PERIPHERAL SEROTONIN TRANSPORTER DNA METHYLATION IS LINKED TO INCREASED SALIENCE NETWORK CONNECTIVITY IN FEMALE ADOLESCENTS WITH ANOREXIA NERVOSA

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INTRODUCTION

- The serotonin system has been associated with mood regulation, anxiety and the modulation of appetite → a neurotransmitter system of interest for anorexia nervosa (AN) (1)
- Existing studies report no evidence for genetic (2) or epigenetic variation (3) of the serotonin transporter gene (SLC6A4) in AN
- Integrating epigenetic (changes in methylation) and neuroimaging data may allow us to test the complex interplay between genes, brain function and abnormal behaviour
- Resting state functional connectivity (rsFC) a imaging technique sensitive to changes in "communication" between spatially separated brain regions and hence has been argued to be more sensitive to the effects of genetic and environmental variation in heterogeneous phenotypes such as psychiatric disorders
- Dysfunctions of the salience network (SN; compromising the anterior cingulate cortex and the insula) has been associated with AN (4) and epigenetic variation of the SLC6A4(5)

Aim: To test the proposed epigenetic-brain-behavior pathway for AN by examining the association between SLC6A4 methylation, SN rsFC and eating disorder symptoms in acutely ill AN patients compared to matched HC.

METHODS

	AN (n=55)	HC (n=55)
Age	16.15 ± 3.07	16.17 ± 3.07
BMI-SDS*	-3.21 ± 1.13	0.09 ± 1.04
Age of onset	13.82 ± 2.63	n.a.
EDI-2 total*	202.27 ± 47.28	142.85 ± 26.82
BDI-II*	21.49 ± 10.92	5.78 ± 6.27
Mean SLC6A4 methylation	5.45 ± 1.51	5.48 ± 2.28

- Collected rsFC data were decomposed using independent component analysis (ICA)
- Two omponents mapping on the SN were identified using spatial correlation with a mask (6)

- We used bisulfite pyrosequencing to analyze blood DNA methylation within the promoter region of SLC6A4
- Quantitative DNA methylation at 15 CpG sites within the promoter-associated CpG island of SLC6A4
- We focussed on 15 CpG sites within the amplicon 3 of a 799-bp region

RESULTS

- Increased rsFC of the SN at the anterior insula
- No group difference in SCL6A4 methylation levels
- We identified a positive relationship between SLC6A4 methylation levels and rsFC between the dorsolateral prefrontal cortex and the SN in patients with AN compared to healthy controls.
- Increased rsFC in the SN mediated the link between SLC6A4 methylation and eating disorder symptoms in patients with anorexia nervosa (r=0.349; p=0.010).
- Results were not influenced by age, intake of SSRI and cigarette consumption
- We confirmed findings of rsFC alterations for CpG-specific methylation at a locus with evidence of methylation correspondence between brain and blood tissue.

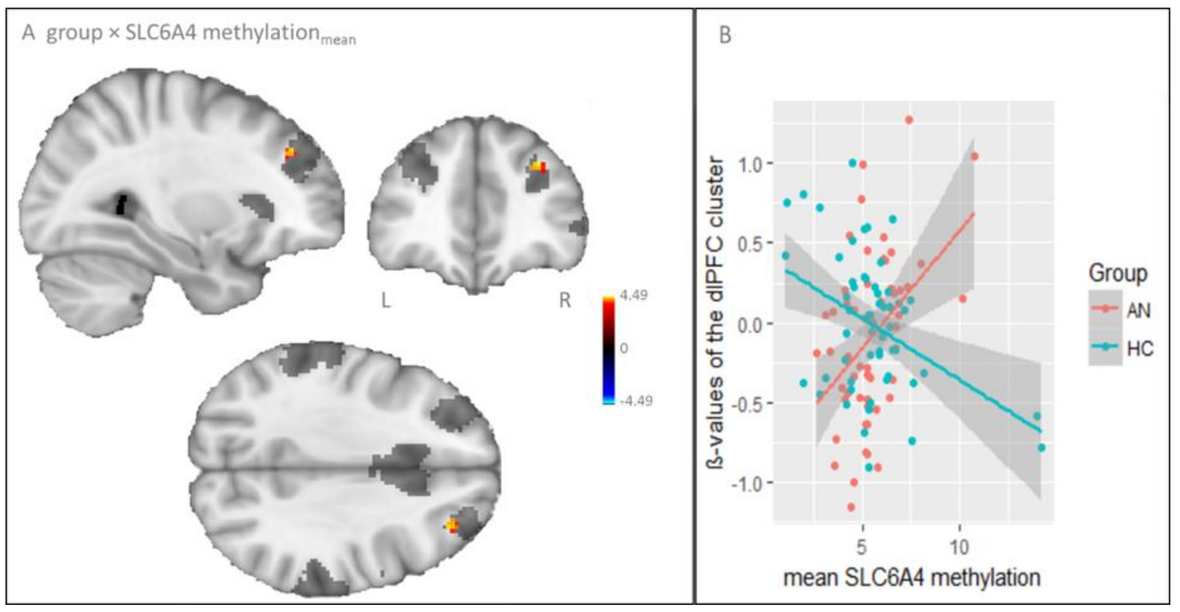

Fig.1) Group × SLC6A4 methylation$_{mean}$ interaction; A) Results of the group × SLC6A4 methylation$_{mean}$ interaction analysis B) Plot of association of the extracted β-values of the dlPFC cluster and mean SLC6A4 methylation separately for AN and HC

CONCLUSION

- The results could be interpreted as an AN-specific methylation-related increased involvement of the dlPFC in the SN and might relate to elevated cognitive or self control – a much debated characteristic of AN.
- Our findings suggest that a serotonin-related epigenetic-brain-behavior pathway is also relevant for AN.
- It sheds light on the neuro-biological mechanism of how epigenetic variation of the SLC6A4 gene may associate with functional connectivity in the SN that is specifically linked to AN symptoms.

Limitation

- the cross-sectional nature of the study does not allow determining a causal link
- methylation measures were assessed in peripheral tissue, which cannot necessarily be generalized to neural tissue

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