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DISORGANIZED THINKING AND EMOTIONAL POVERTY ARE PRIMARY CLINICAL PREDICTORS OF FUNCTIONING IN PSYCHOSES. REANALYSIS OF THE TURKU EARLY PSYCHOSIS STUDY DATA

ABSTRACT

Background: The functional outcomes of patients with a psychotic disorder have been associated with several overlapping clinical, neuropsychological and developmental factors.
Aim: In a prospective study, we aimed to predict functional outcomes in patients with first-episode psychosis or clinically high risk for psychosis by sociodemographic, clinical, neuropsychological and premorbid factors and follow-up symptomatology.
Methods: Altogether, 130 first-episode psychosis and 60 clinical high-risk patients were recruited, and their functioning was assessed at baseline and at 9- and 18-month follow-ups. The total follow-up functioning was predicted by baseline characteristics and factorized dimensions of baseline clinical symptoms, premorbid adjustment, childhood adversities, neuropsychological tests and follow-up symptoms.
Results: Emotional Poverty and Disorganized Thinking, premorbid Sociability and Scholastic Performance, social support, baseline functioning, follow-up Depression/Anxiety and Psychoticism correlated significantly with follow-up functioning. In the regression model, follow-up functioning was significantly associated with Sociability and Scholastic Performance, Disorganized Thinking, work and marital status in the entire sample and in psychotic patients separately. In clinical high-risk patients, Emotional Poverty and follow-up depression/anxiety symptomatology were significantly associated with poor follow-up functioning. The effects of Sociability and School Performance on follow-up functioning were mediated via Emotional Poverty in both patient groups.
Conclusion: In psychotic patients, poor premorbid adjustment, disorganized thinking, poor baseline work status and being single predicted poor follow-up functioning. The effect of premorbid adjustment on follow-up functioning was partly mediated via emotional poverty. In clinical high-risk patients, basic disturbances were affective disorders, and attenuated psychotic symptoms represented their severity.

KEYWORDS: FUNCTIONAL OUTCOME, PSYCHOSIS, CLINICAL HIGH RISK FOR PSYCHOSIS, PREMORBID PSYCHOSOCIAL ADJUSTMENT, DISORGANIZED SYMPTOMS, EMOTIONAL POVERTY, NEGATIVE SYMPTOMS, EMPLOYMENT SITUATION, MARITAL STATUS

INTRODUCTION

PSYCHOSIS

According to Emil Kraepelin [1], classification of mental diseases should be based on illness course and outcome. Using follow-up observations of hospitalized patients, he described dementia praecox with poor and manic-depressive psychoses with good course. Characteristic clinical features of dementia praecox were disturbed courses of thought (Gedankengang), emotional dullness, apathy, lack of interest and volition, diminished work capacity and overall lack of emotional activity. Eugen Bleuler [2] emphasized the need for early diagnosis and the significance of illness symptoms and replaced the dementia praecox with a group of schizophrenic patients with a better but more variable course. In the illness picture, loosening of associations, found in all patients, was primary and behind the fundamental symptoms: formal thought disorders (typically incoherent train of thought) and affect disturbances (typically flattening of affects). Other fundamental symptoms were ambivalence and autism, while delusions, hallucinations and catatonic symptoms were regarded as accessory symptoms [2].

Schneider [3] introduced the concept of first-rank symptoms, which were reliably detectable in all cultures and frequently seen in patients with schizophrenia but also in other severe psychiatric disorders, even in neurological disorders. In a follow-up study, first-rank symptoms were not associated with poor prognosis in schizophrenia [4].

Later, the group of schizophrenias was divided into Kraepelinian nuclear schizophrenia with poor prognosis and schizophreniform psychoses with good prognosis [5] and process/reactive schizophrenia with poor/good premorbid development and poor/good prognosis [6]. In two 7½-year follow-up studies of first-time hospitalized patients, patients with nuclear schizophrenia had poorer outcomes than patients with schizophreniform psychoses [7-8].

Strauss et al. [9] proposed a distinction between positive and negative symptoms. These symptom categories, accepted by other researchers [10], have been adopted in various symptom classifications. In addition to negative symptoms, poor premorbid psychosocial development, educational and work achievement, male gender, single marital status and lack of interpersonal networks have been associated with poor illness course and functional outcomes in patients with schizophrenia [7,8,11,12,13,14,15,16,17,18,19,20,21, 22,23,24].

Patients with schizophrenia have also shown cognitive deficits, including worse intellectual function, learning and memory, attention, working memory, language, executive function and social cognition [25,26,27,28,29,30]. However, baseline neurocognitive impairments have not been associated with clinical outcome [31]. Additionally, childhood adversities have been associated with psychotic disorders [32,33,34] and with persistence of psychotic symptoms and poor outcomes [35,36].

CLINICAL HIGH RISK FOR PSYCHOSIS (CHR)

As early as 1887, Emil Kraepelin [37] described that mental illness (Geisteskrankheit) mostly begins gradually; a sudden beginning is mostly a reaction to external causes. Almost regularly, small changes in emotional life (Gefülsleben) are the first signs, but it may take weeks, months or even years before the onset of a mental illness. This prodromal stage (Stadium der Prodrome) may appear as emotional irritation, restlessness or depressiveness. When the stage of uncharacteristic prodromal disturbances retreats, the characteristic initial symptoms (Initialsymptome) of psychosis become visible. Bleuler's [2] description of "latent schizophrenia" represents a prodromal disturbance without characteristic symptoms of schizophrenia or its 'forme fruste' [38].

Hoch and Polatin [39] described pseudoneurotic forms of schizophrenia with brief and limited psychotic episodes (micropsychoses) and found that 20% of these patients became schizophrenic [40]. In two 8-year follow-up studies, 15.4% of patients with pseudoneurotic schizophrenia became psychotic. Compared with patients with nuclear schizophrenia and schizophreniform psychoses, their outcome was better [7-8].

In the 1960s, Huber [41] described anomalous subjective experiences (basic symptoms) that can develop into psychosis (prodromes) or resolve spontaneously (outpost syndromes) [41,42,43]. Based on these observations, instruments Bonn Scale for the Assessment of Basic Symptoms (BSABS) and Schizophrenia Proneness Instrument, Adult Version (SPI-A) [44,45] were developed for detecting individuals at high risk for psychosis. Using a combination of positive symptoms, changes in functioning and family history, two other instruments, the Comprehensive Assessment of At-Risk Mental States (CAARMS) [46,47,48] and Structured Interview for Prodromal Syndromes/Scale of Prodromal Symptoms (SIPS/SOPS) [49,50], have been developed and widely used.

