Synopsis for EU-GEI Publication

Synopsis no.: *S2.35*

Preliminary title: Polygenic risk scores for major psychiatric disorders explain differences in patterns of clinical and subclinical psychosis dimensions among cannabis users: a case-control analyses

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Publication category: Secondary publication following WP2 cannabis core paper and symptom dimension core paper

Working and writing group: Uli Reininghaus, Diego Quattrone (Dimensions), Craig Morgan; WP2 cannabis: Marta Di Forti, Robin Murray, Giada Tripoli; Cardiff group: Mick O' Donovan and Alex Richards; Jim van Os and Pak Sham

Work Packages involved: WP2 and Cardiff Group

Partners involved from whom candidate co-authors (*additional to working and writing group*) should be nominated: Cathryn Lewis and Paul O'Reilly (SGDP, IOPPN)

Objectives (scientific background, hypothesis, methods, and expected results):

Whereas the existence of a discrete 'cannabis psychosis' is uncertain, there is strong evidence that cannabis use both increases the risk of psychosis and worsens the natural course of the disorder. Indeed, psychotic disorders are extremely complex and there is considerable interest in the possibility that a dimensional approach provides a better basis for investigating their heterogeneity, the underlying biology, and the impact of environmental factors on their course. This method considers the continuous distribution of symptoms such as delusions and hallucinations rather than the traditional Kraepelinian dichotomy. Moreover, psychosis might be manifested at subclinical levels and its expression in the general population is characterized by different levels of severity.

It is still unclear whether genetic liability for major psychiatric disorders, as summarised in Polygenic risk score(s), plays a role in shaping psychopathology among cannabis users.

Aims

- To establish if psychotic patients are heterogeneous in terms of psychopathological presentation and if this reflects their exposure to cannabis use; i.e. symptom dimensions may arise from distinct mechanisms in cannabis-associated psychosis;
- To elucidate the role played by Polygenic Risk scores (PRS) for major mental disorders (MMD) such as: Depression, Bipolar Disorder and Schizophrenia in determining cannabis-associated psychopathology;
- To examine the extent to which cannabis use increases subclinical experiences of psychosis, in the general population in the context of individual differences in MMD PRSs.

Methods

1) In collaboration with Uli Reininghaus and Jim van Os, a) in cases, confirmatory factor analysis will be performed on OPCRIT items with the aim to define specific symptom dimensions and a general psychosis factor. Moreover, b) in controls, positive, negative and depressive symptom dimensions will be examined using the CAPE (Community Assessment of Psychic Experiences, self-administered) and the SIS-R (Structured Interview for Schizotypy, clinical interview).

2) Through the factor analysis we will have obtained distinct dimension scores using regression methods to relate each dimension score to cases with and without cannabis use/tobacco/drug use.

Furthermore, I will relate CAPE and SIS-R subscale scores to controls with and without cannabis/tobacco/drug use. In this way, I will examine the extent to which risk factors such as cannabis use increase subclinical experiences of psychosis, as part of a phenomenological continuity in the general population.

3) In collaboration with Paul O' Reilly and Professor Cathryn Lewis I will generate alongside the Schizophrenia PRS from Cardiff a PRS for Depression and for Bipolar Disorder.
I will investigate how differences in the distribution of each PRS might affects patterns of symptoms and subclinical experiences among cannabis users.

I expect:
1. Psychopathology at psychosis onset to be qualitatively and quantitatively affected by pattern of cannabis use and MMD PRSs.
Specifically, first episode psychotic patients with a premorbid cannabis use, especially daily or high-potency cannabis users, would demonstrate a worse general psychopathology and more positive psychotic symptoms than the patients who did not use cannabis.

2. Psychotic experiences / proneness associated with pattern of cannabis use in healthy controls to be modified by differences in Psychosis PRS.
Specifically, controls using cannabis would present with more positive psychotic experiences than non-users.

3. Cannabis data and PRS scores would explain significantly more variance in both symptom dimensions in cases and separately in subclinical symptom dimensions in controls than pattern of cannabis use data only.

Data needed for the study: CEQ (cannabis and other drugs); OPCRIT (items); TAL (tobacco); SIS-R; CAPE; Basic sociodemographic from MRC1 & 2; WP2 GWAS data

Plan for statistical analysis (overall strategy):
1. To test if the heterogeneity of psychosis is best represented by a general psychosis factor and five symptom dimensions, multidimensional item response model estimations will be conducted on OPCRIT items using Mplus. Different alternative item-response models (unidimensional, multidimensional, bi-factor) will be examined using the log-likelihood, the Akaike information criterion (AIC), the Bayesian information criterion (BIC), and the sample size -adjusted Bayesian information criterion (SABIC).
2. To assess to what degree associations between pattern of cannabis use and symptom dimensions are independent, regression analyses will be conducted correcting for other drugs and tobacco use.
    1. PRSice will be used to generate the PRS
    2. Nagelkerke's R squared analyses of variance will be used to estimate if differences in symptoms dimensions are explained significantly better adding to the model with cannabis use alone also MMD PRS.

Other analyses/methods:
At a later stage Machine learning approaches

Involvement of external Parties (non EU-GEI): Professor Cathryn Lewis, SGDP, IOPPN PhD supervisor

IPR check:

Timeframe: August 2017

Additional comments: