Polygenic Risk Score Analysis of Trajectories of Cognitive Performance in Psychiatric Patients

Sabrina K. Schaupp[1,2], Monika Budde[1], Ivan Kondofersky[3], Sergi Papiol[1,4], Urs Heilbronner[1], Katrin Gade[5], Heike Anderson-Schmidt[5], Janos L. Kalman[1,4,6], Fanny Senner[1,4], Kristina Adorjan[1,4], Till F.M. Andlauer[7], Marcella Rietschel[8], Franziska Degenhardt[9,10], Nikola S. Müller[3], Fabian J. Theis[3,11], Thomas G. Schulze[1]

[1]Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany
[2]Clinic for Psychiatry, Psychotherapy and Psychosomatics, Augsburg, Germany
[3]Institute of Computational Biology, Helmholtz Centre Munich, Germany
[4]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany
[5]Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, Goettingen, Germany
[6]International Max Planck Research School for Translational Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany
[7]Department of Translational Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany
[8]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany
[9]Institute of Human Genetics, University of Bonn School of Medicine & University Hospital Bonn, Bonn, Germany
[10]Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany
[11]Center for Mathematics, Chair of Mathematical Modeling of Biological Systems, Technical University of Munich, Germany

Background

Cognitive deficits are a common symptom in severe mental illnesses like bipolar disorder (BD), schizoaffective disorder (SZA) and schizophrenia (SZ) [1, 2] and are discussed as potential endophenotypes [3] for these disorders with an overlapping psychopathology and polygenic background. While there is more cross-sectional research on the affected cognitive domains as well as the degree of impairment [4, 5, 6], less is known about the long-term course of cognitive deficits [4, 7]. Since cognitive deficits are most prominent in SZ, recent studies also investigate a possible association between polygenic risk scores for SZ (SZ-PRS) and cognitive abilities [8, 9, 10]. However, the long-term course has not been addressed yet. The aims of our study are the identification of cross-diagnostic **longitudinal clusters of cognitive performance (I) and analyze a possible association between these long-term clusters and SZ-PRS (II)**.

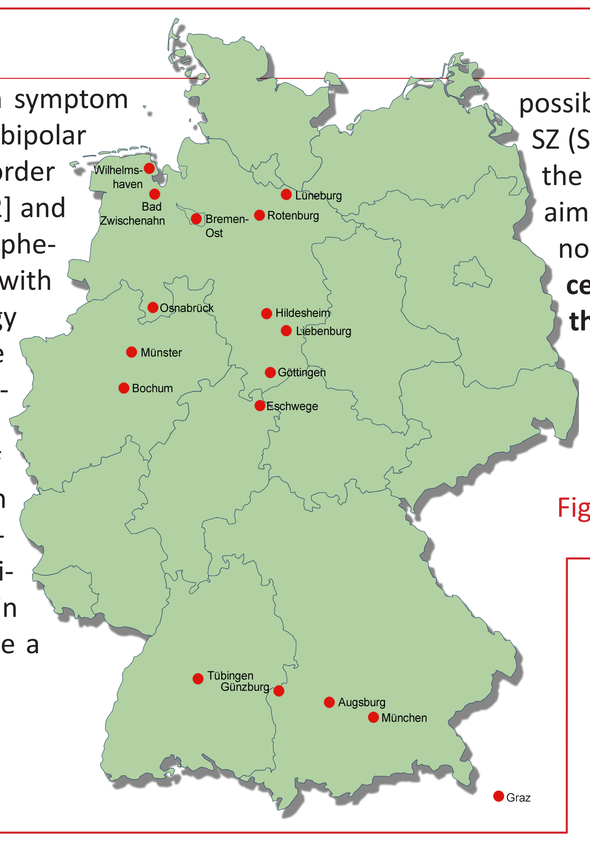

Figure 1. Recruitment network (KFO241/PsyCourse)

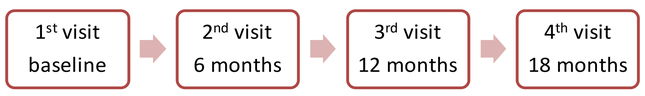

Figure 2. Longitudinal study design

Method

Project: KFO241/PsyCourse (www.kfo241.de; www.psycourse.de)

- Multicenter study in Germany & Austria (Fig.1)
- DSM-IV-diagnosis: BD, SZA, SZ
- Longitudinal and naturalistic study design (Fig. 2)
- Deep phenotyping; blood samples
- Cognitive tests: VLMT (verbal learning memory test), TMT A/B, digit-symbol-test, digit span forward and backward

Sample:

- N = 258
- sex: 45% female
- Mean (SD) age at baseline: 45.5 (12.3) yrs.
- Diagnoses: BD-I: 31%, BD-II: 7%, SZA: 12%, SZ: 50%
- Mean (SD) age at onset: 31.1 (11.8) yrs.
- Mean duration of illness: 14.5 (10.7) yrs.
- Setting at baseline: outpatient: 69.8%, day patient: 3.5%, in-patient: 24.8%, none: 1.9%
- Data from 16 centers

I) DEFINITION OF LONG-TERM COURSE OF COGNITIVE ABILITIES

Methods:

Step 1: Dimension reduction

Principal component analysis on the cognitive data (controlled for age, education, center), with nine variables each measured at three time points (Fig. 3) ➡ 2 dimensions, "general cognitive ability (GCA)" and "consolidation (CON)"

Step 2: Longitudinal clustering

Identification of cross-diagnostic long-term clusters of cognitive performance with FlexMix

Results:

Four different clusters have been identified on the dimensions GCA and CON (Fig. 4 & 5).