Clinical High Risk for Psychosis (CHR) patients are characterized by many clinical disorders, including substance use, affective disorders, suicidal ideation and self-harm, and have impairments in work or in educational and social functioning [51]. In patients with CHR, e.g., long duration of prodromal symptoms, positive symptoms, bizarre thinking, schizotypal personality, substance abuse, low education, depression, disorganization, neurocognitive deficits and poor psychosocial development have been associated with onset of psychosis [52,53,54,55,56,57,58]. According to a systematic review, negative symptoms and disorganized symptoms and cognitive deficits predate frank psychotic symptoms and are risk factors for poor functioning [59].

In CHR patients, impaired emotion recognition and processing speed and deficits in motor speed, verbal memory, verbal learning, verbal fluency and executive function have been associated with the onset of psychosis and poor functioning [58,60,61,62,64]. Additionally, patients with CHR report high levels of childhood adversity [65,66]; this adversity may predict depression, poor social functioning and suicidal thinking [66,67,68].

In terms of premorbid functioning, CHR subjects have not differed from patients with first-episode psychosis or multi-episode schizophrenia [69]. In outcome studies of CHR patients, premorbid psychosocial adjustment, baseline negative symptoms and poor employment/study situations have predicted poor functional outcomes at follow-up [63,64,70,71].

In our previous study, we found that sum scores of premorbid adjustment, assessed by the Premorbid Adjustment Scale (PAS) [72], and sum scores of disorganized symptoms of the Structured Interview for Prodromal Syndromes (SIPS) [49, 73], and one of several neuropsychological (NEUPSY) tests were the major predictors of follow-up functioning in patients with clinical or subclinical psychotic disorders [74,75]. However, PAS and SIPS scores and NEUPSY tests used in analyses are combinations of heterogeneous items. Therefore, in order to reduce heterogeneity of these measurements we factorized PAS, SIPS and NEUPSY items and follow-up symptoms and used these factor dimensions in our analyses. Using more homogeneous explanatory factors, we expected that the practitioner planning interventions for psychotic patients can also receive a more concise and understandable view of the factors predicting patient's functional outcome.

In the present study, our first aim was to predict 9- to 18-month functional outcomes with premorbid, baseline and follow-up factor dimensions in patients with first-episode psychosis (FEP) and clinical high risk for psychosis (CHR). We proposed that PAS can express the effects of very early, like genetic and external, factors that can modulate the clinical factors available at the moment when the clinicians first time meet psychotic patients and concurrently associate with functional outcome. Thus, our second aim was to investigate whether the effect of PAS on follow-up functioning is mediated via baseline clinical factor dimensions. The 18-month follow-up is justified because interventions, aimed at improving both clinical and functional outcomes over longer time periods, should be performed during this critical period.

METHODS

The investigations of the Turku Early Psychosis Study (TEPS) study programme were carried out in accordance with the latest version of the Declaration of Helsinki, and the study design and protocols were approved by the ethical committee of the Turku University Hospital. Written informed consent from participants was obtained after the procedure had been fully explained to them.

SAMPLE AND EXAMINATIONS

The TEPS is a prospective study in which the sample and examinations were described in detail in our previous article [74-75]. Altogether, 130 FEP and 60 CHR patients were recruited from the services of the Turku University Hospital District in Finland between October 2011 and December 2017.

FEP was defined by the Structured Clinical Interview for DSM-IV (SCID-I) criteria and included schizophrenia, delusional and bipolar psychoses, acute and transient psychoses and other psychoses. CHR was defined by the ultra-high risk (UHR) criteria: Attenuated Psychotic Symptoms (APS), Brief Limited Psychotic Symptoms (BLIPS) and genetic risk and reduction of function (GRD) assessed by the 3.0/5.0 version of the Structured Interview for Prodromal Syndromes (SIPS/SOPS) including the Global Assessment of Functioning (GAF) scale [49,73].

At baseline, information on socioeconomic background, premorbid adjustment (PAS) [72], SIPS symptoms (SIPS/SOPS), including GAF [49,73] and Axis I diagnosis (the Structured Clinical Interview for DSM-IV, Axis I) [76] were received in interviews. Neuropsychological tests (NEUPSY) were obtained from 119 (92%) out of 130 FEP and from 54

(90%) out of 60 CHR patients when the patients recovered from their acute psychosis.

Self-rating questionnaires on adverse and traumatic experiences in childhood (the Trauma and Distress Scale (TADS) [77,78]) and social support (Perceived Social Support Scale-Revised (PSSS-R) [79]) received from close confidants were also obtained. The PSSS-R includes 12 questions on social support received. The sum score (range 0-48) was used as an indicator of social support. Details of PAS, SIPS/SOPS, TADS and NEUPSY and their factor analyses are described in the Supplementary Material.

All subjects examined at baseline were invited to follow-up studies 9 (T1) and 18 (T2) months after the baseline examination. For this outcome study, GAF at baseline (GAFT0) and at the follow-up points (GAFT1 and GAFT2) and occurrence of psychosis (yes/no), depression (yes/no) and anxiety (yes/no) symptoms at the follow-up points (T1 and T2) were recorded. Due to follow-up dropouts, information regarding both functioning (GAF) and psychiatric symptoms was supplemented by scrutinizing patients' medical case notes and by telephone interviews with patients and/or their relatives and/or their doctors. GAF and psychosis, depression and anxiety symptoms were obtained for 190 (T0), 189 (T1) and 188 (T2) patients. Thus, there was one dropout at T1 and two dropouts at T2.

STATISTICAL ANALYSES

First, distributions of background factors were cross-tabulated, and means and SD of GAF, SIPS, TADS, PSSS-R, PAS and NEUPSY scores were calculated by diagnostic groups and tested by Chi-square tests and analyses of variance (ANOVAs). The sum of GAFT1 and GAFT2 was calculated, and this sum score was used to describe follow-up functioning (F-GAF).

Principal component factor analyses with varimax rotation were calculated from PAS, SIPS, TADS and NEUPSY items and follow-up symptoms, and the factors received were interpreted (*Supplementary Tables 2-6*). Means of factor dimension scores were calculated by diagnostic groups, and differences were tested with ANOVAs. Pearson correlation coefficients were calculated for the PAS, SIPS, TADS and NEUPSY dimensions and PSSS-R scores.

In multivariate analyses, F-GAF was predicted by background characteristics, PAS, SIPS, TADS and NEUPSY dimensions, and social support scores in linear regression analyses. Thereafter, follow-up psychiatric symptom dimensions were also included in the regression analyses.

