Persistent Negative Symptoms in First-Episode Psychosis: Early Cognitive and Social Functioning Correlates and Differences Between Early and Adult Onset

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ABSTRACT

Objective: To characterize the early cognitive and social functioning characteristics of a sample of first-episode psychosis patients with and without persistent negative symptoms (PNS) and to examine the prevalence and cognitive and functional correlates of PNS in patients with early-onset versus adult-onset first-episode psychosis.

Methods: Participants were 235 patients with first-episode psychosis (51 early-onset, 184 adult-onset) and 240 healthy controls from a multicenter longitudinal study (recruited between 2009 and 2011). Standard instruments were used to evaluate symptoms, cognition, and social functioning. Diagnoses were determined according to *DSM-IV* criteria. PNS proxy was derived from clinical assessments (Positive and Negative Syndrome Scale and Montgomery-Asberg Depression Scale) at 2-, 6-, and 12-month follow-up. Association tests were used to compare the prevalence of PNS in the early-onset versus adult-onset groups. Multivariate analysis of variance was used to examine differences in early cognitive and social functioning (at the 2-month assessment) between patients with and without PNS and between early-onset and adult-onset patients with PNS.

Results: Thirty-eight patients (16.2%) met criteria for PNS during the first year. This PNS group showed a selective deficit in executive functions and in global, community, and occupational functioning ($P < .05$). Having PNS was associated with a diagnosis of a schizophrenia spectrum disorder at the 12-month follow-up. The prevalence of PNS was almost double for those patients with an early-onset (0.25 vs 0.14; OR = 2.18; 95% CI, 1.02–4.64), and this was associated with greater cognitive ($P < .05$) but not social deficits.

Conclusions: There was an early, detectable, social and executive dysfunction associated with PNS in first-episode psychosis and a high risk of having PNS in early-onset first-episode psychosis, which in turn was associated with more widespread cognitive impairment. Specific therapeutic interventions for PNS in early-onset first-episode psychosis might be needed.

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Negative symptoms represent a heterogeneous clinical construct associated with much of the poor long-term functional outcome of patients with schizophrenia, and their treatment remains a major challenge.[1,2] Given that the impact of negative symptoms on functioning is particularly important if they are present early in the course of the illness,[3,4] early detection and intervention might be helpful to prevent the development of further disability in those patients who have negative symptoms that persist despite the treatments currently available. Negative symptoms include those that are primary and enduring, which represent the core of the deficit syndrome,[5] as well as those that are secondary and are due to other factors (eg, depressive symptoms). In first-episode psychosis, the diagnosis of deficit syndrome may be difficult.[6] An alternative approach is based on the identification of persistent negative symptoms (PNS), defined as those negative symptoms that lead to functional impairment, do not respond to usual treatments, and persist during periods of clinical stability.[1] The criteria for PNS are less restrictive and are easier to apply than those required for deficit syndrome, but are conceptually similar.[6] On the other hand, the concept of PNS reduces the heterogeneity of the negative symptoms broadly defined, isolating those negative symptoms that are the most relevant treatment target. In first-episode psychosis, the prevalence of PNS has been reported to range from 3.8% to 34.7%.[3,4,6–10]

Buchanan et al[11] hypothesized that subjects with primary and persistent negative symptoms represent the subgroup of patients who have an early onset of schizophrenia, in which poor premorbid adjustment might in fact be the onset of deficit syndrome. This

Clinical Points

- Persistent negative symptoms are one of the major causes of functional impairment in psychosis. Their early detection might help prevent the development of further disability.
- Social and cognitive dysfunction associated with persistent negative symptoms in first-episode psychosis is detectable early in the course of the illness.
- Patients with onset of psychosis during adolescence are at greater risk of persistent negative symptoms that would be associated with more cognitive deficits than are patients with an onset of disease in adulthood.

hypothesis has received partial support from some studies of adults with schizophrenia[4,12,13] and from the child and adolescent literature,[14,15] but it has been clearly understudied. Only 1 previous study has compared the prevalence of primary negative symptoms between early-onset and adult-onset psychosis, and it found that core primary negative symptoms were more prevalent in the early-onset group.[16] However, this study did not report whether the primary negative symptoms were actually persistent over time. More recently, Parellada et al[17] reported that primary negative symptoms showed continuity over 2 years in a sample of child and adolescent patients with first-episode psychosis. However, the authors made no comparison with an adult-onset group and did not report the prevalence of PNS. No previous studies have directly compared the prevalence of PNS and its early cognitive and social correlates between patients with and without an early-onset of the illness.

The aims of the present study were (1) to compare the early cognitive and functional characteristics of a sample of first-episode psychosis patients with and without PNS, (2) to compare the prevalence of PNS between patients with an early onset and those with an adult onset of the first-episode psychosis, and (3) to examine the similarities and differences in cognitive and functional characteristics between patients with PNS who had an early onset of the illness and those who had an adult onset. We hypothesized that (*a*) patients who had PNS during the first year after the first-episode psychosis would have more cognitive deficits and poorer social functioning early in the course of the illness; (*b*) there would be a higher prevalence of patients with an early onset of the illness among those who showed PNS during the first year after the first-episode psychosis; and (*c*) among patients who had PNS during the first year of the illness, those with an early onset would have more cognitive and social functioning impairments at 2 months after the first-episode psychosis.

