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

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Conflicts of interest

I have no COIs

Background

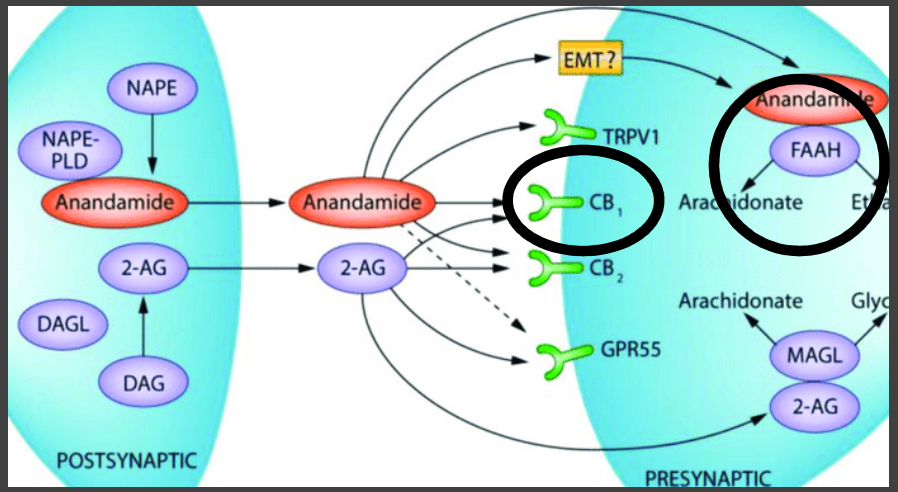
1. Genetic variation accounting for approximately 40% to 60% of the variance of the total risk of *problematic drug use* in vulnerable individuals *(Nestler et al, 2013).*

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)

~~rs806378 T carriers (versus C carriers)~~

FAAH 324420 CC carriers (versus AA/AC 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.

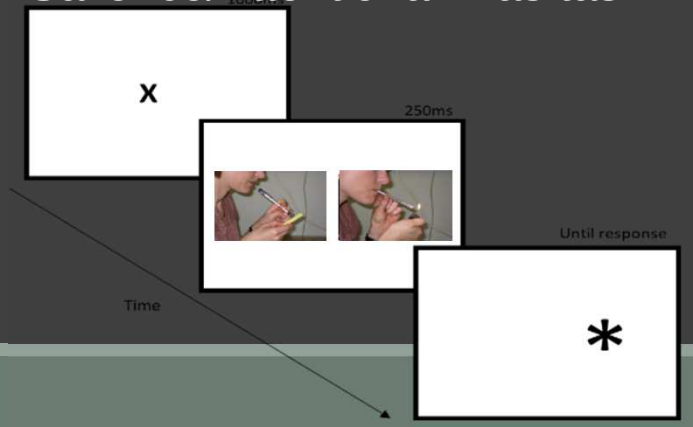
METHOD

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

- Placebo
- 8mg THC
- 8mgTHC +16mgCBD
- 16mg CBD

<u>Endophenotypes</u>

1. Cannabis-induced satiety assess with Bodily Symptoms Scale
2. Cannabis craving as assessed with the Marijuana Craving Questionnaire
3. Drug Cue Salience/Attentional Bias task



RESULTS 1

TABLE 1 Means (SD) for demographic, mental health, and cannabis use variables for each of the genotype groups

