Premorbid academic and social functioning in patients with schizophrenia and its associations with negative symptoms and cognition

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Abstract

Objective

The study aimed to explore premorbid academic and social functioning in patients with schizophrenia, and its associations with the severity of negative symptoms and neurocognitive impairment.

Method

Premorbid adjustment (PA) in patients with schizophrenia was compared to early adjustment in unaffected first-degree relatives and healthy controls. Its associations with psychopathology, cognition, and real-life functioning were investigated. The associations of PA with primary negative symptoms and their two factors were explored.

Results

We found an impairment of academic and social PA in patients ($P \leq 0.000001$) and an impairment of academic aspects of early adjustment in relatives ($P \leq 0.01$). Patients with poor PA showed greater severity of negative symptoms (limited to avolition after excluding the effect of depression/parkinsonism), working memory, social cognition, and real-life functioning ($P \leq 0.01$ to ≤ 0.000001). Worse academic and social PA were associated with greater severity of psychopathology, cognitive impairment, and real-life functioning impairment ($P \leq 0.000001$). Regression analyses showed that worse PA in the academic domain was mainly associated to the impairment of working memory, whereas worse PA in the social domain to avolition ($P \leq 0.000001$).

Conclusion

Our findings suggest that poor early adjustment may represent a marker of vulnerability to schizophrenia and highlight the need for preventive/early interventions based on psychosocial and/or cognitive programs.

Introduction

In line with the neurodevelopmental hypothesis of schizophrenia, a poor premorbid adjustment has been widely reported in individuals affected by the disorder **1**-**3**. Moreover, an impairment of functioning in early epochs of life has been described in unaffected relatives of patients with schizophrenia as compared to healthy controls **4**-**8**.

A worse premorbid adjustment in patients with schizophrenia is associated with severity of negative symptoms, neurocognitive impairment, and poor functional outcome **8**-**13**. To further characterize these associations, several studies explored them by taking into account the distinction of premorbid functioning in two separate subdomains (i.e. the academic and the social one) and/or in different patterns of progression over time (i.e. 'stable-poor', 'deteriorating', and 'stable-good'); however, findings in this regard are not consistent across studies, as summarized below.

The severity of negative symptoms has been associated either with the social subdomain only **8**, **10**, **14**-**20** or with both academic and social aspects of premorbid functioning **21**-**25**. Moreover, some studies reported an association of negative symptoms with specific patterns of progression of premorbid adjustment over time, mainly the 'stable-poor' and/or the 'deteriorating' one **10**, **15**, **26**; a lack of specificity has also been reported **27**.

Heterogeneity in findings on the association between premorbid adjustment and negative symptoms may be due, at least in part, to the lack of distinction between primary (etiologically related to the core pathophysiology of the syndrome) and secondary negative symptoms, that was taken into account in few studies so far **8**, **19**, **25**, **27**, **28**. Furthermore, according to recent literature, negative symptoms include at least two factors, avolition and poor emotional expression, that might be underpinned by different pathophysiological substrates **29**, **30** and show different correlates **31**, **32**. So far, no study investigated separately the relationships of poor premorbid adjustment with the two factors of negative symptoms.

While for negative symptoms the association with poor premorbid adjustment has been consistently reported, and further research is needed to clarify specific aspects of this relationship, whether positive symptoms are related with premorbid adjustment is still unclear as an association has been reported in some studies **33**-**35**, but not in others **21**, **36**.

The severity of neurocognitive impairment has been mainly associated with the academic domain of premorbid adjustment **10**, **15**, **20**, **21**, **37**-**39**, although in some studies deficits of some cognitive domains, such attention and executive functions, have been found more

closely related to the social than to the academic aspects of premorbid adjustment **40**, **41**. The specific cognitive deficits found in association with premorbid adjustment are extremely heterogeneous in the different studies.

As to the association with poor functional outcome, more often premorbid adjustment has been associated with global functioning or with the majority of explored areas of functioning, whereas a consistent pattern of associations with specific areas of functioning has not been described **42**-**46**.

In the light of the strong link between premorbid adjustment and neurodevelopmental aspects of the disorder, as well as of the above-reported controversial findings and open issues, in this study we tried to address the following questions: (i) Is the functional impairment observed in patients before the onset of schizophrenia also observed in their unaffected first-degree relatives during early epochs of life? If yes, does it involve both domains of adjustment? (ii) Are distinct patterns of premorbid adjustment course (i.e. 'stable-good', 'stable-poor', 'deteriorating') associated with the same psychopathological and neurocognitive domains? (iii) Is there a relationship between premorbid adjustment and primary negative symptoms? Is it relevant to both factors of negative symptoms (avolition and poor emotional expression)? (iv) Are different domains of premorbid adjustment related to different negative symptoms factors and/or to different cognitive domains? (v) Is premorbid adjustment related to positive symptoms? (vi) Do different domains of premorbid adjustment have a different impact on specific areas of real-life functioning?

