Acute effects of cannabinoids on addiction endophenotypes are moderated by genes encoding the CB1 receptor and FAAH enzyme


University College London
Conflicts of interest

I have no COIs
1. Genetic variation accounting for approximately 40% to 60% of the variance of the total risk of problematic drug use in vulnerable individuals (Nestler et al., 2013).

2. Meta-analyses have found that polymorphisms in **CNR1** and **FAAH** genes have been associated with cannabis, alcohol, nicotine, and cocaine dependence (Lopez-Moreno et al., 2013).

   - **CNR1** gene encodes CB1 receptor
   - **FAAH** gene encodes FAAH enzyme (breaks down eCBs)

3. Our approach investigate the neurocognitive endophenotypes of CUD after acute cannabinoid administration, which may be more valid than a single dichotomous variable such as a diagnosis of CUD itself.

   Endophenotype = intermediate phenotype

   “quantitative neurobehavioral traits that index genetic susceptibility for a psychiatric disorder”
Aims and hypotheses

To investigate if and how genetic variants in the endocannabinoid system, in particular the CB1 receptor (rs1049353 and rs806378) and the FAAH enzyme (rs324420), would modulate the acute response to cannabinoids, in relation to promising endophenotypes: cannabis-related satiety, the salience of appetitive cues, and craving.

CNR1 rs1045393 A allele carriers (versus G carriers)
rs806378 T carriers (versus C carriers)
FAAH 324420 C carriers (versus A carriers)

would show greater indicators of CUD which would be evidenced by greater drug cue salience, lower satiation and greater craving after intoxication with THC.
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CNR1 rs1045393 A allele carriers (versus G carriers)
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FAAH 324420 CC carriers (versus AA/AC carriers)

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METHOD

48 cannabis users genotyped for CNR1 (rs1049353, rs806378) and FAAH (rs324420)

Placebo
8mg THC
8mg THC + 16mg CBD
16mg CBD

Endophenotypes
1. Cannabis-induced satiety assessed with Bodily Symptoms Scale
2. Cannabis craving as assessed with the Marijuana Craving Questionnaire
3. Drug Cue Salience/Attentional Bias task
Therefore SDS and Last use of cannabis were included in the analysis as covariates, but did not modify the results.
Homozygote GG carriers of CNR1 rs1049353 showed reduced wanting after both THC measures, but A carriers show no such reduction in state satiety.

H1: A carriers show signals of addiction

Drug X Genotype interaction

\[ F_{3,105} = 4.192, \ p = .008, \ \eta^2 = .05 \]
CNR1 rs1049353 GG homozygotes vary by cannabinoid administration. A” carriers’ attentional bias remains relatively constant.

H1: A carriers show signals of addiction

Drug X Genotype interaction

\[ F_{3,120} = 3.108, \ p = .029, \ \eta^2 = .03 \]

Bonferroni corrected p values are displayed for the drug x genotype interaction.
FAAH rs324420 “A” carriers’ attentional bias remains relatively constant whilst CC homozygotes vary by cannabinoid administration.

H1: CC carriers show signals of addiction

Drug X Genotype interaction

$F_{3,126} = 3.385, p = .020, \eta^2 = .003.$

Bonferroni corrected $p$ values are displayed for the drug x genotype interaction.
Strength & Limitations

**STRENGTHS**

1. Our endophenotypes have strong theoretical and empirical clinical relevance to CUD, potentially more than diagnostic criteria alone

2. Highly controlled experimental design.

3. Acute cannabinoid administration

**LIMITATIONS**

1. Behavioral genetics approach – replicability?

2. Sample size based on THC effects not genetics

3. Unable to externally validate the consequences of the SNPS e.g. anandamide plasma levels
TAKE HOME MESSAGE

Variation in eCBs genetics, specifically CNR1 (rs1049353 and rs806378) and FAAH (rs324420) predicted drug cue salience (attentional bias) and feelings of cannabis-induced satiety but not craving. As such, this study provides preliminary evidence of neurocognitive mechanisms through which eCBs genetics may influence vulnerability to cannabis use disorder.
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Chandni Hindocha¹,²,⁵ | Tom P. Freeman¹,²,³,⁴ | Grainne Schafer¹ | Chelsea Gardner¹ | Michael A.P. Bloomfield¹,²,⁵,⁶ | Elvira Bramon⁶,⁷,⁸ | Celia J.A. Morgan¹,⁹ | H. Valerie Curran¹,⁵

http://tiny.cc/CNR1
Thanks for listening!! Questions?

Contact me: c.hindocha@ucl.ac.uk