkins, D., Tsuang, D., McGlashan, T., Heinssen, R., 2008. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. Arch. Gen. Psychiatry 65, 28–37.

Chen, C., Murray, R.M., 2004. How does drug abuse interact with familial and developmental factors in the etiology of schizophrenia? In: Keshavan, M., Kennedy, J., Murray, R. (Eds.), Neurodevelopment and schizophrenia. Cambridge University Press, Cambridge, pp. 248–269.

Cornblatt, B., Lencz, T., Smith, S., Auther, A., 2004. Treatment of schizophrenia prodrome. In: Stone, W.S., Faraone, S.V., Tsuang, M.T. (Eds.), Early Clinical Intervention and Prevention in Schizophrenia. Humana Press, Totowa, New Jersey, pp. 303–323.

French, P., Morrison, A.P., 2004. Early Detection and Cognitive Therapy for People at High Risk of Developing Psychosis: A Treatment Approach. Wiley, Chichester.

Hall, R., 1995. Global Assessment of Functioning: a modified scale. Psychosomatics 36, 267–275.

Haroun, N., Dunn, L., Haroun, D., Cadenhead, K.S., 2006. Risk and protection in prodromal schizophrenia: ethical implications for clinical practice and future research. Schizophr. Bull. 32, 166–178.

Harris, M.G., Burgess, P.M., Chant, D.C., Pirkis, J.E., McGorry, P.D., 2008. Impact of specialized early psychosis treatment programme on suicide: retrospective cohort study. Early Interv. Psychiatry 2, 11–21.

Lemos, S., Vallina, O., Fernández, P., Ortega, J.A., Garcia, P., Gutiérrez, A., García, A., Bobes, J., Miller, T., 2006. Predictive validity of the Scale of Prodromal Symptoms (SOPS). Actas Esp. Psiquiatr. 34, 216–223.

McGlashan, T.H., Miller, T.J., Woods, S.W., Hoffman, R.E., Davidson, L., 2001a. Instrument for the assessment of prodromal symptoms and states. In: Miller, T.J., Mednick, S.A., McGlashan, T.H., Libiger, J., Johannessen, J.O. (Eds.), Early Intervention in Psychotic Disorders. Kluwer Academic, Dordrecht, pp. 135–149.

McGlashan, T.H., Miller, T.J., Woods, S.W., Rosen, J.L., Hoffman, R.E., Davidson, L., 2001b. Structured Interview for Prodromal Syndromes. PRIME Research Clinic. Yale School of Medicine, New Haven, Conneticut.

McGlashan, T.H., Addington, J., Cannon, T., Heinimaa, M., McGorry, P., O'Brien, M., Penn, D., Perkins, D., Salokangas, R.K.R., Walsh, B., Woods, S.W., Yung, A., 2007. Recruitment and treatment practices for help-seeking "prodromal" patients. Schizophr. Bull. 33, 715–726.

McGorry, P.D., Yung, A., Phillips, L., Yuen, H.P., Francey, S., Cosgrave, E.M., Germano, D., Bravin, J., McDonald, T., Blair, A., Adlard, S., Jackson, H., 2002. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. Arch. Gen. Psychiatry 59, 921–928.

McGorry, P.D., Yung, A.R., Bechdolf, A., Amminger, P., 2008. Back to the future: predicting and reshaping the course of psychotic disorder. Arch. Gen. Psychiatry 65, 25–27.

Miller, T.J., McGlashan, T.H., Woods, S.W., Stein, K., Driesen, N., Corcoran, C.M., Hoffman, R., Davidson, L., 1999. Symptom assessment in schizophrenic prodromal states. Psychiatr. Q. 70, 273–287.

Morrison, A.P., French, P., Parker, S., Roberts, M., Stevens, H., Bentall, R.P., Lewis, S.W., 2007. Three-year follow-up of a randomized controlled trial of cognitive therapy for the prevention of psychosis in people at ultrahigh risk. Schizophr. Bull. 33, 682–687.

