



Beyond symptom dimensions: Schizophrenia risk factors for patient groups derived by latent class analysis

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ABSTRACT

Introduction: Patients grouped by latent class analysis of symptoms show some consensus between studies, and may be less etiologically heterogeneous than current diagnoses. If so, the effect size of 'neurodevelopmental' risk factors may be greater than in equivalent DSMIV diagnostic groups.

Method: Two hundred fifty six individuals with neurodevelopmental risk factors recorded in the National Child Development Study (1958) UK birth cohort were grouped by data-driven illness subtypes, derived previously in over 1000 individuals. The effect sizes of these risks were compared between data-derived and DSMIV schizophrenia (295.x) groups.

Results: Compared to DSMIV schizophrenia, the data-driven subtype broadly characterized by the presence of psychotic symptoms in the absence of affective symptoms showed significantly greater effect sizes in eight out of thirteen continuously-rated risk factors: birth weight, cognition, childhood behavioural problems, and neurological softsigns including handedness.

Conclusion: A data-driven subgroup of schizophrenia patients, characterized as lacking co-morbid depressive symptoms, is less heterogeneous with respect to neurodevelopmental etiology.

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1. Introduction

While discrete psychiatric diagnoses are useful in the clinical field, they remain unreliable between rating scales (e.g. for schizophrenia see Jansson et al., 2002) and unstable over time (Baca-Garcia et al., 2007). Dimensional measurement of symptom type and intensity may offer greater clarity, and possibly validity, than the historical categorical constructs enshrined in current diagnostic systems such as DSMIV. The dimensional approach can be seen as stemming from Kraepelin's original distinction between affective and non-affective psychoses (Kraepelin, 1971): The major mental disorders such

as depression, bipolar disorder, schizoaffective disorder, and schizophrenia are just different groups of patients, located in different parts of a two-dimensional 'symptom space' of affective and psychotic variation. In the last two decades, mathematical investigation of the way symptoms vary together has supported the idea that symptoms vary not in two, but in five dimensions of positive symptoms, negative symptoms, symptoms of thought disorganization, depression and manic mood (Liddle, 1987; Andreasen et al., 1995; Lindenmayer et al., 1995; Toomey et al., 1997). However, even if a patient's symptoms are best described by scores on five symptom dimensions, the question still remains how patients group together in 'diagnostic' clusters within this space.

Previously, we used a data-driven process to derive five symptom groups, or subtypes of psychosis (Boks et al., 2007), which resemble the 'schizobipolar', 'schizodepression',

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'hebephrenia', 'classic schizophrenia' and 'major depression' groups described previously by Kendler and others (Kendler et al., 1998; Peralta and Cuesta, 2003; McGrath et al., 2004). While some of these groups superficially resemble familiar historical diagnostic groups, others are novel. There is considerable sharing of DSMIV diagnoses (including bipolar disorder and depression) within each group and none of them are mere DSMIV duplicates. New subtypes like this may reduce the heterogeneity of schizophrenia, and serve as alternative phenotypes in psychiatric etiology research.

Heritability estimates for these new subtypes could test shared genetic origins and thus suitability as phenotypes in genetic research (McGrath et al., 2009; Boks et al., 2008). An alternative way to study the utility of these subtypes is to look at shared pathology – for example brain imaging findings – or etiology. For the purpose of this study we looked at an aggregation of psychosis risk factors within the subtypes. The field of psychosis research is dogged by numerous risk factors of small effect (see Table 5.2 in Cannon et al., 2003), which could reflect heterogeneity in our current definition of schizophrenia. If these new subtypes more accurately reflect symptom variation in patients, the previously-identified risk factors of modest effect could have a larger effect in a subtype for which they truly predispose. For example, a subtype of largely 'neurodevelopmental' origin should show larger effects for previously-identified 'neurodevelopmental' risk factors for schizophrenia.

We tested this idea in the UK 1958 National Child Development Study (NCDS), in whom DSMIV diagnoses and prospectively-gathered 'neurodevelopmental' risk factors (Murray and Lewis, 1987) were known (Done et al., 1994; Leask and Crow, 2006). We hypothesized that bigger effects would be seen solely for the data-driven subtype 'classic schizophrenia', characterized as 'psychosis in the absence of affective symptoms', as this subtype most closely resembles schizophrenia (DSMIV) for which these risk factors are felt to be most specific. If this group shares a neurodevelopmental etiology, and is more precisely defined by shared variation in symptoms, rather than historical concepts of uncertain validity, the effect size of these risk factors should be greater. We maintained the power of our previous study by mapping the subtypes derived from a patient sample of 1056 onto the smaller numbers of patients in the birth cohort.

