High genetic predisposition to schizophrenia is associated with an increased frequency of use of cannabis before illness onset

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ABSTRACT

Objective: Schizophrenia (SZ) and bipolar disorder (BD) are heritable, polygenic disorders with shared clinical and genetic components, suggesting a psychosis continuum. Cannabis use is a well-documented environmental risk factor in psychotic disorders. In the current study, we investigated the relationship between SZ genetic load and cannabis use before illness onset in SZ spectrum and BD spectrum. Since frequent early cannabis use (age <18 years) is believed to increase the risk of developing psychosis more than later use, follow-up analyses were conducted comparing early use to later use and no use.

Method: We assigned a SZ-polygenic risk score (PGRS) to each individual in our independent sample (N=381 SZ spectrum cases, 220 BD spectrum cases and 415 healthy controls CTR), calculated from the results of the Psychiatric Genomics Consortium (PGC) SZ case-control study (N = 81535). SZ-PGRS in patients who used cannabis weekly to daily in the period before first illness episode was compared to those who never or infrequently used cannabis.

Results: Patients with weekly to daily cannabis use before illness onset had the highest SZ-PGRS score (P=0.02, Cohen's d=0.33). The largest difference was found in patients with daily or weekly cannabis use before illness onset <18 years of age compared to never or infrequent use of cannabis (P=0.004, Cohen's d=0.42).

Conclusion: Our study supports an association between high SZ-PGRS and frequent cannabis use before illness onset in psychosis continuum disorders.

INTRODUCTION

Schizophrenia (SZ) and bipolar disorder (BD) are highly heritable disorders with polygenic inheritance (Giusti-Rodriguez and Sullivan 2013;Smoller and Finn 2003;Tesli et al. 2014). Evidence of common genetic risk variants indicates that these two disorders constitute one broad psychosis continuum (Andreassen et al. 2013;Craddock and Owen 2010;Tesli et al., 2014). The polygenic risk score is computed on the basis on large genome-wide association studies (GWAS) of additional explained genetic variance previously not included due to threshold levels of significance (Iyegbe et al. 2014). The method estimating cumulative genetic risk (Purcell et al. 2009) was recently employed to provide molecular validation of the psychosis continuum model (Bigdeli et al. 2014; Tesli et al.,2014).

It is well described in the literature that cannabis use is associated with psychotic like symptoms (such as delusions and hallucinations (Grech et al. 2005)). Current evidence, including the meta-analysis by Marconi et al. (2016), confirms that frequent cannabis use increases the risk of psychotic outcomes and that there is a dose-response relationship between the level of use and the risk for psychosis. However, a causal link between cannabis use and psychosis is not yet established. The first formal evidence relating cannabis use to schizophrenia came from the Swedish Conscript Study from the 1969/70 survey based on more than 45 000 young inductees into the military and followed up for more than 10 years. The study found that those who had used cannabis before age 18 were 2.4 times more likely to have a diagnosis of SZ than those who had never used (Andreasson et al. 1987). The frequency of use was associated with the risk of developing SZ (use on more than fifty occasions); the relative risk of developing SZ increased to 6.0 (95% confidence interval 4.0-8.9) compared to non-users (Andreasson, Allebeck, Engstrom, & Rydberg 1987). Similar findings from the same cohort were later replicated by Zammit et al. (2002). Also the Dunedin multidisciplinary health and development study (a study of a general population birth cohort

of 1037 individuals) showed that cannabis use at age 15, as well as by age 18, was associated with more psychotic like symptoms at age 26 (Arseneault et al. 2002). Specific neighbourhoods of high cannabis use also show greater prevalence of psychosis cases, supporting a link between cannabis use and psychosis (Home Office Research 2008;Kirkbride et al. 2006;Kirkbride et al. 2007).

