PREDICTING FIRST-EPISODE PSYCHOSIS BY BASIC SYMPTOM CRITERIA

Frauke Schultze-Lutter, Joachim Klosterkötter, Heinz Picker, Eckhard-Michael Steinmeyer, Stephan Ruhrmann

Summary

Object: Basic symptoms were suggested as a complement to the 'ultra high risk' approach to an early detection of psychosis, and two criteria were derived from it thought to differ in imminence of psychotic breakdown, the risk criterion cognitive-perceptive basic symptoms (COPER) and the high-risk criterion Cognitive Disturbances (COGDIS). These were compared with regard to their predictive ability and potentially influencing factors.

Method: Criteria were studied prospectively on a sample of 146 putatively prodromal subjects meeting the broader COPER criterion over 19.6±15.4 months with the Schizophrenia Proneness Instrument, Adult version and the PANSS.

Results: 124 COPER subjects also met COGDIS; 51 subjects developed first-episode psychosis within 11.0±9.1 months; 8 of them had only met COPER at baseline. COPER and COGDIS subjects differed significantly on all subscales except the PANSS negative scale (PANSS-N); they did not differ in conversion rate and time or psychotic diagnoses. Comparing converters to non-converters, no differences in psychopathology were found in COPER but in COGDIS subjects; converted COGDIS subjects scored significantly higher on subjective cognitive disturbances, subjective disturbances in experiencing self and surrounding and PANSS-N. Regression models including psychopathology and socio-demographic variables potentially influencing conversion well predicted non-conversion, but failed to predict conversion above chance level.

Conclusions: The previous finding of a good predictive ability of certain basic symptoms was supported, yet not the notion that COPER *per se* delineated a less imminent risk of psychosis than COGDIS. COPER subjects rather appeared as a 'low symptom' subtype of prodromal subjects who might require special prediction.

Key Words: Basic Symptoms – Early Detection Of Psychosis – Risk Criterion Cognitive-Perceptive Basic Symptoms (COPER) – High-Risk Criterion Cognitive Disturbances (COGDIS)

Declaration of interest: None

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Introduction

Since the 1990s, detection of and intervention in putatively prodromal states of first-episode psychosis have been increasingly investigated. In the matter of early detection, two traditions predominate: the 'ultra high risk' (UHR) approach and the basic symptom approach (Olsen and Rosenbaum 2006). The widely applied UHR criteria (Yung et al. 1998, 2004, 2005, 2006, Carr et al. 2000, Phillips et al. 2000, McGorry et al. 2002, Miller et al. 2002, Cornblatt et al. 2003, Ruhrmann et al. 2003, McGlashan et al. 2004, Morrison et al. 2004, Broome et al. 2005, Simon et al. 2006) aim at the description of an imminent risk of psychosis, on a symptomatic level, by attenuated psychotic symptoms (APS) and brief limited intermittent psychotic symptoms (BLIPS); and early studies on UHR subjects had indeed reported first-year transition rates to frank psychosis between 34.6% (Yung et al. 2004) and 54% (Miller et al. 2002) for those not participating in the treatment group of a preventive intervention study. Basic symptoms were suggested as a complementary approach to an even earlier detection (Ruhrmann et al. 2003, Schultze-Lutter et al. 2006). These subtle, subclinical self-experienced disturbances in drive, stress tolerance, affect, thinking, speech, perception and motor action have first been described by Huber (1966, Gross 1989) and operationalized *in extenso* in the 'Bonn Scale for the Assessment of Basic Symptoms' (Gross et al. 1987, Klosterkötter et al. 1997). Basic symptoms are phenomenologically different from mental states known to the patient/subject from what s/he considers his/her

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'normal' self and thus are clearly distinguishable from subtle disturbances described as traits in those at genetic high-risk (Jones 2002, Parnas and Carter 2002). In addition, basic symptoms are phenomenologically clearly distinct from APS and BLIPS as part of the UHR criteria: (1) Basic symptoms are often actively compensated, e.g. by increasing effort, and thus are not necessarily observable by others as are odd thinking and speech, negative symptoms and formal thought disorders. (2) They are regarded by the affected person as originating in him-/herself and, unlike schizotypal perceptual disturbances and hallucinations, are not related to changes in the surrounding; perceptive basic symptoms are therefore often regarded as a disturbance of the affected sense, e.g. as a seeing or hearing problem. (3) Cognitive basic symptoms are disturbances of thought processing, i.e. aberrations from the 'normal' cognitive processes and functions, independent of thought content; thus, unlike magical thinking, ideas of reference, paranoid ideation or delusions, these disturbances do not represent content-related deviations from the subject's former way of perceiving and interpreting the world.

Two partially overlapping basic symptom criteria for defining the initial prodrome of psychosis, esp. schizophrenia, have been suggested based on the data of the prospective Cologne Early Recognition study (Klosterkötter et al. 2001, Schultze-Lutter et al. 2006): One includes ten cognitive-perceptive basic symptoms (COPER; Table 1); it was derived from findings on the predictive accuracy of single basic symptoms. Extended by the additional requirement of the absence of attenuated and transient psychotic symptoms, COPER was included in the early initial prodromal state (EIPS) criteria of the German Research Network Schizophrenia (Häfner et al. 2004, Ruhrmann et al. 2003). The second criterion is based on a methodological study of the same CER-data (Schultze-Lutter 2001), in which a cluster of nine cognitive basic symptoms was repeatedly selected as the most predictive of all seven examined clusters. This cluster was called "Cognitive Disturbances" (COGDIS; Table 1) and employed as an inclusion criterion in the European Prediction Of Psychosis Study, EPOS (Klosterkötter et al. 2005).

