Soc Psychiatry Psychiatr Epidemiol (2016) 51:247–257
DOI 10.1007/s00127-015-1160-9

ORIGINAL PAPER

Depression predicts persistence of paranoia in clinical high-risk patients to psychosis: results of the EPOS project

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Received: 24 August 2015 / Accepted: 17 November 2015 / Published online: 7 December 2015

Abstract

Background The link between depression and paranoia has long been discussed in psychiatric literature. Because the causality of this association is difficult to study in patients with full-blown psychosis, we aimed to investigate how clinical depression relates to the presence and occurrence of paranoid symptoms in clinical high-risk (CHR) patients.

Methods In all, 245 young help-seeking CHR patients were assessed for suspiciousness and paranoid symptoms with the structured interview for prodromal syndromes at baseline, 9- and 18-month follow-up. At baseline, clinical diagnoses were assessed by the Structured Clinical Interview for DSM-IV, childhood adversities by the Trauma and Distress Scale, trait-like suspiciousness by the Schizotypal Personality Questionnaire, and anxiety and depressiveness by the Positive and Negative Syndrome Scale.

Results At baseline, 54.3 % of CHR patients reported at least moderate paranoid symptoms. At 9- and 18-month follow-ups, the corresponding figures were 28.3 and 24.4 %. Depressive, obsessive–compulsive and somatoform disorders, emotional and sexual abuse, and anxiety and suspiciousness associated with paranoid symptoms. In multivariate modelling, depressive and obsessive–compulsive disorders, sexual abuse, and anxiety predicted persistence of paranoid symptoms.

Conclusion Depressive disorder was one of the major clinical factors predicting persistence of paranoid symptoms in CHR patients. In addition, obsessive–compulsive disorder, childhood sexual abuse, and anxiety associated with paranoia. Effective pharmacological and psychotherapeutic treatment of these disorders and anxiety may reduce paranoid symptoms in CHR patients.

Electronic supplementary material The online version of this article (doi:10.1007/s00127-015-1160-9) contains supplementary material, which is available to authorized users.

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Keywords Depression · Anxiety · Paranoia · Persistence · Clinical high risk

Introduction

Pathways to both occurrence and persistence of paranoia and persecutory ideation have always been a topic of great interest in psychiatry research, and their complexity still poses a riddle [1]. One factor that has been extensively discussed as facilitating their occurrence and persistence is emotions, in particular anxiety and depression: for example, Griesinger regarded paranoia as secondary to and always preceded by an affective disorder; while Kraepelin [2] regarded paranoia primarily as an illness of the intellect (Verstand) with an insidious development of the persistent delusional conviction, and affective (depressive) mood as a reaction to the paranoid ideas and experiences [2]. Consequently, Kraepelin [2] first divided paranoia into depressive, expansive and hallucinatory syndromes, and later classified it as an independent illness although manic-depressive patients might have persecutory/paranoid symptoms. Both the ICD and the DSM still follow his view.

In clinical studies, patients with uni- or bipolar affective disorder also reported paranoid or other delusional symptoms [3], while on the other hand, depressive disorders and symptoms were prevalent in patients with delusional disorders [4, 5]. Further, in community samples assessed by lay persons or with self-report measures, depressiveness and anxiety were associated with persecutory ideation [1]. According to Freeman [1], there is a large direct affective contribution, in particular of anxiety, to persecutory experiences, distress and persistence of paranoia. Further, paranoid ideation was put forward as a defence mechanism against low self-esteem and depressive mood [6] in individuals predisposed to anomalous experiences [1] and victims of childhood abuse [7]; yet, this relationship is controversial [1]. Therein, the link between paranoia and emotions in paranoid-prone persons does not appear to be unidirectional but rather to form a vicious circle that should be broken by targeted interventions—preferably before severity of paranoia has reached a delusional degree [1].

Depressive and anxiety disorders are extremely prevalent co-morbidities in clinical high risk of psychosis (CHR) patients [8–10] who frequently report attenuated, not yet delusional paranoia [11]. Generally, in CHR patients, onset of psychosis seems not to be predicted by clinical depression in univariate models [10, 12]; yet, in addition to bipolar and somatoform disorders, unipolar depressive disorders predicted conversion to psychosis in a multivariate model in that anxiety disorders lowered the risk for conversion [1]. However, the role of affective disorders and symptoms in the persistence of attenuated paranoid symptoms in CHR patients has not been studied.