Aims of the study

This study was aimed at exploring whether academic and social functioning during early epochs of life are impaired in a large sample of community-dwelling patients with schizophrenia, as well as in their unaffected first-degree relatives, with respect to healthy controls. In the group of patients, the associations of early functioning with the two distinct factors of primary negative symptoms, avolition and poor emotion expression, as well with neurocognition, social cognition and domains of real-life functioning were also investigated.

Methods

Study design

Premorbid adjustment in the group of patients was compared to adjustment in early age periods (early adjustment) of a group of their unaffected first-degree relatives and one of healthy controls. In the group of patients, the associations of premorbid adjustment with psychopathology, neurocognition, social cognition, and real-life functioning were investigated. The impact of premorbid adjustment on primary negative symptoms, selected by excluding

the confounding effect of depression and/or parkinsonism, as well as on the two distinct factors, avolition and poor emotional expression, was also explored.

Subjects

Patients were recruited among those consecutively seen at the outpatient units of 26 Italian university psychiatric clinics and/or mental health departments from March 2012 to September 2013.

Inclusion criteria were a diagnosis of schizophrenia according to DSM-IV, confirmed with the Structured Clinical Interview for DSM-IV - Patient version (SCID-I-P), and an age between 18 and 66 years. Exclusion criteria were as follows: (i) history of head trauma with loss of consciousness; (ii) history of moderate to severe mental retardation or of neurological diseases; (iii) history of alcohol and/or substance abuse in the last 6 months; (iv) current pregnancy or lactation; (v) inability to provide an informed consent; (vi) treatment modifications and/or hospitalization due to symptom exacerbation in the last 3 months.

For each recruited patient who agreed to involve relatives, two unaffected first-degree relatives were recruited, when available. They were, in order of preference, the two parents, or one parent and one sibling, or two siblings. Healthy controls were recruited through flyers from the community at the same sites as the patient sample. Exclusion criteria for relatives and controls were the same as listed above for patients from (i) to (v), plus a current or lifetime Axis I or II psychiatric diagnosis, as assessed with the SCID-I-Non Patient version and the SCID-II.

All subjects signed a written informed consent to participate after receiving a comprehensive explanation of the study procedures and goals.

Procedures

The study has been conducted in accordance with the principles of the Declaration of Helsinki (59th World Medical Association General Assembly; October 2008). Approval of the study protocol was obtained from the Ethics Committees of the participating centers.

Assessments

Premorbid characteristics

The assessment of premorbid functioning in patients, as well as of early adjustment in relatives and controls, was carried out using the Premorbid Adjustment Scale (PAS) **47**. This instrument assesses five psychosocial domains (sociability and withdrawal, peer relationships, scholastic performance, adaptation to school, and social-sexual functioning), and four age periods (childhood up to 11 years, early adolescence from 12 to 15 years, late adolescence from 16 to 18 years, and adulthood from 19 years on). Social-sexual functioning

is not measured during childhood, whereas school adaptation and school performance are not assessed during adulthood. A more global, 'General' section is included, containing items meant to estimate the overall functioning, for the entire period prior to the first episode, in nine areas (education, employment or school, change in work or school performance between 1 year and 6 months and between 3 years and 6 months before onset, independence, highest level of functioning, social-personal adjustment, degree of interest in life, and energy level).

Ratings are made on a 0- to six-point Likert scale, with 0 indicating normal adjustment and six indicating severe impairment. To gather information about the premorbid period, a semi-structured interview with the participant and her/his family members was used. The PAS defines as 'premorbid' the period ending 6 months before the first episode of illness.

In this study, the following criteria were adopted to analyze the PAS data: (i) scores for the adult age period were not analyzed in order to minimize possible contamination with early prodromal and psychotic symptoms of the illness; (ii) as suggested by other authors **27**, the final 'General' section was not analyzed, because regarded as less reliable than the others; (iii) according to the procedure followed in previous studies **19**, **37**, separate scores were calculated for social and academic premorbid domains of functioning at each age level, by averaging the items sociability, withdrawal, peer relationships, and social-sexual functioning for the social domain and the items scholastic performance and adaptation to school for the academic domain; an academic and a social mean score were then calculated by averaging the scores of the considered age period for each of the two domains; (iv) as in several previous studies **10**, **26**, **27**, the course of premorbid functioning was classified into three different patterns: deteriorating, stable-good, and stable-poor, according to the criteria proposed by Haas and Sweeney **48**. The deteriorating pattern was defined as a progressive decline characterized by a worsening in the PAS global score (sum of scores divided by the highest possible score within each age period) of at least two points between childhood and adulthood, or a proportionate decline for cases in which illness onset was before late adolescence or adulthood (i.e. a change between age groups of at least 0.66). The remaining cases were regarded as stable, and the median value of the PAS global score (0.34 in our study) was used as a cutoff point to categorize the subjects as stable-good or stable-poor.

Psychopathology

The Positive and Negative Syndrome Scale (PANSS) was used to rate symptom severity. Scores for the dimension 'positive symptoms' were calculated according to Wallwork et al. **49**by summing the scores for delusions, hallucinatory behavior, grandiosity, and unusual thought content.