As regards their general predictive accuracy, the two symptom selections hardly differed with areas under the receiver operating characteristic (ROC) curve of 0.83 for the COPER and 0.82 for the COGDIS selection (Schultze-Lutter et al. 2006). The most favourable cut-off was one symptom for the COPER selection and two symptoms for COGDIS (Table 1). At these cut-offs, the two criteria showed satisfying accuracy values with COGDIS tending to be more accurate in ruling in subsequent schizophrenia (Schultze-Lutter et al. 2006). Furthermore, the COGDIS criterion, which defined a subgroup of COPER subjects, seemed to indicate a slightly more imminent risk of psychosis (Schultze-Lutter et al. 2006): 23.9% of those meeting COGDIS converted to schizophrenia within the first year following baseline assessment, 22.4% within the second, 14.9% within the third and 17.9% within more than three years; the corresponding numbers for COPER were 19.8%, 17.0%, 13.2% and 15.1% respectively. Thus with regard to the diagnostic accuracy (McNeil et al. 1975), it was argued that, in terms of intervention studies, the COPER criterion should only be applied when a fairly safe treatment is available that is not causing undue harm if administered to false-positive patients, e.g. a psychotherapeutic treatment focusing on improvement and monitoring of symptoms, whereas the COGDIS criterion would justify even a pharmacological treatment with its potential side-effects to

Table 1. *Basic symptom based definitions of the initial prodromal state of psychosis*

Risk criterion Cognitive-Perceptive Basic Symptoms (COPER)
presence of at least any one of the following ten basic symptoms with a SPI-A score of ≥ 3 within the last three months and first occurrence ≥ 12 months ago:

- thought interference
- thought perseveration
- thought pressure
- thought blockages
- disturbance of receptive speech
- decreased ability to discriminate between ideas/perception, fantasy/true memories
- unstable ideas of reference
- derealisation
- visual perception disturbances (excl. hypersensitivity to light or blurred vision)
- acoustic perception disturbances (excl. hypersensitivity to sounds)

High-risk criterion, Cognitive Disturbances' (COGDIS)
presence of at least any two of the following nine basic symptoms with a SPI-A score of ≥ 3 within the last three months:

- inability to divide attention
- thought interference
- thought pressure
- thought blockages
- disturbance of receptive speech
- disturbance of expressive speech
- unstable ideas of reference
- disturbances of abstract thinking
- captivation of attention by details of the visual field

avoid serious and permanent harm, such as the discussed neurotoxic effects of first-episode psychosis (Copolov et al. 2000, Pantelis et al. 2003).

Recently, Simon and colleagues (2006) conducted a comparison of the symptomatic EIPS criterion, i.e. the COPER criterion extended by the additional requirement of an absence of APS and BLIPS, the UHR and the Clinical High Risk (CHR) criteria, which include attenuated negative symptoms in addition to symptomatic UHR criteria (Cornblatt et al. 2003), in relation to neurocognitive performance. They showed that an inclusion of the EIPS criterion into the UHR criteria led to the definition of a more homogeneous sample of clinically and cognitively impaired subjects. This was thought to suggest that the EIPS criterion were a more sensitive way to predict schizophrenia (Simon et al. 2006).

Thus, the basic symptom concept and the resulting criteria of a potential prodrome of first-episode psychosis appear valuable in the early detection of first-episode psychosis. Yet, they require additional evaluation in prospective studies before final recommendations for their employment can be made. To this aim, both basic symptom criteria were compared for their symptom severity, transition rate, time to transition and type of first-episode psychosis on prospective data of the evaluation study of the Schizophrenia Proneness Instrument, Adult version (SPI-A, Schultze-Lutter et al. unpublished).

Methods

Inclusion, exclusion and transition criteria

The inclusion criterion for an initial prodromal state of psychosis was defined by the COPER criterion (Table 1) irrespective of UHR criteria according to the Structured Interview for Prodromal Syndromes, SIPS (Miller et al. 1999). Subjects were between 16 and 40 years of age (Table 2). Exclusion criteria were: (1) diagnosis of delirium, dementia, amnestic or other neurological cognitive disorders, mental retardation, psychiatric disorders due to a somatic factor or related to psychotropic substances according to DSM-IV (APA 1994), (2) alcohol or drug abuse or dependence within the last three months according to DSM-IV, (3) diseases of the central nervous system (inflammatory, traumatic, epileptic) and (4) current or past diagnosis of any psychotic disorder according to DSM-IV criteria.

A transition to first-episode psychosis was defined by the presence of any one of the following items of the Positive And Negative Syndrome Scale, PANSS (Kay et al. 1987), with a duration of more than seven days: hallucinations (P3≥4), delusions (P1 or P5≥4; P6≥4 for paranoid ideas and P6≥5 for increased mistrust without paranoid ideation), formal thought disorder (P2≥4).

Subjects

146 potentially prodromal subjects gave written informed consent to participate in the study between June 2000 and December 2003. Before, the study had been approved by the local ethical committee The majority of subjects were outpatients who had sought help at the Cologne Early Recognition and Intervention Centre for mental crisis (FETZ); few (n=4) were inpatients of the Department of Psychiatry and Psychotherapy of the University of Cologne and presented to the FETZ for further diagnostic assessment, especially of prodromal criteria (Table 2). About three quarters of potentially prodromal outpatients had been referred by other healthcare professionals, mainly working in private praxis (57.4%), other psychiatric hospitals (16.4%) or counselling services (2.4%); this source of referrals had been facilitated by an intensive awareness campaign about the early course and early warning signs of psychosis in the local healthcare community. 13.9% subjects consulted the FETZ on their own account; the majority of them had learned about it by mass media or had visited its homepage on the internet. Only 9.8% were referred from other sources, such as general hospitals or GPs (Savic et al. 2005).

