

Age-related differences in striatal dopamine D1 receptors mediate subjective drug effects

Peter Manza, ... , Gene-Jack Wang, Nora D. Volkow

J Clin Invest. 2022. <https://doi.org/10.1172/JCI164799>.

Research Letter In-Press Preview Neuroscience

Find the latest version:

<https://jci.me/164799/pdf>



Age-related differences in striatal dopamine D1 receptors mediate subjective drug effects

Peter Manza¹, Ehsan Shokri-Kojori¹, Sukru Baris Demiral¹, Rui Zhang¹, Evan Dennis¹, Allison Johnson¹, Leah Vines¹, Diana Sotelo¹, Dardo Tomasi¹, Gene-Jack Wang¹, Nora D. Volkow¹

¹National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland, USA.

Address correspondence to:

Peter Manza, Ph.D (peter.manza@nih.gov)

Nora D. Volkow, MD (nora.volkow@nih.gov)

Laboratory of Neuroimaging (LNI/NIAAA)

10 Center Dr, Rm B2L124

Bethesda, MD 20892-1013

Phone: (301) 496-1589

The authors have declared that no conflict of interest exists.

The brain dopamine system is critical for cognition, reward, and motivation, and plays a crucial role in the reinforcing effects of drugs with addiction potential but also for some of their therapeutic effects (i.e., stimulants such as methylphenidate (MP)) (1). Importantly, aging is associated with declines in key proteins involved in dopamine signaling, including D1- and D2-like dopamine receptors and dopamine transporters (2), and there is some evidence that elderly individuals are less sensitive to the subjective effects of stimulant drugs than young adults (3). This opens the possibility that age-related declines in dopamine signaling in brain reward regions impact the sensitivity to the positive reinforcing effects of drugs, a key risk factor for the development of a substance use disorder (SUD) (4). This would help explain why substance use and SUD rates are much lower among elderly than younger adults (5). If specific brain markers of dopamine signaling are tied to aging and drug effects, then this information could be leveraged to better understand individual differences in vulnerability to substance misuse and SUD.

We collected measures of D1- and D2-like receptors and estimates of MP-induced ‘dopamine increases’ using PET imaging to study the effect of age on subjective experience of MP in healthy adults. We hypothesized that striatal D1R would show a stronger association with subjective MP effects than striatal D2R, and that striatal D1R availability would mediate the link between age and subjective MP effects.

Methods. Thirty-six healthy adults (23 male, 13 female, age 22-64) participated (for detailed demographics, see **Supplemental Table 1**). All participants provided written informed consent prior to participation. The NIH IRB approved the study.

PET scans measured D1R availability with [¹¹C]NNC-112 and D2R availability with [¹¹C]Raclopride. All [¹¹C]NNC-112 scans were conducted in a baseline state. [¹¹C]raclopride

scans were conducted on two separate days: once 1h after administration of an oral placebo pill and once 1h after administration of 60 mg oral MP, to quantify “dopamine increases” by comparing changes in D2R availability with placebo scans (6). [¹¹C]raclopride scans were single blind and session order was counterbalanced. All participants underwent all three PET scans.

Throughout the sessions participants were periodically asked to rate, on a scale of 1 to 10, several questions about their subjective experience of drug reward in response to MP. We characterized associations between D1R, D2R and dopamine increases with age and subjective drug effects at the voxel level and at the region-of-interest (accumbens and dorsal striatum) level. We then performed mediation analysis, hypothesizing that accumbens D1R would mediate the negative association between age and subjective drug effects. For all analyses, a *p*-value less than 0.05 was considered significant. For more details, see **Supplementary Methods**.

There was a strong negative linear association between D1R and age that was relatively uniform throughout the striatum, whereas the D2R-age association was weaker overall and specific to head of caudate and posterior putamen. There were no significant associations between age and MP-induced dopamine increases. We also observed a positive linear association between D1R and ‘feeling drug effects’ (peak in accumbens; Montreal Neurologic Institute coordinate [14 14 -6]; peak *t* = 3.55). There were no significant associations between ‘feeling drug effects’ and D2R availability nor MP-induced dopamine increases (**Figure 1A**).