METHODS

Subjects

The sample came from a multicenter, longitudinal study designed to assess clinical, neuropsychological, and other variables and social functioning in first-episode psychosis patients (the Phenotype-Genotype and Environmental Interaction: Application of a Predictive Model in First Psychotic Episodes [PEPs] study).[18] A total of 335 patients with a first-episode psychosis were recruited from 16 centers in Spain from 2009 to 2011 and were assessed at baseline and at 2, 6, 12, and 24 months. Sociodemographic data were collected at baseline. Clinical and social functioning data were recorded at baseline and at all follow-up points. Neuropsychological assessment was carried out at 2 and 24 months in patients and at baseline and 24 months in healthy controls. Inclusion criteria for patients were (1) age 7 to 35 years at the time of first assessment, (2) psychotic disorder according to *DSM-IV* criteria of less than 12 months, (3) ability to speak Spanish fluently, and (4) provision of written informed consent. Following Cuesta et al,[19] diagnoses of schizophrenia, schizophreniform, and schizoaffective disorders were categorized into "schizophrenia spectrum disorders," whereas bipolar disorder I and II and manic and depressive episodes with psychotic symptoms were grouped as "affective psychoses," and brief psychotic disorders, psychosis not otherwise specified, and toxic psychoses were categorized as "other psychoses." Exclusion criteria were mental retardation, history of head trauma with loss of consciousness, and organic disease with mental repercussions.

A sample of 253 healthy controls was recruited from the same geographical areas and matched with patients according to age (±10%), sex, and socioeconomic status (SES). Exclusion criteria for healthy controls were the same as for patients plus (1) past or present psychotic symptoms or major depressive disorder and (2) first-degree relative with history of psychotic disorder. The PEPs study was approved by the research ethics committees of all participating centers, and all subjects, and parents/legal guardians in the case of subjects younger than 18 years old, gave their written informed consent.

The PEPsCog study was part of the PEPs study and included those participants who completed more than 1 neuropsychological test.[19] For the purposes of the present study, we examined data on psychosocial and cognitive functioning at 2 months of those patients included in the PEPsCog study for whom Positive and Negative Syndrome Scale (PANSS)[20] and Montgomery-Asberg Depression Rating Scale (MADRS)[21] data were available at 2, 6, and 12 months. The final sample consisted of 475 subjects: 235 patients with first-episode psychosis and 240 healthy controls. Patients were classified as having early-onset first-episode psychosis provided that they were 17 years or younger at onset of psychotic symptoms (51 patients with an early-onset first-episode psychosis, 184 patients with an adult-onset first-episode psychosis). Consensus-based best estimates of age at onset of psychotic symptoms were derived using information from patients and family members with the Symptom Onset in Schizophrenia inventory.[22]

Sociodemographic, Clinical, and Social Functioning Measures

Demographic data, including age, gender, years of patients' education, and parental SES,[23] were collected

for all participants. Diagnoses were determined based on information at 12 months and according to *DSM-IV* criteria with the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I)[24] or the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (Kiddie-SADS),[25] depending on age. The prescribed daily doses of antipsychotics were converted to estimated chlorpromazine equivalents (CPZe) following the international consensus.[26] Severity of psychotic symptoms was assessed with the validated Spanish version of the PANSS,[27] while affective symptoms were assessed with the validated Spanish versions of the MADRS[28] and the Young Mania Rating Scale.[29,30] The Clinical Global Impressions[31] scale was used to assess severity of global symptoms. Patients' social functioning was evaluated using the Global Assessment of Functioning (GAF)[32] scale or its equivalent for subjects under 18 years (Children's Global Assessment Scale)[33] together with the Spanish version of the World Health Organization Disability Assessment Schedule II (WHO-DAS-II).[34]

Cognitive Assessment

A full description of the neuropsychological battery and the derived cognitive domains is reported elsewhere.[19] The battery includes standardized neuropsychological tests validated in the Spanish population and encompassing the cognitive dimensions proposed in the MATRICS battery.[35] Neuropsychological variables were transformed into standard equivalents (*z* scores) based on data from the healthy control group and grouped into the following cognitive domains[19]: *premorbid IQ* (vocabulary subtest of either the Wechsler Intelligence Scale for Children-IV [WISC-IV][36] or the Wechsler Adult Intelligence Scale-III [WAIS-III],[37] depending on age); *processing speed* (Trail Making Test [TMT],[38] form A, and Stroop Test[39]—reading speed of words and colors); *attention* (D prime of the Continuous Performance Test-II)[40]; *working memory* (Digit Span and Letter-Number sequencing subtests of the WISC-IV or WAIS-III); *executive functions* (number of categories, percentage of conceptual responses, total errors and perseverative errors from the Wisconsin Card Sorting Test[41]; TMT, form B; Stroop Test—interference score; F-A-S test[42]); and *verbal memory* (California Verbal Learning Test,[43] immediate and delayed recall). A *global cognition score* was derived from the mean of the aforementioned cognitive domains, except for premorbid IQ.

