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The structure of psychosis revisited: The role of mood symptoms

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Abstract

The heterogeneity of the schizophrenia phenotype is often considered an obstacle for genetic research. We therefore aim to identify subgroups of psychosis patients with a shared symptom profile by means of a fully data-driven analysis, which may serve as an alternative phenotype. We investigated the symptoms of 1056 patients that were referred to our hospital with a psychosis. The lifetime symptoms scores were derived from the current and lifetime ratings of the comprehensive assessment of psychiatric history (CASH) interview. We used latent class analysis (LCA) to identify clusters of patients with a shared symptom profile. The five indicators in our analysis were the total number of symptoms present for each of the five factors identified in a factor analysis of lifetime symptoms. We also analysed the discriminating power of these symptom dimensions in previous LCAs. A six-cluster division of psychotic phenotypes showed substantial overlap with earlier LCA analyses and findings from genetic association studies. The results included a bipolar and a depression subgroup in psychosis and showed that mood symptoms are the best discriminators of subgroups of psychosis. The distinction of subgroups of psychosis patients, in particular those with major mood symptoms could facilitate the unravelling of the genetics of psychotic disorders.

Keywords: Affective disorders; Diagnosis and classification; Genetics; Psychosis; Schizophrenia

1. Introduction

Ever since the description of dementia praecox by Kraepelin, there has been debate about how best to classify the psychotic disorders. Kraepelin (1896) thought that his distinction, between what later became bipolar disorder and schizophrenia, would facilitate the discovery of the aetiology of these disorders. However, there is a substantial overlap in clinical and neuropathological findings between these disorders. Moreover, recent studies have demonstrated that the genetic vulnerability for schizophrenia, bipolar disorder and depression is shared (Cardno et al., 2002; Maier et al., 1993; Berrettini, 2000; Lewis et al., 2003). Consequently there is increasing debate about the current classification of psychotic disorders. Indeed, the identification of groups of patients with a particular vulnerability to underlying neuropathological processes could provide an alternative classification of psychotic disorders of greater utility to psychiatric genetic research as compared to current classifications. Kendler et al. (1989) have argued strongly for a data-driven approach to the classification of psychiatric disorders to address this need. With this study we aim to identify groups of psychosis patients by means of LCA of factor scores of

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symptoms in a large sample of patients. We will investigate the separate contributions of each symptom dimension to the classification of subgroups of psychosis patients in this and previous studies. With the application of a fully data-driven analysis we follow up the historical tradition of classification by analysis of symptom patterns, powered by contemporary statistical tools.

2. Method

We investigated the symptoms of all patients from 1996 to 2005 that were referred to our hospital with psychosis. After complete description of the study to the subjects, written informed consent was obtained. Consensus diagnoses according to DSM IV was reached by two psychiatrists by means of a comprehensive assessment of psychiatric history (CASH) interview (Andreasen et al., 1992). All patients were initially referred with a diagnosis of 'psychosis'. Some of these proved, on examination at our unit, not to be psychotic and since lifetime-rated symptoms were examined, most of these patients had never been psychotic. However, in order to avoid introducing a selection bias to a fully data-driven process we did include these patients. Excluding non-psychotic patients would introduce an artificial boundary between non-psychotic and psychotic patients that would reduce the generalization ability of our subgroups.

A total of 1056 patients were included. Table 1 presents diagnosis and clinical variables for the most relevant diagnostic groups. The miscellaneous diagnosis group ($n=26$) consisted of attention deficit hyperactivity disorder ($n=1$), borderline personality disorder ($n=1$) bipolar disorder not otherwise specified (NOS) ($n=2$), depression NOS ($n=1$), dissociative disorder ($n=1$), dysthymia ($n=4$), pathological gambling ($n=1$), psychosis due to a medical condition ($n=4$), obsessive compulsive disorder ($n=4$), personality disorder NOS ($n=1$), picks disease ($n=1$), posttraumatic stress disorder ($n=2$), schizotypical personality disorder ($n=1$) and Tourettes syndrome ($n=2$).

