Variability in paralimbic dopamine signaling correlates with subjective responses to d-amphetamine

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D-Amphetamine (dAMPH)-induced dopamine (DA) release in the ventral striatum (VS) has been positively associated with either dAMPH-induced euphoria or drug wanting, but these studies were limited in measuring DA D2/3 receptor availability (binding potential, BPND) only in the striatum with [11C]raclopride. The radiotracer [18F]fallypride allows estimation of D2/3 BPND in extrastriatal regions and can index dAMPH-induced DA release, measured as %ΔBPND from baseline/placebo.

Using fallypride PET, we searched for associations between subjective effects of dAMPH and DA signaling across the brain. Participants (n = 46, 23 male, age: 22 ± 2.9) completed PET scans after receiving either placebo or oral dAMPH (0.43 mg/kg). A simplified reference tissue (cerebellum) model was used to estimate BPND across the brain. %ΔBPND [%ΔBPND = (placebo BPND - dAMPH BPND)/ (placebo BPND) × 100%] maps were generated with positive values indicating increased release. Peak positive subjective responses to dAMPH vs. placebo were measured via the Drug Effects Questionnaire (DEQ) Feel, Like, High, and Want More ratings. Initial analyses focused on 35 DEQ responders (22 male, age: 21.9 ± 2.7) as participants lacking subjective responses (nonresponders) could hinder correlational analyses. DEQ ratings were regressed against both placebo BPND and %ΔBPND maps using SPM8. Cluster-level significance was set at p < 0.05 family-wise error corrected.

DEQ High positively correlated with placebo BPND in a large cluster (k, number of voxels) in ventromedial prefrontal cortex (vmPFC; k = 388, T = 4.5). DEQ Want More positively correlated with %ΔBPND in right VS (k = 275, T = 4.4), left insula (k = 215, T = 4.1), and vmPFC (k = 195, T = 4.2). Furthermore, all correlations remained significant when nonresponders were included and after controlling for dAMPH dose, plasma amphetamine levels, age, and sex.

This work indicates that D2 receptor signaling in vmPFC is associated with individual differences in subjective responses to dAMPH: placebo vmPFC BPND was positively correlated with subsequent dAMPH High and vmPFC %ΔBPND tracked with Want More ratings. The observation that differences in DA release in the insula correlated with drug wanting converges with data suggesting the importance of the insula in drug craving. Together these data highlight the importance of variability in DA signaling in specific paralimbic cortical regions in the subjective response to dAMPH, which may confer risk for abusing psychostimulants.