In region-of-interest robust correlation analysis, we observed significant associations with age and D1R, both in dorsal striatum ($r = -.52$, $p_{\text{bonf}} = .0028$), and accumbens ($r = -.50$, $p_{\text{bonf}} = .004$). However, for D2R and MP-induced dopamine increases these associations with age were not significant. We also observed significant associations with ‘feeling drug effects’ and D1R, both in dorsal striatum ($r = .466$, $p_{\text{bonf}} = .008$) and accumbens ($r = .599$, $p_{\text{bonf}} = .0002$). However,

for D2R and MP-induced dopamine increases associations with ‘feeling drug effects’ were not significant (for associations with other brain regions, see **Supplemental Table 2**).

The subjective effects of 60 mg oral MP relative to placebo were negatively associated with age, as hypothesized (**Figure 1B**; $r = -.37, p = .026$).

A Fisher’s z -test for comparing correlations from dependent samples revealed that the accumbens D1R-subjective effects association was significantly stronger than the D2R-subjective effects association ($z = 3.699, p < .001$; **Figure 1C**). Accumbens D1R mediated the link between older age and lower subjective drug effects. (indirect effect coefficient = -2.12 ; 97.5% CI=[$-6.54 -0.37$]; $p = .004$; **Figure 1D**).

In sum, declines in accumbens D1R availability (but not D2R availability nor MP-induced dopamine increases) may explain why people feel stimulant drug effects less strongly as they age, providing a possible neural mechanism for the lower prevalence of stimulant use disorders in the elderly than in young adults (5).

References

1. Volkow ND, Wise RA, Baler R. The dopamine motive system: implications for drug and food addiction. *Nature Reviews Neuroscience* 2017;18(12):741–752.
2. Karrer TM, Josef AK, Mata R, Morris ED, Samanez-Larkin GR. Reduced dopamine receptors and transporters but not synthesis capacity in normal aging adults: a meta-analysis. *Neurobiology of Aging* 2017;57:36–46.
3. Abi-Dargham A, Kegeles LS, Martinez D, Innis RB, Laruelle M. Dopamine mediation of positive reinforcing effects of amphetamine in stimulant naïve healthy volunteers: results from a large cohort. *European Neuropsychopharmacology* 2003;13(6):459–468.
4. de Wit H, Phillips TJ. Do initial responses to drugs predict future use or abuse?. *Neuroscience and Biobehavioral Reviews* 2012;36(6):1565–1576.
5. SAMHSA. *2020 National Survey of Drug Use and Health (NSDUH) [Internet]*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2020:
6. Volkow ND et al. Imaging endogenous dopamine competition with [¹¹C]raclopride in the human brain. *Synapse* 1994;16(4):255–262.

Figure 1. Associations between markers of brain dopamine system function, age, and subjective drug effects. A) regression plots depicting the association of age (left) and subjective drug (right) with striatal dopamine D1 receptors (D1R; top), D2R (middle), and methylphenidate (MP)-induced dopamine increases (bottom). All analyses controlled for body mass index (BMI) and sex. B) Negative association between subjective drug effects and age. To quantify total effects of the drug across the session, we calculated area under the curve (AUC) for all timepoints (every five min from -5 min to 120 min post-MP administration), and subtracted the AUC between the MP and the PLA sessions to get one estimate of the cumulative drug effects per participant. Thus, a negative value for ‘feel drug effects’ indicates a greater subjective response to PLA than MP. C) A selective role for D1R but not D2R in the subjective effects of MP. Nucleus accumbens D1R but not D2R availability was significantly associated with subjective drug effects. The difference in regression slopes was significant ($z = 3.699$, $p < .001$). D) Dopamine D1 receptor (D1R) availability in the nucleus accumbens mediates the negative association between age and subjective drug effects. Note: DVR = distribution volume ratio.

