IMPACT OF FAAH GENETIC VARIATION ON FRONTO-AMYGDALA FUNCTION DURING EMOTIONAL PROCESSING

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INTRODUCTION

- **Endogenous cannabinoid (eCB) system**: involved in emotion processing, anxiety and stress response
- FAAH (fatty acid amide hydrolase) is a catabolic enzyme and primary regulator of anandamide signalling (AEA) in the brain, an eCB and agonist on the CB1 receptor (Cravatt et al., 2001)
- ***FAAH* C385A** is a single nucleotide polymorphism (SNP; rs324420) within the FAAH gene; results in reduced FAAH protein expression, enzymatic activity and increased AEA levels (Chiang, 2004)
- A-allele of *FAAH* C385A is associated with greater **fear extinction**, enhanced **structural** and **functional resting state connectivity** and decreased **anxiety-related behaviors** in both mice and humans (Dincheva et al., 2014; Gee et al., 2016)
- Functional coupling between prefrontal regions and amygdala contributes to successful emotion regulation (Banks et al., 2007; Ochsner et al., 2012; Etkin et al., 2015)

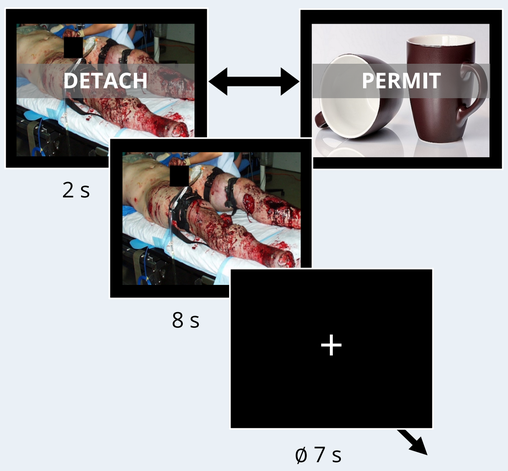
Goal of the study

(1) Replicate the findings of Dincheva et al. (2014) showing stronger fronto-amygdala **resting state connectivity** in A-allele carriers of *FAAH* C385A

(2) Extend these findings on **emotion reactivity** and **emotion regulation** by examining the impact of *FAAH* C385A on task-related **functional connectivity** and **functional activity** during a standard laboratory reappraisal task

METHODS

- Sample: *N* = 48 healthy adults (26♀, 22♂), mean age = 24.7 yrs, SD = 4.0 yrs, range 18–36 yrs
- No history of medical, neurological, or psychiatric illness or treatment, central European origin
- **8-min resting state session, laboratory reappraisal task**



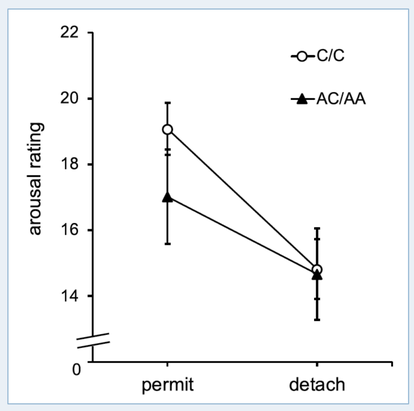
- Design according to Diers et al., 2014 (four blocks, arousal rating at the end of each block)
- 64 negative and neutral IAPS and EmoPics
- **Emotion reactivity**: permit negative > permit neutral
- **Emotion regulation**: detach negative > permit negative

- Genotype frequencies: 58% for C/C (*n* = 28), 38% for C/A (*n* = 18), 4% for A/A (*n* = 2)
- Genotypes were in Hardy–Weinberg equilibrium (*p* = .67)
- Analyses were done with CONN toolbox (16.b) for connectivity and SPM12 for functional activity
- No *FAAH* C385A differences in any of the questionnaires