Negative symptoms were assessed using the Brief Negative Symptom Scale (BNSS) **50**, an instrument designed to overcome the problem of heterogeneity of these symptoms. In fact, in

line with previous research **50**, **51**, this instrument allows the identification of two separate factors: avolition, consisting of anhedonia, asociality and avolition, and poor emotional expression, including blunted affect and alogia. The Italian version of the scale was validated as part of the Italian Network project **52**.

The assessment of depressive and extrapyramidal symptoms was carried out to exclude that negative symptoms were secondary to them. The Calgary Depression Scale for Schizophrenia (CDSS) **53** was used to assess depressive symptoms. This includes nine items (depression, hopelessness, self-depreciation, guilty ideas of reference, pathological guilt, morning depression, early wakening, suicide, observed depression), each rated from 0 (absent) to 3 (severe). Ratings >6 on the total score indicate clinically significant depression **53**. The St. Hans Rating Scale (SHRS) **54** was used to investigate the presence of extrapyramidal symptoms. This is a multidimensional rating scale comprising four subscales: hyperkinesia, parkinsonism, akathisia, and dystonia. Each subscale includes one or more items, with a score ranging from 0 (absent) to 6 (severe). Clinically significant extrapyramidal symptoms, which might confound the assessment of negative symptoms, were defined by a 'mild' (two) rating on at least three items, or a 'mild' rating for tremor or rigidity plus a 'mild' rating on at least another item, or a 'mild-moderate' (three or more) rating on at least one item. Bradykinesia and reduced facial expression were not included among confounding symptoms, due to the high probability that their presence represents a sign of diminished expression.

Neurocognition

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) was used for neurocognitive assessment, as it is regarded as the 'state-of-the-art' neuropsychological battery for research purposes in schizophrenia **55**, **56**. This battery includes tests for the assessment of six distinct cognitive domains: processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning, and problem solving.

Social cognition

The assessment of social cognition, partly carried out by the MCCB Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) managing emotion section, was integrated by the Facial Emotion Identification Test (FEIT) **57**, which examines emotion perception, and The Awareness of Social Inference Test (TASIT) **58**, which is a theory of mind test consisting of seven scales (positive emotions, negative emotions, sincere, simple sarcasm, paradoxical sarcasm, enriched sarcasm, lie), organized into three sections: emotion recognition, social inference-minimal, and social inference-enriched.

Real-life functioning

Real-life functioning was assessed by means of the Specific Levels of Functioning Scale (SLOF) **59**, **60**, an instrument endorsed by the panel of experts involved in the Validation of Everyday Real-World Outcomes (VALERO) initiative as a suitable measure exploring different domains of functioning **61**, **62**. The following domains, characterized by a sufficient level of variability, were analyzed: interpersonal relationships, community activities (e.g. shopping, using public transportation), and working abilities. Higher scores correspond to better functioning.

Data analysis

Co-norming and standardization of the Italian MCCB test scores was carried out as described in Kern et al. **55**, **63**. For cognitive domains including more than one measure, that is working memory and speed of processing, the summary score for the domain was calculated by summing the scores of the tests included in that domain and then standardizing the sum to a *T*-score. In this way, all test scores and domain scores were standardized to the same measurement scale with a mean of 50 and standard deviation of 10. Social cognition variables were standardized with respect to Italian normative data. The mean of standardized scores of MSCEIT, FEIT, and TASIT was used as a composite score. All the other variables were transformed into *z*-scores.

Differences among groups on categorical variables (gender distribution and PAS course categorization) were investigated by using Pearson's chi square test.

Independent one-way analyses of variance (ANOVAs) were used to test group differences on demographic variables. In case of group differences on these indices, group comparisons were performed by entering them as covariates. An exception was made for education, as its assessment is included in the PAS and there is an overlap between premorbid adjustment and educational level **12**, **64**.

Multivariate analyses of variance (MANOVAs) were run to investigate: (i) differences on indices of early adjustment among patients, relatives, and controls, as well as among parents and siblings within the group of relatives in order to control for the possible confounding effect related to the older age and lower education of parents; (ii) differences between patient groups with different premorbid adjustment course (stable-good, stable-poor, and deteriorating) with respect to psychopathology, neurocognition, social cognition, functional outcome, and PAS academic and social profiles. When a group difference or an interaction between groups and domains was statistically significant, univariate effects were examined using Sheffe's *post hoc* test.

To investigate the associations of premorbid adjustment with psychopathological, cognitive, and real-life functioning indices, correlation analyses were carried out by means of Pearson's test. Furthermore, stepwise multiple regression analyses were run, in which mean scores of

PAS academic and social domains were entered as dependent variables, whereas independent variables included gender, as well as psychopathological dimensions and cognitive indices which differed between patient subgroups with different premorbid adjustment course.

