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Predicting Serotonin Transporter Haplotypes Based on Reinforcement Learning.

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Background: Serotonergic neurotransmission has been implicated in risk assessment, processing of negative feedback, and encoding value and time interaction. In humans, central serotonin signals are usually inferred from naturally-occurring polymorphisms in genes that encode key proteins for the synaptic reuptake of serotonin, namely the serotonin transporter (SERT). The SERT gene has two well-studied functional polymorphisms: (1) the 5-HT transporter-linked polymorphic region (5-HTTLPR; long allele (L) = low serotonin, short allele = high serotonin), and (2) the serotonin transporter polyadenylation polymorphism (STPP; C allele = high, A allele = low serotonin).

Objectives: In this study, we investigated the interaction between variations in synaptic serotonin and reinforcement learning. We used machine learning to predict serotonin availability based on the subject's reinforcement learning performance.

Methods: We examined 215 healthy subjects with the haplotypes denoting high serotonin (SS/CC) or low serotonin (LL/AA) in the 5-HTTLPR and STPP polymorphisms. Subjects completed a probabilistic reinforcement learning task that dissociates positive and negative feedback. We

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assessed learning accuracy and response time for positive and negative feedback, prior trial type (positive, negative), and prior trial feedback (positive, negative, no feedback).

Results: Although there were no significant mean differences between the subject groups in the aforementioned measures, their probability distributions revealed unique patterns of variance, skewness, and kurtosis according to the serotonin haplotype. To highlight individual differences underlying the distribution moments, we trained machine learning classifiers to predict individual serotonin haplotypes based on cognitive performance. Classification results identified the high serotonin haplotype (SS/CC) with 92% accuracy (specificity), and the low serotonin haplotype (LL/AA) with 65% accuracy (sensitivity), with a total area under the curve of 84%.

Conclusion: Despite the absence of group mean differences, mathematical and statistical constructs focusing on individual differences can be much more informative for understanding the cognitive effects of serotonin. Given the clinical significance of serotonin in mood and anxiety disorders, our work could start a new research direction to use machine learning to autofill necessary biological variables for fine-tuning of psychotropic treatments.

Research Keywords: Serotonin, reinforcement learning, central tendency, distribution moments, machine learning.

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