Table 1. Descriptive statistics for the behavioral results

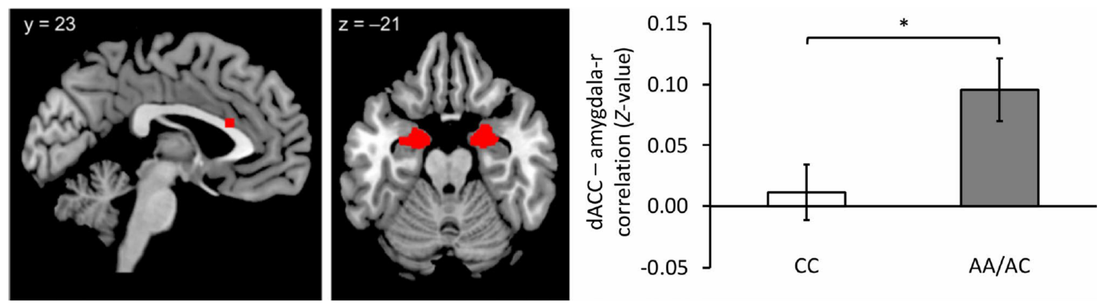
	FAAH C385A A-allele carriers *n* = 20		*FAAH* C385A C/C homozygotes *n* = 28	
	M	*SD*	*M*	*SD*
Sex (female/male)	13/7		13/15	
Age	24.8	3.6	24.6	4.4
STAI-T	42.7	6.5	41.4	7.7
PANAS-NA	21.9	6.4	22.9	5.0
NEO-N	23.3	7.0	20.6	6.6
ERQ reappraisal	27.6	5.6	29.2	5.4
ERQ suppression	14.9	4.1	14.6	4.9
Emotional arousal ratings				
Negative permit	23.1	7.4	25.5	3.9
Negative detach	19.9	7.2	20.5	6.0
Neutral permit	10.9	6.9	12.6	6.3
Neutral detach	9.4	5.9	9.1	5.0

RESULTS



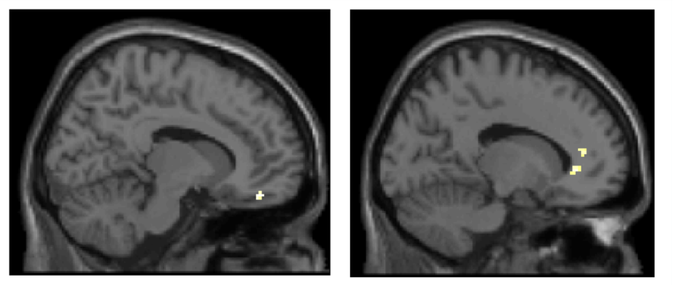
(Left). Self-reported arousal compared between permit vs. detach of negative and neutral pictures in *FAAH* A-allele carriers relative to C/C homozygotes (*p* = .071)

(Down, left). ROI mask in Montreal Neurological Institute standard space of dorsal anterior cingulate (dACC) and left and right amygdala. (Down, right). Resting state functional connectivity of dACC and right amygdala in *FAAH* A-allele carriers relative to C/C homozygotes ($p_{FWE} < .05$)



Region	H	*x*	*y*	*z*	*k*	*Z*	*p* (uncorr)
Emotion reactivity (permit negative > permit neutral)							
FAAH-A > FAAH-C							
Gyrus rectus	R	12	44	− 18	13	3.49	< 0.001
FAAH-C > FAAH-A							
No suprathreshold voxels							
Emotion regulation (detach negative > permit negative)							
FAAH-A > FAAH-C							
Anterior cingulum	R	22	44	0	95	3.62	< 0.001
Anterior cingulum	L	− 14	42	12	10	3.35	< 0.001
White matter	L	− 14	36	0	22	3.55	< 0.001
FAAH-C > FAAH-A							
No suprathreshold voxels							
Emotion regulation (permit negative > detach negative)							
FAAH-A > FAAH-C							
No suprathreshold voxels							
FAAH-C > FAAH-A							
Insula/inferior orbital frontal cortex	L	− 18	34	0	76	3.87	< 0.001
White matter	R	24	42	0	39	3.65	< 0.001

Table 2. Peak voxels and cluster sizes from whole-brain analyses of *FAAH* genotype effects on emotion reactivity and emotion regulation. *p* < .001, uncorrected



Whole-brain analysis for emotion reactivity (left) and emotion regulation (right) depending on *FAAH* C385A genotypes (A>C). *p* < .001, uncorrected

DISCUSSION

- A-allele carriers of *FAAH* C385A show stronger resting state connectivity between amygdala and dACC
- Preliminary evidence for differential functional activity of A-allele carriers during emotion reactivity and emotion regulation
- No differences in task-related connectivity, self-reported anxiety, negative affect and use of emotion regulation strategies
- Further studies should validate and extend these findings using further paradigms on emotional processing, larger sample sizes and polygenetic approaches, as well as gene × environment interactions and epigenetic mechanisms

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