	CNR1 rs1049353			CNR1 rs806378			FAAH rs324420		
	GG	AA/AG	Test Statistic	CC	CT/TT	Test Statistic	CC	AA/AC	Test Statistic
Total *N* (*N* female)	20 (7)	22 (6)	$\chi^2(1)$=.293^{ns}	18 (6)	27 (8)	$\chi^2(1) = 0.069^{ns}$	30 (7)	14 (7)	$\chi^2_1 = 3.129^{ns}$
Age	21.90 (1.94)	21.59 (1.94)	$F_{1,40} = 0.265^{ns}$	21.44 (1.98)	22.00 (1.79)	$F_{1,43} = 0.953^{ns}$	21.87 (1.92)	21.79 (1.72)	$F_{1,43} = 0.018^{ns}$
Race/ethnicity (self-reported)									
White British	14	17		12	20		23	8	
Other ethnic group	6	5	$\chi^2(1) = 0.28^{ns}$	6	7	$\chi^2(2) = 0.005^{ns}$	7	5	$\chi^2_1 = 1.03^{ns}$
Frequency of cannabis	19.75 (10.95)	17.72 (10.21)	$F_{1,40} = 0.394^{ns}$	20.36 (10.15)	17.98 (10.82)	$F_{1,43} = 0.548^{ns}$	19.53 (17.21)	17.21 (10.21)	$F_{1,42} = 0.452^{ns}$
Severity of dependence	4.05 (3.62)	2.09 (2.21)	$F_{1,40} = 4.585$, $p = .038$*	3.55 (3.70)	2.56 (2.47)	$F_{1,43} = 1.187^{ns}$	3.47 (3.26)	1.71 (2.16)	$F_{1,42} = 3.345^{ns}$
Last use of cannabis	3.25 (3.17)	7.81 (25.09	$F_{1,40} = 0.652$	2.94 (1.98)	8.00 (23.14)	$F_{1,43} = 0.848^{ns}$			
Years of cannabis use	6.80 (2.31)	6.02 (3.05)	$F_{1,40} = 0.854^{ns}$	6.00 (2.57)	6.31 (2.91)	$F_{1,43} = 0.138^{ns}$	6.83 (2.64)	4.96 (2.68)	$F_{1,42} = 3.557$, $p = .035$*
SPQ total	19.05 (12.41)	16.55 (15.86)	$F_{1,40} = 0.320^{ns}$	19.83 (13.43	15.15 (14.32)	$F_{1,43} = 1.214^{ns}$	14.07 (9.92)	22.36 (19.46)	$F_{1,42} = 3.542^{ns}$
BDI	13.30 (9.42)	7.91 (8.87)	$F_{1,40} = 3.651^{ns}$	11.96 (10.79)	8.48 (8.25)	$F_{1,43} = 1.485^{ns}$	9.23 (9.16)	10.79 (10.32)	$F_{1,42} = 0.253^{ns}$
STAI	43.50 (11.40)	40.41 (8.81)	$F_{1,40} = 0.976^{ns}$	42.44 (11.55)	40.04 (9.63)	$F_{1,43} = 0.575^{ns}$	40.47 (10.95)	42.14 (10.95)	$F^{1,42} = 0.239^{ns}$

Note. BDI: Beck Depression Inventory; ns; not significant; STAI: State-Trait Anxiety Inventory.

[a]Welch's test.

[b]It includes white other, mixed white and black Caribbean, mixed white and black African, any other mixed background, Asian/British Asian, any other Asian/British Asian background, Black/British Caribbean, Chinese, and any other ethnic group.

*It indicated significant difference at $p \leq .05$.

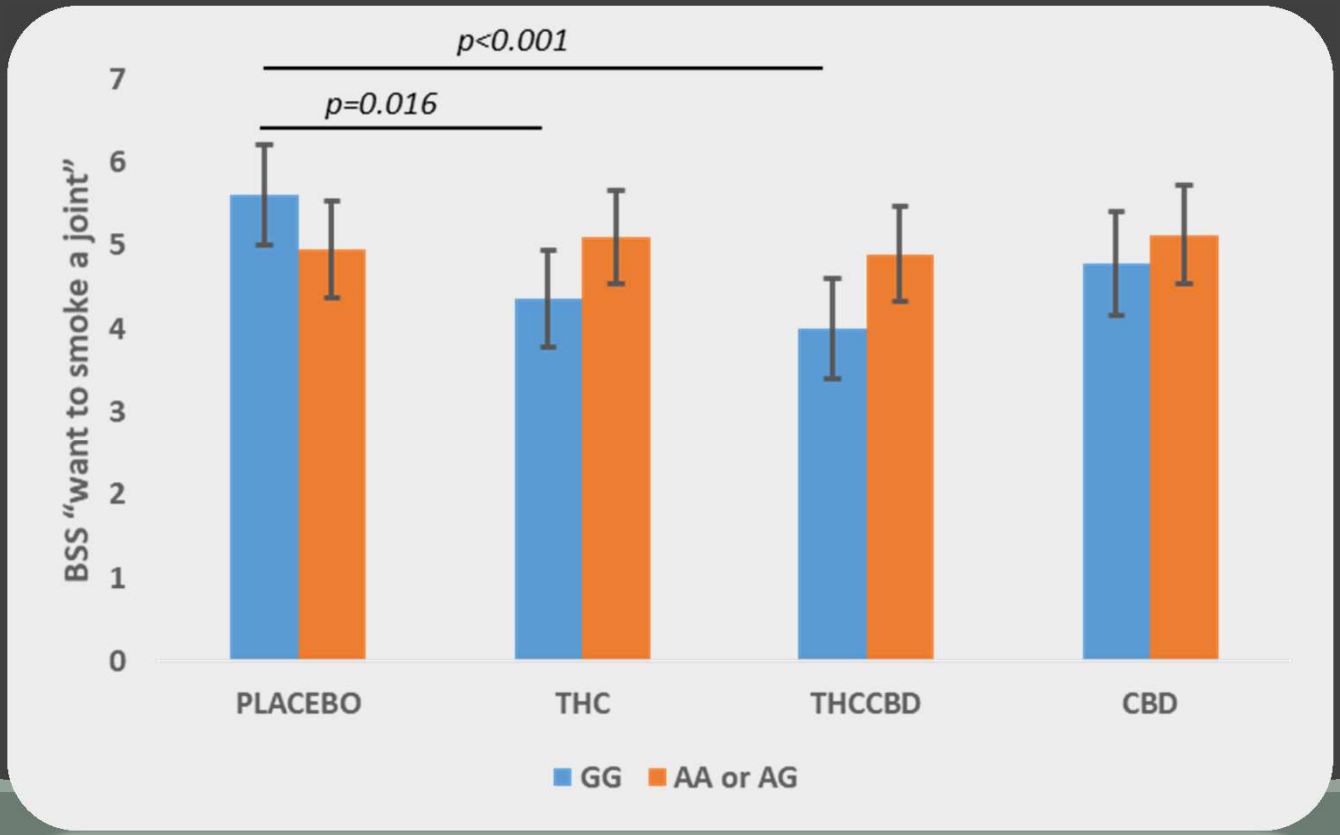
Therefore SDS and Last use of cannabis were included in the analysis as covariates, but did not modify the results

