The Impact of Bipolar and Schizophrenia Polygenic Risk Scores on Familial Features of Bipolar Disorder

Katrin Gade[1,2], Sergi Papiol[1,3], Heike Anderson-Schmidt[1,2], Urs Heilbronner[1], Monika Budde[1], Daniela Reich-Erkelenz[1], Kristina Adorjan[1,3], Janos Kalman[1,3], Fanny Senner[1,3], Till Andlauer[4], Thomas G. Schulze[1]

[1]Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany
[2]Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany
[3]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany
[4]International Max Planck Research School for Translational Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany
*Correspondence: katrin.gade@med.uni-goettingen.de

Background

It has been shown (Schulze et al., 2006) that in bipolar disorder (BD), some disease characteristics such as the occurrence of psychotic symptoms or suicide attempts, the level of psychosocial functioning, disorder subphenotypes like type I/II disorder and comorbidities like alcohol or drug abuse are highly familial. We explored whether polygenic risk scores for bipolar disorder (BD-PRS) or schizophrenia (SZ-PRS) can predict these phenotypes in a sample of German and Austrian patients diagnosed with BD according to DSM-IV-criteria.

Methods

The present study included 327 patients belonging to the German KFO241/PsyCourse cohort (www.kfo241.de; www.PsyCourse.de). Descriptive statistics of the sample are shown in Table 1. The study protocol was approved by the local ethics committees and is in accordance with the 1964 Declaration of Helsinki. Sociodemographic and clinical information on patients was assessed using a comprehensive inventory for phenotype characterization. Association of BD-and SZ-PRS with target variables was tested via logistic regression analyses at several inclusion p-value thresholds (p = 0.00000005 to 1). Polygenic risk scores were calculated using imputed, quality-controlled genome-wide patient genotypes (Illumina Infinium PsychArray) and summary statistics of two large case-control genome-wide association studies (Hou et al., 2016; PGC-Schizophrenia-Working-Group, 2014). The results were corrected for age, sex, recruitment center, duration of illness and population stratification. All analyses were Bonferroni-corrected for the number of phenotypes analyzed in order to control for multiple testing.

Table 1: Descriptive statistics

	n	Min	Max	Mean	Std Dev
Age	327	18	78	45.89	13.38
Duration of illness (years)	327	0	53	15.66	12.58
GAF-score	322	30	97	65.62	12.12

Other sample characteristics		n	%
Sex			
	Male	172/327	52.6
	Female	155/327	47.5
Diagnosis			
	BD I	263/327	80.4
	BD II	64/327	19.6
Lifetime Alcohol Dep.			
	No	239/278	86.0
	Yes	39/278	14.0
Lifetime Drug Abuse			
	No	196/315	62.2
	Yes	119/315	37.8
Lifetime Psychosis			
	No	106/278	38.1
	Yes	172/278	61.9
Lifetime Suicide Attempt			
	No	208/301	69.1
	Yes	93/301	30.9

Results

A higher SZ-PRS was significantly associated with lifetime use of illicit drugs at several p-value-thresholds (Figure 1, strongest association at threshold p = 0.0001, R^2 change 2.7%,p-value=0.0049; corrected p-value=0.0392 after Bonferroni correction). Only with one threshold a slightly positive association with alcohol abuse was observed (p = 0.0000001, R^2 change 3.1%, p = 0.026). BD I patients compared to BD II patients had higher SZ-PRS at several thresholds (Figure 2, strongest association at 0.05 threshold, R^2 change= 2.4%, p=0.020, OR=1.6). However, these results did not survive Bonferroni correction. We found no significant association of SZ-PRS or BD-PRS with other target variables. Especially the lifetime occurrence of psychosis was not predicted by SZ- or BD-PRS, neither in disorder subtype groups nor the whole patient sample.

