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ABSTRACT

Serotonin Transporter Genotype Modulates the Effects of Dopamine Transporter Genotype on Learning from Positive and Negative Feedback

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People vary in their learning from positive or negative feedback. Feedback-based learning is modulated by two main neuromodulators, dopamine and serotonin. Dopamine is a key player in positive feedback processing, where it promotes behavioral activation to seek reward. Serotonin has been linked to negative feedback processing and behavioral inhibition. Dopamine and serotonin levels are regulated in the brain by transporters; the dopamine transporter (DAT) and serotonin transporter (SERT), which are encoded by DAT1 gene and SLC6A4 gene, respectively. Evidence implies that serotonin regulates dopamine release, since dopamine function in reward processing, while serotonin is exhibits behavioral inhibitor which suppresses behavior. The cognitive effects of the interaction between dopamine and serotonin remain to be elucidated. In this study, we are pursuing a multidisciplinary approach to study the molecular and cognitive effects of the interaction of naturally- occurring polymorphisms; the 3'-UTR of the DAT1 gene, a variable number tandem repeat (VNTR) which controls the expression of DAT, and the STTP in the SLC6A4 gene which regulates the expression of SERT mRNA. Also, we will construct a neurocomputational model to study the interactions between dopamine and serotonin in feedback-based learning. We recruited a sample of 450 healthy participants from Al-Quds University. All participants completed a probabilistic categorical feedback-based learning task that differentiates learning from positive and negative feedback. Our results suggest that genes that modulate dopamine and serotonin levels affected reward learning but not punishment learning. When we held SLC6A4 constant and varied DAT1 genotypes, there was better learning from both reward and punishment with higher dopamine levels (9-repeat carriers) in the context



of higher serotonin levels (short allele carriers). Conversely, there was no difference between DAT1 genotypes in learning from positive and negative feedback in the context of low serotonin levels (long allele homozygotes). When we held DAT1 genotypes constant, there were no differences between SLC6A4 genotypes in the context of high (9-repeat carriers) or low (10-repeat homozygotes) dopamine levels. These findings argue in favor of a modulatory role of serotonin on dopamine function. Future 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.