At baseline, subjects who met the COGDIS criterion (n=124) did not differ from those who only met the COPER criterion (n=22) in age (t-test, df=144, p=.627), gender (χ^2-test, df=1, p=.696), graduation (χ^2-test, df=5, p=.159), vocational education (χ^2-test, df=5, p=.518) or current occupation (χ^2-test, df=2, p=.851) but in marital status (χ^2-test, df=2, p=.021) with COPER subjects being less frequently married and presence of attenuated psychotic symptoms, APS, according to the SIPS (χ^2-test, df=1, p=.003) with a higher percentage of COGDIS subjects also reporting APS (Table 3). Transient psychotic symptoms (BLIPS) had only been reported by one COGDIS subject who has not (yet) developed frank psychosis and also reported APS.

The overall mean follow-up time by December 2006 was 20.6±16.1 months (range: 1-70 months; Mdn 18 months). Subjects who had made the transition to a non-affective psychotic disorder were not further followed, thus the mean follow-up time of the as yet 'non-converters' is longer (25.7±16.8; range 1-70; Mdn 24 months) than of the 'converters' (Table 2).

Of the non-converters, 16 (17%) dropped out before 6-month follow-up, 24 (25%) before the 12-month follow-up, and could not as yet (December 2006) be re-contacted. At 24-month follow up, the drop-out rate of non-converters had risen to 40% (n=38); yet drop-outs did not differ from those who stayed in the study in socio-demographic or psychopathologic baseline data. Though high, this drop-out rate is well within the range of the earlier CER study (Klosterkötter et al. 2001), in which 53% could not be re-contacted. Furthermore it is within the range reported for other non-intervention follow-up studies, e.g. 23.4% (11 of 47) potentially non-converted prodromal subjects did not complete 6-months follow-up in an English sample (Broome et al. 2005), and only 21 of 58 (36.2%) potential non-converters could be followed up between 4 and 34 months (mean: 14.6 months) in an Australian sample (Carr et al. 2000).

Instruments and Procedure

Basic symptoms were assessed with the 'Schizophrenia Proneness Instrument, Adult version'

Table 2. *Socio-demographic data of sample fulfilling COPER criterion (N=146)*

		Developed frank psychosis (n=51)	Not (yet) developed psychosis (n=95)	Total sample (N=146)
Age (in yrs.)	***p(t-test)***			***p = .161***
M ± *SD*		23.6 ± 5.6	24.9 ± 4.9	24.4 ± 5.2
range		17 - 39	16 - 36	16 - 39
Mdn		22.0	24.0	24.0
Gender	***p(χ^2-test, df=1)***			***p = .307***
n (%) male		38 (74.5%)	63 (66.3%)	101 (69.2%)
Marital status	***p(χ^2-test, df=2)***			***p = .171***
single		94.1%	85.3%	88.4%
married		2.0%	10.5%	7.5%
separated/divorced		3.9%	4.2%	4.1%
Graduation[1]	***p(χ^2-test, df=5)***			***p = .009***
none		8.0%	-	2.8%
CSE (10 yrs.)		12.0%	2.1%	5.5%
O-level (10 yrs.)		12.0%	15.8%	14.5%
VBD (12 yrs.)		12.0%	13.7%	13.1%
A-level (13 yrs.)		40.0%	54.7%	49.7%
still in school		16.0%	13.7%	14.5%
Vocational educat.	***p(χ^2-test, df=5)***			***p = .075***
none		17.6%	10.6%	13.1%
apprenticeship or similar		13.7%	16.0%	15.2%
master craftsman or similar		3.9%	-	1.4%
college of higher education		-	4.3%	2.8%
university		3.9%	12.8%	9.7%
still in school/ training		60.8%	63.1%	57.9%
Occupation	***p(χ^2-test, df=2)***			***p = .163***
no current occupation		23.5%	12.1%	16.2%
regular incl. education		76.5%	86.8%	83.7%
other		-	1.1%	0.7%
APS (according to SIPS)	***p(χ^2-test, df=1)***			***p = .313***
% present		84.6%	77.7%	80.1%
Time baseline to conversion (in months)		11.0 ± 9.1		
M ± *SD;* range		1 - 37		
Mdn		9.0		

CSE: Certificate of Secondary Education; VBD: Vocational baccalaureate diploma
[1] translated into British graduations (years of school education required to receive the respective graduation)

Table 3. *Socio-demographic data of subjects who did or did not meet COGDIS criterion*