The relationship between genetic load and environmental risk factors in severe mental illness is sparsely investigated and could potentially shed new light on mechanisms behind the development of severe mental disorders. Most individuals who use cannabis never develop a psychotic disorder, and it is proposed that the link between cannabis use and development of psychosis requires an interaction with genetic vulnerability (Loberg et al. 2014). This is supported by the low prevalence psychotic illnesses (estimated to 1%) (McGrath et al. 2008) whilst cannabis use is relatively common in the general population (prevalence estimates of 14%-40% depending on the frequency of use and study location (Home office 2008; WHO 2016). On the other hand, it could be proposed that less genetic risk is needed to develop a psychotic episode in those exposed to cannabis, compared to non-users and that some individuals would have remained healthy if they had not been exposed. For example, Ferraro and colleagues found that patients with a first-episode psychosis who had ever smoked cannabis had significantly higher current IQ and premorbid IQ compared to patients who had never used cannabis (Ferraro et al. 2013). This difference was not found amongst controls. These findings could potentially reflect a subgroup of patients developing psychosis after cannabis use that otherwise would not have developed the illness.

Frequent cannabis use before illness onset could also be seen as an attempt to self-medicate premorbid symptoms (including handling symptoms of anxiety and depression), resulting in a vicious cycle contributing to more severe psychopathology in genetically vulnerable individuals. Another possibility is that risk of using cannabis and developing

psychosis is driven by a common genetic susceptibility. Hence, part of the association between cannabis use and psychosis might reflect the fact that individuals prone to using cannabis are also prone to developing psychosis, and that there is not necessarily a causal link between cannabis use and the pathophysiology of psychosis among these individuals. This theory of shared genetic risk fits with the recent findings by Power et al. demonstrating a higher polygenic risk score for schizophrenia (SZ-PGRS) in healthy cannabis users (Power et al. 2014), indicating a genetic overlap between SZ and vulnerability to cannabis use. Another recent large study (N=14 754) of genetic factors in cannabis dependence include overlapping single-nucleotide polymorphisms in genes associated with SZ, including the CUB And Sushi Multiple Domains 1 (*CSMD1*), and genes related to immune processes, supporting potential overlap in genes for cannabis use and SZ (Sherva et al. 2016). A strong genetic component of cannabis use has also been found in twin studies with a high heritable (h^2) rate, including a high heritability rate for an early onset of use ($h^2 = 80\%$), lifetime use ($h^2 = 76\%$), as well as cannabis abuse or dependence ($h^2 = 21\%$-72%) (Agrawal et al. 2014;Kendler et al. 2015;Lynskey et al. 2012).

Although there are fewer and less consistent studies investigating the link between cannabis and BD, the three year longitudinal study comprised of 4815 individuals from the Netherlands Mental Health Survey and Incidence Study (NEMESIS) reported that use of cannabis increased the risk of manic symptoms during the follow-up period independently of psychotic symptoms (Henquet et al. 2006). Both SZ and in BD cannabis users tend to have an earlier age at onset in a dose dependent manner (i.e. the more use, the earlier age at onset) (Di Forti et al. 2014; Lagerberg et al. 2014) supporting cannabis use as a risk factor across the psychosis continuum.

In the current study we will investigate if cannabis use is frequently used before illness onset. Our study focuses on the relationship between PGRS and cannabis use in psychotic

continuum disorders (SZ and BD). The strength of our study is the well described clinical sample, where we have information on age at illness onset and age at first cannabis use before illness onset, in addition to the premorbid frequency of cannabis use (daily/weekly use compared to no/sporadic use).

We explore the following two hypotheses: According to the hypothesis that cannabis can elicit psychosis in less vulnerable individuals, patients with frequent (daily or weekly cannabis use before illness onset) will have lower SZ-PGRS scores, with the most significant findings for early frequent use (weekly or daily) before 18 years of age. According to the alternative model, suggesting overlapping genetic vulnerability for cannabis use and SZ, those with frequent (daily or weekly) cannabis use before illness onset will have increased SZ-PGRS levels compared to those without frequent cannabis use.