Results

Subjects

The study was carried out in a large sample of community-dwelling patients with a DSM-IV diagnosis of schizophrenia (n = 915), as well as in a group of their unaffected first-degree relatives (n = 368: 249 parents, 119 siblings) and one of healthy controls (n = 778) in the context of the multicenter study of the Italian Network for Research on Psychoses **65**. Group comparisons on demographic variables showed a higher frequency of male gender among patients (69.4%) with respect to both relatives and controls (42.9% and 48.4%, respectively; $P \leq 0.000001$), an older age in relatives (55.0 ± 13.7 years) with respect to patients and controls (40.2 ± 10.7 and 40.5 ± 12.5 years, respectively; $P \leq 0.00002$), due to the fact that also parents were included in the group of relatives (mean age: 61.5 ± 8.4 years for parents, 41.3 ± 12.6 years for siblings; $P \leq 0.000001$), and a higher education level in controls (13.0 ± 4.0 years) than in patients and relatives (11.6 ± 3.4 and 11.3 ± 4.0 years, respectively; $P \leq 0.00002$). In subsequent comparisons among the three groups, gender and age were used as covariates, whereas education was not, as reported in the Methods section.

Comparisons on demographic variables among patients with different premorbid adjustment course (stable-good, n = 329; stable-poor, n = 329; deteriorating, n = 249) showed that age and gender distribution were comparable, whereas education was higher in the stable-good subgroup compared with the other two.

Group comparisons between patients, unaffected relatives, and healthy controls on PAS indices

The MANOVA on PAS academic and social dimensions comparing patients, relatives, and controls showed a significant group effect ($F_{2,1677}$ = 524.83, $P \leq 0.000001$), due to a poorer early adjustment in patients with respect to both controls and relatives for both PAS domains and for all age periods (Fig. 1a).

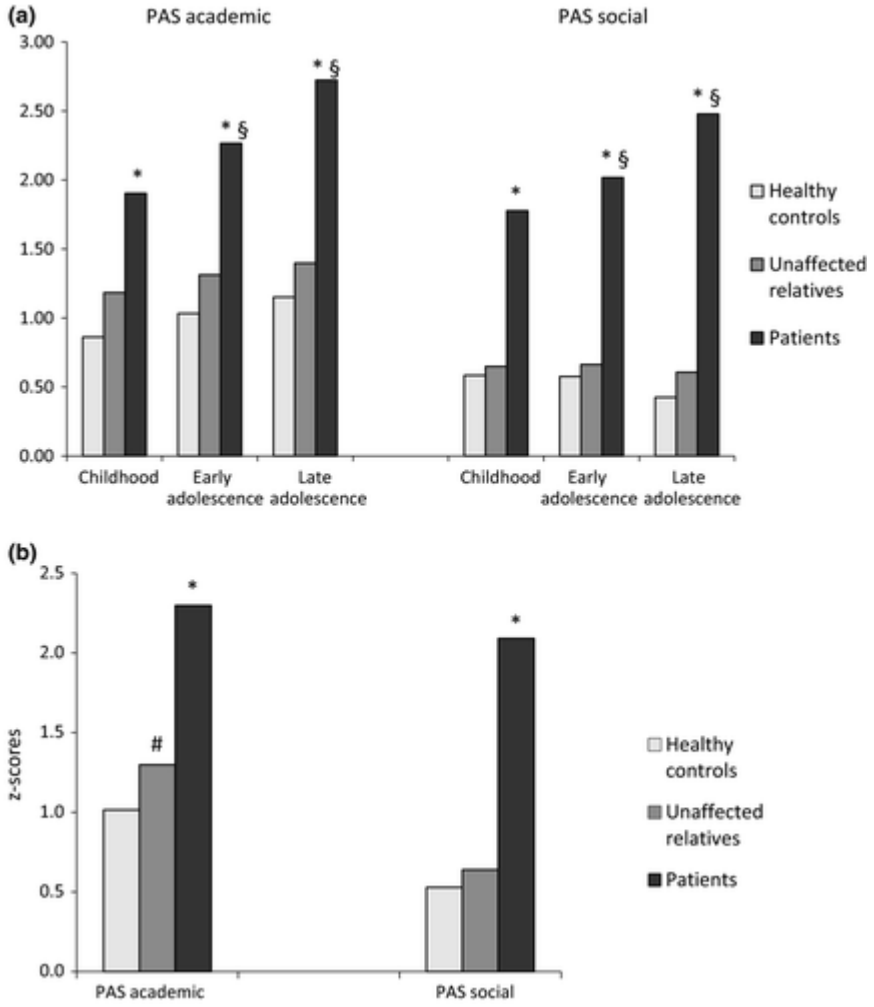

Figure 1

Group comparisons on PAS Academic and Social dimensions. (a) Patients show a greater impairment with respect to both healthy controls and unaffected relatives for both PAS domains, in all age periods, as well as a highly significant worsening over time, not observed in the other two groups. *Statistically significant difference with respect to unaffected relatives and healthy controls: $P < 0.000001$. §Statistically significant difference with respect to the previous age period: $P < 0.000001$. (b) A greater impairment is observed, independently from age periods, in patients with respect to the other two groups for both Academic and Social PAS domain, as well as in unaffected relatives with respect to healthy controls only for the Academic domain. *Statistically significant difference with respect to unaffected relatives and healthy controls: $P < 0.000001$. #Statistically significant difference with respect to healthy controls: $P < 0.01$.