2. Method

In our original analysis (Boks et al., 2007) we used lifetime-ever symptom ratings from the Comprehensive Assessment of Symptoms and History (CASH) interview (Andreasen et al., 1992) administered to a Dutch sample of 1056 patients referred with psychosis, reducing the 120 symptoms to 5 factor scores using factor analysis, then using factor sumscores from each patient as ordinal indicators in a latent class analysis (LCA – a statistical method that identifies homogeneous groups, or classes, from multivariate data), yielding five diagnostic subtypes.

This process was blind to clinical diagnosis. The factor analysis explored how symptoms vary 'together', and concluded that there are five factors – mania, depression, positive symptoms, negative symptoms and disorganization – which can be considered independent axes of variation. We then used

LCA to consider how patients group together in this new 'symptom space' (see Supplementary Fig. 1 in the Appendix) which concluded there are five patient subgroups, agreeing to a large extent with previous work in this field. A review including previous studies of this type concluded that the symptoms that most clearly distinguish between the types of psychosis are affective, not psychotic (Boks et al., 2007).

We reproduced these psychosis sub-groups in 256 members of the NCDS birth cohort (Shepherd, 1985) admitted to mainland UK psychiatric hospitals between 1974 and 1995 whose case notes had been perused to obtain consensus-rated lifetime-ever DSMIV diagnoses, and OPCRIT (operational criteria checklist for psychotic symptoms, McGuffin et al., 1991) symptom items (Done et al., 1994; Leask and Crow, 2006). We calculated factor sumscores using OPCRIT items that were equivalent to the CASH questionnaire items in our original factor analysis. Patients were assigned to the previously-identified subtypes based on the parameter estimates from the original LCA as implemented in version 4.5 of the Latent Gold software (Vermunt and Magidson, 2008).

A number of 'neurodevelopmental' risk factors were recorded in childhood for these patients in the 1958 cohort database (Table 1). These include several neurological 'soft signs', minor neurological signs indicating non-specific rather than focal cerebral dysfunction, which are associated with psychotic illness (Dazzan and Murray, 2002). We compared the effect sizes of these risk factors for both the new subtypes, and for a group with consensus-derived case note diagnoses of DSMIV schizophrenia (295.xx).

After transforming the risk factor scores into z-scores, a 2×13 (two models, thirteen risk factors) design mixed-effects ANOVA was performed to test for differences in risk factor effects between the DSMIV and the novel diagnoses. The significances quoted are for comparisons between models with the DSM diagnosis as the only predictor, and both the DSM and the novel diagnosis as predictors, i.e. testing whether the new diagnosis yielded a significant improvement in prediction of the risk factors. Analyses were performed by the R package and Latent Gold 4.5 (Vermunt and Magidson, 2008; R Development Core Team, 2006).

3. Results

The birth cohort patients were 50% male. The sharing between diagnostic types is shown in Table 2. The mean z-

Table 1

Risk factors previously identified in the birth cohort dataset (Done et al., 1994; Crow et al., 1995; Leask and Crow, 2001).

1	Birth weight
2	Verbal IQ at 11
3	Non-verbal IQ at 11
4	Bristol Adjustment Guide, score at 7
5	Bristol Adjustment Guide, score at 11
6	Relative Hand Skill laterality index at 11
7	F1: Left preference
8	F2: Unsteadiness on feet
9	F3: Fine coordination
10	F4: "Neurological problem"
11	F5: Tics/twitches
12	F6: Speech impairment
13	F7: Incontinence

F1-7 = Neurological Soft Sign Factor sumscores at age 11.

scores for each risk factor by diagnostic grouping are shown in Fig. 1 along with the significances of ANOVAs comparing the two model fits. Note that signs have been changed for risk factors 1 (birth weight), 2 (verbal IQ), 3 (non-verbal IQ) and 6 (relative hand skill), as these would be expected to be decreased, not increased, in schizophrenia.

For the DSMIV 295.x diagnosis, we see the expected effects: Reduced birth weight, verbal and non-verbal performance, and relative hand skill. Social (mal) adjustment is greater, and there are more neurological soft-signs, with the exception of 'tics and twitches'. The majority of the risks show z-scores much greater for DSMIV than for most of the subtypes, some subtypes even showing effects of the opposite sign.

The exception is LCA subtype 'classic schizophrenia', best described as 'psychosis in the absence of mood symptoms' (Boks et al., 2007). Subjects in this group show effects that are similar or greater in 12 of the 13 measures, significantly greater, up to more than twice those for subjects with DSM-IV diagnoses of schizophrenia, in 8 of the 13 measures.

Table 3 summarizes the counts (cases with and without the risk factors) for the 3 largest effects. None of these ratios differed significantly by chi-squared testing. The specificity of the risk factors ('true positive'/'true positive' + 'false negative', e.g. from Table 3, sensitivity of 'neurological soft sign factor 2' for DSMIV schizophrenia = 21/21 + 4 = 0.84) were higher for the LCA subtype. The positive predictive values (PPV = 'true positive'/'true positive' + 'false positive') were uniformly smaller for the LCA subtype, unsurprising since we have fewer cases/'true positives', but pretty much the same (huge) number of 'false positives', for each risk factor.