	COGDIS criterion not met (COPER)			**COGDIS criterion met**		
	Developed psychosis (n=8)	Not (yet) developed psychosis (n=14)	Total (n=22)	Developed psychosis (n=43)	Not (yet) developed psychosis (n=81)	Total (n=124)
Age (in yrs.)			***p = .701***			***p = .176***
M ± *SD*	24.4 ± 6.0	25.2 ± 4.2	24.9 ± 4.8	23.4 ± 5.6	24.8 ± 5.1	24.3 ± 5.3
range	19 - 35	19 - 34	19 - 35	17 - 39	16 - 36	16 - 39
Mdn	21.5	25.0	25.0	23.0	24.0	23.5
Gender			***p = 1.0***			***p = .305***
n (%) male	6 (75.0%)	10 (71.4%)	16 (72.7%)	32 (74.4%)	53 (65.4%)	85 (68.5%)
Marital status			***p = .527***			***p = .068***
single	75.0%	92.9%	86.4%	97.7%	84.0%	88.7%
married	-	-	-	2.3%	12.3%	8.9%
separated	25.0%	7.1%	13.6%	-	3.7%	2.4%
Graduation			***p = .289***			***p = .033***
none	12.5%	-	4.5%	7.0%	-	2.4%
CSE (10 yrs.)	12.5%	-	4.5%	11.6%	2.5%	5.6%
O-level (10 yrs.)	-	-	-	16.3%	18.5%	17.7%
VBD (12 yrs.)	12.5%	7.1%	9.1%	11.6%	14.8%	13.7%
A-level (13 yrs.)	62.5%	78.6%	72.7%	34.9%	50.6%	45.2%
still in school	-	14.3%	9.1%	18.6%	13.6%	15.3%
Vocational educat.			***p = .608***			***p = .089***
none	25.0%	14.3%	18.2%	16.3%	10.0%	12.2%
apprenticeship	-	14.3%	9.1%	16.3%	16.3%	16.3%
master craftsman	-	-	-	4.7%	-	1.6%
college	-	-	-	-	5.0%	3.3%
university	12.5%	21.4%	18.2%	2.3%	11.3%	8.1%
still in training	62.5%	50.0%	54.5%	60.5%	57.5%	58.5%
Occupation			***p = .527***			***p = .276***
none	25.0%	7.1%	13.6%	23.3%	13.0%	16.7%
regular	75.0%	92.9%	86.4%	76.7%	85.7%	82.5%
other	-	-	-	-	1.3%	0.8%
APS (acc. to SIPS)			***p = 1.00***			***p = .153***
% present	50.0%	57.1%	54.5%	90.9%	81.3%	84.7%
Time baseline to conversion (in months)	10.9 ± 10.9 2 - 29 4.0			11.1 ± 8.7 1 - 37 9.0		

For abbreviations and tests see TABLE 1

(SPI-A). The 34-item SPI-A comprises of 6 subscales of 5 to 6 items each:

- 'affective-dynamic disturbances' (ADYN) including impaired stress tolerance, a change in general mood and a decrease in general as well as positive emotional responsiveness,
- 'cognitive-attentional impediments' (ATTENT) including some cognitive basic symptoms that were found to be less specific to subjects later developing psychosis (Klosterkötter et al. 2001), i.e. attention and short-term memory deficits, concentration problems as well as slowed-down thinking and lack of purposive thoughts,
- 'cognitive disturbances' (COGNIT) comprising of the more peculiar cognitive basic symptoms found to be rather specific to truly prodromal subjects (Klosterkötter et al. 2001), i.e. indecisiveness with regard to minor choices, thought interference and blockages, disturbances of immediate recall, of receptive as well as expressive speech,
- 'disturbances in experiencing self and surroundings' (SELF) including self-reported pressure of thoughts unrelated to each other and unstable ideas of reference in that the knowledge of the lack of correspondence of this felt reference in reality is immediate and, unlike in true ideas of reference as part of APS, the experience is never considered to have a counterpart in the environment; furthermore, disturbances in the visual perception of others, a decreased capacity to distinguish between different kinds of emotions and an increased emotional reactivity in response to routine social interactions are rated in this subscale,
- 'body perception disturbances' (BODY) comprising of coenesthetic phenomena, i.e. unusual perceptive experiences related to the body in a non-delusive way,
- 'perception disturbances' (PERCEPT) with hypersensitivity to optic and/or acoustic stimuli, photopsia, micro-/macropsia, changes in the perception of the intensity/quality of acoustic stimuli and somatopsychic bodily depersonalization.

For the quantitative rating, a seven-points severity scale was introduced with maximum frequency of occurrence within the last three months as the guiding criterion; i.e. from '0' equal 'symptom absent' to '6' equal 'present daily'. Within a semi-structured interview, the SPI-A was assessed together with the PANSS by four experienced raters, all of them were members of the FETZ-team trained either as psychologists or psychiatrists. Their overall concordance rate with an expert rating (F.S.-L.) in rating a taped interview was 91%.

Exclusion criteria, i.e. current or past diagnosis of any psychotic disorder, psychiatric disorders due to a somatic factor or related to psychotropic substances as well as alcohol or drug abuse or dependence within the last three months, were assessed with the Structured Clinical Interview for DSM-IV (SKID-I, German version; Wittchen et al, 1997). When the anamnestic interview revealed any indication of a neurological or other disease of the central nervous system, subjects were referred for the appropriate diagnostic procedures to specialised services of the university clinic. In addition, every subject had received a clinical brain imaging, MRI or CT, to control for organic mental disorders. The same step-wise procedure was applied to rule out mental retardation: only when indications of a mental retardation were present in the interview and in the educational history, the Hamburg-Wechsler-Intelligenztest für Erwachsene (HAWIE-R; Tewes 1991) was conducted.

In subjects who made the transition to psychosis, outcome DSM-IV diagnoses of psychosis were given according to the clinical picture; diagnoses were supported by the PANSS-data.

Data analyses

Data analyses were conducted with SPSS version 11.0. For analyses of group differences in baseline psychopathology in terms of the nine subscale totals of SPI-A and PANSS, Mann-Whitney tests with error adjustment for multiple testing across all scales according to the sequential method of Holm (1979) were calculated. An adjustment across the different scales and not only across each individual scale was chosen, because Spearman correlation analyses of the subscale totals of the whole sample (n=146) had revealed highly significant ($p<.01$) correlations for all but two of the 36 correlations; these two were between the PANSS negative scale (PANSS-N) and BODY ($r_s=.124$) and PERCEPT ($r_s=.142$), respectively. BODY generally showed the least correlation with other scales; here, an at least small effect of 10% commonly explained variance was only found in correlation with PERCEPT ($r_s=.351$).