METHODS

Participants

The participants were recruited consecutively from psychiatric units (outpatient and inpatient) in four major hospitals in Oslo, as part of the larger Thematically Organized Psychosis (TOP) research study. A total of 601 patients were recruited to this study: N=381 had a schizophrenia spectrum disorder (SZ) [224 schizophrenia; 22 schizophreniform disorder; 45 schizoaffective disorder and 90 with other psychosis]; and N=220 had a bipolar disorder with or without a history of psychosis (BD) [141 bipolar I; 65 bipolar II; 14 bipolar NOS]. The mean age of the patients was 32.7±10.3; and 51.5% were females. In addition, 415 heathy controls were included in the study (mean age 34.6±10.0 and 49.9% females, see Table 1) for validation of the method (assessment of explained variance of case-control status). All participants were Caucasians. Exclusion criteria for all groups were: An unstable or

uncontrolled medical condition that interferes with brain function, age outside the range of 18–65 years. The Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate approved the study. All participants gave written informed consent.

-Insert Table 1 here-

Clinical Assessment

Trained medical physicians and clinical psychologists carried out the clinical assessment. Diagnosis was based on the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I). Diagnostic reliability was found satisfactory (Ringen et al. 2008a) with overall agreement for DSM-IV diagnostic categories of 82% and the overall κ 0.77 (95% CI: 0.60-0.94). Age at illness onset was defined as the age of the first SCID-verified psychotic episode. For BD patients without information on the first psychotic episode (N=101), first mood episode was used to define the onset of illness. Cannabis assessment: Patients were asked regarding the time of use and frequency of use (no, sporadic, weekly or daily use), also see (Ringen et al. 2016). For the purpose of this study, we divided the sample into patients with daily or weekly use (frequent use) compared to no use or sporadic use (no use) before illness onset. Lifetime use was also reported. Thirty-three cases were missing data on age at illness onset and cannabis use.

Polygenic risk score (PGRS)

All participants were genotyped at Expression Analysis Inc (Durham, NC, USA) using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix Inc, Santa Clara, CA, USA). Quality control was performed using PLINK (version 1.07; http://pngu.mgh.harvard.edu/purcell/plink/) (25). SNPs were imputed with MACH (26)

(http://www.sph.umich.edu/csg/abecasis/MACH/download/1000G-PhaseI-Interim.html) using the European samples in the Phase I release of the 1000 Genomes project. Genotyping and imputation procedures are described in further details elsewhere (Athanasiu et al. 2010;Djurovic et al. 2010;Finseth et al. 2014).

The polygenic risk score (PGRS) for the schizophrenia phenotype was computed based on imputed SNPs following the method developed by Purcell et al. 2009. Using PLINK version 1.07 (http://pngu.mgh. harvard.edu/ purcell/plink/), a meta-analysis including all Psychiatric Genomics Consortium (PGC) sub studies (PGS, except ours (TOP 8; n = 377 schizophrenia cases and 403 controls) was performed to obtain risk allele effect sizes (ln(OR)) for all imputed SNPs. The SNPs remaining after removal of those within MHC or with MAF < 0.01 were pruned using PLINK's –clump option (r^2 < 0.1, 500 kb windows) to select representatives with lowest P-values from all linkage disequilibrium blocks (102,635 SNPs). PGRSs were then computed for each individual in our sample by summing up the effect sizes of the selected SNPs multiplied by the number of risk alleles expected to be carried by that individual (dosage). A total of ten PGRS were computed based on different P-value thresholds (P = 1, 0.5, 0.4, 0.3, 0.2, 0.1, 0.05, 0.01, 0.001, and 0.0001) for SNP inclusion. The AUC for case-control status prediction is reported for PGC2 schizophrenia polygenic risk scores based on different P-value thresholds for SNP inclusion (Fig S1 Suppl Mat). For use in the analyses to follow, we selected the most parsimonious threshold that gave a significant increase in the AUC with respect to the threshold preceding it (P = 0.05).