Finally, a PROCESS macro in SPSS (model template 4) created by Hayes [80] was used. In cross-sectional samples, this macro tests the direct and indirect effects of an independent variable (X) on a dependent variable (Y) while modelling a process in which X affects a mediator (M), which in turn affects Y. The models tested the effect of X (PAS) on Y (F-GAF) with mediators (SIPS, TADS and NEUPSY dimensions and PSSS-R scores). Five thousand bootstrap samples and 95% confidence intervals were used for all analyses. The PROCESS macro was developed for cross-sectional analyses, but in the present study, it was applied in a prospective design.

Analyses were performed for all study subjects and in sensitivity analyses for FEP and CHR patients separately. Data were analysed using the Statistical Programme for the Social Sciences (SPSS) v26.0, and p values <0.05 were considered statistically significant.

RESULTS

BASELINE ANALYSES

In FEP patients, 33.8% had affective and 66.2% had non-affective psychosis. A majority of the CHR patients suffered from depression (56.7%) and anxiety (26.7%) disorders. The FEP patients reported more social support and, by diagnostic definition, more SIPS-positive symptoms. Otherwise, there was no difference in background characteristics, SIPS symptoms, TADS or PAS scores. At baseline, GAF was lower in FEP patients than in CHR patients. During follow-up, GAF in the FEP ($p<0.001$) and CHR ($p=0.007$) groups improved. However, at follow-up, there was no difference in F-GAF between the diagnostic groups (*Table 1*).

Table 1. Sociodemographic background and baseline characteristics of the Turku Early Psychosis Study (TEPS) sample

	FEP	CHR	All	p
Gender	n=130	n=60	n=190	0.336
Male	56.2	51.7	54.7	
Female	43.8	48.3	45.3	
Age (years)	n=130	n=60	n=190	0.124
18-23	37.7	53.3	42.6	
24-29	33.1	23.3	30.0	
30-49	29.2	23.3	27.4	
mean (SD)	26.5(5.9)	25.0(6.2)	26.1(6.0)	0.111
Marital status	n=130	n=60	n=190	0.999
Single	72.3	71.7	72.1	
Ever married/divorced	27.7	28.3	27.9	
Basic education	n=130	n=60	n=190	0.347
Elementary school or less	40.0	41.7	40.5	
High school	13.8	6.7	11.6	
College	46.2	51.7	47.9	
Professional education	n=130	n=60	n=190	0.254
None	43.8	48.3	45.3	
Vocational school	41.5	43.3	42.1	
University	14.6	8.3	12.6	
Years of education; mean (SD)	13.8(3.1)	13.2(2.9)	13.6(3.0)	0.207

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	FEP	CHR	All	p
Employment situation	n=130	n=60	n=190	0.574
Employed	60.0	58.3	59.5	
Unemployed	19.2	30.0	22.6	
Sick leave	10.8	6.7	9.5	
Temporary pension	10.0	5.0	8.4	
Social support	n=104	n=48	n=152	
mean, SD	31.4(11.5)	27.4(10.7)	30.2(11.4)	0.046
SCID Diagnosis (%)	n=130	n=60	n=190	<0.001
None	0.0	8.3	2.6	
Bipolar	16.9	3.3	12.6	
Depression	16.9	56.7	29.5	
Non-affective Psychosis	66.2	5.0	46.8	
Anxiety	0.0	26.7	8.4	
SIPS symptoms	n=125	n=60	n=185	
Positive (0-30)	16.5(5.3)	10.6(5.9)	14.6(5.6)	<0.001
Negative (0-30)	11.0(7.2)	11.4(6.5)	11.1(6.9)	0.760
Disorganized (0-24)	5.4(4.0)	4.9(3.4)	5.3(3.9)	0.325
General (0-24)	6.8(4.5)	7.7(3.3)	7.1(4.2)	0.162
TADS mean (SD)	n=107	n=48	n=155	
EmoAb (1-5)	4.7(4.3)	5.3(4.4)	4.9(4.3)	0.449
PhyAb (1-5)	1.7(2.1)	1.8(2.6)	1.8(2.2)	0.831

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	FEP	CHR	All	p
SexAb (1-5)	1.2(3.1)	0.6(1.6)	1.0(2.7)	0.242
EmoNeg (1-5)	6.8(5.0)	7.5(5.1)	7.0(5.0)	0.469
PhyNeg (1-5)	3.4(2.8)	3.3(3.1)	3.4(2.9)	0.831
PAS mean (SD)	n=124	n=57	n=181	
-11 years (0-24)	6.2(3.6)	6.8(3.3)	6.4(3.5)	0.278
12-15 years (0-30)	10.1(5.2)	10.8(4.9)	10.3(5.1)	0.427
16-18 years (0-30)	10.9(5.6)	10.9(5.9)	10.9(5.6)	0.998

FEP = First-episode psychosis; CHR = clinical high-risk to psychosis;
EmoAb = Emotional abuse; PhyAb = Physical abuse; SexAb = Sexual abuse; EmoNeg = Emotional neglect;
PhyNeg = Physical neglect; PAS = Premorbid adjustment

In neurocognitive tests of attention, speed of processing, verbal learning and visual learning, the CHR patients performed better than FEP patients (*Supplementary Table 1*). In other tests, there was no difference between FEP and CHR patients.

FACTOR ANALYSES ON SIPS SYMPTOMS, NEUROPSYCHOLOGICAL TEST PARAMETERS, TADS DOMAINS AND FOLLOW-UP SYMPTOMS

Factor analysis of SIPS items yielded four dimensions: emotional distress, emotional poverty, disorganized thinking and delusions/hallucinations (*Supplementary Table 2*). Social anhedonia/withdrawal and avolition loaded on the Emotional Distress and Emotional Poverty dimensions, indicating some overlap and decrease in mood and emotional response in these dimensions. Odd behaviour/appearance loaded on Emotional Poverty and Disorganized Thinking dimensions describing the inability to take care of appearance and to behave coherently.

Factor analyses for NEUPSY yielded four factor dimensions: executive functions, cognitive performance, perceptual disturbances and verbal skills. For TADS domain there was one factor, childhood trauma. For PAS items, there were two factors, sociability and school performance. For follow-up symptoms, there were two factor dimensions, depression/anxiety and psychoticism (*Supplementary Tables 3-6*).

In CHR patients, Emotional Distress, Cognitive Performance and Depression/Anxiety dimension scores were higher than in FEP patients, whereas in Disorganized Thinking and Delusionary/Hallucinatory and Psychoticism dimensions, the situation was reversed (*Supplementary Figure 1*).

The employment situation, GAFT0, SIPS dimensions Emotional Poverty and Disorganized Thinking, PAS Sociability and School Performance, social support, and follow-up Depression/Anxiety and Psychoticism correlated significantly with F-GAF. It was notable that the NEUPSY and Childhood Trauma had no significant correlation with the F-GAF (*Table 2*).

