## **Dopaminergic Network Differences** in Human Impulsivity

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ndividuals vary widely in their capacity to deliberate on the potential consequences of their choices before they act. Highly impulsive people frequently make rash, destructive decisions, and trait differences in impulsivity strongly predict risk for externalizing psychiatric disorders (1-3).

Dopamine (DA) has been theorized to play a key role in impulsivity (4, 5), but the precise systemslevel mechanisms linking variation in DA signaling to trait differences in impulsivity remain unclear, particularly in humans. Extrapolating from preclinical and human findings of impulsivity-linked alterations in DA functioning, we have developed a neurobiological model of individual differences in human impulsivity. According to this model, highly impulsive individuals are characterized by diminished midbrain autoreceptor availability, which leads to enhanced DA cell firing and potentiated DA release in terminal fields following exposure to novel, salient, or rewarding stimuli.

To test this model, we scanned 32 physically and psychiatrically healthy volunteers with positron emission tomography and [18F]fallypride, a D2/D3selective ligand that labels striatal and extrastriatal receptors, at placebo and after oral administration of 0.43 mg/kg d-amphetamine (AMPH) (6). Each participant completed the Barratt Impulsiveness

Scale (BIS-11) (3). For each participant, we calculated voxelwise statistical parametric maps (SPMs) of D2/D3 receptor availability (binding potential, BP<sub>ND</sub>) and AMPH-induced DA release (percent change in [18F]fallypride binding from placebo; fig. S1) and correlated these SPMs with participants' BIS-11 total scores (6).

Trait impulsivity was inversely correlated with D2/D3 autoreceptor availability in the substantia nigra/ventral tegmental area (SN/VTA; Fig. 1A) and positively correlated with the magnitude of AMPH-induced DA release in the striatum (Fig. 1A). Consistent with an inhibitory influence of midbrain autoreceptors on DA release in terminal fields (7), SN/VTA D2/D3 BP<sub>ND</sub> was inversely correlated with striatal DA release after AMPH administration (r = -0.42 and -0.35 for left and right striatum, respectively, each P < 0.05). We used path modeling (mediation analysis) to test our mechanistic hypothesis that lower SN/VTA autoreceptor availability leads to impulsivity by enhancing stimulated DA release in the striatum. This analysis confirmed that the ability of SN/VTA D2/D3 BP<sub>ND</sub> to predict impulsiveness is at least in part mediated through the impact of SN/VTA autoreceptor availability on AMPH-induced striatal DA release (Fig. 1B).

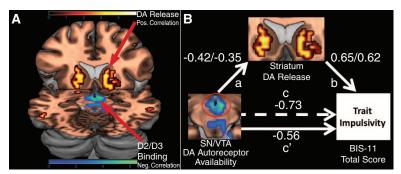


Fig. 1. (A) Rendering of two separate SPMs depicting negative correlations between BIS-11 scores and D2/D3 BP<sub>ND</sub> (cool colors) and positive correlations between BIS-11 scores and AMPH-induced DA release (warm colors) ( $P_{\text{corrected}} < 0.05$ ; image thresholded at t > 3). For D2/D3 BP<sub>ND</sub>, inverse associations emerged in the DA midbrain [anteriorly in the VTA, centered at 6, -3, -11 (x, y, z; Montreal Neurological Institute space)]. Peak coordinates for the striatal AMPH-induced DA release correlations are -16, 15, 5 (left) and 20, 23, -3 (right); cluster sizes are 167 voxels (left) and 216 voxels (right). Color bars represent z-statistic values. SPMs rendered on a T1-weighted magnetic resonance image template brain, with cuts at z = -11 and y = 16. (B) Path analysis demonstrating that the influence of midbrain D2/D3 availability on trait impulsivity is mediated through an impact on striatal AMPH-induced DA release. Path a shows coefficients for the effect of midbrain D2/D3 BP<sub>ND</sub> (cluster outlined with red circle) on right and left striatal DA release. Path b shows the coefficients for the effect of striatal DA release on trait impulsivity. Paths c and c' show coefficients for the total (dashed line) and direct (solid line) effects of midbrain D2/D3 BP<sub>ND</sub> on trait impulsivity. All coefficients standardized. Sobel test for mediation: Z = -1.94, P = 0.05.

To explore the relevance of enhanced striatal release to risk for substance abuse, we examined the relationship between AMPH-induced striatal DA release and subjective responses to AMPH. Increased striatal DA release predicted stronger subjective desire for more drug after AMPH treatment (drug "wanting" ratings from the drug effects questionnaire; r = 0.48 and 0.47 for left and right striatum, respectively, each P < 0.01). Given that heightened subjective "wanting" responses to initial stimulant exposure is a risk factor for future drug dependence (8) and that BIS-11 scores predict drug craving in substance-dependent individuals (9), the present data suggest a neurobiological link between human impulsiveness and drug abuse vulnerability.

These results show that individual differences in midbrain autoreceptor availability are associated with the expression of impulsivity in humans, an effect that appears to be mediated, in part, through diminished inhibitory autoreceptor control over stimulated striatal DA release. Our findings suggest that dysregulation within ascending dopaminergic projection pathways subserving reward and motivation may produce deficits in impulse control, a critical feature of the psychopathological architecture underpinning substance abuse. Further, they provide a specific, plausible mechanism that links individual variability in DA network functioning to differences in human impulsivity.

## **References and Notes**

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## Supporting Online Material

www.sciencemag.org/cgi/content/full/329/5991/532/DC1 Materials and Methods SOM Text

Fig. S1

References

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