Thus, based on the data of the European Prediction of Psychosis Study (EPOS) [13], we examined whether (1) there is an association between affective and other axis-I disorders and affective symptoms, and paranoid symptoms, and whether (2) depression and anxiety predict persistence of paranoid symptoms during follow-up. In analysing these associations, we also aimed to take into account the effects of childhood adverse experiences and trait suspiciousness.

Subjects and methods

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. Local Ethics Committees of the participating universities and healthcare agencies approved the study. After complete description of the study, written informed consent was obtained from all participants and from their parents if minors.

Design and study subjects

EPOS is a naturalistic, prospective follow-up study of 245 CHR patients recruited between August 2002 and April 2006 in six centres: Cologne and Berlin, Germany; Turku, Finland; Amsterdam, The Netherlands; and Birmingham and Manchester, UK. Details of study design, inclusion and exclusion criteria, and assessments have been described previously [13, 14]. Inclusion criteria comprised the basic symptom criterion "cognitive disturbances, COGDIS" [15] and/or ultra high-risk (UHR) criteria: attenuated psychotic symptoms (APS), brief limited psychotic symptoms, and genetic risk and reduction of function. Exclusion criteria were: past or present psychotic episode lasting more than 1 week, symptoms relevant for inclusion arising from a known general medical disorder or the effect of a psychotropic substance, or drugs or alcohol dependency, and low verbal IQ (<85).

Assessments were carried out at baseline, and at 9- and 18-month follow-ups, or until a conversion to psychosis was detected. Therefore, data were available at baseline for 245, at 9 months for 187, and at 18 months for 156 patients. There were no systematic statistical differences in socio-demographic or clinical characteristics between the patients with or without 9- or 18-month follow-up [14].

The patients recruited were treated according to the local treatment standard. On average, they received 0.70 psychosocial interventions (counselling/support/monitoring); 22 % received neuroleptics, 28 % antidepressants and 47 % no medication.

Clinical assessments

COGDIS was assessed with a short version of the Schizophrenia Proneness Instrument, Adult version (SPI-A) [15], and UHR criteria with the 3.0 version of the structured interview for prodromal syndromes (SIPS) [16]. The SIPS comprises positive, negative, disorganised and general symptoms, as well as assessment of a family history of psychotic disorders, and global psychosocial functioning. Each syndrome-like item is rated on a Likert scale as follows: '0' (absent), '1' (questionably present), '2' (mild), '3' (moderate), '4' (moderately severe), '5' (severe but not psychotic), and '6' (severe and psychotic). The second SIPS positive item (P2), "suspiciousness/persecutory ideas" served as the independent variable in the analyses. Its rating comprises: wariness ('1'), doubts about safety and hypervigilance without clear source of danger ('2'), persecutory ideas of reference, suspiciousness or paranoid thinking, and presenting a guarded or openly distrustful (APS-level: '3'–'5') attitude that may intrude on the interview and/or behaviour and reflect delusional conviction (psychotic level: '6'). Henceforth, P2-ratings will be referred to as "paranoia" (PAR) although it describes a continuum of paranoid ideas with increasing severity from non-pathological experiences ('1'–'2') via attenuated ('3'–'5') to psychotic symptoms ('6').

The baseline examination included socio-demographic information and extensive clinical assessments [13, 14], including the Structured Clinical Interview for DSM-IV (SCID-I) [17], the Positive and Negative Syndrome Scale (PANSS) [18], the Trauma and Distress Scale (TADS) [19], and the Schizotypal Personality Questionnaire (SPQ) [20]. Follow-up assessments took place at 9 and 18 months from baseline. Altogether 37 transitions to psychosis (TtPs) during the whole follow-up were identified and operationalized as a continuation of BLIPS, one or more psychotic symptoms persisting for more than 1 week [14].

In the SCID-I assessment, the following current non-psychotic disorders were identified: bipolar disorders, unipolar depressive disorders, anxiety disorders, obsessive–compulsive disorder, somatoform disorders, eating disorders, and other DSM-IV axis-I disorders. SCID diagnoses at baseline were available for all 245 patients.

The PANSS [18] comprises seven positive, seven negative, and 16 general symptoms. Each item is rated as follows: '1' (absent), '2' (minimal), '3' (mild), '4' (moderate), '5' (moderately severe), '6' (severe), and '7' (extreme). In our analyses, the general symptoms anxiety (G2) and depression (G6) were considered.