We only examined lifetime-rated symptoms and observational items in these patients because they are a better reflection of genetic vulnerability compared to present state measures alone. The lifetime symptom scores were derived from the current and lifetime ratings of the CASH. We avoided imposing arbitrary measures of 'intensity' of symptoms, instead considering symptoms as categorically present or absent. We considered ratings of 0 and 1 on the present state score of the CASH (absent or doubtful) as absent. We then employed factor analysis to reduce the number of variables before the latent class analysis. In preference to inserting categorical variables into a factor analysis, we employed the MPlus framework, which for this purpose more correctly considers categorical variables as probabilistic cut-offs on continuous distributions (Muthen and Muthen, 1998). An exploratory factor analysis (EFA) with Promax rotation was used to determine the number of factors and

Table 1
Demographic and clinical characteristics by diagnostic group

Diagnosis	*N*	Age (SD)	No. of male (%)	Age onset (SD)	No. of episodes (SD)	Married (%)[a]	Years of education (SD)
Paranoid schizophrenia	439	33.7 (12.3)	314 (71.5)	26.0 (9.2)	2.3 (2.1)	49 (11.2)	11.7 (3.1)
Undifferentiated schizophrenia	109	34.7 (13.4)	75 (68.8)	26.1 (9.0)	2.5 (2.3)	10 (9.2)	11.4 (2.7)
Psychosis NOS	73	27.7 (8.4)	55 (75.3)	25.5 (8.4)	1.4 (1.7)	10 (14.3)	11.5 (2.4)
Schizophreniform disorder	72	24.6 (6.1)	52 (72.2)	23.2 (4.7)	1.1 (0.4)	2 (2.9)	12.3 (2.4)
Schizoaffective disorder	65	35.0 (11.3)	45 (69.2)	27.5 (10.0)	2.6 (2.2)	8 (13.3)	11.3 (3.5)
Depression	50	42.2 (12.0)	22 (44)	40.1 (14.2)	1.1 (0.5)	18 (36.0)	12.5 (2.6)
Disorganized schizophrenia	49	36.6 (11.8)	33 (67.3)	28.0 (11.9)	2.9 (2.6)	1 (2.0)	11.1 (3.1)
Bipolar disorder I	49	31.0 (10.4)	27 (55.1)	26.1 (9.8)	2.4 (2.4)	11 (24.4)	12.3 (2.7)
Residual schizophrenia	39	39.0 (15.0)	28 (71.8)	27.9 (10.6)	2.2 (1.2)	5 (12.8)	11.5 (3.0)
Psychotic depression	28	34.6 (11.9)	14 (50)	31.3 (11.8)	1.5 (0.8)	7 (25.9)	10.9 (3.5)
Miscellaneous	26	41.0 (13.2)	14 (53.8)	38.2 (16.2)	2.3 (2.2)	8 (30.8)	12.6 (2.2)
Drug induced psychosis	17	27.7 (10.0)	15 (88.2)	25.7 (9.4)	2.4 (1.2)	1 (6.7)	10.3 (2.8)
Brief psychosis	16	30.7 (8.9)	9 (56.3)	27.5 (6.6)	2.3 (1.9)	4 (26.7)	11.9 (2.5)
Catatonic schizophrenia	10	36.1 (15.0)	9 (90.0)	26.3 (6.4)	1.4 (1.6)	0 (0)	11.6 (3.9)
Bipolar disorder 2	7	37.0 (16.7)	3 (42.9)	37.7 (17.7)	2.2 (1.6)	2 (33.9)	15 (1.6)
Delusional disorder	7	31.1 (10.8)	6 (85.7)	29.3 (10.9)	2.2 (2.2)	0 (0)	15.2 (1.8)
Total	1056	33.5 (12.3)	721 (68.3)	27.3 (10.4)	2.1 (2.0)	136 (14.2)	11.6 (3.0)

[a] Percentages are true percentages after exclusion of missing values.

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to select items. Confirmatory factor analysis (CFA) under the MPlus framework was employed on a random half of the dataset, examining model fit for different thresholds of item loading from the EFA. Having obtained a satisfactory fit, we confirmed this model by calculating fit indices for the second random half of the dataset.

We used latent class analysis (LCA) with the LatentGold software (Vermunt and Magidson, 2003) to identify clusters of patients with shared symptom profile. The five indicators (observed response variables) in our analysis were the total number of present symptoms for each of the factors encountered in the CFA. Age of onset was dichotomised by median split. In LatentGOLD, these five observed scores were treated as ordinal rather than as continuous scales because the assumption of normally distributed scores within classes seemed to be much too restrictive. In the more robust ordinal specification, the relationship between class membership and responses is restricted by means of an ordinal logit model.