Table 2. Correlation between baseline functioning (GAFT0), follow-up functioning (F-GAF) scores, Structured Interview for Prodromal Syndromes (SIPS), neuropsychological tests (NEUPSY), Premorbid Adjustment Scale (PAS), Trauma and Distress Scale (TADS) dimensions, Perceived Social Support Scale-Revised (PSSS-R) scores and follow-up symptom dimensions

	0	1.	2.	3.	4.	5.	6.	7.
0. GAFT0	1	**.438****	**-.220****	**-.216****	**-.307****	**-.159***	-.031	**.222****
1. F-GAF (GAFT1+GAFT2)	**.438****	1	-.119	**-.368****	**-.240****	-.003	.083	.131
SIPS dimensions								
2. Distress	**-.220****	-.119	1	.000	.000	.000	.026	-.009
3. Emotional Poverty	**-.216****	**-.368****	.000	1	.000	.000	**-.162***	**-.246****
4. Disorganized Thinking	**-.307****	**-.240****	.000	.000	1	.000	-.006	-.049
5. Delusionary/Hallucinatory	**-.159***	-.003	.000	.000	.000	1	.045	**-.237****
NEUPSY dimensions								
6. Executive Functions	-.031	.083	.026	**-.162***	-.006	.045	1	.000
7. Cognitive Performance	**.222****	.131	-.009	**-.246****	-.049	**-.237****	.000	1
8. Perceptual Disturbances	**223****	.134	-.107	-.135	**-.205****	-.009	.000	.000
9. Verbal Skills	.084	.141	**-.232****	-.143	-.001	.029	.000	.000
PAS dimensions								
10. Sociability	**-.222****	**-.278****	**.296****	**.385****	.076	.034	-.059	-.063
11. Scholastic Performance	-.079	**-.354****	.028	**.373****	.001	-.024	-.146	**-.333****
TADS domain dimension								
12. Childhood Trauma	.063	-.117	.115	**.171***	-.091	.050	.034	.024
PSSS-R scores								
13. Social support	.124	**.243****	**-.331****	**-.304****	.077	-.025	-.091	.113
Follow-up symptom dimensions								
14. Depression/Anxiety	-.138	**-.402****	**.186***	.098	-.084	**-.152***	**-.150***	.004
15. Psychoticism	**-.197****	**-.569****	-.110	.138	**.217****	**.188***	.044	**-.159***

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	8.	9.	10.	11.	12.	13.	14.	15.
0. GAFT0	**.223****	.084	**-.222****	-.079	.063	.124	-.138	**-.197****
1. F-GAF (GAFT1+GAFT2)	.134	.141	**-.278****	**-.354****	-.117	**.243****	**-.402****	**-.569****
SIPS dimensions								
2. Distress	-.107	**-.232****	**.296****	.028	.115	**-.331****	**.186***	-.110
3. Emotional Poverty	-.135	-.143	**.385****	**.373****	**.171***	**-.304****	.098	.138
4. Disorganized Thinking	**-.205****	-.001	.076	.001	-.091	.077	-.084	**.217****
5. Delusionary/Hallucinatory	-.009	.029	.034	-.024	.050	-.025	**-.152***	**.188***
NEUPSY dimensions								
6. Executive Functions	.000	.000	-.059	-.146	.034	-.091	**-.150***	.044
7. Cognitive Performance	.000	.000	-.063	**-.333****	.024	.113	.004	**-.159***
8. Perceptual Disturbances	1	.000	-.027	-.066	-.021	-.011	-.112	-.022
9. Verbal Skills	.000	1	-.037	**-.327****	.120	.072	.021	.037
PAS dimensions								
10. Sociability	-.027	-.037	1	.000	**.238****	**-.459****	.121	.031
11. Scholastic Performance	-.066	**-.327****	.000	1	.059	-.156	**.216****	**.164***
TADS domain dimension								
12. Childhood Trauma	-.021	.120	**.238****	.059	1	**-.354****	**.183***	-.043
PSSS-R scores								
13. Social support	-.011	.072	**-.459****	-.156	**-.354****	1	-.152	.011
Follow-up symptom dimensions								
14. Depression/Anxiety	-.112	.021	.121	**.216****	**.183***	-.152	1	.000
15. Psychoticism	-.022	-.037	.031	**.164***	-.043	.011	.000	1

**. Correlation is significant at the 0.01 level (2-tailed)
*. Correlation is significant at the 0.05 level (2-tailed)

MULTIVARIATE PREDICTION OF FOLLOW-UP FUNCTIONING

In linear regression analysis, baseline marital status (single), poor employment situation, Disorganized Thinking, difficulties in premorbid Sociability and School Performance associated with poor F-GAF (*Table 3 A*). In FEP patients, the associations were the same as in the entire sample (*Table 3 B*). In CHR patients, only Emotional Poverty significantly associated with F-GAF (*Table 3 C*).

Table 3. Regression analyses for follow-up functioning in the total sample (A.) and in the patients with first-episode psychosis (B. FEP) and with clinical high risk for psychosis (C. CHR) separately

A. TOTAL SAMPLE

R^2 0.342	B	p	CI95%	
Marital status (single)	10.047	0.038	0.588	19.507
Employment situation	-8.782	<0.001	-13.186	-4.377
Disorganized thinking	-7.492	<0.001	-11.608	-3.376
Sociability	-6.122	0.006	-10.472	-1.772
Scholastic Performance	-11.498	<0.001	-15.666	-7.330

B. FEP

R^2 0.400	B	p	CI95%	
Marital status (single)	15.519	0.011	3.622	27.416
Employment situation	-8.391	0.002	-13.711	-3.070
Disorganized thinking	-8.351	0.001	-13.062	-3.640
Sociability	-5.601	0.044	-11.052	-.151
Scholastic Performance	-13.066	<0.001	-18.287	-7.845

