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Methylation of HPA axis related genes in men with hypersexual disorder

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Highlights:

1. Patients with hypersexual disorder had reduced levels of methylation in a locus of the CRH gene.
2. Patients with hypersexual disorder had higher (TNF)-α levels compared to healthy volunteers.

Hypersexual Disorder (HD) defined as non-paraphilic sexual desire disorder with components of compulsivity, impulsivity and behavioral addiction, and proposed as a diagnosis in the DSM 5, shares some overlapping features with substance use disorder including common neurotransmitter systems and dysregulated hypothalamic-pituitary-adrenal (HPA) axis function. In this study, comprising 67 HD male patients and 39 male healthy volunteers, we aimed to identify HPA-axis coupled CpG-sites, in which modifications of the epigenetic profile are associated with hypersexuality.

The genome-wide methylation pattern was measured in whole blood using the Illumina Infinium Methylation EPIC BeadChip, measuring the methylation state of over 850 K CpG sites. Prior to analysis, the global DNA methylation pattern was pre-processed according to standard protocols and adjusted for white blood cell type heterogeneity. We included CpG sites located within 2000 bp of the transcriptional start site of the following HPA-axis coupled genes: Corticotropin releasing hormone (CRH), corticotropin releasing hormone binding protein (CRHBP), corticotropin releasing hormone receptor 1 (CRHR1), corticotropin releasing hormone receptor 2 (CRHR2), FKBP5 and the glucocorticoid receptor (NR3C1). We performed multiple linear regression models of methylation M-values to a categorical variable of hypersexuality, adjusting for depression, **dexamethasone** non-suppression status, Childhood Trauma Questionnaire total score and plasma levels of TNF-alpha and IL-6.

Of 76 tested individual CpG sites, four were nominally significant ($p<0.05$), associated with the genes CRH, CRHR2 and NR3C1. Cg23409074 – located 48 bp upstream of the **transcription start site** of the CRH gene