Both socio-demographic variables that had shown significant differences between groups, marital status and graduation (Tables 2 and 3), did not show any relevant correlation of at least 10% commonly explained variance with any subscale; thus both variables were not considered as potential covariates in group comparisons of psychopathology; the only statistical significant correlations were for graduation (higher graduation equalled higher appointed value) and COGNIT ($r_s=-.225$, $p=.006$) and ATTENT ($r_s=-.176$, $p=.028$) and for ATTENT and marital status ($r_s=-.172$, $p=.038$).

To test for variables most predictive of transition, stepwise logistic regression models (Wald method with a classification threshold of p=.5, p=.05 as entry and p=.10 as exclusion criterion of variables) were calculated. Both forward and backward selection methods were calculated to account for a variable selection bias. To be able to estimate the potential bias for a tailor-made classification, a random selection of 66% cases (n=97) was used as a model development, the remaining 49 cases as a model validation group. Only variables that had shown a significant difference between transited and non-transited subjects entered the model. Due to the small size of the COPER sample, no regression analyses were calculated separately for COGDIS and COPER. Classification rates in the subgroups were tested for significant differences from random assignment using 1-dimensional χ^2-tests with an unadjusted critical $\chi^2_{(1;95\%)}=3.84$.

Table 4. *Classification results of the logistic regression equation and results of 1-dimensional χ^2-tests for difference from random classification* (critical $\chi^2_{(1;95\%)}$=3.84)

Equation	Group	% correct positive classifications	% correct negative classifications	% correct classifications
Logistic regression 1 (p=0.105 × PANSS negative scale - 1.986)	Model development (n=97)	15|38 (39.5%) $\chi^2_{emp.}$=1.68; ***n.s.***	50|59 (84.7%) $\chi^2_{emp.}$=28.49; p<.001	55|97 (67.0%)
	Model validation (n=49)	8|13 (61.5%) $\chi^2_{emp.}$=0.69; ***n.s.***	31|36 (86.1%) $\chi^2_{emp.}$=15.16; p<.001	39|49 (79.6%)
	Model development, COPER (n=17)	1|8 (12.5%) $\chi^2_{emp.}$=4.50; p<.05	7|9 (77.8%) $\chi^2_{emp.}$=2.78; ***n.s.***	8|17 (47.1%)
	Model development, COGDIS (n=80)	14|30 (46.7%) $\chi^2_{emp.}$=0.13; ***n.s.***	43|50 (86.0%) $\chi^2_{emp.}$=25.92; p<.001	57|80 (71.3%)
	Model validation, COPER (n=5)		5|5 (100%) $\chi^2_{emp.}$=5.00; p<.05	5|5 (100%)
	Model validation, COGDIS (n=44)	8|13 (61.5%) $\chi^2_{emp.}$=0.69; ***n.s.***	26|31 (83.9%) $\chi^2_{emp.}$=14.26; p<.001	34|44 (77.3%)
Logistic regression 2 (p=0.103 × PANSS negative scale - 0.280 × graduation - 0.916)	Model development (n=97)	16|38 (42.1%) $\chi^2_{emp.}$=0.95; ***n.s.***	50|59 (84.7%) $\chi^2_{emp.}$=28.49; p<.001	66|97 (68.0%)
	Model validation (n=49)	7|13 (53.8%) $\chi^2_{emp.}$=0.08; ***n.s.***	28|36 (77.8%) $\chi^2_{emp.}$=11.11; p<.001	35|49 (71.4%)
	Model development, COPER (n=17)	2|8 (25.0%) $\chi^2_{emp.}$=2.00; ***n.s.***	8|9 (88.9%) $\chi^2_{emp.}$=5.44; p<.025	10|17 (58.8%)
	Model development, COGDIS (n=80)	14|30 (46.7%) $\chi^2_{emp.}$=0.13; ***n.s.***	42|50 (84.0%) $\chi^2_{emp.}$=23.12; p<.001	56|80 (70.0%)
	Model validation, COPER (n=5)		4|5 (80.0%) $\chi^2_{emp.}$=1.8; ***n.s.***	4|5 (80.0%)
	Model validation, COGDIS (n=44)	7|13 (53.8%) $\chi^2_{emp.}$=0.08; ***n.s.***	24|31 (77.4%) $\chi^2_{emp.}$=9.32; p<.01	31|44 (70.1%)

n.s. not significant

Results

Psychopathology in COPER and COGDIS

The majority of subjects selected for the COPER criterion also met the COGDIS criterion (n=124, 84.9%). Compared to subjects only meeting the COPER criterion (n=22), COGDIS subjects exhibited significantly higher subscale totals in all scales at baseline. Except for PANSS-N ($p_{unadj.}$=.026), differences remained significant after error adjustment (ADYN [$p_{adj.}$=.0015], ATTENT [$p_{adj.}$=2.30e-008], COGNIT [$p_{adj.}$=3.34e-010], SELF [$p_{adj.}$=9.60e-006], BODY [$p_{adj.}$=.0295], PERCEPT [$p_{adj.}$=.0018], PANSS positive scale, PANSS-P [$p_{adj.}$=8.61e-006], and general psychopathology scale, PANSS-G [$p_{adj.}$=.0052]).

Transition rate and time

51 (34.9%) subjects have meanwhile developed a frank psychosis, 8 (36.4%) of the COPER and 43 (34.7%) of the COGDIS subjects. The mean time between baseline and conversion that only showed a trend towards normal distribution (Kolmogorov-Smirnov-Z=1.26, p=.082) did not differ between the two groups (Mann-Whitney test, p=.57; Table 3). Five (22.7%) COPER and 31 (25.0%) COGDIS subjects transited to frank psychosis within 12 months following baseline; all of the COPER and 18 (14.5%) of the COGDIS subjects within 6 months; an additional 2 (9.1%) of the COPER and 10 (8.1%) of the COGDIS subjects transited within 13 to 24 months. Only one subject fulfilling COGDIS transited within one month.