Definition of Persistent Negative Symptoms

Criteria for PNS were adapted from criteria proposed by Galderisi et al[6] to define PNS in patients with first-episode psychosis: (*a*) PANSS scores ≥ 4 for at least 1 of the following symptoms: blunted affect, emotional withdrawal, poor rapport, passive withdrawal, and lack of spontaneity and (*b*) absence of or only mild depressive symptoms (MADRS score of 19 or less). When all of these criteria were met at 2 months and maintained at 12 months, or met at 6 months and maintained at 12 months, the negative symptoms were defined as *persistent* (PNS). Severity of extrapyramidal symptoms was controlled for in a subsample of 175 patients (74.5% of the patient sample), for whom the Simpson-Angus Scale (SAS)[44] was available at the same follow-up assessments, allowing us to determine the presence of neuroleptic-induced parkinsonism.[45]

Statistical Analyses

Demographic, clinical, cognitive, and social functioning data in patients with and without PNS (PNS and NoPNS groups) and healthy controls were compared using the χ^2 test, Fisher exact test, or analysis of variance (ANOVA) with Bonferroni post hoc tests, as appropriate. Analysis of covariance (ANCOVA) was used to examine differences between groups in cognitive and social functioning, controlling for the effect of demographic (parental SES) and clinical (CPZe and PANSS positive and general symptoms scores) differences among the groups. Crosstabs with the χ^2 test were used to examine differences between the early-onset first-episode psychosis and adult-onset first-episode psychosis groups in the prevalence of patients who met criteria for PNS. Odds ratio (OR) and the 95% confidence interval (CI) for the association between type of onset and prevalence of PNS were computed. ANCOVAs were run to study differences between patients with early-onset first-episode psychosis with PNS and patients with adult-onset first-episode psychosis with PNS, controlling for differences in age and in clinical symptoms (MADRS score) between the groups. All tests were 2-tailed, and the significance threshold was set at $P < .05$. All analyses were conducted using IBM SPSS Statistics for Windows (version 18, SPSS Inc, Chicago, Illinois).

RESULTS

Sociodemographic and Clinical Characteristics

During the first year of the illness, 38 patients (16.2%) met criteria for PNS (Table 1). The PNS and NoPNS groups had lower parental SES than healthy controls, and the PNS group had lower parental SES than the NoPNS group. Education level was lower in both groups of patients than in healthy controls.

At 2 months, the PNS group had higher scores on all PANSS subscales than the NoPNS group, and CPZe was also higher in the PNS group. There were no differences between the groups in neuroleptic-induced parkinsonism at 2- and 12-month follow-up ($\chi^2 = 2.83$, $P = .139$; $\chi^2 = 0.16$, $P = .713$, respectively). However, the prevalence of neuroleptic-induced parkinsonism was higher at 6 months in the PNS group ($\chi^2 = 8.58$, $P = .009$). Having PNS during the first year after the first-episode psychosis was associated with a diagnosis of a schizophrenia spectrum disorder at 12-month follow-up.

Differences in Early Cognitive and Social Functioning Between the PNS, NoPNS, and Healthy Control Groups

At 2 months, the PNS and NoPNS groups scored lower than healthy controls in all cognitive domains except

Table 1. Sociodemographic and Clinical Characteristics of the PNS and NoPNS Groups

Characteristic	PNS (n = 380)	NoPNS (n = 197)	HC (n = 240)	Statistic (F, χ^2)	P	Post Hoc
Sociodemographic variable						
Age, mean (SD), range, y	22.8 (6.2), 15–35	23.3 (5.9), 9–36	24.0 (6.1), 9–38	0.96	.383	…
Sex, male:female (% male)	27:11 (71.1)	133:64 (67.5)	155:85 (64.6)	0.83	.660	…
Socioeconomic status, n (%)						
High/medium-high	9 (24.3)	61 (31.1)	99 (41.8)	20.45	<.001	PNS < NoPNS < HC
Medium	5 (13.5)	57 (29.1)	72 (30.4)	…	…	…
Medium-low/low	23 (62.2)	78 (39.8)	66 (27.8)	…	…	…
Education, n (%)						
Primary	14 (36.8)	41 (20.9)	16 (6.7)	63.89	<.001	PNS = NoPNS < HC
Secondary	22 (57.9)	124 (63.3)	123 (51.5)	…	…	…
University	2 (1.5)	31 (15.8)	100 (41.8)	…	…	…
Clinical variable						
Age at onset, mean (SD), y	22.8 (6.1)	22.94 (5.91)	…	0.03	.862	…
Diagnoses, n (%)						
Schizophrenia spectrum disorders	29 (76.3)	81 (41.1)	…	15.89	<.001	…
Affective psychoses	3 (7.9)	44 (22.3)	…	…	…	…
Other psychoses	6 (15.8)	72 (36.5)	…	…	…	…
PANSS, mean (SD)						
Positive	12.9 (4.83)	11.1 (4.84)	…	4.26	.040	…
Negative	21.7 (6.38)	15.6 (6.46)	…	29.95	<.001	…
General	33.0 (9.38)	28.6 (9.94)	…	6.34	.012	…
MADRS, mean (SD)	9.73 (5.75)	9.74 (8.48)	…	0.00	.997	…
YMRS, mean (SD)	2.39 (3.91)	2.66 (4.62)	…	0.11	.745	…
CPZe, mean (SD); range	596.23 (315.05); 100–1,888	436.64 (299.18); 75–2,100	…	5.49	.020	…
CGI Illness severity, mean (SD)	3.89 (0.92)	3.51 (1.16)	…	3.77	.053	…