Statistics

Data were analyzed using the Predictive Analytic software (PASW), Version 21 (formerly SPSS Statistics). For the primary analysis, a *t*-test was used to assess potential differences in SZ-PGRS scores in those with daily or weekly cannabis use before age at onset

of their psychotic disorder, compared to those without daily or weekly cannabis use before age at onset. Since the age of initiation of cannabis use has been identified as a risk factor for developing a severe mental disorder, we performed a follow up analysis investigating the association between SZ-PGRS in patient groups separated based on age at initiation of cannabis use. A cutoff of < 18 years was chosen based on the initial study by Andreasson,et al., (1987) showing that cannabis use < 18 years of age was linked explicitly to developing a psychotic illness in the large Swedish cohort. Other studies suggested a cut off at age <15 (Di Forti et al., 2014) but our sample would have been too small for that (N=15 individuals with cannabis initiation <15, versus N=46 for initiation at <18)). Regression analyses correcting for sex and population principal components were also performed. All individuals were included from the same catchment area in Oslo, Norway with similar socioeconomic background. A follow up analysis was performed dividing into SZ spectrum and BD spectrum. Effect sizes were computed for the main analysis of cannabis and genetic correlates in patients with a psychosis continuum diagnosis using Cohen's *d* (Cohen 1977). According to Rosenthal and Rosnow (Rosenthal and Rosnow 1984) effect sizes were considered small for values between 0.20 and 0.50, moderate for values between 0.50 and 0.80, and large for values greater than 0.80. A pre-set significance level of 0.05 was used for the main analysis of SZ-PGRS and cannabis use before illness onset.

To validate the SZ-PGRS method case-control variance an ANOVA model was applied to determine SZ-PGRS differences between SZ spectrum cases, BD spectrum cases, and healthy controls, with post hoc Tukey's test comparing groups pairwise, adjusting *P*-values for numbers of tests (see Supplementary material).

RESULTS

Demographics of the sample

Sixty-two percent of the patients reported ever trying cannabis. No significant difference in lifetime cannabis use was observed between SZ and BD (X^2=0.41, df=1, P=0.53). Lifetime cannabis use was associated with an earlier age at onset (see Table 2). The mean age of first using cannabis was eighteen years (18.2±5.3 mean±SD). For the validation of the SZ-PGRS method as well as the diagnostic investigation of cannabis use, please see Table 2, and Supplementary Material (Figure S1-S5; Table S1).

-Insert Table 2 here-

SZ-PGRS and cannabis use before illness onset

In patients with SZ or BD daily or weekly cannabis use before age at onset was associated with higher SZ-PGRS (t-test=-2.45, P=0.02, Cohen's d =0.33, see Figure 1). Correcting for sex and population principal components, a trend was observed for higher PGRS in patients with daily or weekly cannabis use before age at onset (ß=0.08, t=1.87, P=0.067).

- Insert Figure 1 here-

Dividing the sample into early cannabis users [N=46] (< 18 years), later [N=20] (≥ age 18) cannabis users, and non-frequent cannabis users [N=502], the largest difference in SZ-PGRS was observed between the early users and the non-frequent users (t=-3.02, P=0.003, Cohen's d =0.42). A dose relationship was observed with the highest SZ-PGRS in the early

frequent users (< age 18) with intermediate SZ-PGRS in the late frequent users (≥ age 18; ANOVA: *f*=4.64, *P*=0.01; Figure 2). Comparing late frequent users [N=20] to non-frequent users [N=502] no significant difference was observed in SZ PGRS (*t*=-1.42, *P*=0.16). Correcting for sex and population principal components, significant higher PGRS score was observed in early users compared to all other groups (ß=0.09, t=2.05, *P*=0.04).

- Insert Figure 2 here-

Dividing the sample into SZ spectrum and BD spectrum, both groups showed a trend towards higher SZ-PGRS in the frequent cannabis users (see Supplementary Material S5A, S5B) with the strongest association for the young (age < 18) SZ group (*t*=-2.28, *P*=0.02, Cohen's *d* =0.37). Correcting for for sex and population principal components, a significant trend was observed for higher PGRS in SZ in early cannabis users ((ß=0.11, t=1.99, *P*=0.05).

DISCUSSION

In the whole group, patients with weekly to daily cannabis use before illness onset had higher SZ-PGRS than those who never or infrequently used cannabis before illness onset. The largest difference was found in patients who started their daily or weekly cannabis use before the age of 18. Dividing the sample into SZ and BD spectrum both groups showed a trend towards higher PGRS in the frequent cannabis users, with the strongest association in the young (age <18) SZ group.