No group difference showed for the distribution of psychotic DSM-IV diagnoses in general (χ^2-test, df=5, p=.39; Figure 1), the frequency of a schizophrenic disorder (Fisher's test, df=1, p=.14) or of the paranoid

schizophrenic subtype (Fisher's test, df=1, p=.25). The subject who had first developed psychotic features within a major depression fulfilled DSM-IV criteria of a schizoaffective disorder in a second psychotic episode two years later.

Psychopathology and transition

Whereas the 51 converters had generally shown more pronounced symptoms in both scales, this became significant only for COGNIT ($p_{unadj.}$=.028) and SELF ($p_{unadj.}$=.037), and for PANSS-N ($p_{unadj.}$=.004) and PANSS-G ($p_{unadj.}$=.043). After adjustment for multiple testing, only PANSS-N ($p_{adj.}$=.036) remained significant. Moreover, no group differences in baseline psychopathology between those who developed schizophrenia (paranoid or undifferentiated) and non-schizophrenic psychoses or between those who developed paranoid schizophrenia and other psychoses unveiled.

When comparing psychopathology at baseline between transited and not (yet) transited subjects separately for the groups with and without COGDIS, no differences showed within the group only meeting the COPER criterion (Figures 2 and 3): Here, the largest difference occurred for ATTENT ($p_{unadj.}$=.27) with the non-transited subjects scoring higher, the smallest for PANSS-P ($p_{unadj.}$=.97). In contrast, several significant group differences with higher scores in the transited subjects showed in the COGDIS group (Figure 2 and 3); after adjustment for multiple testing, group differences remained significant for COGNIT ($p_{adj.}$=.032), SELF ($p_{adj.}$=.035) and PANSS-N ($p_{adj.}$=.027).

Predictors of transition

In the regression analyses of the six subscales that had shown significant unadjusted group differences in the COGDIS group (Figures 2 and 3), PANSS-N was solely chosen (Table 4); the model explained 9.5% of the variance. Adding graduation and the interaction of highly correlating subscales of the same instrument (ADYN*COGNIT, r_s=.516; ADYN*SELF, r_s=.567; PANSS-P*PANSS-G, r_s=.661), PANSS-N was again chosen as the sole psychopathological variable supplemented by graduation (Table 4); this model explained 14.5% of the variance. Both models were significant on a 1%-level, performed slightly better in the validation than in the development group and in the COGDIS better than in the COPER group. No differences between forward and backward selections occurred for the respective analyses.

Failing to show significant difference from random

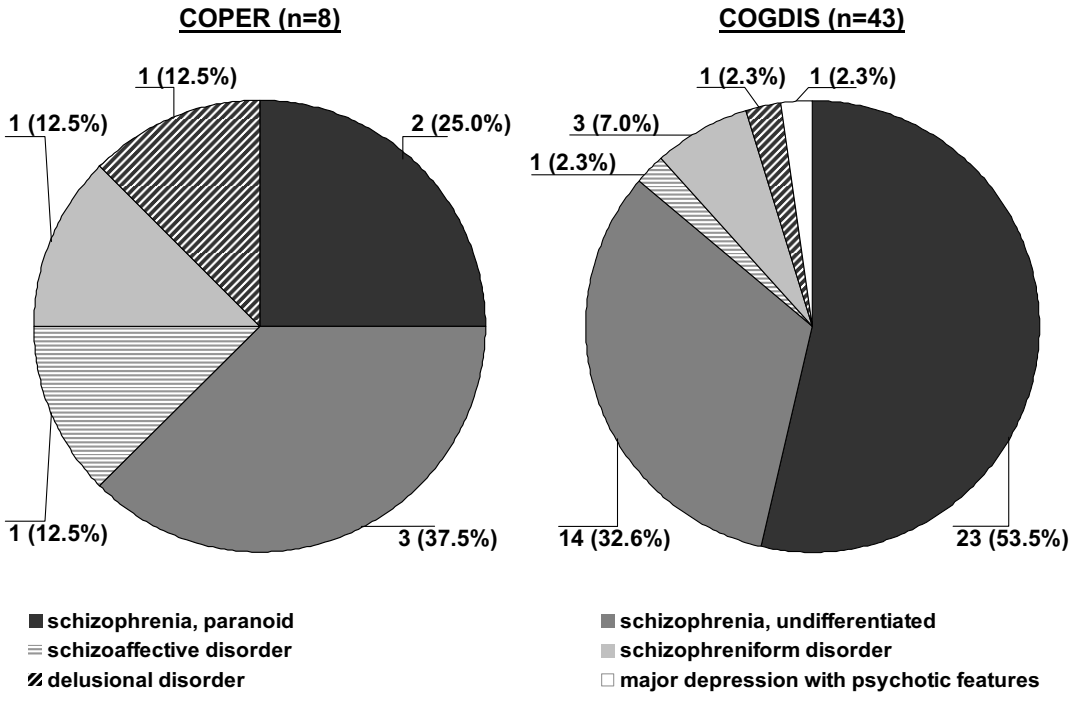

Figure 1. *Distribution of psychosis diagnoses according to DSM-IV in the COPER (n=22) and COGDIS sample (n=124).*