Determining the numbers of clusters in latent class analysis is far from straightforward, especially because different criteria can point to different solutions. In our study we made use of the most accepted measure, the Bayesian Information Criterion (BIC). We also investigated the bivariate residuals reported by LatentGOLD, which indicate how well the model describes the pairwise relationships between the indicators i.e. how well the underlying local independence assumption holds. A third measure we considered was the estimated proportion of classification errors, since we want not only a well-fitting model but also a model with a good classification performance. After classifying cases to the class with the highest membership probability (easily done in the Latent Gold program) we further examined the relationship between class membership and the DSM IV diagnosis, and with demographical variables. We compared the 6 clusters we encountered with respect to their demographic and clinical characteristics. Depending on the scale type of the variable and the homogeneity of error variances, we used ANOVA with post hoc tests, Kruskal Wallis with post hoc Chi-square tests and Chi-square goodness-of-fit tests to test for significance of the difference between groups.

We also performed a meta-analysis of previous studies of this type, to investigate the relative importance of the symptom dimensions to the delineation of subgroups of psychosis. We calculated R^2 for each symptom dimension from previous LCAs, based on the cluster size indicators and endorsement frequencies of individual symptoms in the classes. We took the mean of the endorsement frequencies of those symptoms that were included in each symptom group (from the factor analysis) to give an indication of how much they each contributed to the final subgroup differentiation.

3. Results

Demographic and clinical characteristics are presented in Table 1.

3.1. Factor analysis

The scree plot indicated the presence of 5 factors which accounted for 54% of the total variance and therefore a substantial part of the variability between the outcome is not explained by the symptoms but by either other measures, or just noise (Scree plot and Promax rotated loadings are available on request). Model fit of a confirmatory five-factor model, in which each symptom is related only to the factor for which its loading turned out to be highest in the EFA, was examined under the MPlus framework. Satisfactory fit in a random half of the dataset required the removal of one item with borderline significant loading (thought blocking: Est/S.E=1.91). This was confirmed in the other half of the sample: CFI/TFI=0.976/0.975, RMSEA=0.046 in the 1st half, CFI/TLI=0.962/0.961, RMSEA=0.052 in the 2nd half (Table 2).

3.2. Latent class analysis

We investigated the fit measures for the 1 to 9 class models (data available on request). The 6-class model is the best model based on both the Bayesian Information Criterion (BIC) and the proportion of classification error. Also the bivariate residuals for this model were low (not reported), and were not reduced much more if the number of classes was further increased. We also looked at other information criteria such as AIC and AIC3 (Akaike Information Criterion and a variant that uses a constant of 3 instead of 2), based on which we could select a model with more than six classes: AIC3 points at seven classes and AIC at nine classes. However, for both measures we found that the gain in fit reduced markedly after six clusters.

Fig. 1 presents the symptom profiles for the 6 classes. The *Y*-axis represents the class-specific mean scores as proportions of the maximum score for the indicator concerned. The *X*-axis contains the five symptom dimensions as defined by the factor analysis — these served as indicators in the LCA. For each cluster, the lines connect the means of the five symptom dimensions. For the relationship between class membership

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Table 2
Symptom in the 5 'symptom dimensions'

	Factor				
	Disorganization	Negative symptoms	Positive symptoms	Depression	Mania
Symptoms	Tangentiality	Paucity of expressive gestures	Commenting voices	Loss of interest	Pressure of speech
	Derailment	Decreased spontaneous movements	Auditive hallucinations	Loss of energy	Overactive
	Illogicality	Unchanging facial expression	Thought insertion	Dysphoria	Euphoria
	Perseveration	Lack of vocal inflections	Mind reading	Feelings of worthlessness	Decreased need for sleep
	Incoherence	Affective non-responsivity	Conversing voices	Diminished ability to think	Inflated self-esteem
	Distractibility	Poverty of speech	Thought broadcasting	Loss of appetite	Flight of ideas
	Thought blocking	Poor eye contact	Thought withdrawal	Recurrent suicide thoughts	Distractibility
	Disorganized speech	Increased latency response	Being controlled	Psychomotor retardation	Poor judgement
	Age of onset	Stupor	Visual hallucinations	Hypersomnia	
	Unusual behavior	Rigidity	Tactile hallucinations	Decreased weight	
			Olfactory hallucinations	Insomnia	
			Persecutory delusions		
			Ideas of reference		

and demographic and clinical classification see Tables 3 and 4, respectively.

