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GENETIC DETERMINANTS OF MONOAMINE TURNOVER IN HUMAN CEREBROSPINAL FLUID: ASSOCIATIONS WITH 5-HT SEASONALITY AND MOOD SYMPTOMS

J. Luykx[1]

[1]Psychiatry, UMC Utrecht, Utrecht, Netherlands

Although monoamines are thought to be involved in seasonal mood disorders, it is unknown how such concentrations may impact seasonal variation in mood symptoms. Studies of monoaminergic seasonality and a possible influence of the serotonin transporter gene, *SLC6A4*, on serotonin seasonality have yielded conflicting results. To study this comprehensively, we first performed a genome-wide association study (GWAS) of monoamine metabolites in human cerebrospinal fluid (CSF). We then examined whether the S/L promoter polymorphism of the serotonin transporter gene (5-HTTLPR) affects seasonal changes in CSF serotonin metabolite levels. To translate our findings to the behavioral level, we tested for correlations of 5-HT seasonality values with mood symptoms.

The GWAS yielded a locus significantly associated with monoamine metabolite levels 20kb from *SSTR1* ($P = 4.92 \times 10^{-8}$), a locus that was shown to control expression of PDE9A, a gene previously implicated in monoaminergic transmission, major depressive disorder and antidepressant response. We additionally show evidence for involvement of the S allele with 5-HT seasonality (standardized $\beta = 0.12$, $P = 0.020$). Moreover, 5-HT seasonality correlated positively with depressive symptoms (Spearman's rho = 0.13, P = 0.018).

We demonstrate how genetic variation in a range of genes involved with neuronal activity influences monoamine metabolite levels in human CSF. We furthermore highlight a dose-dependent association of the 5-HTTLPR with 5-HT seasonality and a positive correlation between 5-HT seasonality and depressive symptomatology. The presented data provide new insights into the genetic determinants of 5-HT seasonality and its role in affective disorders.

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