Several hypotheses have emerged regarding the relationship between cannabis and psychosis (for a detailed description, see Van Winkel and Kuepper (2014)). Our findings support the notion that genetic risk for SZ also implies a higher risk of cannabis use. New

studies are needed to determine in what way genetic risk for SZ influences risk for cannabis use. One possibility is that frequent cannabis use before illness onset could be seen as an attempt to self-medicate premorbid symptoms resulting in a vicious cycle contributing to increased psychopathology in genetic vulnerable individuals. Hence, increased cannabis use as a reflection of higher symptomatic load might not explain the relationship between cannabis use and psychosis. Another possibility supported by our findings is that risk of using cannabis and risk of developing psychosis partly share genetic susceptibility. This suggests that individuals prone to developing psychosis are also prone to start using cannabis, regardless of any causality between cannabis use and the pathophysiology of psychosis. Our findings are in line with a recent large study of healthy individuals demonstrating that polygenic risk of SZ is correlated with cannabis use (Power, et al.,2014, Verweij *et al.*, 2017). Overlapping genetic components between cannabis use and schizophrenia are also reported in the recent large (N=14754) study by Sherva, et al., (2016) of CUB And Sushi Multiple Domains 1 (*CSMD1*) as well as inflammatory genetic components linked to both cannabis abuse and schizophrenia.

Several limitations to the current study should be mentioned: Most importantly, we did not have cannabis data in our control sample; therefore we were not able to investigate the role of cannabis and SZ-PGRS in a case-control design. However, controls were selected from the population of Norway, and healthy individuals report much less frequent cannabis use. For example the study by Ringen et al. (2008b) showed an increase of 44% of illicit use in SZ and in BD compared to use in the general population from the same catchment area in Oslo. To investigate overlap between cannabis, genetic risk and psychosis, case-control studies are needed. Secondly, the explained variance of the SZ-PGRS was low (Nagelkerke r^2 0.12 and 0.05 for SZ and BD respectively). As suggested by Tesli et al., (2014) improvement of the SZ-PGRS method could potentially increase the variance explained by the SZ-PGRS, which

should be investigated in future studies. It could also be that the relatively low explained variance could be influenced by the nature of the two competitive hypotheses proposed in this study. However when dividing the sample into frequent cannabis users before age at onset and non-frequent cannabis users before age at onset, we found the highest r2 in the group with frequent cannabis use (r2=0.122), compared to the larger group without frequent cannabis use before age at onset (r2=0.09), indicating higher PGRS in cannabis users. Similar findings were observed in patients with lifetime cannabis use compared to controls (r2=0.11), and patients without lifetime cannabis use compared to controls (r2=0.059). We also used a cutoff score of before 18 year of age in the follow up analysis investigating frequent early use of cannabis and SZ-PGRS, similar to the study by Andreasson, Allebeck, Engstrom, & Rydberg (1987). More recent studies indicate that frequent early use before age 15 could be an even better cutoff age (Di Forti et al., 2014). The study by Arseneault et al. (2002) found that both cannabis users by age 15 and by 18 were associated with more psychotic like symptomatology in high risk individuals, supporting 18 as a valid cutoff age. Also our sample was too small to divide into younger than 18 year of age. It should also be noted that our results could also merely be a result of higher cannabis use among SZ cases than controls in the PGC study, which may have led to SNPs associated with cannabis use being misclassified as schizophrenia risk alleles. This could specifically be an issue if GWAS controls have been selected based on more stringent substance misuse criteria's than patients.

In conclusion, our data support a weak increase in SZ-PGRS in those with frequent cannabis use before illness onset, suggesting overlapping genetic susceptibility. If there is a genuinely (rather than methodologically) increased rate of cannabis use in PGC SZ cases (as we might expect given the association between cannabis use and SZ), we might find alleles that increase SZ risk via increased risk of cannabis use (or vice versa). As the effect sizes were small the findings should be interpreted with caution. Further investigation of genetic

overlap between SZ and cannabis are warranted, such as comparing SZ PGRS to PGRS cannabis use in independent GWAS samples.

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