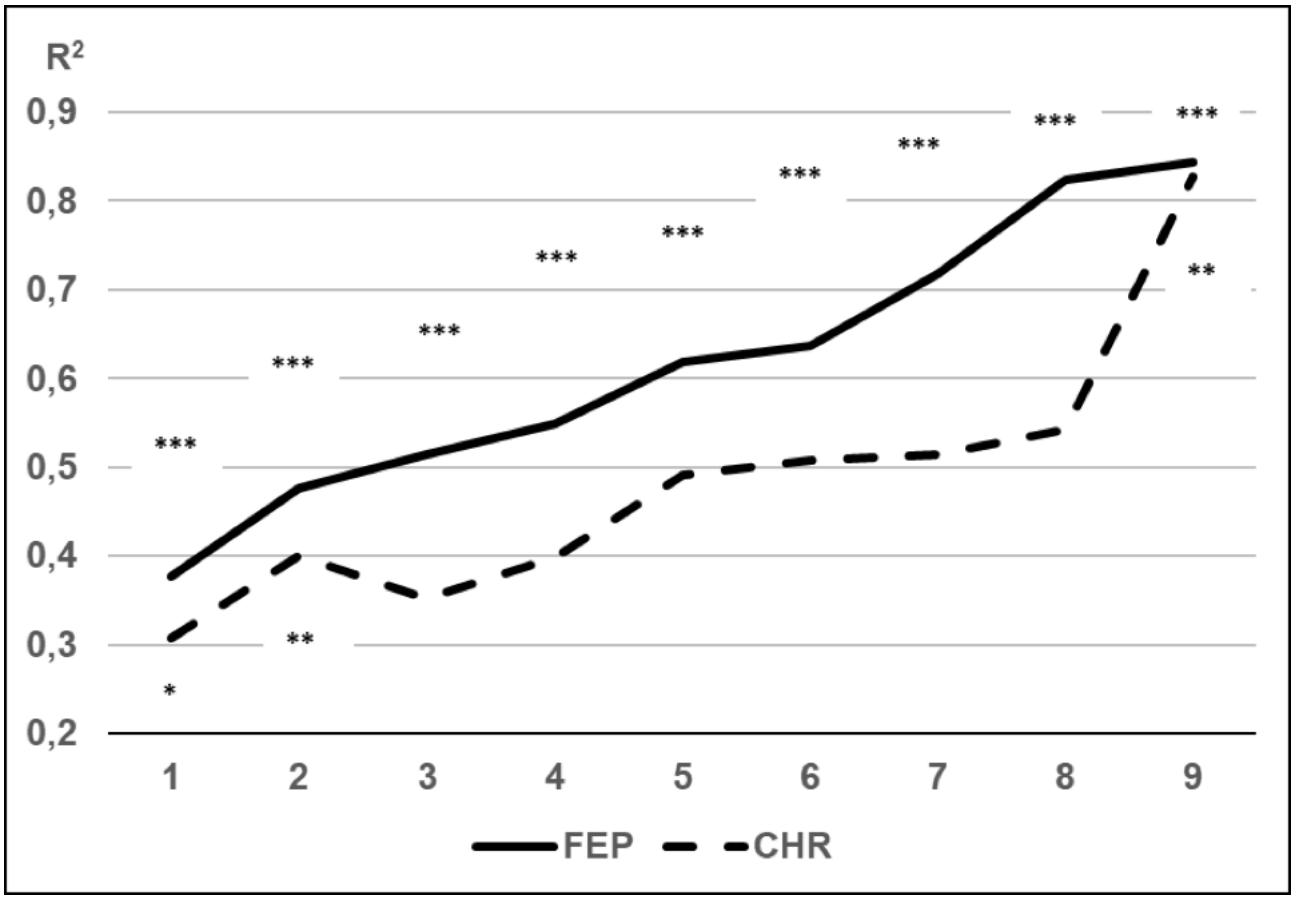
C. CHR

R^2 0.149	B	p	CI95%	
Emotional poverty	-10.378	0.003	-17.075	-3.681

In the regression models for FEP patients, the proportion of explained variance (R2) increased steadily when explanatory factors were added, and the regression models were statistically significant at each stage. In CHR patients, the effects of PAS dimensions were significant. Thereafter, regression models were non-significant until the follow-up depression/anxiety dimension was included. Simultaneously, R2 increased considerably (*Figure 1*).

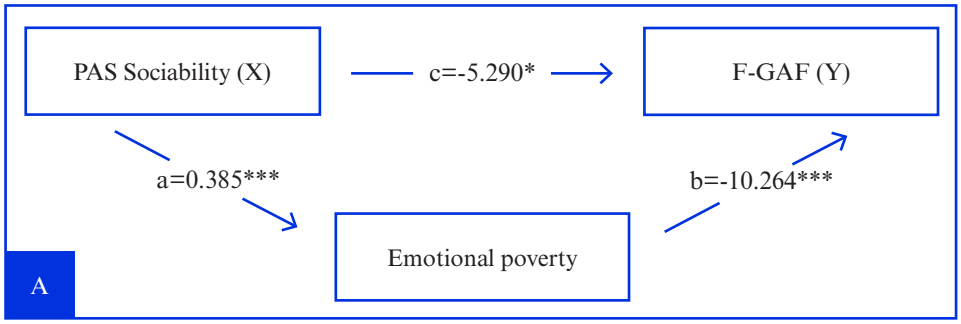
In mediation analyses of the total sample (*Figure 2*) and in FEP and CHR patients separately (*Supplementary Figures 2a-2d*), the effects of PAS Sociability and PAS Scholastic Performance on F-GAF were significantly mediated via SIPS Emotional Poverty. This finding explains why SIPS Emotional Poverty was not included into the regression model. In the total sample and FEP patients separately, the direct effect of PAS Sociability and Scholastic Performance on F-GAF was also significant, but not in CHR patients. Other SIPS dimensions and Childhood Trauma and NEUPSY dimensions and social support scores did not act as mediators between PAS and F-GAF.

Figure 1. Proportions of explained variation (R^2) in prediction models by stages of added explanatory factors in linear regression analyses for the patients with first-episode psychosis (FEP) and clinical high risk for psychosis (CHR)



Predictors: 1. Premorbid (PAS) Scholastic performance; 2. previous and premorbid (PAS) Sociability; 3. previous and Trauma and Distress Scale (TADS) dimension; 4. previous and neuropsychological (NEUPSY) dimensions; 5. previous and social support (PSSS-R) scores; 6. previous and Structured Interview for Prodromal Syndromes (SIPS) dimensions; 7. previous and background factors; 8. previous and follow-up Psychoticism; 9. previous and follow-up Depression/Anxiety
Significance of regression models in each stage: *** p<0.001, ** p<0.01, * p<0.05

Figure 2. Path analyses for the effects of Premorbid Adjustment Scale (PAS) Sociability (A) and PAS Scholastic Performance (B) to follow-up functioning (F-GAF, Global Assessment of Functioning)



Note:

