Polygenic risk scores and substance abuse comorbidity in patients with schizophrenia and bipolar disorders

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Introduction

Cannabis is the most widely used illicit drug in the world. It is well established that substance abuse comorbidity i.a. cannabis use is much higher among patients with schizophrenia (SCZ) and bipolar disorders (BD) than in the general population. However, the relationship between SCZ, BD and cannabis use might be more complicated than it initially seems. Previous studies have revealed that a genetic predisposition to SCZ might be associated with increased use of cannabis in healthy individuals. Given this relationship, we intended to study whether polygenic risk scores (PRS) for SCZ predict cannabis use in patients with SCZ and BD. In addition we want to test whether cannabis PRS have an impact on cannabis use in these two subgroups.

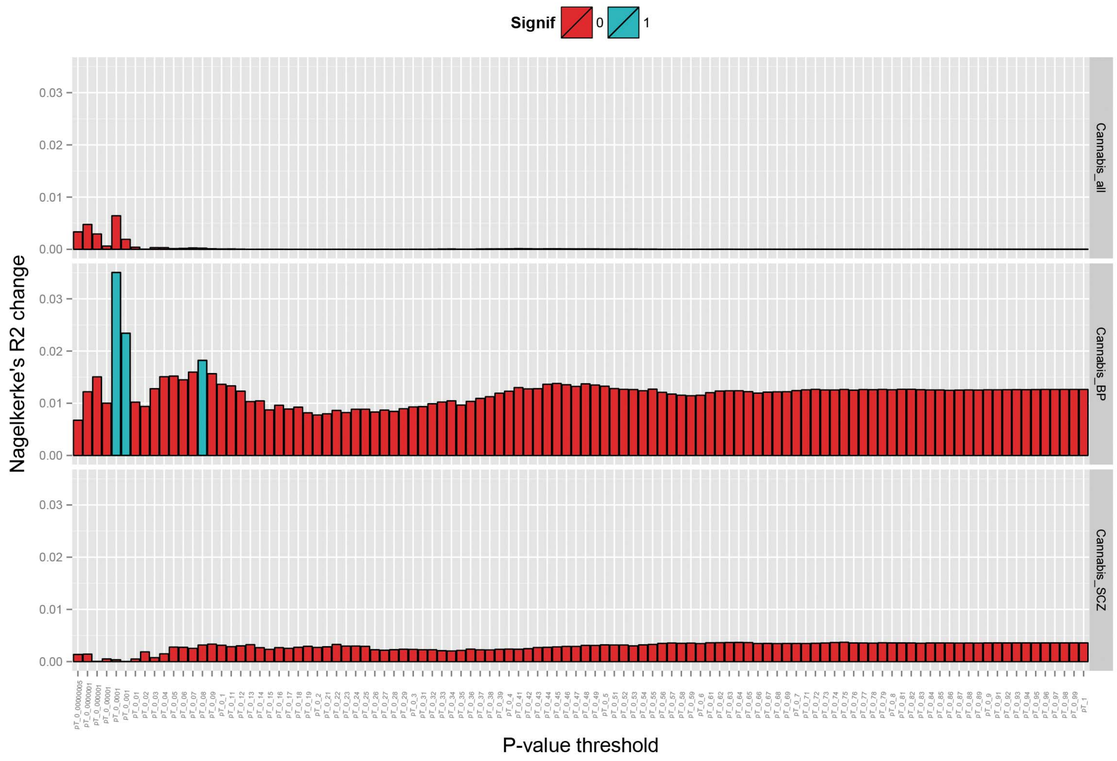
Methods

1. In a sample of 630 individuals (N= 367 SCZ, and N= 263 BD) in the KFO/PsyCourse cohort (www.kfo241.de; www.PsyCourse.de), we tested whether PRS for SCZ predict cannabis use in patients with SCZ and BD. PRS reflect the cumulative burden of risk alleles carried by an individual according to the well-powered genome-wide association study (GWAS) investigated by the Psychiatric Genomics Consortium (PGC).
2. We will test whether cannabis use PRS calculated according to a recent GWAS from the International Cannabis Consortium (ICC) explains cannabis use in patients with SCZ and BD in our cohort.
3. We tested the replicability of our results in an independent sample from the USA (GAIN/TGen), with a sample size of 1.150.

