PsyCourse: A transdiagnostic study on the course of severe mental disorders

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Background

Although classified as separate categorical entities in current diagnostic systems, affective and psychotic disorders partially share psychopathological features and are genetically correlated (Bulik-Sullivan et al., 2015). Moreover, patients suffering from a disorder of either group are highly heterogeneous regarding their course of illness and functional outcome. Longitudinal studies with phenotypes beyond mere diagnoses might help to biologically and clinically stratify patients. We have therefore designed the PsyCourse study (www.psycourse.de; Budde et al., 2018), an ongoing transdiagnostic longitudinal study of the affective-to-psychotic continuum. Here, we give an update on the sample that is currently available and re-analyze depressive, manic and psychotic symptoms as well as level of functioning in clinical participants with predominantly affective versus predominantly psychotic symptoms. Moreover, we update our analyses in patients on polygenic risk scores (PRS) as predictor of diagnostic group.

Methods

The PsyCourse Study

- Multi-center study with 19 centers in Germany and Austria
- Observational study; both in- and outpatient treatment possible at recruitment
- Adult participants (clinical participants and controls)
- Clinical participants with DSM-IV diagnoses of recurrent major depression (re-MDD), bipolar disorder I and II (BD-I and BD-II), schizoaffective disorder (SZA), brief psychotic disorder (BPD), schizophreniform disorder (SZD), schizophrenia (SZ)
- Longitudinal study design: assessments at baseline (V1), 6months (V2), 12 months (V3) and 18 months (V4)

Phenotypic analyses

- **Comparing diagnostic groups of clinical participants with predominantly affective (re-MDD, BD) vs. predominantly psychotic (SZA, BPD, SZD, SZ) symptoms**
- Cross-sectional phenotype data: Pearson's chi-squared and t-tests (R)
- Longitudinal data: linear mixed-effect regression (R)
  - Outcome: acute depressive (IDS-C30), manic (YMRS) and psychotic (PANSS Positive Scale) symptoms as well as psychosocial functioning (GAF) at V1, V2, V3 and V4 (natural logarithm transformation)
  - fixed effects: age at baseline, psychiatric treatment at first study visit, sex, diagnostic group, time, interactions between sex, diagnostic group and time
  - random effects: subject and clinical center
  - p-values false discovery rate (FDR) corrected

Genotyping and imputation

- DNA samples of 825 clinical participants genotyped using Illumina Infinium PsychArray
- Imputation after quality control using SHAPEIT2 and IMPUTE2 (reference panel: 1000 Genomes Project dataset)

Calculation of polygenic risk scores

- Calculated using PLINK 1.90
- Discovery GWAS for SZ-PRS: [5]
- Discovery GWAS for BD-PRS: [4]

Polygenic risk score analyses of diagnostic group

- Blockwise logistic regression analyses (SPSS)
  - Outcome: diagnostic group (affective vs. psychotic)
  - First step: covariates, namely sex, age, age², sex*age interaction, first five ancestry principal components
  - Second step: z-standardized BD-PRS at 11 different p-value thresholds
- Results of analyses with SZ-PRS as predictor taken from [1]

Results

The data presented here are a current snapshot of this ongoing study. The number of subjects who completed baseline and follow-up assessments respectively is shown in Table 1.

Clinical participants: We compare groups of clinical participants with predominantly affective symptoms (n=480 [366 with BD-I, 90 with BD-II and 24 with re-MDD]) and predominantly psychotic symptoms (n=567 [456 with SZ, 94 with SZA, 11 with SZD and 6 with BPD]). Cross-sectional comparisons on demographic variables between the predominantly affective and predominantly psychotic groups are presented in Table 2.

Control participants: 60.4% of control participants are female. The mean age in the control sample is 37.0 years (range: 18-77 years). 68.4% have never been married and 51.4% report that they have relatives suffering from a psychiatric disorder.

The course of acute depressive (IDS-C_{30}), manic (YMRS) and psychotic (PANSS Positive Scale) symptoms as well as psychosocial functioning (GAF) is displayed in Figures 1-4, respectively. Table 3 summarizes the results of the linear mixed-effect regression models (for detailed statistical values please ask the presenting person).

Table 1. Current PsyCourse sample at baseline and follow-up.