Symbol: … = not applicable.
Abbreviations: CGI = Clinical Global Impressions scale, CPZe = estimated equivalent amount of chlorpromazine, HC = healthy control group, MADRS = Montgomery-Asberg Depression Rating Scale, NoPNS = first-episode psychosis without persistent negative symptoms, PANSS = Positive and Negative Syndrome Scale, PNS = first-episode psychosis with persistent negative symptoms, YMRS = Young Mania Rating Scale.

Table 2. Cognitive Functioning Differences Between PNS, NoPNS, and Healthy Control Groups

Cognition Measure[b]	PNS Group, Mean (SD)	NoPNS Group, Mean (SD)	ANOVA Results			ANCOVA Results[a]	
			F	P Value	Post Hoc	F	P Value
IQ	−1.36 (1.02)	−1.06 (1.11)	62.52	<.001	PNS = NoPNS < HC	1.01	.316
Processing speed	−1.32 (1.0)	−0.92 (1.0)	69.07	<.001	PNS = NoPNS < HC	2.48	.117
Attention	−0.84 (0.58)	−0.13 (3.11)	2.09	.125	PNS = NoPNS = HC	0.91	.340
Working memory	−0.70 (0.78)	−0.80 (0.82)	50.92	<.001	PNS = NoPNS < HC	1.09	.298
Executive functions	−1.22 (0.97)	−0.80 (0.96)	61.94	<.001	PNS < NoPNS < HC	3.94	.049
Verbal memory	−1.68 (1.23)	−1.23 (1.17)	88.24	<.001	PNS = NoPNS < HC	1.49	.224
Global cognition	−1.35 (0.77)	−0.86 (0.97)	81.37	<.001	PNS < NoPNS < HC	3.68	.057

[a]Differences between PNS and NoPNS groups controlling for CPZe and PANSS positive and general symptoms.
[b]Standardized scores. HC: mean = 0, SD = 1.
Abbreviations: ANOVA = analysis of variance, ANCOVA = analysis of covariance, CPZe = estimated equivalent amount of chlorpromazine, HC = healthy control group, IQ = intelligence quotient, NoPNS = first-episode psychosis without persistent negative symptoms, PANSS = Positive and Negative Syndrome Scale, PNS = first-episode psychosis with persistent negative symptoms.

attention (Table 2). The PNS group scored lower than the NoPNS group in executive functions and also had a lower global cognitive score. Parental SES differences between groups emerged as a significant variable in the models ($P < .05$) but did not change the main results. Controlling for CPZe and PANSS positive and general symptoms differences between groups, only differences in executive functions remained significantly lower in PNS patients.

Regarding social functioning, the PNS group scored lower than the NoPNS group on all measures (Table 3). However, only differences in GAF and in the community functioning and occupational WHO-DAS subscales remained significantly lower ($P < .005$) in the PNS group when controlling for parental SES differences between groups. Controlling for CPZe and PANSS positive and general symptoms, the same pattern of results emerged, showing a main effect of PNS versus NoPNS group only in GAF and in the community functioning and occupational WHO-DAS subscales.

Prevalence of PNS Among Patients With an Early-Onset First-Episode Psychosis and an Adult-Onset First-Episode Psychosis

Among patients with an early onset, 25.5% (n = 13 of 51) met criteria for PNS during the first year after the onset of first-episode psychosis (expected frequency was 8; PNS prevalence = 0.25; 95% CI, 0.16–0.39). The corresponding figure among those with an adult onset was 13.6% (n = 25

Table 3. Social Functioning Differences Between PNS and NoPNS Groups

Variable	PNS Group, Mean (SD)	NoPNS Group, Mean (SD)	ANOVA Results		ANCOVA Results[a]	
			F	*P* Value	*F*	*P* Value
WHO-DAS[b]						
Personal care	0.84 (1.08)	0.47 (0.83)	5.67	.018	0.56	.454
Occupational tasks	2.76 (1.32)	1.90 (1.37)	12.95	<.001	4.86	.029
Family functioning	1.58 (1.11)	1.12 (1.19)	4.77	.030	0.37	.545
Community functioning	2.68 (1.32)	1.67 (1.34)	18.16	<.001	8.05	.005
GAF/CGAS	56.31 (13.21)	64.30 (14.32)	9.68	.002	4.38	.038

[a]Differences controlling for CPZe and PANSS positive and general symptoms.
[b]Higher scores mean lower social functioning.
Abbreviations: ANOVA = analysis of variance, ANCOVA = analysis of covariance, CGAS = Children's Global Assessment Scale, CPZe = estimated equivalent amount of chlorpromazine, GAF = Global Assessment of Functioning scale, NoPNS = first-episode psychosis without persistent negative symptoms, PANSS = Positive and Negative Syndrome Scale, PNS = first-episode psychosis with persistent negative symptoms, WHO-DAS = World Health Organization Disability Assessment Schedule-II.