Clusters have different sizes: Cluster A = 20%, Cluster B = 9%, Cluster C = 27 and Cluster D = 44% There are no significant between-group differences regarding diagnosis, sex, duration of illness and age at onset. Patients in cluster A and C have a significantly lower mean score across all study visits on the global assessment of functioning (GAF) scale (p=.00067) compared to patients from cluster C and are less likely to work full time (p=.029). The mean GAF score also significantly differs between cluster A and D (p=.018). The overall course of illness is rated more severe for patients in cluster A compared to clusters B (p=.047) and C (p=.017). All reported p-values are corrected for multiple testing (FDR correction).

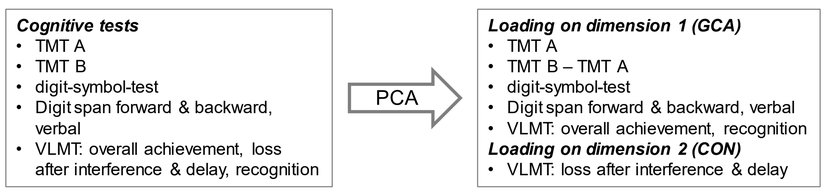

Figure 3. Reduction of dimension of quantitative data

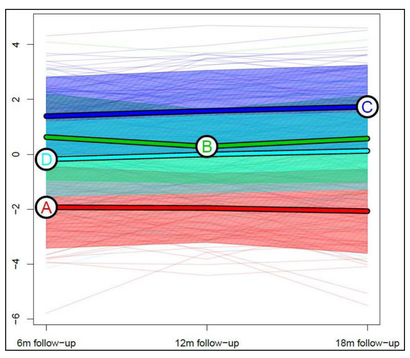

Figure 4. Clusters on GCA: A = poor performance, B = average with loss, C = good performance, D= average

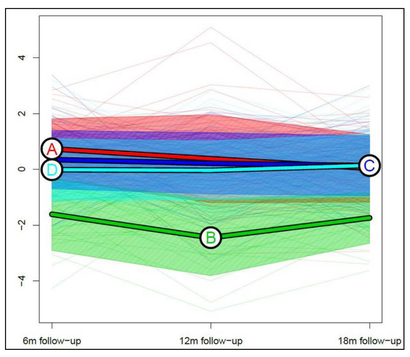

Figure 5. Clusters on CON : A= average with loss, B= poor performance, C = average, D = average

II) ASSOCIATION OF LONGITUDINAL CLUSTERS AND SZ-PRS

Background:

SZ-PRS are associated with cognitive abilities in the general population and in patients. How much variability of cluster membership in the dimensions GCA and CON can be explained by SZ-PRS?

Methods:

Genotyping and imputation

- DNA samples genotyped using Illumina PsychChip
- imputed using the 1000 Genomes Phase 3 reference panel

Calculation of SZ-PRS

- calculated for all individuals with PLINK1.07
- allellic effect-sizes and P-values obtained from the PGC2 SZ summary results (SZ Working Group of the PGC 2014, Nature)

Statistical analyses

- multinomial regression of cluster membership on SZ-PRS (11 P-value thresholds)
- covariates: age, age2, sex, age x sex, diagnosis, 5 ancestry principal components

Results:

Ten out of eleven SZ-PRS explain less than 1% of the variability of cluster membership. There is no significant association (Fig. 6).

Figure 6. Multinomial regression of cluster membership on SZ-PRS

References

1) Mark W and Toulopoulou T, Curr Opin Neurobiol, 2016.
2) Kim D et al., Clin Psychopharmacol Neurosci, 2015.
3) Gottesmann II and Gould TD, Am J Psychiatry, 2003.
4) Czepielewski LS et al., Eur Neuropsychopharmacol, 2015.
5) Lee RSC et al., J Psychiatr Res, 2014.
6) Torniainen M et al., J Nerv Ment Dis2012.
7) Budde M and Schulze TG, Harv Rev Psychiatry, 2014.
8) Nakahara S et al., Schizophr Res, 2018.
9) Lencz T et al., Mol Psychiatry, 2014.
10) McIntosh AM et al., Biol Psychiatry, 2013.

Acknowledgements

German Research Foundation (Deutsche Forschungsgemeinschaft; DFG), Grant/Award Numbers SCHU 1603/4-1, 5-1, 7-1, FA241/16-1;
German Federal Ministry of Education and Research (BMBF), Grant/Award Numbers: Integrated Network IntegraMent 01ZX1614K, 01ZX1614G, and 01ZX1614A;
German Federal Ministry of Education and Research (BMBF), BipoLife Network;
Dr. Lisa Oehler Foundation BONFOR Programme of the University of Bonn

Summary

We identified four cross-diagnostic clusters of trajectories (one year) on the two cognitive dimensions GCA and CON over a period of one year. Cluster A shows poor performance on GCA and an average performance on CON compared to the other clusters. Furthermore, patients in cluster A have a lower mean GAF, a lower rate of employment and a more severe course of illness. The performance in Cluster B is average on GCA and poor on CON with a kink in the course, respectively. The course of cognitive performance on dimensions GCA and CON is stable for clusters A, C and D. There is no significant association between cluster membership and the SZ-PRS.

Limitations:

- Short period to define a course, one year with three measurements
- Unknown premorbid status
- Medication effects are not addressed yet

Outlook:

- Increasing power by repeating analyses with updated database
- Comparison to healthy controls
- Define longitudinal clusters based on single tests
- Consider differences in cognitive abilities during acute episodes and euthymic status