Figure 1. Higher SZ-PRS associated with lifetime use of illicit drugs in BD patients

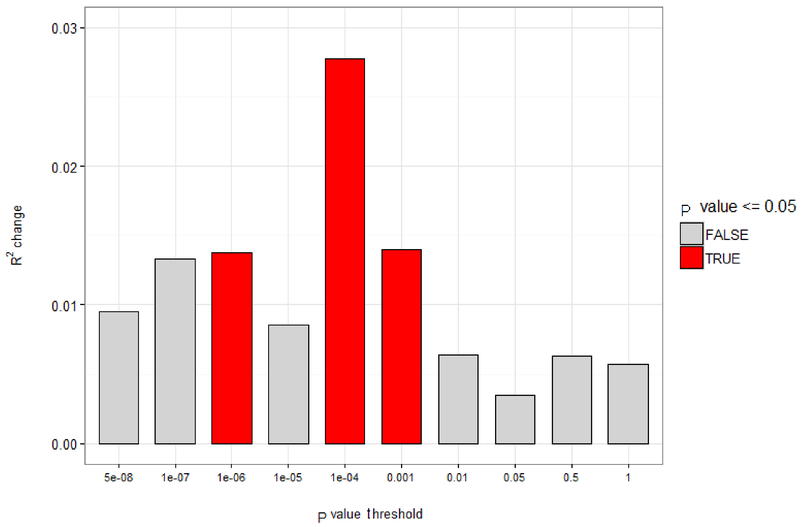
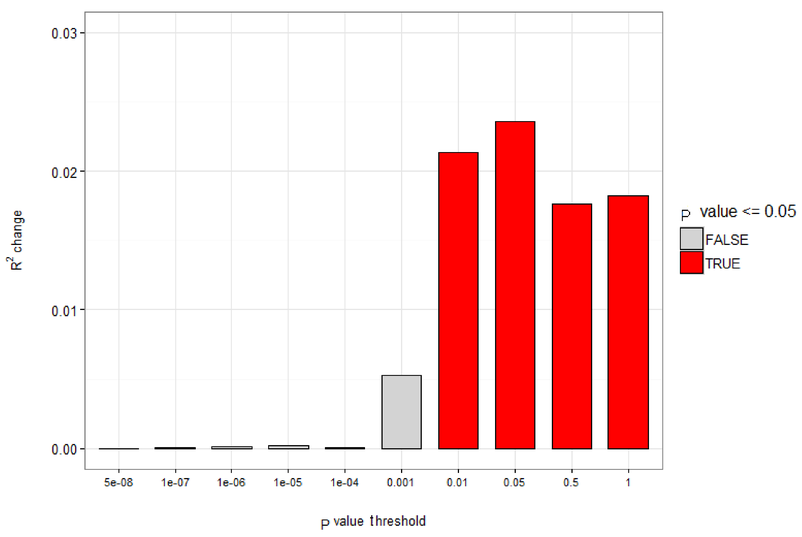


Figure 2. Higher SZ-PRS in BD I patients compared to BD II patients



Discussion

Our results suggest that a higher polygenic SZ risk score is associated with lifetime use of illicite drugs in BD patients while the polygenic BD risk score is not. Interestingly, a study by Reginsson et al. found higher SZ-PRS as well as BD-PRS associated with increased risk of alcohol and certain substance use disorders in otherwise mentally healthy subjects. Therefore, higher SZ-PRS may have a negative effect in BD patients regarding substance abuse.

Although the association of higher SZ-PRS with BD I compared to BD II disorder in our sample did not remain significant after Boferroni correction, our findings are in line with previous literature (e.g. Charney et al., 2017). There may be a stronger genetic overlap between schizophrenia and BD I disorder subtype than between schizophrenia and BD II disorder subtype. This effect even seems to be independent from the occurrence of psychosis, as even in the subgroup of BD I disorder patients this variable was not associated with higher SZ-or BD-PRS.

References

Schulze TG et al. What is familial about familial bipolar disorder? Resemblance among relatives across a broad spectrum of phenotypic characteristics. Arch Gen Psychiatry 2006, 63(12): 1368-76.

Hou L et al. Genome-wide association study of 40,000 individuals identifies two novel loci associated with bipolar disorder. Hum Mol Genet.2016, 25(15): 3383-94.

Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature 2014, 511(7510): 421-7.

Reginsson GW et al. Polygenic risk scores for schizophrenia and bipolar disorder associate with addiction. Addict Biol 2017, Feb 23. doi: 10.1111/adb.12496.

Charney AW et al. Evidence for genetic heterogeneity between clinical subtypes of bipolar disorder. Transl Psychiatry 2017, 7(1): e993.

Funding

This project was supported by the Deutsche Forschungsgemeinschaft (DFG) within the framework of the projects

www.kfo241.de and www.PsyCourse.de (SCHU 1603/4-1, 5-1, 7-1).

Thomas G. Schulze is further supported by the Dr. Lisa Oehler Foundation (Kassel, Germany).

The authors declare no conflicts of interest.