Total effect of X on Y

Effect	se	t	p	LLCI	ULCI
-9.240	2.467	-3.745	<0.001	-14.109	-4.370

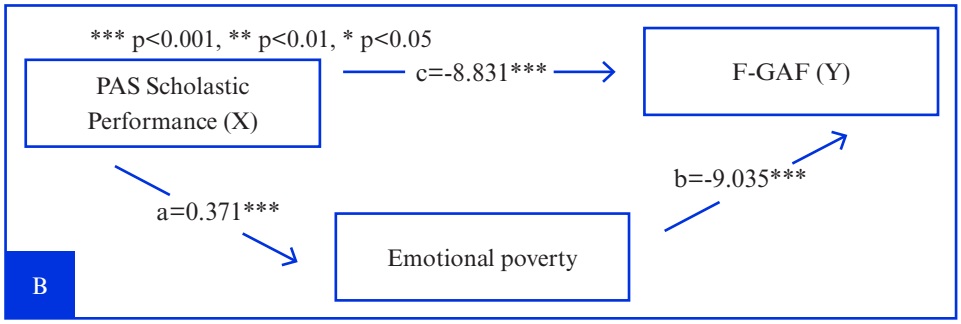
Direct effect of X on Y

Effect	se	t	p	LLCI	ULCI
-5.290	2.556	-2.070	0.040	-10.336	0.245

Indirect effect(s) of X on Y:

	Effect	BootSE	BootLLCI	BootULCI
Emotional Poverty	-3.949	1.158	-6.409	-1.914

*** p<0.001, ** p<0.01, * p<0.05



Note:

Total effect of X on Y

Effect	se	t	p	LLCI	ULCI
-12.184	2.386	-5.107	<0.001	-16.892	-7.475

Direct effect of X on Y

Effect	se	t	p	LLCI	ULCI
-8.831	2.478	-3.564	<0.001	-13.722	-3.940

Indirect effect(s) of X on Y:

	Effect	BootSE	BootLLCI	BootULCI
Emotional Poverty	-3.353	1.036	-5.497	-1.514

*** p<0.001, ** p<0.01, * p<0.05

Additionally, in the total sample and in FEP patients separately, the effect of PAS Sociability on F-GAF was significantly mediated via employment situation (all: effect -1.944; CI -3.709 to -0.516; FEP: effect -2.554; CI -4.799 to -0.724), but the effect of PAS School Performance on F-GAF was not mediated significantly via employment situation. In CHR individuals, the effect of PAS Sociability or Scholastic Performance on F-GAF was not mediated via work situation. In these analyses for all patients and FEP and CHR patients separately, employment situation was significantly associated ($p<0.05$) with F-GAF.

DISCUSSION

DISORGANIZED THINKING AND DIMINISHED EMOTIONALITY: CORE FEATURES OF PSYCHOSES

In the combined sample of FEP and CHR patients, four dimensions, emotional distress, emotional poverty, disorganized thinking and delusions/hallucinations, were formed from the SIPS symptoms. Numerous previous factor analyses on patients with schizophrenia [81,82,83 ,84,85,86,87,88,89,90,91,92,93,94,95], on a heterogeneous group of psychiatric patients [96], early affective and non-affective psychoses [97] and on help-seeking youths with early FEP or CHR [98] have yielded negative, disorganized, affective and psychotic symptom dimensions resembling the symptom dimensions found in the present study. Names of dimensions may vary between different studies, but the SIPS symptom dimensions found in the present study fit quite well with the four main symptom dimensions found in other studies.

Of note, the SIPS items social anhedonia/withdrawal and avolition loaded on both emotional distress and emotional poverty dimensions, indicating that these symptom dimensions describing acute decreases in mood (depression) and long-standing decreases in emotional responsiveness (negative symptoms) are partly joined together [99]. Additionally, the SIPS item odd behaviour/appearance loaded on Emotional Poverty and Disorganized Thinking dimensions describing an inability to take care of cleanness and appearance and inability to behave coherently having the same origin as Disorganized Thinking.

DISORGANIZED THINKING AND DIMINISHED EMOTIONALITY: MAJOR PREDICTORS OF FUNCTIONAL OUTCOMES

Kraepelin [1] and Bleuler [2], who both intensively followed their patients for years, regarded thought and emotional disturbances as essential features in psychotic disorders. The former spoke about the disturbed course of thoughts and emotional dullness, and the latter spoke about the loosening of associations and flattening of affect. The Disorganized Thinking and Emotional Poverty symptom dimensions come close to Kraepelin's and Bleuler's symptom descriptions and support Liddle's [100] suggestion that diminished mental activity (psychomotor poverty) and disorganization form core deficits of classic schizophrenia, even core features of schizotypal and CHR subjects.

In line with previous studies concerning negative symptoms and their central components [7,8,18,22,23,101,102] and formal thought disorders [103], emotional poverty and disorganized thinking, in the present study, were strongly correlated with poor functioning (F-GAF). In regression models, Emotional Poverty's effect on F-GAF was explained by PAS dimensions, except in the CHR sample. Thus, disorganized thinking and emotional poverty seem to have major independent effects on functional outcomes and probably different neural correlates, which are described in the Appendix.

Instead, in line with previous studies [104,105,106,107,108,109], the dimension including delusions and hallucinations and Bleulerian accessory symptoms played no role in the prediction of functional outcome. This finding concerns CHR patients specifically. The CHR cases are most often defined by subclinical delusional and hallucinatory symptoms, and their severity predicts conversion to psychosis [110]. However, more than 70% of CHR patients did not become psychotic during two years of follow-up [111]. Transition to psychosis hardly has much effect on functioning in the long run, and successful interventions preventing transition to psychosis have not improved the functional outcome of patients with CHR [112].

FUNCTIONAL OUTCOME HAS ITS ROOTS IN EARLY PREMORBID ADJUSTMENT

Premorbid adjustment is generally considered a global factor. In the present study, PAS was factorized into two separate dimensions: sociability and scholastic performance. Regression analyses showed that scholastic performance had a stronger association with functioning

than sociability, but sociability had an independent effect on functioning.

In line with previous studies, both premorbid dimensions correlated with emotional poverty and functional outcome [7,8,16,17,18,19,22,23,104,113,114] both directly and via emotional poverty so strongly that in regression modelling, emotional poverty did not enter the model in FEP patients. In the CHR patients, however, the effect of PAS dimensions was totally mediated via emotional poverty, whose association with functioning was emphasized as in another CHR study [115].

The fact that the effects of premorbid sociability and scholastic performance on F-GAF were mediated via emotional poverty but not via disorganized thinking, which had only a direct effect on F-GAF, indicates that emotional poverty has its roots in the very early psychosocial development of patients with psychosis. Contrary to a previous meta-analysis [36], in the present study, childhood adversity had no association with functional outcome.