Table 4. Sociodemographic and Clinical Characteristics of Adult-Onset First-Episode Psychosis With PNS and Early-Onset First-Episode Psychosis With PNS Groups

Characteristic	Adult-Onset With PNS	Early-Onset With PNS	Statistic (F, χ^2)	*P* Value
Sociodemographic variable				
Age, mean (SD), range, y	26.12 (5.06), 18–35	16.54 (1.05), 15–18	45.02	<.001
Sex, male:female (% male)	17:8 (68)	10:3 (76.9)	0.33	.714
Socioeconomic status, n (%)				
High/medium-high	4 (16)	5 (41.7)	3.53	.161
Medium	3 (12)	2 (16.7)		
Medium-low/low	18 (72)	5 (41.7)		
Education, n (%)				
Primary	7 (28)	7 (53.8)	3.06	.301
Secondary	16 (64)	6 (46.2)		
University	2 (8)	0 (0)		
Clinical variable				
Age at onset, mean (SD), range, y	25.64 (4.99), 18–35	16.18 (1.17), 14–17	37.89	<.001
PANSS, mean (SD)				
Positive	13.16 (4.79)	12.31 (5.06)	0.26	.613
Negative	22.16 (6.50)	20.92 (6.32)	0.32	.578
General	33.88 (9.51)	31.15 (9.23)	0.72	.403
MADRS, mean (SD)	11.25 (5.89)	6.92 (4.41)	5.36	.027
YMRS, mean (SD)	1.79 (3.83)	3.58 (3.94)	1.72	.199
CPZe, mean (SD)	585.18 (420.05)	618.33 (248.38)	0.06	.803
CGI Illness severity, mean (SD)	3.92 (1.04)	3.85 (0.69)	0.05	.819

Abbreviations: CGI = Clinical Global Impressions scale, CPZe = estimated equivalent amount of chlorpromazine, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, PNS = persistent negative symptoms, YMRS = Young Mania Rating Scale.

of 184) (expected frequency was 29.8; PNS prevalence = 0.14; 95% CI, 0.09–0.19). The association between having an early onset of the illness and having PNS was significant ($\chi^2 = 4.17$, $P = .041$), with an OR of 2.18 (95% CI, 1.02–4.64).

Early Differences in Clinical Characteristics and Cognitive and Social Functioning Between Patients With an Early Onset of the Illness and PNS and Patients With an Adult Onset and PNS

As expected, the early-onset group with PNS was younger and had an earlier age at onset. No other sociodemographic differences were found (Table 4). Regarding clinical characteristics, the adult-onset group with PNS had more depressive symptoms. CPZe were similar between the groups, as was the prevalence of neuroleptic-induced parkinsonism at 2, 6, and 12 months ($P > .171$).

Compared with the adult-onset group with PNS and controlling for differences in age, the early-onset group with PNS was cognitively more impaired at 2 months, showing lower scores on global cognition, executive functions, and verbal memory (Table 5, Figure 1). Differences remained statistically significant after controlling for depressive symptoms. No differences were found in social functioning. These differences were not found when comparing the early-onset and adult-onset groups without PNS (see Supplementary eTable 1 at PSYCHIATRIST.COM). Therefore, the finding of more impaired global cognition, executive function, and verbal memory scores in the early-onset group with PNS was not attributable to general differences between adult and early types of onset.

DISCUSSION

This study, which covered a wide age span of patients with a first-episode psychosis, showed that having an early onset of psychosis increased the odds of meeting criteria for PNS during the first year after the first-episode psychosis by 2.18 points compared with an adult onset. In addition, among patients who had PNS, those with an early onset were more cognitively impaired early in the course of the illness. Also, the results showed that regardless of age at onset, patients who met criteria for PNS during the first year after the first-episode psychosis had a selective deficit in executive functions that was detectable early in the course of the illness and also presented greater difficulties in several areas of social functioning. Moreover, having PNS during the first year was associated with a diagnosis of a schizophrenia spectrum disorder at 12-month follow-up. To our knowledge, this is the first study comparing the prevalence of PNS in patients with early-onset first-episode psychosis and adult-onset first-episode psychosis. Furthermore, the early cognitive and functional correlates between patients with PNS of early or adult onset have not been studied to date.