Moreover, a statistically significant group-by-age period interaction ($F_{4,3354} = 90.46$, $P \leq 0.000001$) was observed. According to the *post hoc* analysis, it was due to a significant worsening of premorbid adjustment over time (childhood vs. early adolescence as well as early vs. late adolescence), independently of the PAS domain, in the group of patients, whereas such a progression was not observed in the other two groups (Fig. 1a).

A significant interaction group-by-dimension was also observed ($F_{2,1677} = 28.89$, $P \leq 0.000001$) that, according to *post hoc* analysis, was due to a greater impairment in patients with respect

to the other two groups for both domains, and to a poorer functioning in relatives with respect to controls only for the academic domain, independently by the age period (Fig. 1b).

The MANOVA on PAS academic and social dimensions comparing parents and siblings within the group of relatives showed no statistically significant interaction with kinship.

The comparisons among the three groups on the frequency of different patterns of course of early adjustment showed that a poor early adjustment was more frequent in patients (63.7%) with respect to relatives and controls (9.5% and 5.4%, respectively; $P \leq 0.00001$) and, to a less degree, in relatives with respect to controls ($P \leq 0.01$).

Comparisons among patient groups with different course of premorbid adjustment

Comparisons among the three subgroups of patients with different course of premorbid adjustment revealed the lack of differences for all the investigated psychopathological, cognitive, and real-life functioning indices between patients with the stable-poor pattern and those with the deteriorating one. Therefore, these two subgroups were collapsed in a single class named 'poor premorbid adjustment' (poor-PA, $n = 578$) that was compared to the remaining one named 'good premorbid adjustment' (good-PA, $n = 329$). The only difference between the two subgroups on demographic variables was a higher level of education in the good-PA with respect to the poor-PA group. The MANOVA on psychopathological variables comparing poor-PA vs. good-PA patients showed a significant group effect ($F_{1,905} = 33.04$, $P \leq 0.000001$) and a significant group-by-symptom interaction ($F_{2,1810} = 4.02$, $P \leq 0.02$), due to a greater severity of both negative symptoms subdomains (poor emotional expression and avolition) in the poor-PA group (Fig. 2a).

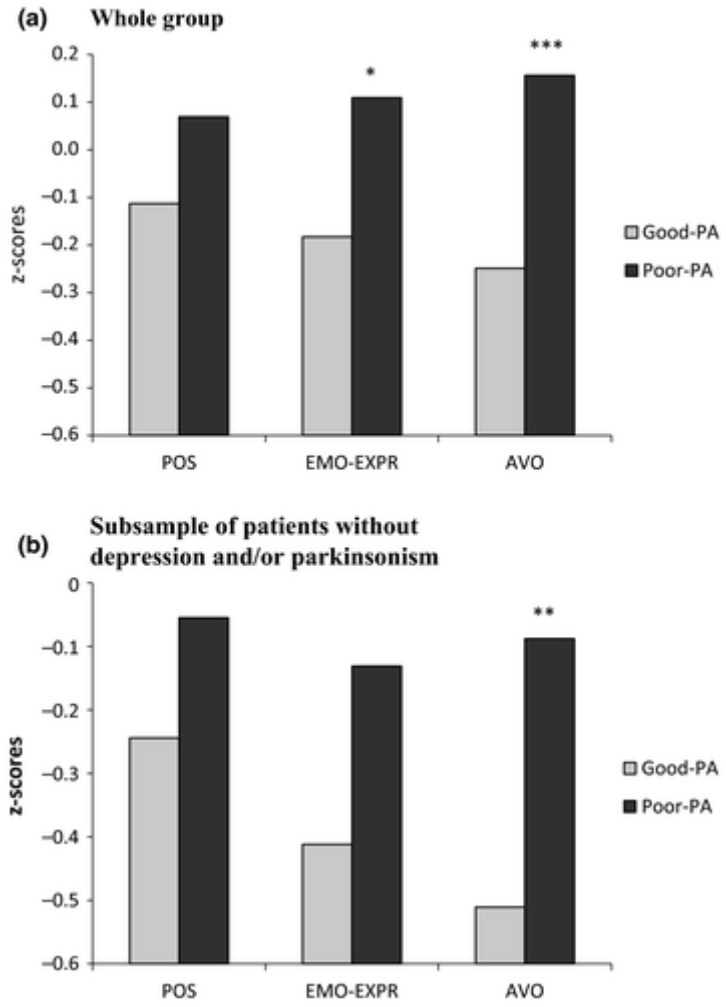

Figure 2

Comparisons on psychopathological variables between patients with good premorbid adjustment (Good-PA) and patients with poor premorbid adjustment (Poor-PA). (a) In the whole sample of patients, both domains of negative symptoms (Poor Emotional expression and Avolition) are more severe in the poor-PA group with respect to the good-PA one. (b) After the exclusion of patients with clinical significant depression and/or parkinsonism, only Avolition is more severe in the poor-PA group with respect to the good-PA one. POS = positive symptoms; EMO-EXPR = Reduced emotional expression; AVO = Avolition. *Statistically significant group difference: *$P \leq 0.003$; **$P \leq 0.0005$; ***$P \leq 0.00001$.