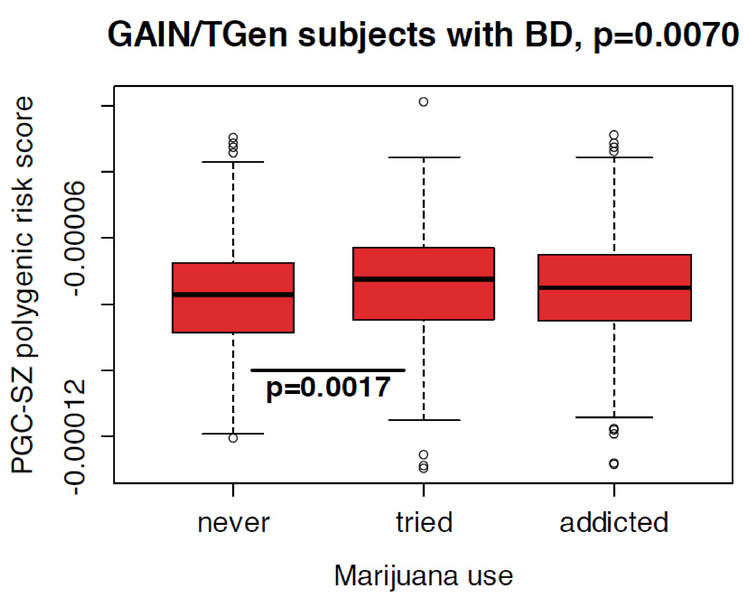
First results

PRS for SCZ showed positive associations (R2=3.5 % p=0.0067) for “use” versus “never use” of cannabis in BD with the strongest association of PRS that were based on SNPs with a p-value ≤0.0001 in the original SCZ GWAS. This finding replicated in an independent sample of BD patients where higher PRS were also associated with a higher probability of cannabis use (OR=1.20 for increase of PRS by 1 sample sd, p=0.0105). Comparisons of PRSs in the groups „use“ vs. „never use“ showed repeated nominal significance (p <= 0.0436). No association was found in the same analyses for SCZ patients. Further analyses of cannabis PRS in the same samples will be conducted.

PGC-SZ polygenic risk sccores in the KFO/PsyCourse cohort



PGC-SZ polygenic risk sccores in GAIN/TGen-BD



Analysis with 3 groups (N = 1148)

Marijuana use	never	tried	addicted
Sample size	292	394	462

- subjects who tried marijuana had higher PGC-SZ polygenic risk scores (less genetic protection against SZ) by 0.23SD (p=0.0026, rank-sum test p=0.0017)
- subjects who are addicted to marijuana also had higher PGC-SZ polygenic risk scores (less genetic protection against SZ) by 0.12SD (p=0.1084, rank-sum test p=0.0790)

SD=standard deviation of the PGC-SZ polygenic risk score within GAIN/TGen BD who had a PGC-SZ polygenic risk score and information on marijuana use
Rank-sum tests yielded slightly more powerful statistics although score data appear fairly normal.

Conclusion

First results suggest that individuals with BD and an increased polygenic risk for SCZ are more likely to use cannabis. The association between BD and cannabis use might be not simply one of an environmental risk factor, but rather involves gene–environment interaction, as individuals choose and shape their own environment according on their own innate preferences.

Analysis with 2 groups (N=1150)

- gives essentially the same results
t-test p=0.0108, score is higher by 0.17SD in subjects who ever used marijuana
Rank-sum test p=**0.0068**
Multiple logistic regression with Ever-used-marijuana (yes/no) as binary target and PGC-SZ polygenic risk score, sex, and age-at-onset as potential predictors yields

- OR=1.20 of having ever used marijuana (vs. never) when individual PGC-SZ polygenic risk score increased by +1sample SD, p=0.0105 (subjects with higher PRS are more likely of ever using/ trying marijuana)
- OR=1.29 for men compared to women to ever have used marijuana, p=0.0872 (men tend to use/try marijuana more likely than women)
- OR=0.97 of having ever used marijuana (vs. never) when age of onset is later by 1 year, p=6.6·10-7 (younger age-of-onset associates with higher probability of marijuana use)

Remark for other target (GAF): PRS is not significant on GAF (linear model, p=0.7072) also not on GAF extremes (logistic model, p=0.3583), but being male, longer DOI are risks for lower GAF (p<0.05) and ever tried/using marijuana tends to harm GAF-outcome as well.

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