The TADS [19] was developed for EPOS. It assesses 43 childhood adversities (rated on a Likert scale as '0' = never, '1' = rarely, '2' = sometimes, '3' = often, '4' = nearly always) that form five domains of five items each: emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect.

The SPQ [20] includes 74 items (yes/no) included in nine subscales: ideas of reference, excessive social anxiety, odd beliefs or magical thinking, unusual perceptual experiences, odd or eccentric behaviour, no close friends, odd speech, constricted affect and suspiciousness. The suspiciousness subscale was used as indicator of premorbid paranoid traits. A full baseline data set including SIPS, SCID, PANSS, TADS and SPQ was available for 223 patients.

Statistical analyses

First, median PAR ratings at baseline (PAR0), 9-month (PAR9) and 18-month follow-ups (PAR18) were calculated for background characteristics and current clinical diagnoses, and differences tested by the Mann–Whitney or Kruskal–Wallis test. Changes in PAR0, PAR9 and PAR18 scores were tested by the Friedman test. Kendall's tau-*b* correlations were calculated between PAR and TADS domains, PANSS anxiety and depressive scores, and SPQ suspiciousness.

In multivariate analyses, generalised repeated ordinal logistic modelling was carried out for PAR scores over the whole study period (baseline to 9–18 months) when time factor was controlled. In logistic modelling, independent variables were added in three blocks. The first block contained background characteristics, the second block clinical DSM-IV axis-I diagnoses, and the third block the five TADS domains, PANSS anxiety and depression scores and SPQ suspiciousness scores. Factors with non-significant effect ($p \geq 0.1$) were omitted from the model before proceeding to the next stage. Finally, non-significant predictors were one by one omitted from the model of the 3rd block at a significance level of $p \geq 0.05$.

In a sensitivity analyses for conversion to psychosis within 18 months, the final analysis was repeated (a) with conversion as an additional predictor and (b) in the larger subgroup of non-converters ($N = 208$). Finally, PAR18 was predicted in ordinal regression analysis by significant factors of the initial regression model when the effect of PAR0 was controlled. Analyses were performed with the SPSS (22 for Windows). $p < 0.05$ (two-tailed) was considered statistically significant.

Results

Socio-demographic background and paranoid symptoms

At baseline, 54.3 % of CHR patients ($n = 133$) reported at least moderate PAR ($\geq$'3' on SIPS-P2). At 9- and 18-month

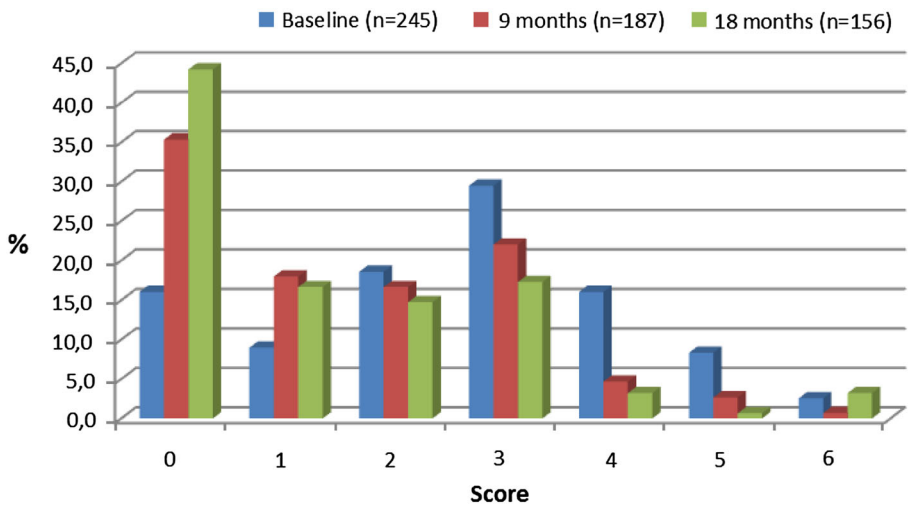

Fig. 1 Distributions of SIPS paranoia scores at baseline, 9- and 18-month follow-up