When the MANOVA was run in the subsample without clinically significant depression and/or parkinsonism ($n = 480$), significant effects of group ($F_{1,478} = 19.32$, $P \leq 0.000001$) and of symptom subdomain ($F_{2,956} = 4.86$, $P \leq 0.01$) were observed, whereas the group-by-symptom domain interaction only approached the statistical significance ($F_{2,956} = 2.65$, $P \leq 0.07$). *Post hoc* analysis in this subsample revealed a statistically significant greater severity of avolition only in the poor-PA group (Fig. 2b).

The MANOVA on neurocognitive domains showed a significant effect of group ($F_{1,860} = 16.58$, $P \leq 0.00005$) and domain ($F_{5,4300} = 62.44$, $P \leq 0.000001$), and a significant group-by-domain interaction ($F_{5,4300} = 2.17$, $P \leq 0.05$) that, according to *post hoc* analysis, was due to a more severe impairment of working memory in the poor-PA group with respect to the good-PA one

(Table 1). The MANOVA on the social cognition index showed a significant effect of group ($F_{1,897}$ = 8.15, $P \leq 0.004$), due to a greater impairment in the poor-PA group with respect to the good-PA one (Table 1).

Table 1. Comparisons on cognitive domains and areas of real life functioning between patients with good premorbid adjustment (good-PA) and patients with poor premorbid adjustment (poor-PA)

	Patients with good-PA (n = 329)	Patients with poor-PA (n = 578)
Psychopathological domains (z-scores)		
PANSS positive	−0.11 ± 1.01	0.07 ± 0.98
BNSS reduced emotional expression	−0.18 ± 1.02	0.11 ± 0.98*
BNSS avolition	−0.25 ± 1.04	0.16 ± 0.94**
Neurocognitive domains (T-scores)		
Speed of processing	33.27 ± 10.25	30.50 ± 11.75
Attention/vigilance	37.83 ± 11.31	36.36 ± 11.43
Working memory	37.73 ± 11.38	33.53 ± 11.90*
Verbal learning	36.69 ± 10.85	34.36 ± 12.20
Visual learning	33.58 ± 15.05	31.44 ± 14.51
Problem solving	39.19 ± 10.45	36,85 ± 9.92
Social cognition (composite score)	−1.26 ± 1.15	−1.47 ± 1.08*
Areas of real-life functioning (z-scores)		
Interpersonal relationships	0.26 ± 0.97	−0.16 ± 0.97**
Community activities	0.17 ± 0.95	−0.10 ± 1.01**
Work abilities	0.28 ± 0.15	−0.15 ± 0.99**

PANSS, Positive and Negative Syndrome Scale; BNSS, Brief Negative Symptom Scale.
Statistically significant group difference: *$P \leq 0.01$; **$P \leq 0.00001$.

A pattern of group differences analogous to those reported above emerged by the MANOVArun on SLOF areas, showing a significant group effect ($F_{1,885}$ = 46.29, $P \leq 0.000001$) and a significant group-by-area effect ($F_{2,1770}$ = 3.32, $P \leq 0.04$). *Post hoc* analyses showed a greater impairment of all the considered areas of real-life functioning in poor-PA with respect to good PA (Table 1).

Correlation analyses in the patient sample

Results of correlation analyses are reported in Table 2. Statistically significant positive correlations were observed between both academic and social PAS domains and the three considered psychopathological indices (poor emotional expression, avolition, and positive symptoms; $P \leq 0.0001$ for all of them), indicating that a worse premorbid adjustment is associated to more severe psychopathology. The association was slightly stronger for

avolition (r = 0.16) with respect to the other two symptom dimensions (r = ≤0.13), in particular in the subsample of patients without clinically significant depression and/or parkinsonism (n = 482; r = 0.32 for avolition, r ≤ 0.26 for the remaining two dimensions).

Table 2. Results of correlation analyses

	Whole-patient sample (n = 915)				Subsample of patients without depression and/or parkinsonism (n = 482)			
	PAS academic		PAS Social		PAS academic		PAS social	
	P	*r*	*P*	*r*	*P*	*r*	*P*	*r*
Psychopathology								
Reduced emotional expression	**0.0001**	0.13	**0.0001**	0.22	**0.01**	0.11	**0.0001**	0.26
Avolition	**0.0001**	0.16	**0.0001**	0.28	**0.0001**	0.17	**0.0001**	0.32
Positive symptoms	**0.0001**	0.12	**0.0001**	0.14	**0.01**	0.12	**0.002**	0.14
Cognition								
Speed of processing	**0.0001**	−0.20	**0.0001**	−0.14	**0.0001**	−0.21	0.1	−0.07
Attention/vigilance	**0.0001**	−0.16	0.07	−0.06	**0.002**	−0.15	0.6	−0.02
Working memory	**0.0001**	−0.30	**0.0001**	−0.18	**0.0001**	−0.32	**0.0001**	−0.16
Verbal learning	**0.0001**	−0.19	**0.0001**	−0.10	**0.0001**	−0.21	0.07	−0.08
Visual learning	**0.0001**	−0.18	0.06	−0.06	**0.0001**	−0.40	0.4	−0.04
Problem solving	**0.0001**	−0.14	**0.0001**	−0.11	**0.001**	−0.15	0.1	−0.07
Social cognition	**0.0001**	−0.19	0.1	−0.05	**0.0001**	−0.22	0.1	−0.08
Real-life functioning								
Interpersonal relationships	**0.0001**	−0.16	**0.0001**	−0.27	**0.0001**	−0.19	**0.0001**	−0.27
Community activities	**0.0001**	−0.17	**0.0001**	−0.19	**0.0001**	−0.19	**0.0001**	−0.18
Work abilities	**0.0001**	−0.23	**0.0001**	−0.18	**0.0001**	−0.21	**0.0001**	−0.18