Navari, S., Dazzan, P., in press. Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. Psychol. Med. doi:10.1017/S0033291709005315.

Nelson, B., Yung, A.R., 2007. When things are not as they seem: detecting first-episode psychosis upon referral to ultra high risk ('prodromal') clinics. Early Interv. Psychiatry 1, 208–212.

Nordentoft, M., Thorup, A., Petersen, L., Ohlenschlaeger, J., Melau, M., Christensen, T.O., Krarup, G., Jorgensen, P., Jeppesen, P., 2006. Transition rates from schizotypal disorder to psychotic disorder for first-contact patients included in the OPUS trial: a randomized clinical trial of integrated treatment and standard treatment. Schizophr. Res. 83, 29–40.

Pantelis, C., Yücel, M., Wood, S.J., McGorry, P.D., Velakoulis, D., 2003. Early and late neurodevelopmental disturbances in schizophrenia and their functional consequences. Aust. N. Z. J. Psychiatry 37, 399–406.

Phillips, L.J., McGorry, P.D., Yuen, H.P., Ward, J., Donovan, K., Kelly, D., Francey, S.M., Yung, A.R., 2007. Medium term follow-up of a randomized controlled trial of interventions for young people at ultra high risk of psychosis. Schizophr. Res. 96, 25–33.

Power, P., McGorry, P.D., 2008. First episode psychosis inpatient services: a comparison of the EPPIC and LEO inpatient units. Early Interv. Psychiatry 2 (Suppl. 1), A14.
SAS Institute, 2007. The MIXED Procedure, SAS/STAT User's Guide, SAS Online Documentation. SAS Institute Inc., Cary, North Carolina.
Smieskova, R., Fusar-Poli, P., Allen, P., Bendfeldt, K., Stieglitz, R.D., Drewe, J., Radue, E.W., McGuire, P.K., Riecher-Rössler, A., Borgwardt, S.J., 2009. The effects of antipsychotics on the brain: what have we learnt from structural imaging of schizophrenia? — a systematic review. Curr. Pharm. Des. 15, 2535–2549.
Vallejo, G., Arnau, J., Ato, M., 2007. Comparative robustness of recent methods for analyzing multivariate repeated measures designs. Educ. Psychol. Meas. 67, 410–432.
Velthorst, E., Nieman, D.H., Becker, H.E., van de Fliert, R., Dingemans, P.M., Klaassen, R., de Haan, L., van Amelsvoort, T., Linszen, D.H., 2009. Baseline differences in clinical symptomatology between ultra high risk subjects with and without a transition to psychosis. Schizophr. Res. 109, 60–65.
Willhite, R.K., Niendam, T.A., Bearden, C.E., Zinberg, J., O'Brien, M.P., Cannon, T.D., 2008. Gender differences in symptoms, functioning and social support in patients at ultra-high risk for developing a psychotic disorder. Schizophr. Res. 104, 327-245.
Yung, A.R., McGorry, P.D., McFarlane, C.A., 1996. Monitoring and care of young people at incipient risk of psychosis. Schizophr. Bull. 22, 283–303.
Yung, A.R., Phillips, L.J., McGorry, P.D., McFarlane, C.A., Francey, S., Harrigan, S., Patton, G.C., Jackson, H.J., 1998. Prediction of psychosis: a step towards indicated prevention of schizophrenia. Br. J. Psychiatry 172 (Suppl. 33), 14–20.
Yung, A.R., Phillips, L.J., Yuen, H.P., McGorry, P.D., 2004. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. Schizophr. Res. 67, 131–142.
Yung, A.R., Stanford, C., Cosgrave, E., Killackey, E., Phillips, L., Nelson, B., MCgorry, P.D., 2006. Testing the ultra high risk (prodromal) criteria for the prediction of psychosis in clinical sample of young people. Schizophr. Res. 84, 57–66.
Yung, A.R., Yuen, H.P., Berger, G., Francey, S., Hung, T., Nelson, B., Phillips, L., McGorry, P., 2007. Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? Schizophr. Bull. 33, 673–681.