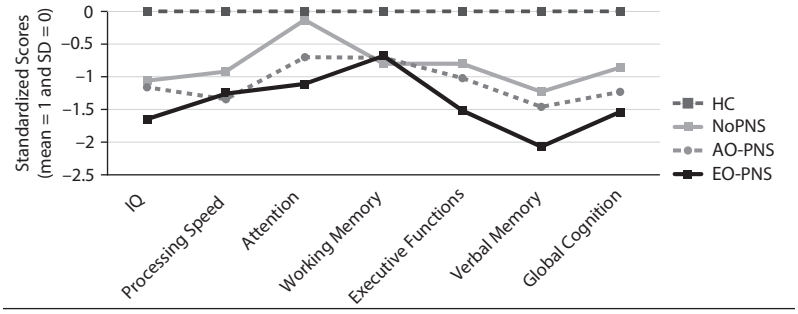
The prevalence of PNS in our total sample was within the range reported in previous studies of first-episode psychosis,[3,4,6–10] but it was almost twice as high in patients with an early onset of the illness. This finding is in line with that reported by Ballageer et al[16] in patients with early onset, although our prevalence rate for PNS is much lower than that reported by their study. This difference could be due to the fact that our definition of PNS highlighted the persistence of negative symptoms, whereas Ballageer et al based their

Table 5. Cognitive and Social Functioning Differences Between Adult-Onset First-Episode Psychosis With PNS and Early-Onset First-Episode Psychosis With PNS Groups Controlling for Age Differences Between Groups

Variable	Adult-Onset With PNS, Mean (SD)	Early-Onset With PNS, Mean (SD)	ANOVA Results		ANCOVA Results[a]	
			F	*P* Value	*F*	*P* Value
Cognition[b]						
IQ	−1.16 (0.88)	−1.65 (1.17)	1.57	.220	1.29	.265
Processing speed	−1.35 (1.01)	−1.26 (1.03)	2.02	.165	3.83	.060
Attention	−0.70 (0.54)	−1.11 (0.59)	0.89	.353	0.43	.519
Working memory	−0.71 (0.71)	−0.68 (0.92)	2.27	.142	2.73	.108
Executive functions	−1.02 (1.00)	−1.52 (0.86)	8.66	.007	6.32	.018
Verbal memory	−1.46 (1.19)	−2.07 (1.23)	4.86	.035	4.94	.034
Global cognition	−1.23 (0.74)	−1.54 (0.82)	8.54	.007	7.72	.010
Social functioning						
WHO-DAS[c]						
Self-care	0.92 (1.15)	0.69 (0.65)	0.03	.861	0.03	.862
Occupational tasks	2.92 (1.41)	2.46 (1.13)	0.33	.568	0.34	.566
Family functioning	1.68 (1.15)	1.38 (1.04)	0.73	.398	0.29	.591
Community functioning	2.76 (1.40)	2.54 (1.20)	0.35	.556	0.15	.701
GAF/CGAS	56.96 (13.06)	55.00 (14.00)	0.68	.417	0.56	.459

[a]Controlling for age and depressive symptoms differences between groups.
[b]Standardized scores. Healthy control group: mean = 0, SD = 1.
[c]Higher scores mean lower social functioning.
Abbreviations: ANOVA = analysis of variance, ANCOVA = analysis of covariance, CGAS = Children's Global Assessment Scale, GAF = Global Assessment of Functioning scale, IQ = intelligence quotient, PNS = persistent negative symptoms, WHO-DAS = World Health Organization Disability Assessment Schedule-II.

Figure 1. Cognitive Functioning Scores of Healthy Control, NoPNS, AO-PNS, and EO-PNS Groups



Abbreviations: AO-PNS = adult-onset first-episode psychosis with persistent negative symptoms, EO-PNS = early-onset first-episode psychosis with persistent negative symptoms, HC = healthy controls, IQ = intelligence quotient, NoPNS = first-episode psychosis without persistent negative symptoms.

figure only on symptoms at intake. It is known that negative symptoms are rather unstable during the first months after the first-episode psychosis,[7] with a dramatic decrease in their rate at 3 months.[4] Overall, the increased prevalence of PNS in patients with early onset highlights the burden of the onset of psychosis when it coincides with a momentous neurodevelopmental period such as adolescence.[46]

Regarding neurocognition, patients with PNS showed, as a whole, a selective deficit in executive functions. The executive dysfunction was not explained by parental SES differences or differences in positive and general symptoms between groups. Executive deficits have been found by some previous studies of patients with PNS[4] and of patients with deficit syndrome features,[12,47–49] although not by all.[3,6,7] The meta-analysis by Cohen et al[50] found that deficit syndrome was associated with a more severe global neuropsychological impairment, as well as selective impairments in language and social cognition. Our results also showed that patients with PNS had lower scores in all cognitive domains, although the result did not remain significant when controlling for positive and general symptoms.