follow-ups, the corresponding figures were 28.3 % ($n = 53$) and 24.4 % ($n = 38$) (Fig. 1). PAR0 correlated moderately with PAR9 (Kendall's tau $b = 0.329$, $p < 0.001$) but only slightly with PAR18 ($b = 0.172$, $p = 0.008$), while PAR9 and PAR18 correlated strongly with each other ($b = 0.454$, $p < 0.001$). During follow-up, PAR decreased significantly in severity (PAR0: median 3.00; PAR9: median 1.00; PAR18: median 1.00; Δ (PAR0, PAR9): $\chi^2 = 40.679$, $df = 1$, $p < 0.001$; Δ (PAR9, PAR18): $\chi^2 = 7.385$, $df = 1$, $p = 0.007$, Friedman test), as well as in frequency of at least moderate PAR (PAR0: 54.3 %; PAR9: 28.3 %; PAR18: 24.4 %; Δ (PAR0, PAR9): $\chi^2 = 35.714$, $df = 1$, $p < 0.001$; Δ (PAR9, PAR18): $\chi^2 = 5.143$, $df = 1$, $p = 0.023$, Friedman test), indicating significant clinical improvement over time (Fig. 1). At 9 months, 10 (18.9 %) out of 53 PAR9 subjects had newly developed PAR ($\geq$'3' on SIPS-P2); at baseline they had been non-paranoid (<'3' on SIPS-P2). At 18 months, the corresponding figures were 13 (34.2 %) out of 38 PAR18 subjects.

There was no consistent pattern of association between PAR at any time and background characteristics. While no group difference was significant at baseline, PAR9 scores were higher in women, those 20 years of age or younger and non-whites; and PAR18 scores higher in singles and those with poor occupational functioning (Table 1).

Clinical diagnoses and paranoid symptoms

CHR patients with unipolar depressive disorder at baseline (35 %) showed higher PAR scores than those without at 9 and 18 months but not at baseline; and baseline PANSS depression scores were positively correlated with PAR only at 18 months (Table 2). Baseline PANSS anxiety scores correlated significantly at small with moderate effect sizes with PAR throughout, although baseline presence of an anxiety disorder (33 %) revealed no significant effect. Further, PAR9 and PAR18 but not PAR0 were more severe in the small number of patients with obsessive–compulsive (6 %) or somatisation disorder (7 %). Of the TADS domains, only sexual and emotional abuse showed consistent correlation with PAR (Table 2), although of only small effect size. As expected, baseline SPQ suspiciousness correlated significantly with PAR throughout at moderate effect size (Table 2).

Multivariate modelling

Generalised repeated ordinal logistic modelling was carried out across the three assessment times in a block-wise design with time factor being controlled. In the first block of sociodemographic variables, female gender, single marital status, inability to work, and non-white ethnicity associated significantly ($p < 0.10$) with paranoid symptoms (see Supplementary Table 1).

Adding to these axis-I diagnoses in the second block, depressive and obsessive–compulsive disorders associated significantly ($p < 0.10$) with paranoid symptoms (see Supplementary Table 2).

In the third block that additionally considered other clinical and background baseline factors, single marital status, depressive and obsessive–compulsive disorders from the second block, and from TADS, PANSS and SPQ factors physical abuse, sexual abuse, emotional neglect, physical neglect, anxiety, and trait suspiciousness ($p < 0.001$, OR 1.344, 95 % CI 1.252–1.442) associated significantly ($p < 0.10$) with paranoid symptoms (see Supplementary Table 3).

When non-significant variables ($p \geq 0.05$) were one by one omitted from these variables, depressive and obsessive–compulsive disorders, sexual abuse, anxiety and trait suspiciousness associated positively, and physical neglect negatively, with paranoid symptoms in the final model

Table 1 Distributions of background characteristics and respective subgroup comparisons of SIPS paranoia scores at baseline, 9-month and 18-month follow-ups

	Baseline ($n = 245$)		9 months ($n = 187$)		18 months ($n = 156$)	
	%	Median	%	Median	%	Median
All	100	3.00	100	2.00	100	1.00
Gender[a]						
Men	55.9	2.00	55.1	1.00*	51.9	1.00
Women	44.1	3.00	44.9	2.00	48.1	1.00
Age (mean 22.4 years; range 15–35)[a]						
−20	46.9	3.00	46.0	2.00*	47.4	1.00
21+	53.1	3.00	54.0	1.00	52.6	1.00
Marital status[a]						
Single	81.2	3.00	81.8	1.00	81.4	1.00*
Ever married	18.8	2.00	18.2	1.00	18.6	0.00
Education years[a]						
−12	43.7	3.00	41.7	1.00	43.6	1.00
13+	56.3	2.00	58.3	1.00	56.4	1.00
Work situation[b]						
Working	66.9	3.00	67.4	1.00	65.4	1.00*
Unemployed	14.3	3.00	13.9	1.00	15.4	1.00
Unable to work	18.8	3.00	18.7	2.00	19.2	2.00
Ethnicity[a]						
White	83.7	3.00	84.0	1.00**	83.3	1.00
Non-white	16.3	3.00	16.0	2.00	16.7	1.50

* $p < 0.05$, ** $p < 0.01$

[a] Differences tested by Mann–Whitney test and [b] Kruskal–Wallis test

(Table 3). It is noteworthy, that altogether 42.9 % of patients with obsessive–compulsive disorder also had depressive disorder.