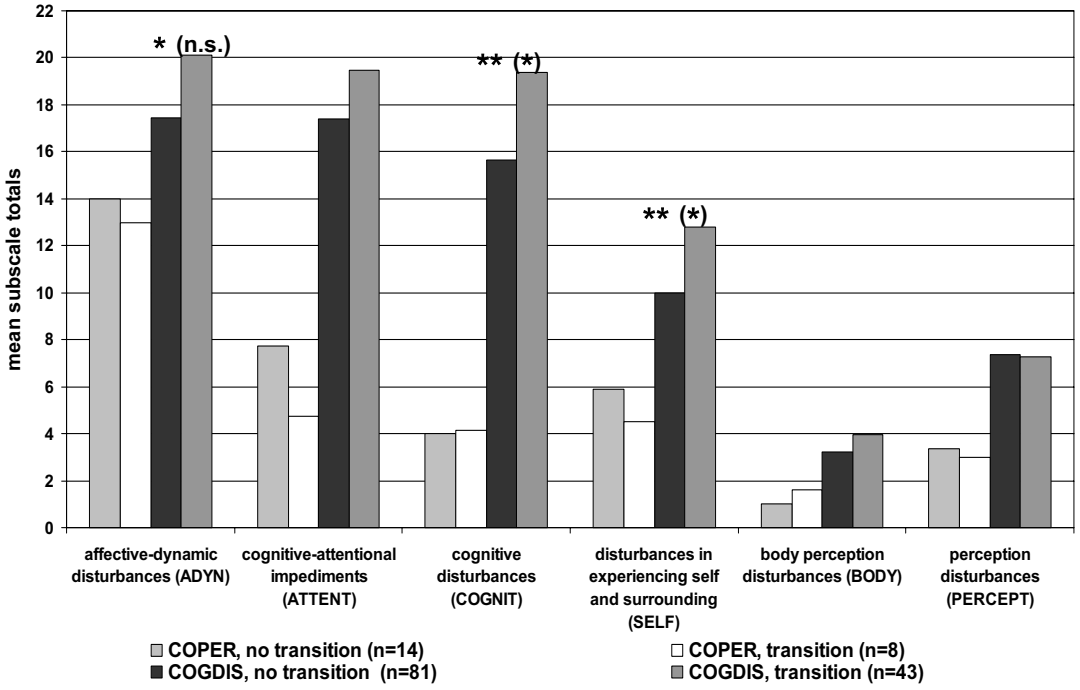

Figure 2. *Mean SPI-A subscale totals by group and transition n.s. pe≥.05; * p<.05; ** p<.01 (Mann-Whitney tests); significance level after adjustment for multiple testing in parenthesis*

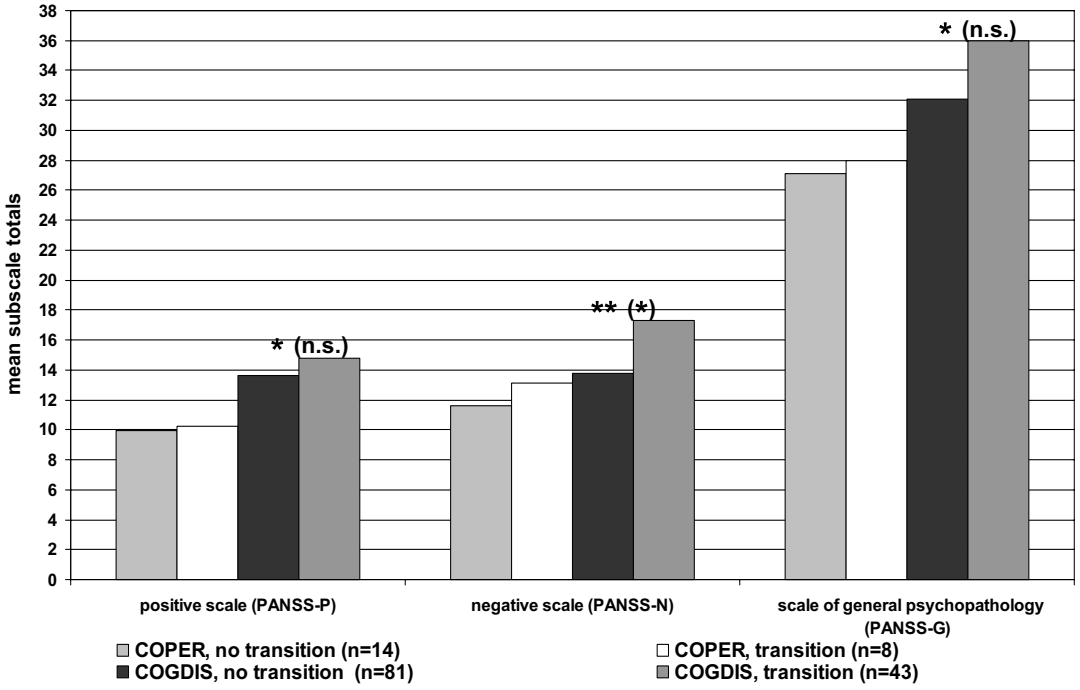

Figure 3. *Mean PANSS subscale totals by group and transition for explanation see Figure 2*

group assignment in the expected direction, both models were insufficient in classifying, i.e. predicting, conversion to psychoses (Table 4). However, right prediction of non-conversion was significantly different from random assignment, except in two sub-samples of n=9 and n=5 in that the percentage of right predictions, 77.8% and 80.0%, were comparable to other non-converter sub-samples, but failed level of significance due to the small sample size (Table 4).

Discussion

Cognitive and perceptive basic symptoms were suggested as a complementary approach to the UHR criteria as they are thought to occur during a very early state of the illness as the first psychopathological expression of the underlying organic cause; thus the term 'basic' (Huber 1966, Gross 1989, Klosterkötter et al. 2001, Schultze-Lutter et al. 2006, Ruhrmann et al. 2003). The suggested cognitive-perceptive basic symptoms can be well distinguished from subtle disturbances described as traits in genetic high-risk persons as well as from attenuated or frank psychotic symptoms as employed in the UHR criteria. Furthermore, the cognitive basic symptoms that are included in both basic symptom criteria describe specific and peculiar subjective aberrations in thought processing that are different from (attenuated) negative symptoms affecting thinking and decision-making as part of attentional impairment or avolition.