Although the numbers of cases was even smaller, we then explored this LCA subtype compared with conventional DSMIV schizophrenia subtypes, instead of just 'schizophrenia'. The LCA subtype again showed superior effect sizes in the majority of risk factors, and the effects of adding this LCA subtype to each model were significant (vs. paranoid $p = 0.03$, vs. disorganized $p < .001$, vs. undifferentiated $p < 0.001$).

4. Discussion

This is the first study attempting to validate purely data-driven diagnostic subtypes by looking at risk factors. We have shown that whereas most of the risks factors showed no significant differences between the subtypes and a DSMIV 295.xx diagnosis, the subtype characterized by psychosis in the absence of mood symptoms showed significantly greater scores for 8 out of the 13 measures. This subtype might constitute a

more 'pure' form of schizophrenia with respect to neurodevelopmental etiology.

This does not merely replicate previous observations that neurodevelopmental risks are more associated with psychosis without affective symptoms (e.g. Hultman et al., 1999), since the grouping procedure used here was purely data-driven, blind to diagnostic mores.

The study has strengths. The 1958 birth cohort risk factor measures rated at ages 7 and 11 were systematically and prospectively gathered, and thus lack recall biases. Study power was maximized by building upon the LCA from our original study, in a large sample of patients with diverse diagnoses (not just schizophrenia), instead of determining groups de novo in the smaller group of cohort patients. While OPCRIT and CASH differ in some ways, such as symptom duration required to be rated, and focus upon different symptom domains, both seek to incorporate all available information, and differences in detail for a particular symptom are reduced when considering symptom groups.

There are clear methodological weaknesses too. It is perhaps to be expected that any study designed to accumulate the large amounts of symptom data needed to create subtypes will seldom be the sort of study that prospectively records risk factors. The symptom ratings were derived from case notes, never the most reliable of sources, although comparisons were improved by both the OPCRIT ratings and the DSMIV consensus diagnoses being based upon the same notes. Significant publications have already derived from these casenote diagnoses in birth cohort data, since this tends to be the only source of clinical diagnostic data in birth cohort databases. It may also be considered that 'lifetime-ever' symptom lists do not capture clinically, genetically or otherwise etiologically-important variations in presentation. The cohort data also limited this study to examine neurodevelopmental factors; there is no indication whether the LCA subtypes show greater effects of other risk factors e.g. childhood trauma, cannabis exposure or genes.

Cohorts are huge, but the numbers of cases are small, which weakens this study. In some instances the number of cases is less than the number of predictors, and interpretation of differences clearly becomes somewhat subjective, whatever the p -values are. Correction for multiple comparisons (for example by the Bonferroni method) therefore needs consideration, and would render the interesting finding non-significant. However, patients were assigned to one subtype only and therefore the groups were not independent, making such correction perhaps too stringent. Also, post-hoc analysis

Table 2

Table comparing diagnoses (DSMIV and LCA groups) in NCDs cohort sample.

	LCA: No diagnosis	"Schizophrenia"	"Hebephrenia"	"Schizobipolar"	"Schizodepression"	"Depression"
DSMIV: "No diagnosis"	123	0	0	0	1	29
Schizophrenia	3	19	19	2	0	2
Other psychosis (drugs etc)	6	2	10	1	1	1
Affective psychosis	0	0	5	3	5	0
Other (mainly Anxiety)	6	1	2	0	0	0
Affective disorder without psychosis	6	1	0	1	3	4
	144	23	36	7	10	36

N.B. The LCA subtypes have names (in quotes) to give a flavour of symptoms that are to the fore, but it should be noted that these are not merely subsets of conventional diagnoses, and include patients from diverse diagnoses.