When we took into account the early-onset versus adult-onset variable, a more widespread pattern of deficits emerged. Early-onset patients with PNS performed more poorly on 4 of 6 cognitive domains, with these differences reaching statistical significance on executive functions, verbal memory, and the global cognitive score. Furthermore, the results showed that while early-onset patients with PNS had more severe cognitive difficulties, patients with early onset but without PNS did not. It is known that negative symptoms in general are closely related and share many characteristics with cognitive deficits, although they are separable and independent domains of the illness.[1,51] As for patients with deficit syndrome features, it is still not clear whether they are affected by a differential pattern of neuropsychological impairment or whether they merely represent a subgroup of the schizophrenia population with more severe cognitive impairment.[50,52] Also, in patients with PNS, previous neuropsychological studies reported inconsistent findings, with one reporting a greater impairment in executive functions and attention,[4] another reporting greater verbal impairment in the PNS group,[53] and 2 studies reporting no differences between the PNS and NoPNS groups.[6,7] It has been suggested that a third variable might be responsible for the group differences in neuropsychological functioning between patients with and without deficit features.[50] In view of our findings, we propose that having an early onset of the first-episode psychosis might explain some of these differences given that neurodevelopmental disturbances in the form of cognitive dysfunction were greater among patients with PNS who also had early illness onset. Thus, this finding could help to explain the heterogeneity of the cognitive deficits that have been associated with deficit features and PNS.[50,52]

Regarding social functioning, PNS patients as a group had specific deficits in global, community, and occupational functioning that were not attributable to parental SES differences between groups or to differences in positive and general symptoms. This result was consistent with previous studies.[54,55] However, early-onset

patients with PNS did not show greater difficulties than their adult-onset counterparts with PNS. This was unexpected since greater cognitive impairment is known to be related to greater psychosocial deficits over the lifespan.[56] We speculate that social dysfunction associated with PNS may be related more to other factors such as social cognition[57] or dysfunctional attitudes[58] and that these may be independent of the age at onset. Clearly, more research is warranted.

The results of the early clinical characteristics of patients with and without PNS also merit some comment. First of all, even though, as expected, the mean difference between groups was clearly higher in the negative symptoms of the PANSS subscale, both groups presented variations in the severity of negative symptoms and the group characterized as not having PNS still had negative symptoms. This was to be expected, since the PANSS scores are by definition continuous and implied that the 2 groups were not totally separable as 2 distinct homogeneous groups. It is known that the severity of global negative symptoms together with cognitive deficits is the major cause of the marked functional disability that is often associated with first-episode psychosis and accounts for much of the long-term morbidity and poor outcomes.[59,60] However, the definition of PNS focused not only on the severity of specific negative symptoms but on their endurance as well, since they had to persist during the follow-up and not respond to the usual treatments. Specifically, the presence of PNS in first-episode psychosis has been associated with poorer improvement of all psychopathological dimensions and worse global functioning after 1 year of treatment.[6] Consistent with these findings, in our sample, the presence of PNS during the first year after the first-episode psychosis was associated with a diagnosis of a schizophrenia spectrum disorder at 12-month follow-up and with an early and selective impairment in several areas of social functioning.

The temporal stability of negative symptoms seems to be a crucial point, since it has been demonstrated that transitory negative symptoms differ markedly from deficit ones.[61] Moreover, instability over time of the negative symptoms broadly defined, which is clearly present during the first months after the first-episode of psychosis,[4,7] can confound research findings.[52] Thus, even though the use of ratings of overall negative symptoms is highly informative about the prognostic and clinical importance of negative symptoms, it is unlikely to lead to the development of effective treatment for symptoms that persist during clinical stability and do not improve with currently available treatments. The PNS construct represents a clear improvement over ratings of negative symptoms broadly defined because it can define a patient population with a clinically relevant symptomatology that is significant enough to be targeted, selected, and studied. This can facilitate research efforts into finding clinically effective treatments, which is still a major challenge.[1,2,52] Our study adds to previous studies of PNS that patients with an early-onset first-episode psychosis are at increased risk for having PNS, which, in turn, is associated with greater cognitive impairment than in patients with an adult onset. To the best of our knowledge, these findings have not been previously described and are consistent with Buchanan and colleagues' hypothesis[11] that subjects with primary and persistent negative symptoms represent the subgroup of patients who have an early onset of schizophrenia.

Finally, the examination of the other PANSS subscales showed that the PNS group had higher scores on the positive and general symptoms subscales and were receiving higher CPZe dosage at 2-month follow-up. The results are consistent with other studies with first-episode psychosis patients that also found a similar clinical profile in the PANSS dimensions at baseline between patients with and without PNS.[6] As discussed below, our approach to define PNS was in line with the concept of "prominent" negative symptoms,[62] which is more suitable in a sample of patients with first-episode psychosis defined by meeting criteria for a psychotic disorder of less than 12 months. Further analysis of longitudinal data may indicate whether these results are maintained at longer follow-up assessments. But meanwhile, it seems important to consider PNS as a therapeutic target in first-episode psychosis, taking into account its early association with cognitive and social functioning deficits and, in the light of the results regarding a more widespread cognitive dysfunction in those patients with PNS and an early onset of the first-episode psychosis, paying special attention to this subgroup.