Two basic symptom based criteria have been proposed (Schultze-Lutter et al. 2006), COPER and COGDIS (Table 1), that show an overlap of about 50% of their respective symptoms. Although theoretically allowing for the single appearance of both criteria, all subjects meeting COGDIS had also met COPER within the CER study (Schultze-Lutter et al. 2006); and of 402 potentially prodromal subjects who had been examined in the FETZ between 1998 and 2003, only 4 (0.995%) met COGDIS but not COPER, whereas 107 (26.6%) met COPER but not COGDIS; additional 268 subjects (66.7%) met both (unpublished own data). Thus, the inclusion of study subjects according to the COPER criterion is not likely to have introduced a selection bias in disfavour of subjects meeting the COGDIS criterion.

In the light of the CER-data, COPER and COGDIS were assumed to differ with regard to imminence of psychosis and level of risk for psychosis (Schultze-Lutter et al. 2006). As expected from a criterion delineating a more imminent risk of psychosis, subjects meeting the COGDIS criterion suffered from significantly more and/or more severe symptoms across all scales at baseline and more frequently reported APS. However surprisingly, compared to the COPER group, this significantly more severe psychopathology was neither associated with a higher transition rate, with shorter time intervals between baseline assessment and transition nor with an accumulation of more severe, i.e. schizophrenic, psychotic disorders in the COGDIS group. Since the two groups hardly differed in their general data this lack of difference in transition rate, time to transition and type of psychosis does not appear to be mediated by a socio-demographic selection bias.

In addition, although a certain degree of uncertainty is associated with the drop-out rate in the non-converters and some of them might have been wrongly treated as false-positive predictions in the analyses, a systematic drop-out bias in favour or disfavour of converters is not likely as baseline data between those lost to the 24-month follow-up and those who participated in it did not differ. However, the observation period in the CER study (Klosterkötter et al. 2001) was on average nearly ten years with a minimum of five years, thus some differences between COPER and CODGIS criterion in predicting psychoses might only become apparent within longer follow-up times.

As regards the first year conversion rate, the current data nearly mimicked the CER data (Schultze-Lutter et al. 2006), whereas the second year transition rates were considerably lower. This might partly be due to the drop-out rate; whether the 40% of cases not known to have developed psychosis and not followed up at 24 months are really the non-converters as whom they are treated in the analyses is not known. With no difference in psychopathology and socio-demographic variables at baseline, some transitions to psychosis are likely to have occurred in this drop-out group, too. However, at first year transition rates of more than 20% and overall transition rates around 35%, both basic symptom based criteria, COPER and COGDIS, performed well within a range lately reported for the UHR criteria (Carr et al. 2000, Morrison et al. 2004, Broome et al. 2005, Cornblatt and Auther 2005, Lemos et al. 2006, Riecher-Rössler 2006, Yung et al. 2005, 2006). These decreased transition rates in UHR samples seem to indicate that the UHR criteria really delineate at least a less imminent risk of psychosis in less selected and/or earlier referred samples (Yung et al. 2006). At the recent transition rates of UHR criteria, basic symptom criteria might *de facto* be complementary to the UHR criteria not only in terms of time, i.e. indicating an earlier state of the initial prodrome, but of psychopathological characteristics of the prodromal state and might indeed support the definition of more "homogeneous" high-risk groups (Simon et al. 2006), at least in terms of their clinical profile.

In addition, although the rate of correct classifications of transitions by the generated logistic regression was generally dissatisfying at about chance level, it was well below chance level in the COPER group. However, the COPER group was small so that conclusions about model fit are greatly limited. None the less, assuming this result will hold in future studies, it indicates that, despite no differences in acute outcome, the prodromal course of COPER and COGDIS subjects might differ considerably with the COPER group representing a kind of 'low symptom' group. Whether this low level of psychopathology is due to less insight or whether it corresponds to different long-term outcome can not be answered within this study. Furthermore, the question what variables might be good predictors of conversion in the COPER group, e.g. neurocognitive functioning, newly or re-occurring substance abuse, family climate, coping, life events etc., requires future studies on larger samples. Such additional variables might also enhance prediction in the COGDIS group, in which more severe attenuated

negative symptoms in combination with lower levels of graduation predicted transition - though insufficiently. However, this finding underlines the important role of attenuated negative symptoms in the development of psychosis, the mean severity of the PANSS-N items was between 'minimal' (score=2) and 'mild' (score=3). The value of attenuated negative symptoms in the prediction of psychosis was earlier emphasised by their inclusion in the CHR criteria (Cornblatt et al. 2003), although they do not seem specific enough to be employed as predictors in their own right (Cornblatt and Auther 2005, Schultze-Lutter et al. in press).

In all, the results of this study underline the earlier notion that certain cognitive and perceptive basic symptoms can be valuable predictors of first-episode psychosis. Yet with no differences between COPER and COGDIS in terms of transition rate, time between baseline and transition and acute outcome but in general severity of psychopathology, the results point towards potential different subtypes in the prodromal course roughly in line with what has been suggested by Cornblatt and colleagues (2003, Cornblatt and Auther 2005). They thus caution to look at the psychotic prodrome in a unitary way, as there might be different subgroups of prodromal patients, and to narrow the focus on potentially predictive symptoms too early as well as underline the need for further studies of longer observation periods in order to get a picture of the predictive ability of current criteria less blurred by as yet unknown outcomes.

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