Cluster 1 was the largest group of the six, including 33.1% of the patients. Patients presented with the second highest number of disorganization symptoms, the highest number of negative symptoms and the second highest number depression symptoms, and by far the highest number of mania symptoms. The fact that both depression and mania are high in this class can be understood bearing in mind that these are life-time rating of symptoms. Sixty-one percent of the bipolar disorder I patients and 52% of the schizo-affective disorder patients were represented in this group.

The second cluster included 26% of the patients. Patients showed low numbers of disorganization symptoms, some positive and mania symptoms, substantial negative and the highest number of depression symptoms. Sixty-seven percent of the 'psychotic depression' patients fell into this group. There was a significantly higher percentage of females as compared to the other clusters (Chi square=36.8, df=5, p<0.001) and the second highest number of married people.

The third cluster included 14% of the patients. Patients showed the highest number of disorganization and positive symptoms the second highest number of negative symptoms but almost no depression or mania symptoms. Forty percent of the patients with 'schizophrenia-disorganized type' were classified in this group. This group also was less educated (see Table 5) (F=4.2 df=5, p=0.001) and suffered the highest number of episodes, although the latter may be due to their higher age.

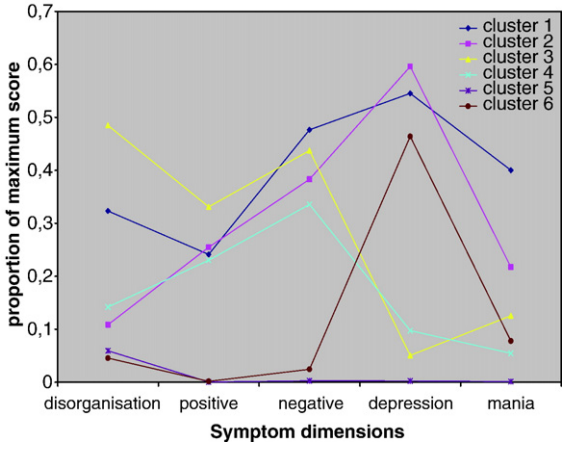

Fig. 1. Symptom profile of six latent classes.

Table 3
Assignment (%) of DSM IV diagnosis in the 6 clusters

Diagnosis	Cluster					
	1	2	3	4	5	6
Bipolar disorder I	61.1	21.5	4.9	1.4	5.9	5.3
Bipolar disorder II	40.0	35.7	0.1	4.3	0.8	19.2
Brief psychosis	25.9	36.8	12.5	15.3	6.0	3.4
Catatonic schizophrenia	18.8	10.8	24.2	37.0	8.9	0.2
Delusional disorder	6.9	25.4	8.8	20.0	7.5	31.4
Depression	5.1	17.3	0.0	0.8	27.0	49.8
Disorganized schizophrenia	36.4	6.1	40.1	9.5	7.6	0.2
Drugs induced psychosis	27.1	19.8	11.7	16.0	17.1	8.3
Schizophreniform disorder	33.2	24.5	10.5	25.1	2.5	4.2
Miscellaneous	11.0	13.2	2.8	2.4	49.8	20.8
Paranoid schizophrenia	34.6	26.7	15.9	16.5	4.4	2.0
Psychosis NOS	24.7	39.2	6.4	18.8	5.2	5.7
Psychotic depression	12.9	67.8	0.1	2.7	0.0	16.5
Residual schizophrenia	35.7	22.1	15.8	23.3	2.8	0.3
Undifferentiated schizophrenia	33.2	20.1	22.6	13.5	7.2	3.4
Schizoaffective disorder	54.1	32.5	6.3	1.2	4.5	1.4

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Table 4
Meta-analysis of relative importance of the symptom dimension in the current and previous LCAs to the delineation of psychosis subgroups

	Utrecht (N=1054)	Kendler '98 (N=343)	Kendler '97 (N=580)	Peralta (N=660)	Mean (SD)
Disorganization	0.336	0.290	N/A	0.263	0.296 (0.03)
Positive	0.160	0.239	0.080	0.015	0.123 (0.08)
Negative	0.337	0.313	0.341	0.467	0.364 (0.05)
Depression	0.348	0.678	0.088	0.297	0.353 (0.16)
Mania	0.569	0.759	0.320	0.192	0.460 (0.20)

Presented numbers are R^2.
Kendler '98 (Kendler et al., 1998).
Kendler '97(Kendler et al., 1997).
Peralta (Peralta and Cuesta, 2003).