In the first sensitivity analysis of the effect of conversion, conversion was selected into the model in addition to depressive and obsessive–compulsive disorders, sexual abuse, anxiety and trait suspiciousness, while the negative association of physical neglect failed to become significant (see Supplementary Table 4). In the second analysis on non-converters, depressive disorder, sexual abuse, anxiety and trait suspiciousness again associated significantly with paranoid symptoms, while the associations of both physical neglect and obsessive–compulsive disorder became non-significant (Supplementary Table 5).

In ordinal regression analysis, depressive and obsessive–compulsive disorders, sexual abuse, anxiety and trait suspiciousness but not physical neglect associated significantly with PAR18 when the effect of PAR0 was controlled (Table 4).

Discussion

Persecutory experiences are the most frequent forms of frank and attenuated delusions in psychotic and CHR patients [11, 21], and, at the time of help-seeking, about a half of CHR patients participating in EPOS reported attenuated paranoid symptoms. Therefore, the clinical relevance of paranoia in psychosis, as well as in its risk states, is clearly high. The occurrence as well as persistence of delusional and sub-clinical paranoia have so far been examined in clinical and general population samples, though in the latter group rarely with validated clinical assessments [1], thus only providing an approximation of clinician-assessed paranoia and their potentially constituting factors [22]. We, therefore, studied factors related to the occurrence as well as persistence of clinician-assessed attenuated paranoid symptoms in a sample already considered symptomatically at risk for psychosis, mainly for attenuated psychotic symptoms and/or cognitive basic symptoms.

Although the proportion of CHR patients with attenuated paranoid symptoms clearly decreased during the 18-month follow-up period, indicating improvement in their clinical state in this respect, about a quarter of CHR patients reported attenuated paranoid symptoms at follow-ups. Of these, a third was newly developed. Thus, a quarter of patients still had to be considered at high clinical risk of developing a psychotic disorder with persecutory delusions.

Table 2 Comparisons of SIPS paranoia median scores by baseline DSM-IV diagnosis, differences tested by Mann–Whitney test, and Kendall's tau correlations with TADS domains, PANSS anxiety and depression and SPQ suspiciousness

	Baseline ($n = 245$)		9 months ($n = 187$)		18 months ($n = 156$)	
	%	Median	%	Median	%	Median
Bipolar disorder						
Yes	4.1	1.50	4.3	0.50	5.1	0.00
No	95.9	3.00	95.7	1.00	94.9	1.00
Depressive disorder						
Yes	34.7	3.00	34.8	2.00***	34.0	2.00***
No	65.3	2.00	65.2	1.00	66.0	0.00
Anxiety disorder						
Yes	33.1	3.00	33.2	2.00	36.5	1.00
No	66.9	3.00	66.8	1.00	63.5	1.00
Obsessive–compulsive disorder						
Yes	5.7	2.50	6.4	3.00*	6.4	3.00**
No	94.3	3.00	93.6	1.00	93.6	1.00
Somatisation disorder						
Yes	6.5	3.00	7.5	3.00*	8.3	3.00*
No	93.5	3.00	92.5	1.00	91.7	1.00
Eating disorder						
Yes	1.6	2.50	2.1	0.50	2.6	0.50
No	98.4	3.00	97.9	1.00	97.4	1.00
Any disorder						
Yes	66.5	3.00	67.4	2.00**	69.9	1.00**
No	33.5	2.00	32.6	0.00	30.1	0.00
TADS						
Emotional abuse		0.145**		0.115*		0.179**
Physical abuse		0.096		0.153*		0.119
Sexual abuse		0.151**		0.162**		0.174*
Emotional neglect		0.067		0.042		0.066
Physical neglect		0.067		−0.012		0.017
PANSS						
Anxiety		0.135**		0.296***		0.236***
Depression		0.095		0.098		0.213**
SPQ						
Suspiciousness		0.307***		0.300***		0.306***