CHR PATIENTS SUFFER FROM AFFECTIVE DISORDERS

While the baseline Delusion/Hallucination dimension and transition to psychosis [75] had no effect on F-GAF and the effect of follow-up Psychoticism on F-GAF was moderate, the follow-up Depression/Anxiety dimension increased strongly explanatory power in the regression model indicating that in CHR patients, continuation of affective symptomatology is more strongly associated with decreased functioning than psychotic symptoms. Moreover, the effect of both premorbid sociability and scholastic performance on F-GAF was mediated via emotional poverty. This, together with the finding concerning follow-up affective symptoms, indicates that there is an affective continuum from premorbid stage via baseline emotional poverty and follow-up depression/anxiety to deficits of functioning. In patients with depression, poor premorbid adjustment is associated with negative symptoms [99], indicating that negative symptoms are not specific to psychoses but are also found in depression. Moreover, in a study of CHR patients, lower levels of negative and mood/anxiety symptoms were related to an increased likelihood of both symptomatic and functional recovery [116].

The discussion above and the fact that disorganized thinking played no role in predicting functioning in CHR patients suggest that the CHR group fundamentally differs from the FEP group and, BLIPS excluded, represents a group of affective disorders with temporary or durable psychotic-like symptoms indicating the severity of affective disorders. In a long-term outcome study of CHR patients, SIPS disorganized symptoms predicted functional outcomes [110]. However, SIPS disorganization symptoms represent a heterogeneous group that also includes negative symptoms (in the present factor analysis, 'odd behaviour and appearance' was partly loaded on Emotional Poverty, also representing negative symptoms).

For functional outcome, these findings challenge the CHR/Ultra-High Risk (UHR) paradigm. A great majority of CHR patients have non-psychotic clinical disorders, mostly anxiety and depression [117,118,119], as in the present study, and the occurrence of anxiety and depressive disorders is associated with impaired global functioning and suicidality [68,118]. Among UHR patients, affective symptoms, not subthreshold psychotic symptoms, are the most commonly reported reasons to seek help, and patients reporting affective symptoms had poorer functional outcomes than patients with subthreshold psychotic symptoms [119]. In a 6-year follow-up study, 45% of non-converted UHR patients remained functionally impaired, and persistence or recurrence of non-psychotic comorbid mental disorders was associated with poorer global functional outcomes [120]. All these findings strongly indicate that in the great majority of patients with CHR, the focus of attention should shift from prevention of transition to psychosis to active interventions of actual affective clinical disorders [121].

WORK STATUS IS A CENTRAL INDICATOR OF FUNCTIONAL OUTCOME IN FEP

Baseline work status was an independent, non-clinical predictor of functional outcome in patients with FEP. Contrary to FEP patients, in CHR patients, work status played no role in the prediction of functional outcome, emphasizing a basic difference between FEP and CHR patients. Although neurocognitive deficits are common in FEP [25,26,27,28,29,30,122] and in CHR patients [60,61,62,63,64,58] and, in the present study, correlated with GAFT0, they, in line with some other studies [31,110], did not predict functional outcome in our modelling in which premorbid school performance and emotional poverty, as in a network analysis [123], and work situation explained the effect of baseline neurocognitive deficits on functional outcome. Similarly, although social support correlated strongly with F-GAF, in modelling, its effect on functional outcome was explained away by premorbid sociability,

indicating that perceived social support at the time of onset of psychosis has its roots in premorbid social and peer relations. Baseline work status is a result of long-term development affected by several preceding and current factors, such as premorbid adjustment, neurocognitive performance, and deficit (emotional) and productive (positive) clinical symptoms, and is therefore one of the most important factors when treatment interventions are planned.

ADVANTAGES AND LIMITATIONS

Moderately low number of study participants limits results' generalizability. Also, the follow-up period (18 months) can be seen as a limitation. However, the first two years form the most important period in treatment of psychotic patients. Thereafter, the changes in patients' functioning are smaller (e.g., 171). The GAF, which measures mainly illness-related functioning, was used as an indicator of functioning. This finding may have emphasized associations between symptoms and GAF scores, especially at the baseline examination. In any case, GAF is a good enough indicator of real-life functioning. The small number of CHR subjects limits the generalizability of the CHR group findings. On the other hand, we were able to collect follow-up GAFs from all except two subjects, which clearly strengthens the certainty of the conclusions. We also believe that assessment of GAF scores from case notes and phone interviews gave a sufficiently reliable picture of the real-life functioning of the patients dropping out of treatment. A considerable number (18%) of TADS and social support questionnaires remained incomplete. However, GAF scores between the patients who did or did not complete the questionnaires (analyses available by request) did not differ significantly. In the present study, individual treatment interventions and their possible effects on functional outcome were not assessed. These aspects will be presented in later publications. Preliminarily, no association was found between baseline medication and follow-up functioning [75].

IMPLICATIONS

Regarding the functional outcomes of patients with psychosis, the significance of positive psychotic symptoms, although central in the diagnostic process, is minor. In the present study, the delusion/hallucination dimension played no role in predicting follow-up functioning because these symptoms remitted spontaneously or due to antipsychotic medication that was given to 90% of FEP patients.

Emotional poverty and disorganized thinking are the key clinical factors affecting functioning, and therefore, deserve major diagnostic weight in the group of functional psychotic disorders. Concerning emotional poverty, psychosocial interventions (e.g., cognitive behavioural therapy and cognitive remediation [124], social skills training), pharmacological medication (e.g., partial dopamine agonists, antidepressants and other pro-dopaminergic drugs) and non-invasive brain stimulation (e.g., repetitive transcranial magnetic stimulation [125]) should start from the earliest stage of the illness.

Special rehabilitative measures for improving functioning can be directed towards studying and working [126]. We have a considerable amount of evidence that supporting education and employment can improve school participation and the ability to work in FEP patients [127], and that individual placement and support (IPT) can improve the ability to work and learn, leading to competitive employment when compared with traditional vocational rehabilitation [128]. Neurocognitive remediation combined with supported employment may further improve severely mentally ill patients' working ability [129,130].

In CHR patients, who most often suffer from affective disorders, the primary focus of interventions should be on the active treatment of these clinical disorders [131] and to consider the treatment of subclinical psychotic symptoms. There is some evidence that in CHR patients, mood disorders are associated with transition to psychosis [117]. Thus, it is possible that in addition to prevention of transition to psychosis, intensive interventions for mood disorders will improve the functioning of CHR patients more than interventions narrowly focused on prevention of the onset of psychosis. To further improve their functioning, the most severely ill CHR patients need the same psychosocial interventions as described above for psychotic patients. However, because lower momentary self-esteem seems to be associated with an increased intensity of psychotic experiences in daily life, self-esteem support interventions may reduce the intensity of, and distress caused by, psychotic experiences and prevent illness progression in both CHR and FEP patients at an early stage of their illness [132].

