**Background**

Bipolar disorder (BD), schizoaffective disorder (SZ-A) and schizophrenia (SZ) are severe mental illnesses that share - at least in parts - psychopathological features and an underlying polygenic nature. One characteristic of all three diagnoses is the highly variable disease course and outcome. This heterogeneity is one of the biggest challenges in studying the underlying biological mechanisms. Therefore, defining more homogeneous subgroups across diagnoses is a promising approach. However, there are no clear criteria as how to define a “good” or “poor” course of illness as different domains can be considered such as psychopathology, cognitive performance, psychosocial functioning, or quality of life (QoL).

**Aims**

I) Identification of cross diagnostic longitudinal clusters of patients as a basis for biological studies

II) Testing the association of these clusters with schizophrenia-polygenic risk scores (SZ-PRS)

**I) Identification of longitudinal clusters**

**Project:** KFO241/PsyCourse [www.kfo241.de; www.pyscourse.de]

- Multi-site project in Germany & Austria (Fig.1)
- DSM-IV diagnoses: SZ, SZ-A, BD
- Longitudinal, naturalistic study design (Fig.2)
- Extensive phenotyping; blood samples
- Recruitment ongoing

![Figure 1: Recruitment network (KFO241/PsyCourse)](image1)

**Sample**

- N = 198 (completed all 4 study visits)
- Sex: 46% female
- Mean (SD) age at baseline: 46.92 (12.43) years
- Diagnoses: SZ: 49%; BD: 38%; SZ-A: 12%
- Mean (SD) age at onset: 29.67 (11.09) years
- Mean (SD) duration of illness: 17.25 (11.64) years
- Sex: 46% female
- Age: 46.92 (12.43) years
- Diagnoses: SZ: 49%; BD: 38%; SZ-A: 12%
- Mean (SD) age at onset: 29.67 (11.09) years
- Mean (SD) duration of illness: 17.25 (11.64) years
- Treatment at baseline: 78% outpatients;
- 22% hospitalized
- Data from 16 centers

**Methods**

**Step 1: Dimension reduction (Fig.3)**

- Apply factor analysis for mixed data (FAMD) to a set of 106 variables each measured at 4 time points ➔ identify main latent dimension behind these data
- Result: individual trajectories across time on dimension 1

**Step 2: Longitudinal clustering (Fig.4)**

- k-means clustering for longitudinal data on individual trajectories on dimension 1

![Figure 3: Dimension reduction of phenotype data](image3)

**Results**

Based on the Calinski-Harabasz criterion, three clusters of longitudinal trajectories were identified on the dimension “psychosocial functioning”. “Good” (A): patients who scored highly across all time points (57%); “poor” (B): patients with consistently low scores (26%); “improve” (C): patients who improved from baseline to the last follow up (17%).

There were no significant between-group differences regarding sex, age, diagnoses, center, age at onset, and duration of illness. The mean difference in GAF score between clusters “good” and “poor” was 10-15 points. Significantly fewer patients in the “poor” group were fully employed compared to the other groups.

**Association of longitudinal clusters and SZ-PRS**

SZ-PRS are associated with chronicity in SZ patients (Meier et al., 2016, Mol Psychiatry)

How much variability of cluster membership in the dimension “psychosocial functioning” can be explained by SZ-PRS?

**Methods**

Genotyping and imputation

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

Calculation of SZ-PRS

- calculated for all individuals with PLINK 1.07
- allele effect sizes and P-values were obtained from the PGC2 SZ summary results (SZ Working Group of the PGC 2014, Nature)

**Statistical analyses**

- multimedial regression of cluster membership on SZ-PRS (11 P-value thresholds)
- covariates: age, sex, 5 principle ancestry components

**Results**

From a P-value threshold of 0.05 on, up to 6% of the variability of cluster membership could be explained by SZ-PRS (significant after FDR correction for multiple testing: Fig. 5). Polygenic loading for SZ was highest in the “poor” cluster and lowest in the “improve” cluster. However, these differences between single clusters did not turn out to be significant.

**References**