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

Table 3 Multivariate modelling for SIPS paranoia scores

Baseline variables	Model (PAR0 to PAR9 to PAR18)[a]			
	df	*p*	OR	95 % CI
Depressive disorder	1	<0.001	2.345	1.687–3.259
Obsessive–compulsive disorder	1	0.006	2.495	1.301–4.784
TADS sexual abuse	1	<0.001	1.092	1.046–1.141
TADS physical neglect	1	0.001	0.941	0.906–0.977
PANSS anxiety	1	<0.001	1.335	1.176–1.515
SPQ suspiciousness	1	<0.001	1.350	1.264–1.443

PAR0 baseline SIPS paranoia scores, *PAR9* 9-month SIPS paranoia scores, *PAR18* 18-month SIPS paranoia scores

[a] Generalised repeated ordinal logistic modelling when the effect time factor is controlled

Table 4 Ordinal regression analysis for PAR18 when the effect of PAR0 was controlled

Baseline variables	*df*	*p*	Estimate	95 % CI
Depressive disorder	1	<0.001	1.185	0.530–1.839
Obsessive–compulsive disorder	1	0.001	2.151	0.925–3.378
TADS sexual abuse	1	0.007	0.117	0.032–0.203
TADS physical neglect	1	0.427	−0.040	−0.138–0.058
PANSS anxiety	1	0.015	0.002	0.000–0.004
SPQ suspiciousness	1	<0.001	0.297	0.164–0.429

Predictors of persistent paranoid experiences

Depressive disorders that were present in about a third of patients at baseline but not level of depressiveness as assessed at baseline with the PANSS were a main predictor of persistence of attenuated paranoid symptoms. The association between depressive disorders and paranoid symptoms was highly significant also when the effects of transitions to psychosis were taken into account, and in the CHR subsample without transitions to psychosis. Additionally, depression predicted paranoid symptoms at the end of follow-up although the effect of baseline paranoid symptoms was controlled. All these results indicate that clinical depression plays a central role in persistence and possibly also in occurrence of paranoia. In the PANSS, depression is defined by feelings of sadness, discouragement, helplessness and pessimism, and rated on the basis of patient's report of depressed mood during the course of interview, and its clinician observed influence on attitude and behaviour. This item might have less or little additional information on presence of depressive disorder, and therefore has not been selected as an additional predictor in the model. Additionally, it is possible that the effect of clinical depression on the persistence of paranoid symptoms partly goes via lowered baseline functioning. This was supported by the fact that in post hoc analyses (not shown), clinical depression correlated with reduced baseline functioning more strongly than the PANSS depressive symptoms and low baseline functioning (GAF) associated significantly with follow-up paranoid symptoms.

In addition to depressive disorders, obsessive–compulsive disorder predicted follow-up paranoid symptoms. However, because of its low prevalence and high co-occurrence with depressive disorders, its overall role in the persistence of attenuated paranoia in CHR patients can be assumed to be a minor one that possibly lies rather in its role as an indicator of greater clinical severity.

In line with previous studies [1], anxiousness but not anxiety disorders associated strongly with follow-up paranoid symptoms. Anxiety is defined in the PANSS by the patient's subjective experience of nervousness, worry, apprehension or restlessness, ranging from excessive concern about the present or future to feelings of panic. The bases for rating are the patient's verbal report during the course of interview and clinician observed corresponding physical manifestations. Only at the two most severe levels ('6' and '7'), are criteria of an anxiety disorder likely to be met as well; though the overlap between definitions of axis-I disorder and PANSS symptom is less than in the case of depression. Thus, this item might better reflect anxiety related to paranoia than does anxiety related to other stimuli and defining anxiety disorders. In any case, paranoid patients commonly suffer from anxiety symptoms, which together with paranoid experiences might greatly disturb their interpersonal relations to the degree of a social phobia. In fact, social phobia was consistently the main and most frequent anxiety disorder reported in the CHR sample [22].

Furthermore, both anxiety and depression may play a dual role in paranoia: patients with paranoid experiences become anxious or depressed and these emotions force them to seek help. Supporting this view, a recent study on clinician-assessed APS according to the SIPS and help-seeking for mental problems in a general population sample reported that APS were never named as a reason for help-seeking in an open question, while depressive mood and anxiety were among the top three reasons named by persons with any lifetime APS [23].