	Clinical participants (n)	Controls (n)
V1 (Baseline)	1,047	288
V2	608 (58%)	238 (82.6%)
V3	466 (44.5%)	99 (34.4)
V4	415 (39.6%)	49 (17.0%)

Figures 1-4. Violin plots of the course of depressive symptoms depressive (IDS-C_{30}), manic (YMRS) and psychotic (PANSS Positive Scale) symptoms as well as psychosocial functioning (GAF), separately for both patient groups. Individual trajectories are plotted in gray color.

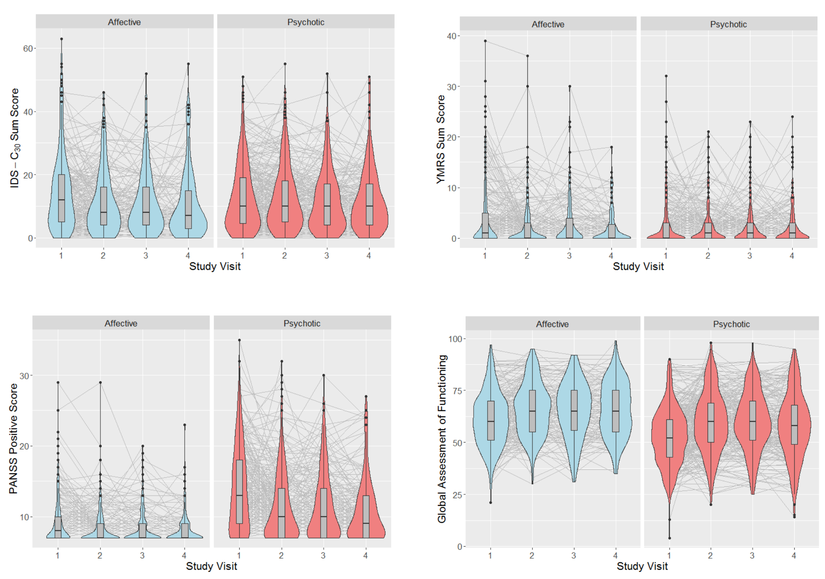


Table 2. Comparisons between patient groups with predominantly affective versus predominantly psychotic disorders on demographic variables at the first study visit (V1). Abbreviations: DF – degrees of freedom.

	Affective	Psychotic	Test statistic	DF	P
Female sex, n (%)	233 (48.5)	226 (39.9)	7.61 (X^2)	1	0.006
Age at first interview, mean (range)	44.9 (18-78)	40.6 (18-73)	5.43 (t)	980.40	<0.001
Age at illness onset, mean (range)	33.2 (7-73)	27.6 (7-73)	7.61 (t)	800.64	<0.001
Marital status single (never married), n (%)	206 (42.9)	368(64.9)	48.59 (X^2)	1	<0.001
Family history of psychiatric illness, n (%)	360 (75.0)	365 (64.4)	17.39 (X^2)	1	<0.001
In- or day patient at first study visit, n (%)	173 (36.0)	341 (60.1)	55.04 (X^2)	1	<0.001

Table 3. Summary of longitudinal analyses of depressive (IDS-C_{30}), manic (YMRS) and psychotic (PANSS Positive Scale) symptoms as well as psychosocial functioning (GAF). R^2 for the models [95% confidence interval] were: IDS-C_{30}: 6.1% [5.0, 8.8]; YMRS: 2.2% [1.8, 4.2]; PANSS Positive Scale: 14.4% [12.5, 17.4], GAF: 15.9% [13.0, 18.0].

	IDS-C_{30}	YMRS	PANSS Positive Scale	GAF
Main effects				
Age at first study visit	x	x	x	x
In-or day patient at first study visit	✓	x	✓	✓
Sex	✓	✓	✓	x
Dx group	x	✓	✓	✓
Time (Study visit)	x	✓	✓	✓
Interaction effects				
Sex*Dx group	x	x	x	✓
Sex*Time (Study Visit)	x	x	x	x
Dx group* Time (Study visit)	x	✓	x	x
Sex*Dx group*Time (Study visit)	x	x	x	x

✓ : significant effect after FDR correction; x: non-significant

Discussion

The results presented here are an update of the analyses previously published [1]with additional 156 subjects. While mild depressive symptoms were still comparable between diagnostic groups, manic symptoms differed between the groups in the updated sample, although to less extent than psychotic symptoms and psychosocial functioning.

