Synopsis no.: *S2.40*

Can Polygenic Risk Scores explain the differences in Premorbid Social and Academic Adjustment, and current Cognition between those Psychotic patients who use cannabis compared to those who don't?

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Publication category: WP2 paper following paper on premorbid and cannabis, main PRS and cannabis core papers

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Work Packages involved: WP2and the Cardiff team

Partners involved from whom candidate co-authors (*additional to working and writing group*) should be nominated: (all for sample access)

Scientific background

The background of this hypothesis is based on a previous study (Synopsis on premorbid and cannabis). I showed that psychotic patients who used cannabis in their lifetime had higher IQ scores and better premorbid adjustment than those who had not used cannabis. The same was true in a control group. The study also suggested that the better premorbid social adjustment of patients with cannabis-use might have contributed to contact with the substance; thus cannabis use increased the risk of psychosis in a subgroup of patients with less neurodevelopmental vulnerability.

Both patients and control cannabis heavy-users (everyday use), had a lower premorbid academic adjustment but an IQ comparable with non-users. Patients but not controls, had also higher premorbid social adjustment, compared with non-users and occasional recreational users. Taken together, these results are able to rule out the explanation of a neuroprotective role of cannabis use on cognition, in favour of the hypothesis of a complex relationship between premorbid predisposition and different pattern of cannabis use in determining the paradoxical result of the better IQ in cases who are recreational cannabis-users (i.e. less than everyday users).

Polygenic risk scores (PRSs) are promising candidates to successfully summarize genome-wide effects of genetic variants in several mental illnesses, included schizophrenia and bipolar disorders, starting from the meta-analysis conducted by the Psychiatric Genomics Consortium[1].

Several studies have paid attention to general cognitive functioning and robust polygenic correlations have been found between cognitive performance and educational attainment[2,3]. Other studies have reported a polygenic overlap between autism spectrum disorders and cognition in the general population[4] and between schizophrenia, cognition and educational attainment, with negative correlations[5]. Along with cognition deficits, social communication difficulties show common genetic overlap with both disorders[6]. However, no important sharing of common risk alleles have been demonstrated between autism and schizophrenia[5,7]. Interestingly, a more generic genome-wide association study on social and non-social autistic-like-traits in the general population was conducted, leading to controversial results [8].

Starting from this rising and diversified landscape, it would be very interesting to combine selected risk profile scores that could predict different phenotypes and environmental risk factors, in the EU-GEI case/control sample, which dataset includes common variant genotype data.

Aims

to test whether (schizophrenia) SCZ and (bipolar disorders) BD risk profile scores (PRS), based on

PGC case/control training datasets, have a relationship with premorbid scores and current IQ, and if and how this relationship is related to different patterns of cannabis use. Additionally, I plan to use PRS for educational attainment (EA) and the PRS for social communication difficulties (SCD) (in a preliminary phase this PRS will be compared with autism or autistic-like traits PRSs), as possible non-clinical markers of premorbid academic and social adjustment scores respectively across cases and controls.

The final aim is to test which of these 4 PRSs, alone or in interaction with the others, is able to better explain the discrepancy between IQ, premorbid academic and social adjustment of cases and controls with different patterns of cannabis use, once inserted into the model.

Methods

In a preliminary phase, proportion of variance explained and the different statistical power of each hypothesized PRSs will be explored[9] and tested on the available dataset. The sample will be made of 1,895 subjects (834 cases and 1,061 controls) they all having complete information on socio-demographics, cannabis use and premorbid adjustment at least. To build the PRS we will use the PRSice program. Risk profile scores will use the most powerful GWAS studies currently available from the PGC as training sets.

Hypotheses

1. We expect that: a) social communication difficulties PRS correlates more with schizophrenia PRS than bipolar PRS and better predict premorbid sociability across cases and controls; b) educational attainment PRS correlates more significantly with bipolar PRS than schizophrenia PRS and better predict premorbid academic adjustment across cases and controls.

We hypothesize that social communication difficulties and educational attainment PRSs interact with cannabis use in determining dissimilar trajectories of life in both cases and controls. Specifically:

2. PRS for educational attainment does not differ between subjects with recreational and heavy cannabis use, given that this latter group could have suffered additional impairment in educational adjustment and career, due to cannabis heavy-use.
3. social communication difficulties PRS is lower in cannabis-users and predicts a better premorbid sociability (in interaction with cannabis use).

We expect a different schizophrenia/bipolar PRS profile combined with different pattern of cannabis use in cases and controls in determining IQ, premorbid social and academic adjustment;

4. We hypothesize that a higher schizophrenia PRS will be able to predict a lower IQ in cases heavy cannabis- users, alone or in interaction with a lower educational attainment PRS, compared to controls.
5. a) We hypothesize that educational attainment PRS is higher in cases and controls recreational cannabis-users, compared with non-users; b) We hypothesize that bipolar PRS will be able to predict a higher IQ in cases that are lifetime cannabis recreational-users, alone or in interaction with a higher educational attainment PRS.
6. We hypothesize a different schizophrenia/bipolar PRS profile in cases who never used cannabis compared to heavy-users; i.e. higher schizophrenia PRS in cannabis non-users, alone or in interaction with higher social communication difficulties.

Additionally, we plan to test (reverse model) if cannabis heavy-use in cases and in controls is better predicted by: lower social communication difficulties or higher schizophrenia PRS scores, once have taken into account other pattern of cannabis use (type and potency in THC of cannabis use and age at first use).

References:

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Data needed for the study:

- Genotype data from WP2cases and controls.
- Psychosis Polygenic (Schizophrenia and Bipolar) scores data from PGC training
- Training sets data to build Educational Achievement and Autism like-trait PRSs
- PAS
- WAIS
- MRC1 and 2
- CEQ
- TAL and CEQ other drugs (for confounders)
- OPCRIT

Plan for statistical analysis (overall strategy): as principal analysis,risk profile scores will be inserted into the original model, already used to obtain the results in the first study, in order to achieve statistically comparable results, i.e. a factorial ANCOVA where PRSs, group belonging, different pattern of cannabis use will be the main predictors of premorbid adjustment scores (main effects and possible interactions).
Exploratory analyses will be performed by reversing the model into a multinomial regression with different patterns of cannabis use as outcome and premorbid and PRSs as independent predictors (once tested for significance).
Country and several other confounders (age, gender, ethnicity, country…other drugs) will be inserted in each of the the analysis and tested for significance.

Other analyses/methods: will be later developed once conducted preliminary analyses

Involvement of external Parties (non EU-GEI): no

IPR check:

Timeframe: Analysis and first writing to occur by the end of2018.