Also in line with previous studies [7, 24, 25], childhood sexual abuse had a strong association with paranoid symptoms. The consistent association between sexual abuse and paranoid symptoms may indicate a specific association between childhood adversity and adult psychopathology in rather severely ill CHR patients. In a population study, sexual abuse associated with paranoia only in those who were brought up in institutional care [26], in another community sample, childhood neglect was specifically associated with paranoia [27], while in the present CHR patients, neglect had no or a negative effect on paranoid symptoms. In a community sample [28], a strong link between sexual abuse and psychosis was mainly mediated by depressive symptoms. In a clinical sample of CHR patients, depressive disorders seem to have a rather strong direct association with paranoid symptoms.

Finally, it is well in line with the persistence model [1] that trait suspiciousness was also a significant predictor of paranoid symptoms at follow-ups, and associated with baseline paranoid symptoms. This trait suspiciousness might be regarded as a manifestation of the hostility, as well as cognitive and attentional biases described to provide confirmatory evidence for the "belief". It might also have mediated the role of childhood abuse: childhood abuse might have abetted the development of trait suspiciousness already early in life, thus not acting as a further independent predictor of the persistence of paranoid symptoms later in life. Further, the predictive role of trait suspiciousness is in line with the assumption that persecutory delusions have their origin in early development: family genetic studies suggested that patients with paranoid delusional disorders are more likely to have family members who show more suspiciousness, jealousy, even paranoid illness than controls [29, 30]. This finding indicates the possible presence of additional neurobiological, genetic factors in both the formation and persistence of paranoid symptoms.

Depression, paranoia and the dopaminergic system

The associations between clinical diagnoses and paranoia may also arise from a common neurobiological vulnerability. Generally, patients with depression have lower, while patients with psychosis have elevated and dysregulated, striatal dopaminergic activity [31]; in first-episode neuroleptic-naive schizophrenic patients, depressive symptoms and feeling of guilt were associated with low, but suspiciousness and persecutory ideas with higher striatal presynaptic dopamine function [32]. In CHR patients, elevated striatal dopamine function was linked to risk signs of schizophrenia [33] and was even predictive of conversion to psychosis [34]. This suggests that striatal dopaminergic tone is one of the factors modulating the relationship between concurrent depressive and paranoid symptoms. Further, potent dopamine releaser amphetamine or dopamine agonists used in patients with Parkinson's disease caused paranoid and other positive symptoms [35, 36]. Moreover, intravenous delta 9-tetrahydrocannabinol, a potent releaser of striatal dopamine, increased paranoia concurrently with negative affects (anxiety, worry, depression, negative thoughts about self) and anomalous experiences in persons with paranoid ideations, suggesting that generation of negative affects and anomalous experiences may be closely related to manifestation of paranoia [37]. In patients with major depression, a polymorphism (A allele) in the dopamine beta-hydroxylase gene was suggested to predispose patients to paranoia [38].

The dopaminergic system is sensitive to various stressors, and repetitive challenge by stressors, such as childhood abuse; sexual abuse in particular, may sensitise the dopaminergic system to an increased dopaminergic response to different challenges [39]. It was proposed that a dysregulated, hyperdopaminergic state might lead to an aberrant assignment of salience to external objects and internal representations, and that delusions were efforts to make sense of these experiences of aberrant salience [40]. A dysregulated dopaminergic system might, thus, first manifest as depression (decreased transmission), while in persons with additional internal (e.g. genetic or personality) and/or external vulnerability factors, the dysregulated dopaminergic system may lose its coherence, and increased transmission leads to paranoia.

Strengths and limitations

The main advantage of our study was the prospective study design and the assessment of disorders and symptoms by well-trained mental health professionals. It enabled prospective prediction when the effects of baseline states were taken into account. We did not study psychotic paranoid disorders but attenuated paranoid symptoms defined by one SIPS symptom "suspiciousness/persecutory ideas". Thus, the conclusions related to paranoia should be limited to the symptomatic or dimensional level (e.g. ideations or experiences). For clinicians, it is important to acknowledge their patients' first paranoid ideations or signs and take them into account when they are planning and executing interventions to prevent their patients from sliding into full-blown psychosis. Paranoid symptoms were most prevalent already at baseline and, therefore, although the effect of baseline paranoid symptoms (in post hoc analysis) was controlled, our results rather allow conclusions about their persistence; the conclusions about their occurrence during the follow-up are at least partly limited. Future longitudinal studies on CHR samples with a higher percentage of cognitive basic symptoms (or, in other words, anomalous experiences) might, however, be able to study the onset of attenuated paranoid symptoms.