The fourth cluster included 14% of patients. Patients showed low numbers disorganization symptoms, substantial negative and positive symptoms, and a low number of mood symptoms. This group was the youngest (although the difference was not significant) and included 37% of the catatonic schizophrenia patients.

Cluster 5 included 7% of the patients. It mainly represented patients with hardly any psychotic symptoms. It contained less than 2% of the schizophrenia patients and about 50% of the miscellaneous patients. Patient in this group suffered significantly fewer episodes compared to all other groups (Kurskal–Wallis, with post hoc Chi square; Chi square=32.14, df=5, p<0.001).

The sixth cluster included 6% of the patients. Patients showed few symptoms apart from depression. Fifty percent of the depression patients were represented in this group as well as around 30% of the delusional disorder patients. These patients had a significantly higher age of onset (F=31.0, df=5, p=<0.001) and a higher percentage were married (Chi square=68.9, df=5, p<0.001) compared to the other groups (see Table 5).

3.3. Meta-analysis

Table 4 shows the relative importance of different symptom dimension in the delineation of cluster from the current (Utrecht) and previous analysis presented by R^2. Overall, mania was the best discriminator of subgroups of psychosis.

4. Discussion

We present a six-cluster division of psychotic phenotypes based on a fully data-driven procedure. The clusters were derived by means of latent class analysis (LCA) from a large sample of patients (N=1056) rated by two psychiatrist by means of standardised diagnostic interview (CASH). Mood symptoms, rather than psychotic symptom types, contributed the most to the delineation of subgroups of psychosis patients in this LCA, and in previous LCAs.

This study is the first fully data-driven analysis of the psychosis phenotype in a large sample (N=1056). We have captured all the information on symptoms obtained by two psychiatrists by means of standardised diagnostic interview (CASH) by applying factor analysis,

Table 5
Overview of characteristics of the six clusters

Cluster	N	Mean age (SD)	No. of male (%)[a]	Mean age onset (SD)	No. of episode (SD)	Married (%)[a]	No. of years education (SD)
1	350	31.5 (10.3)	247 (70.6)	23.97 (7.6)	2.3 (1.9)	37 (10.7)	11.6 (3.0)
2	271	32.6 (11.2)	167 (61.6)[b]	28.4 (10.0)	1.7 (1.7)	49 (18.4)	12.2 (3.1)
3	142	39.1 (15.9)	111 (78.2)	25.5 (9.5)	2.9 (2.6)	13 (9.3)	10.9 (3.1)[c]
4	153	31.3 (11.7)	110 (71.9)	26.5 (9.1)	1.9 (2.0)	12 (8.1)	11.5 (2.6)
5	78	36.2 (14.6)	60 (76.9)	36.1 (14.6)[d]	0.9 (0.9)[b]	1 (1.3)	13.2 (2.7)
6	62	38.5 (11.5)	26 (49.9)	35.3 (13.3)[d]	2.2 (2.0)	24 (52.2)[e]	12.5 (2.9)

[a] Percentages are true percentages after exclusion of missing values.
[b] Kurskal–Wallis, with post hoc Chi square, p<0.001, compared to groups 1–4 and 6.
[c] ANOVA, p=0.001, compared to groups 1, 2, 4, 5, and 6.
[d] ANOVA, p<0.001 compared to groups 1–4.
[e] Chi square, p<0.001, compared to group 1–5.

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representing each 'symptom type' by a sumscore for each factor, rather than selecting an arbitrary subset of 'important' symptoms. In contrast to most factor analyses using numerical techniques (sometimes for ordinal data of uncertain validity), we employed a factor analysis for categorical responses and used lifetime ratings for the presence or absence of symptoms. The fact that the derived symptom dimensions reflected earlier factor-analyses adds to the validity of this study. One other factor analysis for categorical responses has been published ($N=1043$) (McGrath et al., 2004). In addition to a positive, negative and disorganization factor they found an early onset/developmental factor instead of a separate depression and mania factor: We did find age of onset to be an important contributor to the largest "disorganization" factor.

