Polygenic burden analysis of longitudinal clusters of psychopathological features in a cross-diagnostic group of individuals with severe mental illness

E.C. Schulte1,2, I. Kondofersky3, M. Budde1, K. Adorjan1,2, F. Senner1,2, H. Anderson-Schmidt4, K. Gade2, U. Heilbronner2, J. Kálmán1, S. Papiol2, F. J. Theis3, F. J. Theis3, P. G. Falkai1, N. S. Mueller3, T. G. Schulze2

1Klinik für Psychiatrie und Psychotherapie, Ludwig-Maximilian Universität München, Munich, Germany
2Institute of Psychiatric Phenomics and Genomics (IPPG), Medical Center of the University of Munich, Munich, Germany
3Institute of Computational Biology, Helmholtz Zentrum München, Munich, Germany
4Department of Psychiatry and Psychotherapy, University Medical Center, Georg-August University, Göttingen, Germany

Background

Bipolar disorder (BD), schizophrenia (SZ) & schizoaffective disorder (SZA) are associated with severe psychiatric symptomatology, often with overlapping psychopathological features between diagnostic groups (e.g. Craddock & Owen, 2010 Br J Psychiatry).

More severe psychopathological features are associated with a less favorable outcome (e.g. Gitlin MJ et al., Am J Psych 1995).


BD, SZ & SZA are common complex genetic diseases with a polygenic genetic architecture in the majority of cases (e.g. Ferreira MA et al., Nat Genet 2008; O’Donovan MC et al., Nat Genet 2008).

Phenotypic heterogeneity poses a challenge to identification of disease mechanism and clinical management — clustering could identify high risk individuals for intensified clinical intervention.

Workflow

(1) Identification of Clusters of Psychopathology
Five clusters were identified as the most stable solution. These comprised individuals who were/had:

(A) stably well
(B) most severe overall psychopathology
(C) psychotic symptoms at baseline
(D) manic symptoms at baseline
(E) chronic low-level symptoms

Clustering was driven by:

(A) PANSS items N2 (emotional withdrawal), N3 (poor rapport), N1 (blunted affect)
(B) IDS-C items 5 (sad mood), 20 (energy level), 16 (self image)
(C) YMRS items 2 (increased motor activity/energy), 6 (rate & amount of speech), 1 (elevated mood)

Results

(1) Identification of Clusters of Psychopathology
Five clusters were identified as the most stable solution. These comprised individuals who were/had:

(A) stably well
(B) most severe overall psychopathology
(C) psychotic symptoms at baseline
(D) manic symptoms at baseline
(E) chronic low-level symptoms

Clustering was driven by:

(A) PANSS items N2 (emotional withdrawal), N3 (poor rapport), N1 (blunted affect)
(B) IDS-C items 5 (sad mood), 20 (energy level), 16 (self image)
(C) YMRS items 2 (increased motor activity/energy), 6 (rate & amount of speech), 1 (elevated mood)

(2) Factors influencing Clustering
Significant influences on Clustering:

- Diagnosis (schizophrenia-spectrum diagnoses more common in clusters B, C and E)
- Disease course
- Global Assessment of Functioning (GAF)
- Work status

(3) No Association between SZ-PRS and Cluster Membership
SZ-PRS loading did not differ between clusters. Cluster membership was not significantly associated with the SZ-PRS in either cluster.

Discussion

- Longitudinal clustering to identify cross-diagnostic homogeneous subgroups of individuals appears to be feasible
- Reason why more severe psychopathological features were not associated with increased genetic risk burden needs to be explored further

Caveats:

- Small, heterogeneous sample over relatively short time frame
- No replication in independent sample
- Clinical relevance?

Disclosure

The authors of this work have no financial disclosures to report.