According to neuropsychological models [1], selectively biased attention to threatening salient information, along with an externalising attribution style with regard to negative events, and deficits in understanding other people's mental states (theory of mind) might explain the formation and maintenance of persecutory delusions in persons predisposed to anomalous experiences. In the present study, we were unable to evaluate the role of these neuropsychological factors which may moderate and mediate social cognitive processing between depression and paranoia. Further, we concentrated on the clinical disorders and symptoms most important for clinicians when they treat CHR patients, and neglected the role of possible resilience factors such as good coping strategies or self-efficacy.

Future studies of the development and persistence of paranoid symptoms in CHR patients should take these factors into account, in particular as their role might be different at the risk state than in manifest psychosis. In a study, patterns of aberrations in self-efficacy and external control beliefs in CHR patients resembled those of depressive patients rather than those of first-episode psychosis patients [41].

The EPOS was a naturalistic follow-up study in which many factors remained uncontrolled, e.g. effects of various interventions were not systematically controlled for. Thus, effects of potential drug or psychological treatment on associations between diagnoses and paranoid symptoms remain unclear. However, as treatment, and in the case of depression, even drug treatment is more likely the more severe the disorder, any potential treatment was either of little efficacy or had little effect on the association of initial diagnosis and persistence of paranoid symptoms, at least in those already prone to them according to higher trait suspiciousness. Finally, it must be kept in mind that modelling on the basis of a single study (despite the large sample) can overestimate associations. Further studies will be necessary to validate our predictive modelling based on clinical diagnoses.

Conclusions

Paranoid symptoms are prevalent in help-seeking CHR patients; about a quarter of these patients seem to suffer from paranoid symptomatology for more than 18 months. Among clinical disorders, depression is the most important clinical factor associating with and predicting persistence of paranoid symptoms in CHR patients. Additionally, obsessive–compulsive disorder and anxiety symptoms associate strongly with paranoid symptoms. Interventions focused on reducing these disorders and symptomatology may, therefore, help to reduce severity of paranoid symptoms in CHR patients and possibly prevent their proceeding to delusional level. Antidepressants and cognitive-behavioural therapy have proved to be effective in the treatment of depression, obsessive–compulsive disorder and anxiety [42, 43], and cognitive-behavioural therapy has recently been recommended as first-choice treatment of CHR states [44]. These interventions may also reduce the paranoid thinking and interpersonal sensitivity often found in CHR patients [45].

Acknowledgments The International Advisory Board 'European Prediction of Psychosis' (EPOS) group comprises Patrick D. McGorry, Australia; Thomas H. McGlashan, USA; Martin Knapp, UK. The authors thank the following scientists for their work for EPOS: Reinaud van der Fliert, Rianne Klaassen (Department of Psychiatry, AMC, University of Amsterdam, The Netherlands); Heinz Picker, Meike Neumann, Anke Brockhaus-Dumke, Ralf Pukrop (Department of Psychiatry and Psychotherapy/FETZ, University of Cologne, Cologne, Germany); Jukka Huttunen, Terja Ristkari (Department of Psychiatry, University of Turku, Finland); Tanja Svirskis (Department of Psychiatry, University of Helsinki, Helsinki, Finland); Amanda Skeate (ED: IT, Early Intervention Service, Birmingham, UK); Yehonala Gudlowski (Charité, Berlin, Germany); Seza Ozgürdal, Henning Witthaus (Charité, Berlin, and Ruhr-University, Bochum, Germany); Shôn Lewis, Antony Morrisson (School of Psychological Sciences, University of Manchester, Manchester, UK).

Compliance with ethical standards

Funding This study was funded by Grant QLG4-CT-2001-01081 from the 5th Framework Program Quality of Life and Management of Living Resources of the European Commission. Additional local funding was provided by the Social Insurance Institution of Finland, the Medical Faculty of Cologne (Köln Fortune Program), the Research Council of The Netherlands (ZorgOnderzoek Nederland/NWO-Medische Wetenschappen, project # 2630.0001), the National Institute for Health Research (NIHR) through the Collaborations for Leadership in Applied Health Research and Care for Birmingham and the Black Country (CLAHRC-BBC)' and Oy H. Lundbeck AB, Finland.

Conflict of interest None.

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