A number of other considerations are required when interpreting the results. Given that SAS data were not available for the whole sample, and since there was an increased prevalence of neuroleptic-induced parkinsonism at the 6-month follow-up among patients with PNS, we cannot differentiate primary from secondary PNS in some of our patients. However, no between-group differences in neuroleptic-induced parkinsonism prevalence were present at 12-month follow-up. Secondary negative symptoms due to severe positive symptoms were not excluded. In this respect, our approach was in line with the concept of "prominent" negative symptoms, which considers positive and negative symptoms as independent domains and focuses on the severity of negative symptoms, irrespective of their status as primary or secondary.[62] The findings about cognition and social functioning were based on the 2-month follow-up assessment, which allowed us to study the early cognitive and functional correlates of PNS. Further longitudinal studies of PNS that take into account the early-onset versus adult-onset distinction are warranted.

The main limitation of the study was the relatively small sample size of the early-onset first-episode psychosis group. Finally, another limitation was that statistical correction for multiple comparisons was not systematically applied. The main strengths included the use of a large patient sample with recent first-episode psychosis, the large age span analyzed, the inclusion of a large group of healthy controls, and the follow-up design that allowed us to study the persistence of negative symptoms. The inclusion of diagnoses of affective and other psychoses could be

controversial, although it might also be seen as a strength since it provided a broad and more realistic picture of the entire population of first-episode psychosis.[18]

In summary, we found an early, detectable social and executive dysfunction associated with PNS in first-episode psychosis, a high risk of meeting criteria for PNS if the onset of the psychosis was during adolescence, and, in those patients with early illness onset, a more widespread cognitive dysfunction that was not associated with greater social impairment. Future studies should take into account the patients' developmental period at psychosis onset when examining the prevalence and correlates of PNS. Moreover, the results suggest the existence of critical periods of development associated with a greater risk of developing PNS. The findings are of relevance because they could help the early identification of patients with a first episode of psychosis who will have enduring and treatment-resistant negative symptoms and for whom intervention efforts are especially needed. Given that there are greater plasticity and structural reorganization during adolescence,[46] specific interventions for negative symptoms during this period would appear to be particularly relevant.

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Potential conflicts of interest: **Dr Bioque** has been a consultant for, received honoraria from, and/or been on the speakers/advisory board of Adamed, Ferrer, Janssen-Cilag, Lundbeck, Otsuka, and Pfizer. **Dr Lobo** has been a consultant to or has received honoraria or grants from CIBERSAM, ISCIIII, Janssen-Cilag, Lilly, Bial, Lundbeck, Ministerio de Ciencia e Innovación, Ministerio de Sanidad, Ministerio de Economía y Competitividad. **Dr Bernardo** has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, AlmirAll, AMGEN, Boehringer, Eli Lilly, Ferrer, Forum Pharmaceuticals, Gedeon, Hersill, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Roche, and Servier and has obtained research funding from the Spanish Ministry of Health, the Spanish Ministry of Science and Education, the Spanish Ministry of Economy and Competiveness, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), by the Government of Catalonia, Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), and the 7th Framework Program of the European Union. The other authors and the PEPs Group declare that there are no conflicts of interests in relation to the subject of this study.

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Supplementary Material

Article Title: Persistent Negative Symptoms in First-Episode Psychosis: Early Cognitive and Social Functioning Correlates and Differences Between Early and Adult Onset

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List of Supplementary Material for the article

1. **eTable 1** Cognitive and Social Functioning Differences Between Adult-Onset Without PNS and Early-Onset Without PNS Groups Controlling for Age Differences Between Groups

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Supplementary eTable 1. Cognitive and social functioning differences between adult-onset without PNS and early-onset without PNS groups controlling for age differences between groups

			ANOVA results	
	Adult-onset without PNS	Early-onset without PNS	F	P value
Cognition[*]				
IQ	-1.00 (1.08)	-1.28 (1.22)	1.64	0.203
Processing speed	-0.89 (1.01)	-1.03 (0.94)	0.36	0.549
Attention	-0.05 (3.46)	-0.83 (0.54)	1.80	0.182
Working memory	-0.77 (0.80)	-0.93 (0.92)	0.00	0.961
Executive functions	-0.71 (0.95)	-1.20 (0.95)	1.09	0.299
Verbal memory	-1.20 (1.14)	-1.39 (1.30)	1.58	0.211
Global Cognition	-0.78 (1.01)	-1.23 (0.70)	1.23	0.270
Social functioning				
WHO-DAS [#]				
Self-Care	0.47 (0.81)	0.50 (0.89)	0.38	0.540
Occupational tasks	1.91 (1.37)	1.87 (1.36)	1.55	0.215
Family functioning	1.13 (1.16)	1.08 (1.32)	1.09	0.299
Community functioning	1.69 (1.30)	1.61 (1.53)	0.01	0.909
GAF/C-GAS	64.88 (13.20)	61.78 (18.40)	0.52	0.474

Abbreviations: PNS= persistent negative symptoms; IQ=Intelligence quotient; WHO-DAS= World Health Organization Disability Assessment Schedule-II; GAF=Global Assessment of Functioning scale; C-GAS= Children Global Assessment Scale.

[*] Standardized scores. Control group: mean=0, SD=1.

[#] Higher scores mean lower social functioning.