Variability of diagnostic group could significantly be predicted with SZ-PRS, but not BD-PRS. This is very likely an effect of the higher power the SZ discovery GWAS [5] had compared to the BD GWAS [4, 3].

The PsyCourse study is one of the first transdiagnostic longitudinal projects in the field of psychiatric genetics and is therefore a great resource for future analyses. A wealth of phenotypic and biological data has already been collected and the sample size will increase further during the next months. While not in the public domain, data will be available to bona fide researchers all over the world based on mutually agreed memoranda of understanding.

Polygenic risk score analyses of diagnostic group

A subset of 771 clinical participants with available PRS and covariates were analyzed, 57.3% of whom were in the group with predominantly psychotic symptoms. While SZ-PRS significantly explained variability of diagnostic group (Figure 5, results from [1]), BD-PRS did not (Figure 6). Figures 5 and 6 show the increase in Nagelkerke's R^2 due to effects of PRS. Along with the increase in SZ-PRS, the odds of being in the predominantly psychotic group increase.

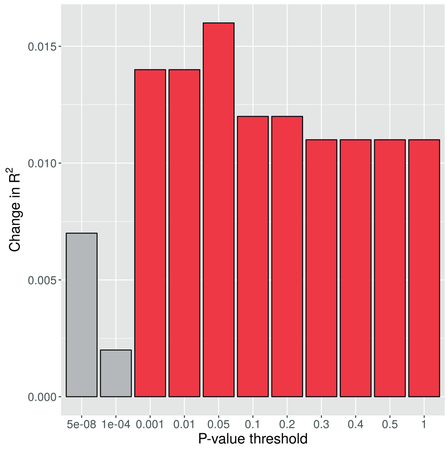
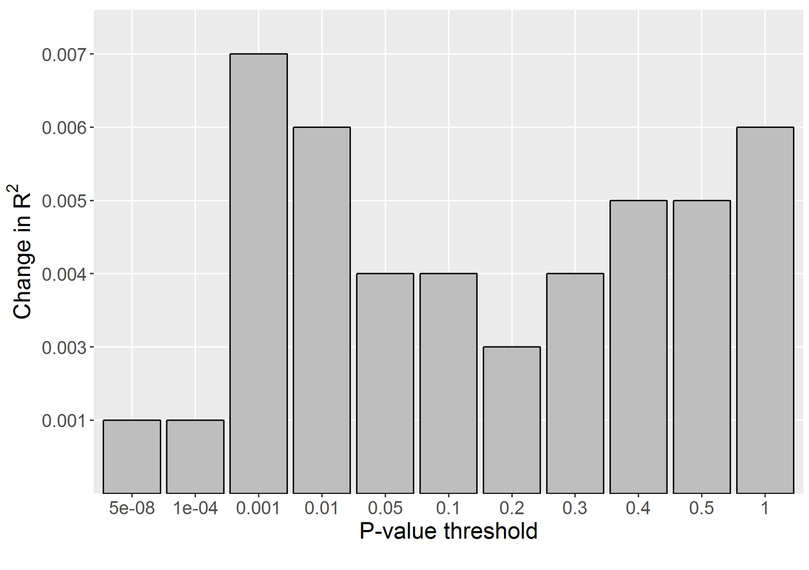


Figure 5. Effects of SZ-PRS on diagnostic group. P-values significant after FDR correction in red color (baseline model with covariates only: R^2=0.091; FDR corrected p-values for the models with p-value thresholds from 5e-08 – 1: 0.059; 0.29; 0.022; 0.022; 0.022; 0.022; 0.022; 0.024; 0.022; 0.022; 0.022) [1]

Figure 6. Effects of BD-PRS on diagnostic group. P-values significant after FDR correction in red color (baseline model with covariates only: R^2=0.091; FDR corrected p-values for the models with p-value thresholds from 5e-08 – 1: 0.571; 0.836; 0.209; 0.209; 0.209; 0.209; 0.240; 0.209; 0.209; 0.209; 0.209).



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