

Dopamine polymorphisms, striatal response and individual differences in reward-related behavior

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In the last decade, there has been tremendous progress in describing the neurobiology of appetitive drive. The collective results of animal and human studies implicate the amygdala, prefrontal cortex, thalamus and ventral striatum (VS) as main elements of the brain's appetitive circuitry. Pharmacological and genetic studies have demonstrated that the function of this distributed circuitry, particularly the VS, is exquisitely modulated by dopamine (DA). In the VS, DA availability is largely regulated by the dopamine transporter (DAT), and alterations in DAT function in the VS have been implicated in the pathophysiology of addiction. A putatively functional 40-bp VNTR element in the 3' UTR of the human DAT gene is associated with altered DAT density. The most common variants in European Americans are the 9- and 10-repeat alleles, found at frequencies of 30% and 70%, respectively. Although reported effects for neural, behavioral and clinical phenotypes have been variable, it has been suggested that the 10-allele represents a 'risk' factors in nicotine and alcohol addiction as well as ADHD. Using our imaging genetics strategy, we recently explored the impact of the DAT 3'VNTR 9- & 10-repeat alleles, which presumably affect DAT expression and subsequent DA availability in corticostriatal circuits, on the functional reactivity of the VS associated with positive and negative feedback in the context of monetary reward. Our BOLD fMRI data revealed significantly greater VS activation in 9-repeat carriers in comparison to 10-repeat

homozygotes. Moreover, the magnitude of VS activation was positively correlated with both novelty seeking and delay discounting, measures associated with behavioral impulsivity and increased risk for addiction. Prior in vivo imaging and in vitro data suggest that the 10-repeat is associated with relatively higher striatal DAT than the 9-repeat. In the context of our imaging genetics data, it is plausible that carrying a 9-repeat results in relatively lower striatal DAT and subsequently higher striatal DA, which in turn results in greater VS activity associated with reward. This genetically mediated bias could also contribute to increased sensitivity to rewarding behaviors/stimuli and increased risk for addiction. Our current findings, while preliminary, highlight the effectiveness of bridging different methodologies (e.g. neuroimaging and genetics) and increasing transdisciplinary dialogue in efforts to elucidate the biological mechanisms leading to the emergence of individual differences in appetitive behavior and risk for addiction.