There is substantial overlap between the identified patient groups in our analysis and previous analyses in somewhat smaller groups (Peralta and Cuesta, 2003; Kendler et al., 1998, 1997) ($N=343$, $N=580$ and $N=660$ respectively). The first cluster, including patients with a high number of mania symptoms, resembles the cluster named bipolar-schizomania (Kendler et al., 1998) or schizobipolar (Peralta and Cuesta, 2003) in previous LCAs. Compared to these studies we found higher numbers of negative symptoms, probably the result of a broader definition of negative symptoms in our analysis. The relatively high numbers of disorganization symptoms in this cluster was partly due to the early age of onset in this group, which loaded in the disorganization dimension. The second cluster, with the highest depression score, shows considerable overlap with the schizodepression groups of previous LCAs (Peralta and Cuesta, 2003; Kendler et al., 1998, 1997). The presence of a "schizodepressive" subgroup of schizophrenia patients in all 3 LCAs conducted to date, is further support for the importance of mood symptoms in psychotic patients. The third cluster, including patients with the highest number of disorganization and positive symptoms and a limited number of mood symptoms, resembles the "hebephrenia" group of Kendler (Kendler et al., 1998). There are fewer mania symptoms in our group, although we note that distractibility and unusual behavior, included in the 'mania' symptom in their study, loaded on the 'disorganization' dimension in our factor analysis, which may account for this difference. The fourth cluster shows many similarities with the classic "schizophrenia" groups of previous LCAs (Peralta and Cuesta, 2003; Kendler et al., 1998), including patients with low numbers of disorganization symptoms, substantial negative and positive symptoms and low numbers of mood symptoms. In our study only 14% of patients were assigned to this group compared to 26% and 38% respectively in the other studies (Kendler et al., 1998; Peralta and Cuesta, 2003).

In contrast to these LCAs we did not find a cluster with mild positive and negative symptoms and mood symptoms which they called "schizophreniform" and "atypical schizophrenia" respectively (Kendler et al., 1998; Peralta and Cuesta, 2003). Instead we found a cluster that contained most of the patients suffering from a non-psychotic illness, a group of patients not present in previous studies. It therefore appears that the presence of a non-psychosis group in our data has led to the relocation of patients with mild psychotic symptoms to the non-psychosis subgroup and the other subgroups. Cluster 6 strikingly resembles Kendler et al.'s (1998) "major depression" subtype of psychosis. These patients showed almost exclusively depressive symptoms. This group included 31% of the delusional disorder patients and 50% of the depression patients (although only 16% of the psychotic depression patients). Consistent with Kendler's findings, this group had a significantly higher age of onset and a higher percentage of married subjects compared to the other groups.

Overall, our data point to the presence of distinct subgroups within the current schizophrenia concept. The partial replication of earlier LCAs supports the existence of subgroups of psychosis patients with fairly consistent patterns of symptoms resembling bipolar and depression subgroups. The presence of a group of patients in our data that does not suffer from any psychotic symptoms points to the ability of this model to distinguish between psychosis and non-psychosis patients.

Our data and the meta-analysis of previous studies show that mania symptoms contribute the best discriminators of subgroups of psychosis patients. It is therefore not surprising that Kraepelin picked up on this difference in the 19th century. However, our delineation is inconsistent with the Kraepelinian distinction between schizophrenia and bipolar disorder (Crow, 1998; DeLisi, 1999; Craddock et al., 2006): the subgroup of psychosis patients with many mania symptoms suffered with high levels of disorganization and negative symptoms as well. A substantial proportion of patients with a diagnosis of schizophrenia according to the DSM IV (34%) and the majority of bipolar disorder I patients (61%) were included in this group, which would suggest that the boundaries between bipolar disorder and schizophrenia according the DSM IV are not optimally defined. The presence of a "bipolar-schizomania" (Kendler et al., 1998) or schizobipolar (Peralta and Cuesta, 2003) subgroup is consistent with recent findings by Green et al. (2005) who demonstrated an

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association of the core haplotype of neuroregulin 1 with cases that had both manic episodes and mood incongruent psychotic features.