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

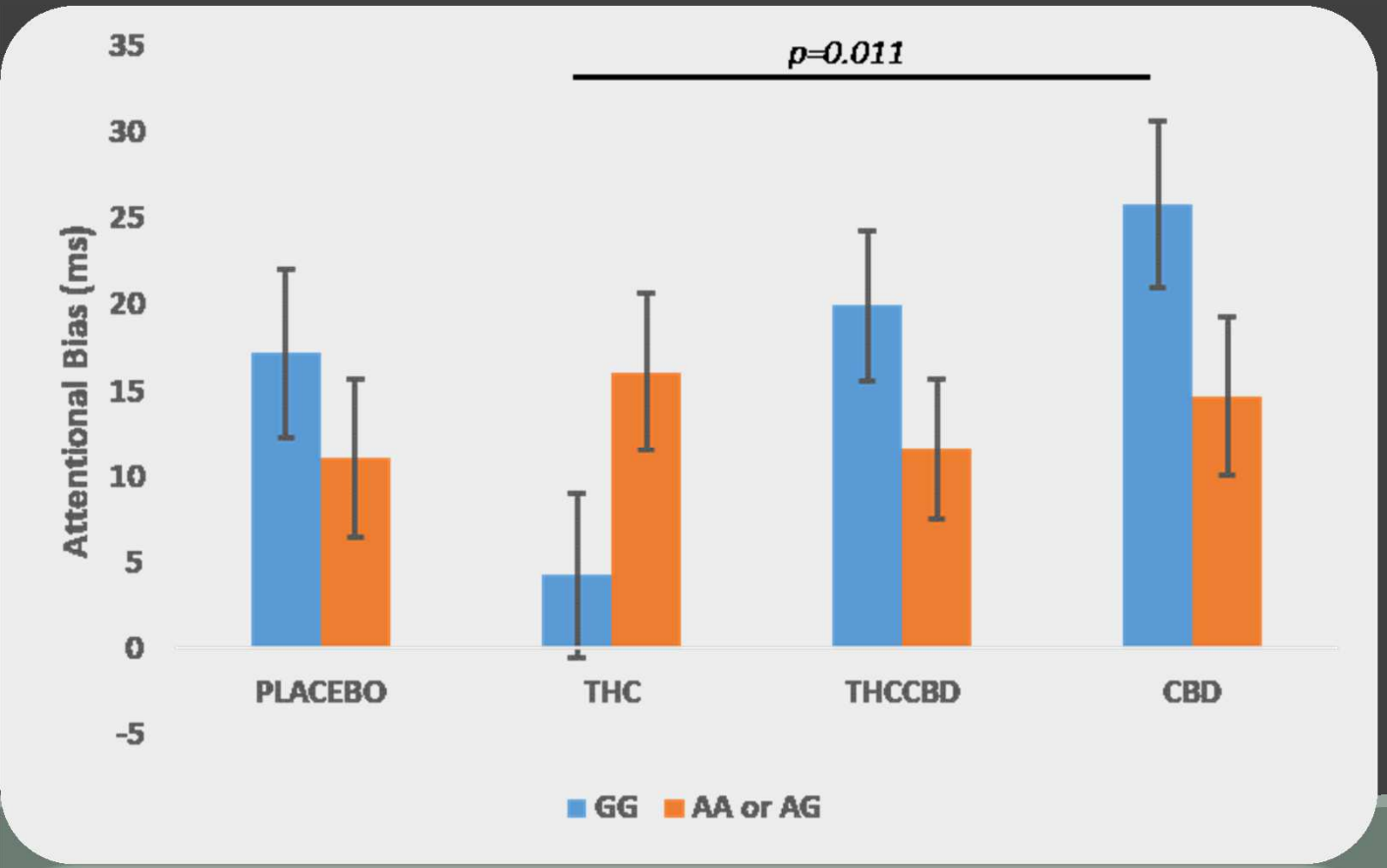
Drug X Genotype interaction

$F_{3,105} = 4.192$, $p = .008$, $\eta_2 = .05$



Bonferroni corrected p values are displayed for the drug x genotype interaction.