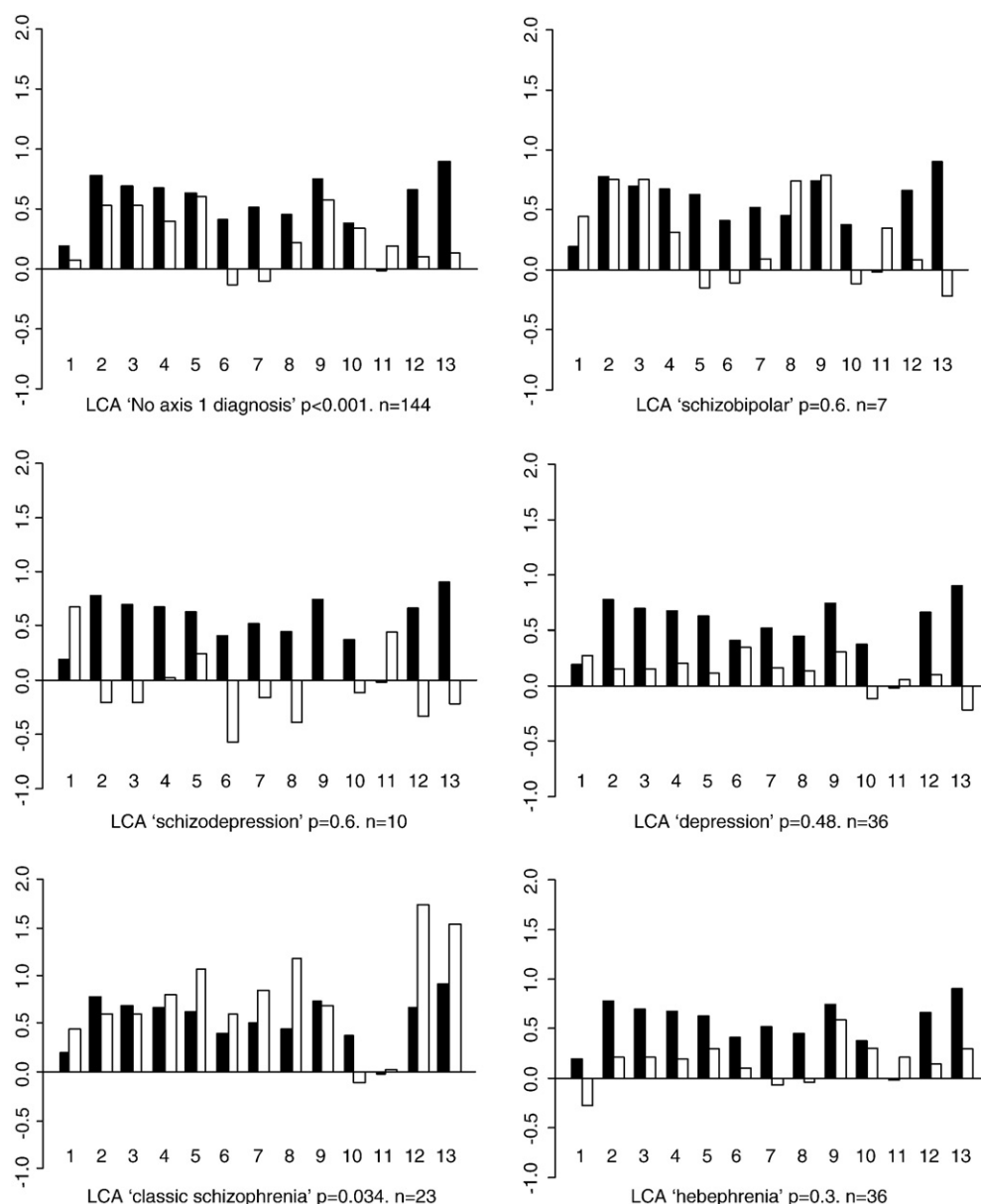


Fig. 1. Mean z-score for each risk factor: DSMIV 295.x (black) and every subtype defined by the LCA (white). *p*-value refers to the difference between ANOVAs with and without the novel diagnostic grouping. NB. For clarity, the sign of the effect for birth weight, IQ and relative hand skill have been reversed, as these are anticipated to be decreased, not increased, in schizophrenia.

Table 3
Counts of cases.

	F2	F6	F7
DSMIV	4:21	18:7	19:6
LCA	0:8	4:4	5:3

"Number of cases without risk factor": "Number of cases with risk factor", for the largest differences i.e. the 8th, 12th and 13th risk factors, for DSMIV schizophrenia and LCA 'classic schizophrenia'.

NB. The numbers of cases have dropped from Table 2, as risk factor data was not available in the cohort database for all cases. Interpretation of ratios when numbers are so small, is clearly somewhat subjective.

looking at all 6 subtypes added to 6 comparable DSM categories confirmed a significant effect ($p = 0.016$). In small numbers like this, there remains too the risk of type II error. However, the smaller risk effects in the 'no diagnosis' group is to be expected, and also achieves significance, suggesting that this study is seeing real effects.

Overall, these findings suggest that delineation of subtypes using latent class analysis in this way can meaningfully reduce the etiological heterogeneity of schizophrenia.

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None.

Contributors

Dr Leask carried out the initial diagnostic data-gathering in the birth cohort, contributed to the study design, literature review, statistical analysis and the manuscript. Dr Vermunt performed the Latent Class analyses. Dr Done, Professor Crow and Dr Blows contributed to the diagnostic data-gathering in the birth cohort. Dr Boks contributed to the study design, literature review, statistical analysis and the manuscript.

Conflict of Interest

The authors declare they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.schres.2009.09.017](https://doi.org/10.1016/j.schres.2009.09.017).

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