Bold, statistically significant.

All neurocognitive domains, as well as the social cognition index, were negatively correlated with both PAS domains. These correlations indicate that a worse premorbid adjustment is associated to a worse neurocognitive and social cognition performance. They were statistically significant for all neurocognitive domains (P ≤ 0.0001 for all of them) and for social cognition (P ≤ 0.0001) when considering the academic PAS domain, and only for speed of processing, working memory, verbal learning, and reasoning and problem solving (P ≤ 0.0001 for all of them) when considering the social PAS domain. In the subsample of patients without depression and/or parkinsonism, the same pattern of results was observed for the academic domain, whereas for the social domain the only statistically significant association was with working memory.

Statistically significant negative correlations were also observed between both PAS domains and the three SLOF areas (P ≤ 0.0001 for all of them), indicating that a worse premorbid adjustment is associated to worse real-life functioning in all the examined domains. Slightly stronger associations were observed between the PAS academic domain and work abilities (r = −0.23 vs. r ≤ −0.17), as well as between social PAS domain and interpersonal relationships (r = −0.27 vs. r ≤ −0.19). This pattern of correlations did not change after the exclusion of patients with clinically significant depression and/or parkinsonism.

Stepwise multiple regression analyses in the patient sample

Results of multiple regression analyses are reported in Table 3. The mean score on the PAS academic domain was associated with the working memory neurocognitive domain ($F_{3,868}$ = 87.8, R^2 = 0.09), avolition ($F_{3,868}$ = R^2 = 0.01), and gender ($F_{3,868}$ = 7.7, R^2 = 0.008) (the worse the academic premorbid adjustment, the poorer the performance on the tests exploring working memory, the more severe the avolition, and the higher the percentage of males). The mean score on the PAS social domain was associated with avolition ($F_{2,894}$ = 74.6, R^2 = 0.08) and working memory ($F_{2,894}$ = 17.3, R^2 = 0.02) (the worse the social premorbid adjustment, the more severe the avolition, and the poorer the performance on working memory test). After excluding subjects with clinically significant depression and/or parkinsonism, the association between academic PAS domain and working memory, as well as that between social PAS domain and avolition, became slightly stronger (R^2 = 0.10 for both).

Table 3. Results of multiple regression analyses

Table 3. Results of multiple regression analyses

	Whole-patient sample (n = 915)		Subsample of patients without depression/ parkinsonism (n = 482)	
	$F_{3,868}$	R^2	$F_{3,454}$	R^2
PAS Academic				
Gender	7.7	0.008**	9.4	0.02**
Reduced emotional expression				
Avolition	12.8	0.01**	4.8	0.01*
Attention/vigilance				
Working memory	87.8	0.09***	51.9	0.10***
Verbal learning				
Visual learning				
Problem solving				
Social cognition index				

	Whole-patient sample (n = 915)		Subsample of patients without depression/ parkinsonism (n = 482)	
	$F_{2,894}$	R^2	$F_{2,473}$	R^2
PAS social				
Gender				
Reduced emotional expression				
Avolition	74.6	0.08***	55.8	0.10***
Working memory	17.3	0.02***	6.02	0.01*
Verbal learning				
Problem solving				

*$P \leq 0.05$; **$P \leq 0.005$; ***$P \leq 0.0001$.

Discussion

According to our findings, premorbid adjustment in patients with schizophrenia, as compared to early adjustment in healthy controls and patients' unaffected first-degree relatives, is poorer for both social and academic domains during childhood and early and late adolescence. This finding is in line with a large body of literature reporting an impairment of premorbid adjustment in patients with schizophrenia with respect to healthy controls **64**, **66**, **67**.

Unaffected relatives also differed from healthy controls, although to a lesser extent than patients, by showing a poorer early adjustment only for the academic domain and independently of the age period, as well as a slightly greater frequency of poor early adjustment. These findings, in line with those of other studies exploring early adjustment in patients' relatives **4**-**8**, **64**, support the hypothesis that poor early adjustment may represent a marker of vulnerability to schizophrenia.

The exclusive involvement of the academic domain in relatives, already reported by other authors **4**, **5**, could be related to a mild cognitive dysfunction that has been described by several authors **68**-**73** and found in the sample of relatives recruited in the present multicenter study **63**, **74**.