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, *η*2 = .03

Bonferroni corrected p values are displayed for the drug x genotype interaction.

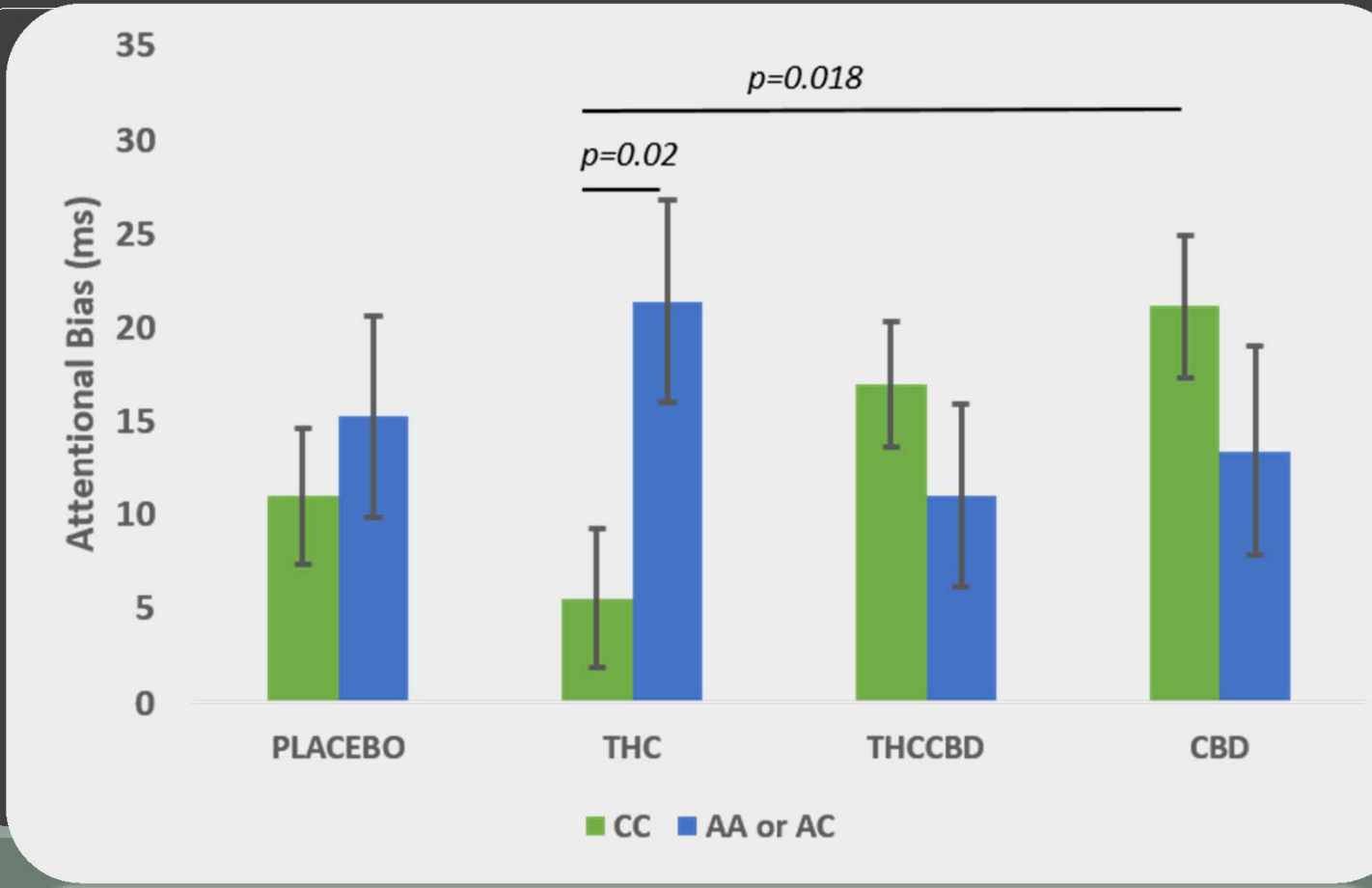
FAAH rs324420 "A" carriers' attentional bias remains relatively constant whilst CC homozygotes vary by cannabinoid administration.

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.

ORIGINAL ARTICLE

WILEY Addiction Biology SSA

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

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http://tiny.cc/CNR1

Thanks for listening!! Questions?

@UCL_CPU

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