APPENDIX

NEURAL CORRELATES OF DISORGANIZED THINKING AND EMOTIONAL POVERTY

1. Disorganized thinking – Deficit in neural coherence

What is the possible neural basis of disorganized thinking? Both Kraepelin [37] and Bleuler [2] proposed that psychosis was a disease of the cortex. Neuroimaging research has verified that psychotic patients have extensive defects in their cortex (grey matter) and subcortical structures (white matter) [133,134]. Deficits of white matter, indicating altered myelination, are also associated with lower regional grey matter volumes (synaptic layer) and poor outcomes in schizophrenia [135].

Weinberger et al. [136] hypothesized that schizophrenia is a disorder of neuronal connectivity. This dysconnectivity may be due to alterations in neural myelination [135] and/or synaptic pruning [137] reaching its peak at puberty when disorganized symptomatology manifests in psychotic states. Deficits in myelination may lead to lengthening and scattering conduction times (dysconnectivity) and reduced capacity of the neural system to synchronize particular neural frequencies (desynchronization) [138], while excessive pruning may result in diminished, blocked, or otherwise disturbed connectivity (dysconnectivity), and the occurrence of delusions and hallucinations may be possible [139]. These deficits in myelination and neuropil connections affect various neural tracts and cortex areas and can manifest as various forms of disorganization in thinking, speaking, perception and behaviour. Formal thought disorders in schizophrenia are often, but not always, associated with structural and functional aberrations in the language network (e.g., the inferior frontal gyrus; Brodmann Area, the frontal operculum, the superior temporal gyrus, the middle temporal gyrus) [140], suggesting that thought disorders are indicators of extensive neural dysconnectivity.

Disorganized thinking may relate to disturbed neural conduction and connections with difficulties in synchronizing and coherently directing stimuli from multimodal sources [141]. One candidate of these sources is the cerebellum [142] and the cerebello-thalamo-cortical circuitry [143]. Increased connectivity in the cerebello-thalamo-cortical circuitry is a pattern found in patients with CHR (more pronounced in converters) and schizophrenia associated with disorganized symptoms [144]. Increased connectivity in the cerebello-thalamo-cortical circuitry may be a heritable trait associated with the genetic risk of schizophrenia [145]. Signs of thought disorders are often seen in close relatives of patients with schizophrenia [146,147], further suggesting that disorganized thinking and its neural correlates may have a genetic background.

Disorganized thinking and behaviour manifest most clearly at the acute phase of psychosis. In acute psychosis, vigorous turmoil of synaptic transmitters due to overactivity of basal structures [148,149] and axonal leakage of electric signals violate connectivity of the genetically vulnerable neural network, and consequently lead to incoherent (synaptic level) and idiosyncratic (signal leaking) thinking and behaviour. During recovery from psychosis, disorganized thinking decreases [150] but retains its significance as an indicator of poor outcome, even if it is hardly detectable anymore. However, even in a recovered stage, there are signs of neural disorganization, such as impaired facial emotion recognition [151] and emotion-specific (neural) face processing [152]. In the case of schizophrenia, "restitutio ad integrum" does not occur [2]. Repetitive psychotic episodes may have toxic effects on the unstable neural network and lead to chronic thought disorders. Neuroleptics, such as synaptic blockers and anti-inflammatory [153] agents, can facilitate the recovery of acute processes but have little effect on long-term functional outcomes. In follow-up studies, daily doses of neuroleptics mainly correlate with the severity of illness.

In summary, in patients with psychosis, disorganized thinking seems to be an indicator of a general structural and functional disorganization of the central nervous system, and the magnitude of its effect on functional outcome depends on the extent of neural disorganization.

2. Emotional Poverty – Deficit in neural energizing processes

Contrary to disorganized thinking, which manifests after puberty, emotional poverty has its roots in early childhood/adolescence. Premorbid sociability and scholastic performance comprise emotional and cognitive components of apathy that are typical in schizophrenia [154] but are also found in depression [99] and across different pathological conditions [155]. Very recently, in an 18-month follow-up study, the negative factor characterized by high negative symptoms and high premorbid deficits was loaded over patient groups with ROP (Recent Onset of Psychosis) (55%), CHR (31%) and non-psychotic depression (14%) [156]. Additionally, in the present study, sociability correlated with the distress dimension, indicating its association with depression/anxiety symptomatology. Thus, emotional poverty is not specific to psychotic disorders but also relates

to other disorders, particularly to depression. Regarding depression, the distinction between primary ("thought to be intrinsic to the pathophysiology of schizophrenia") and secondary ("thought to be related to other factors, such as psychiatric or medical comorbidities, treatment adverse effects or environmental factors") negative symptoms may be artificial [156].

Neuroimaging studies have suggested that abnormalities within the fronto-basal ganglia network, including the thalamus [155,156,157,158,159], structures representing motivation-relation circuits [160,161], are most consistently associated with apathy, a key component of negative symptoms, across the different pathological conditions. Emotional apathy is associated with damage to the orbitofrontal (ventromedial prefrontal) cortex ventral striatum and the anterior cingulate cortex, while cognitive apathy correlates with the dorsolateral prefrontal cortex and dorsal caudate nuclei [158,162]. Kirschner et al. [163] suggested that orbitofrontal-striatal abnormalities associated with negative symptoms may predate the occurrence of schizophrenia.

Recently, Wang et al. [164] found that the intrinsic functional connectivity and structural properties (fractional anisotropy and fibers) of the left frontal white matter corresponded to individual negative symptoms in adolescent-onset schizophrenia. A decreased number of fibers in the serotonergic network (raphe nuclei, anterior and posterior cingulate cortices, and prefrontal and inferior parietal cortices) and frontal white matter cingulum network contributed to negative symptom severity. There was also abnormal functional and structural connectivity between the interhemispheric frontal white matter; the decreased fiber counts between frontal hemispheres correlated inversely with the negative symptoms. The finding regarding the serotonergic neural network is interesting. Serotonergic antidepressants have some effect on negative symptoms in patients with schizophrenia [165]. More specifically, the 5-HT2A receptor has been considered a potential target for reducing negative and cognitive deficits [166]. Mirtazapine, an antidepressant with 5HT2A antagonistic properties [167], has been effective in reducing negative symptoms in patients with schizophrenia [168], and roluperidone, an antipsychotic agent with a 5HT2A receptor antagonist, has improved reduced emotional experience (avolition-anhedonia) and reduced emotional expression (affective blunting and alogia), which are key components of negative symptoms [169]. Another study related to roluperidone also emphasized the central role of avolition within the treatment of negative symptoms [170]. However, the role of the serotonergic network in negative symptoms is unclear.

In summary, emotional poverty seems not to be specific to psychosis but reflects unspecific deficits in neural structures related to motivational and energizing Central Nervous System processes, and can manifest as difficulties in psychosocial relations and intellectual performance in childhood and adolescence.

Supplementary Material

Supplementary data are available at Psychiatrica Fennica online.

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Declaration of interest

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