It should be noticed that the differences in early adjustment we observed between relatives and controls were small, although statistically significant. An underestimation of impairment in early epochs of life in relatives cannot be excluded; it might be due to a retrospective recall bias that could be greater in this group since it includes also parents (for which a long time elapsed since early epochs of life and no further source of information was available). As a matter of fact, more marked differences were reported when the group of relatives consisted of offspring of patients **5**. It should be acknowledged that the inclusion of parents together with siblings in the group of relatives represents a limitation of our study design, as it introduces a potential bias due to the fact that parents are older and less educated than siblings; therefore we controlled for this potential bias by comparing PAS severity among parents and siblings, and found no statistically significant interaction with kinship.

Our data also confirm the previously reported impact of poor premorbid adjustment on negative symptoms **9**, **11**, **75** but not on the positive ones **21**, **36**. In this study, for the first time to our knowledge, the impact of premorbid dysfunction was investigated on the two factors of the negative psychopathological dimension, that is avolition and poor emotional expression. When considering the subsample of patients without clinically significant depression and/or parkinsonism, we found a greater severity of avolition in the poor-PA group with respect to the good-PA one, and an association of academic and social premorbid impairment with both negative factors. Furthermore, regression analyses revealed the lack of

associations between the two PAS domains and the negative factor poor emotional expression, whereas both academic and social PAS domains were significantly associated with avolition; this association resulted slightly stronger with the social PAS domain, in particular after excluding the confounding effect of depression and/or parkinsonism. These findings are in line with the hypothesis that the two distinct dimensions of negative symptoms are subtended by different pathophysiological mechanisms and neurobiological correlates. According to recent literature, a key role in the pathophysiology of poor emotional expression seems to be played by a dysfunction of amygdala and hippocampus, known to be involved in emotion recognition and expression, whereas avolition has mainly been associated with abnormalities in prefrontal-subcortical circuits involved in motivation and goal-directed behaviour **32**, **76**, and is a much stronger predictor of functioning than is poor emotional expression **77**, **78**. Our finding of a stronger association of poor premorbid functioning, especially of its social component, with avolition than with poor emotional expression, suggests that the former is more likely related to neurodevelopmental abnormalities with respect to the latter and that such abnormalities may involve neural circuits implicated in goal-oriented behavior.

A greater impairment of working memory and social cognition was observed in patients with poor-PA with respect to those with good-PA. An association between premorbid dysfunction and impairment in working memory has already been reported **10**, **39**, whereas the relationship between social cognition and premorbid adjustment was explored for the first time in this study. Different patterns of association of poor-PA with other neurocognitive domains have also been found **15**, **21**, **79**, **80**. Such discrepancies may be related to the great heterogeneity among different studies in the choice of the test battery and selection of cognitive domains.

Regression analyses showed that working memory was more strongly associated to the PAS academic domain than to the social one, especially in the subsample of patients without clinically significant depression and/or parkinsonism, whereas avolition was more strongly related to the social than to the academic PAS domain. These two different patterns of associations have been reported in the majority of previous studies (**8**, **10**, **15**-**18**, **20**, **21**, **37**), with some exception **23**-**25**, **40** and are confirmed in this study when excluding the confounding effect of depression and/or parkinsonism.

As to real-life functioning, we found that all the investigated areas were more impaired in the group of patients with poor-PA, and that their impairment was associated to both PAS domains. This confirms the impact of premorbid dysfunction on real-life functioning, as reported by several authors **42**-**46**.

In conclusion, our findings confirm the presence of a global impairment of premorbid adjustment in patients and an impairment of early adjustment in patients' unaffected first-

degree relatives mainly involving the academic domain. Our data confirm that the two PAS domains show different patterns of associations, with the academic domain mainly associated with cognitive deficits, in particular working memory, and the social domain mostly associated with primary negative symptoms, in particular avolition. Instead, premorbid adjustment domains are not associated with the severity of positive symptoms, whereas both of them are associated with social cognition and real-life functioning.

The impairment of functioning occurring in patients before the illness onset, as well as in their unaffected relatives during early epochs of life, suggests that poor early adjustment may represent a marker of vulnerability to schizophrenia. However, the possibility that it is a consequence of cognitive deficits and/or avolition cannot be ruled out based on available findings.

Findings from our study have some potential clinical implications. First of all, they suggest the inclusion of a comprehensive assessment of academic and social aspects of early functioning in subjects at ultra-high-risk for developing psychosis in algorithms implemented to predict psychosis. In addition, such an assessment of early functioning in these subjects, as well as its historical assessment in patients at their first episode of psychosis, may be informative for the implementation of individually tailored preventive/early intervention strategies, such as psychosocial and/or cognitive rehabilitation programs, based on the domain of early functioning resulting impaired. Early interventions on social and/or academic aspects of functioning may impact, respectively, the course of negative symptoms and cognitive deficits, which in their turn strongly influence the outcome in people with schizophrenia.

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Declaration of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

Appendix

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