The second most discriminating symptom dimension in our analysis and that of Kendler et al. (1998) was depression. In the meta-analysis it was the third contributing factor, just after negative symptoms. There were also two subgroups of psychosis patients that stood out through the presence of depressive symptoms, those with marked negative and positive symptoms in cluster 2 (the "schizodepression" cluster), and those with almost no other symptoms in cluster 6 (the "major depression" cluster) (Kendler et al., 1998). The importance of depressive symptoms in psychosis patients is consistent with a shared genetic vulnerability for schizophrenia with major depression (Maier et al., 1993) and underlines the importance of mood symptoms in delineating subgroups of psychotic disorders. Williams et al. (2006) demonstrated an association of variation at the DAOA/G30 locus with mood episodes in a combined group of schizophrenia and bipolar disorder patients.

Negative symptoms are the third most discriminating symptoms in our and Kendler et al.'s (1998) analysis, and the second most important according our meta-analysis. It is possible, indeed likely, that negative symptoms reflect the persistent symptoms on which Kraepelin originally based his distinction between bipolar disorder and dementia praecox; the absence of negative symptoms was typical of the two subgroups (cluster 5 and 6) that included the lowest number of schizophrenia patients.

Overall we found that a majority (65.1%) of the patients, including those with a diagnosis of schizophrenia, were part of a subgroup with affective symptoms. This reiterates the question weather the Kreapelinian distinction between schizophrenia and affective disorders holds (Craddock and Owen, 2005). Studies in first episode and high risk subjects have previously pointed out that affective symptoms are a prominent part of schizophrenia (Hafner et al., 2005; Owens and Johnstone, 2006) in the early stages of the disease. The presence of affective symptoms in the later stages has also been widely recognized and has lead to the inclusion of the diagnosis post-psychotic depression in the appendix of the DSM IV. Our data provide further support for the notion that affective symptoms are an intrinsic part of schizophrenia.

In addition to a shared genetic vulnerability of schizophrenia and affective disorders there are other mechanisms that are likely to contribute to this association of psychotic and affective symptoms. Apart from the normal comorbidity with unipolar depression there are likely to be factors such as social deprivation, marginalization and the reaction to the diagnosis of schizophrenia that inflate the risk of depression. In addition, post-psychotic depression may arise as a result of the stress induced by the psychosis (Siris, 2000). Thirdly there is evidence of an association between depression and substance abuse that may also inflate the prevalence of depression in psychosis patients (Siris et al., 2001).

Several limitations of this study should be noted. Firstly, we cannot rule out selection bias. Although we aimed to include all patients referred to our ward with a suspected psychosis, it is possible that inclusion of other groups of patients would have altered the outcome. However considering the similarities with previous LCAs (Peralta and Cuesta, 2003; Kendler et al., 1998, 1997) there seems to be substantial stability of the clusters. There are also limitations of the applied statistical techniques. Latent class analysis assumes local independence within the resultant clusters; this is certified in our dataset by means of a check of the residual bivariate relationships between the observed variables within classes. However LCA can only describe, and does not prove, the existence of clusters. The meta-analysis of the relative importance of the symptom groups to the delineation of subgroups of psychosis is vulnerable to bias as a result of the availability of symptoms over the 4 studies. For instance, it was not possible to calculate the importance of the disorganization dimension in one of the studies (Kendler et al., 1997). The meta-analysis therefore reflects the contribution of some signs of our symptom dimensions to the latent class structure of the particular study. The differences between the studies may to a large extent be the result of this limitation. However there is no reason to assume these differences had a systematic effect. The major limitation of this study however is the lack of any heritability estimate. Twin data, and to a lesser extent family data could provide a clue whether the derived subgroups of psychosis show a stronger relationship to genotype than current classifications. Indeed, the incorporation of genetic data into the analysis of psychosis subgroups may lead to the identification of psychotic subgroups with improved value for psychiatric genetic research (Cardno et al., 2002).

Overall this study supports the presence of distinct subgroups in psychosis patients, in particular those with major mood symptoms, which may facilitate the unravelling of the genetics of psychotic illnesses.

5. Contributors

M.P.M. Boks and S. Leask have conceived the idea and methodology of the paper. K.S. Vermunt particularly contributed to the methodology and statistical

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analysis. R.S. Kahn contributed to the data acquisition, methodology and write up. All authors contributed to and have approved the final manuscript.

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