Transdiagnostic symptom dimensions and genetic risk scores at first episode psychosis

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Background
The hot question in psychiatric nosology

• Categorical diagnostic classification may not reflect clear biological entities

Kraepelin

Manic-depressive insanity

Dementia praecox

Affective Psychosis
(Bipolar disorder, Psychotic Depression)

Non Affective Psychosis
(Schizophrenia, Schizoaffective disorders)
Aims and hypotheses

1. Examining the dimensional structure of psychopathology in the EUGEI study

2. Examining how cannabis use shapes psychopathology at illness onset

3. Examining the effects of common genetic variants associated with Major Mental Disorders, on general and specific psychotic symptom dimensions
First Episode Psychosis (FEP) sample

Final sample size:
2182 FEP cases with available psychopathology information
Measurements

• Medical Research Council (MRC) Sociodemographic Schedule was used for sociodemographics (Mallett, 1997)
• The OPerational CRITeria (OPCRIT) system was used to assess all the different aspects of psychopathology (McGuffin et al., 1991)
• The Schedule for Deficit Syndrome (SDS) was used to assess negative symptoms (Kirkpatrick et al., 1989)
• The Cannabis Experience Questionnaire – modified version (CEQ_{EU-GEI}) was used to collect extensive information on cannabis use (Di Forti et al.)
• Samples were genotyped using Illumina HumanCoreExome-24 BeadChip array
Aims and hypotheses

1. Examine the dimensional structure of psychopathology in the EUGEI study
   i. Does a general factor of psychopathology encompass affective and non-affective psychosis?
Bi-factor conceptualization of psychosis

(☐) Observed variables (No. of OPCRIT items)
(⊙) Unobserved variables (latent factors)
(→) Standardized item loading onto latent factors

Aims and hypotheses

1. Examine how cannabis use shapes psychopathology at illness onset
   i. Is psychopathology at FEP different in those using cannabis?

Donald Trump said he never smoked cannabis

Boris Johnson admitted having used cannabis as a student
Positive Dimension & Cannabis Use

Frequency
Less than everyday: 🌿
Everyday: 🌿🌿

Potency:
More than 10% THC: 🌿

HP=High Potency

Variance explained, $R^2=\text{6\%}$

Negative Dimension & Cannabis Use

Contrasts of Predictive Margins of Patterns of Cannabis Use

Negative symptom dimension

Never use
Less than daily - no HP
Less than daily - HP
Daily - no HP
Daily - HP

HP = High Potency
Aims and hypotheses

1. Examine effects of common genetic variants associated with Major Mental Disorders on general and specific psychosis dimensions
   i. We expect that schizophrenia PRS would be associated with more positive / negative symptoms; bipolar PRS with manic symptoms
Positive and Manic Dimensions & SZ - BIP PRS
Negative Symptoms & SZ PRS

Schizophrenia PRS

[Graph showing the relationship between Negative symptoms and SZ PRS quantiles]
What do we know about positive symptoms in the EUGEI so far

1. Does cannabis use impact on positive symptoms?
   Yes, it has a moderate effect consistently with some previous report (Ringen et al, 2016; Seddon et al., 2016)

2. Does SZ PRS impact on positive and negative symptoms?
   Yes, however the effect is small

3. Does cannabis use interact with SZ PRS in predicting positive symptoms?
   No, the effects are independent with each other
Endocannabinoids (eCB) - AEA (anandamide); 2-AG
Metabolizing enzymes - e.g., FAAH; NAAA; MAGL
Receptors - e.g. CB1R; CB2R; TRPV1

**Research questions**

To examine:
1) eCB risk alleles and psychosis outcomes
2) eCB risk alleles X cannabis use and psychosis outcomes;
3) eCB risk alleles and clinical presentation

Part of the eCB pathway based on Kyoto Encyclopaedia of Genes and Genomes database
Conclusions

• The psychosis structure at FEP can be conceptualized as being composed of one general psychosis factor and five specific symptom dimensions
• FEP patients using cannabis, especially daily users of high potency types, expressed more psychopathology, in particular positive symptoms
• There was a small effect for SZ PRS on positive and negative symptoms, and for BIP PRS on manic symptoms
• Further research will examine the impact of endocannabinoid signaling and transdiagnostic symptom dimension