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The Effects of Naturally-Occurring Interactions of Dopamine Vs. Serotonin Levels on Reinforcement Learning in Healthy Individuals

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Background: The neuromodulators dopamine and serotonin play key roles in reinforcement learning. While dopamine modulates positive feedback processing, serotonin facilitates aversive learning and behavioral inhibition. The dopamine transporter (DAT), coded by the DAT1 gene, regulates synaptic dopamine levels in the brain is. DAT1 exhibits a naturally-occurring variable number of tandem repeats polymorphism (VNTR) in its 3' untranslated region (3'-UTR). Similarly, the serotonin transporter (SERT) controls synaptic serotonin levels in the brain. SERT is coded by the SLC6A4 gene that has a polyadenylation polymorphism influencing the balance of two polyadenylation forms of SERT in the brain (STPP).

Objectives: Here, we investigate the impact of interaction between naturally-occurring dopamine and serotonin levels on reinforcement learning.

Methods: We examined the variable number of tandem repeats polymorphism (VNTR) in the 3' untranslated region (3'-UTR) of DAT1 alongside the serotonin transporter polyadenylation

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polymorphism (STPP) of SLC6A4 in 143 healthy volunteers. We grouped subjects into DAT1 VNTR 9-repeat homozygotes (high dopamine) and 10-repeat homozygotes (low dopamine), and SLC6A4 STPP C-allele homozygotes (high serotonin) and A-allele homozygotes (low serotonin).

Results: All subjects completed a probabilistic reinforcement learning task that dissociates learning from positive and negative feedback. Dopamine and serotonin levels affected learning from positive, but not negative, reinforcement. Dopamine levels modulated learning from positive reinforcement differently only in the context of low serotonin, with low dopamine under low serotonin being associated with better learning. Under high dopamine, subjects with high serotonin learned better from positive reinforcement. In the context of low dopamine, the opposite pattern ensued.

Conclusion: Our results argue in favor of an inverted U-shaped modulatory effect of serotonin on dopamine and reinforcement learning. Subsequent studies will investigate this gene-gene interaction in Parkinson's disease and major depressive disorder as it relates to cognitive function and response to treatment.

Research Keywords: Dopamine, serotonin, naturally-occurring genetic polymorphisms, reinforcement learning, inverted-U-shaped function.

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