NEUROSCIENCE

Dopamine promotes cognitive effort by biasing the benefits versus costs of cognitive work

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Stimulants such as methylphenidate are increasingly used for cognitive enhancement but precise mechanisms are unknown. We found that methylphenidate boosts willingness to expend cognitive effort by altering the benefit-to-cost ratio of cognitive work. Willingness to expend effort was greater for participants with higher striatal dopamine synthesis capacity, whereas methylphenidate and sulpiride, a selective D2 receptor antagonist, increased cognitive motivation more for participants with lower synthesis capacity. A sequential sampling model informed by momentary gaze revealed that decisions to expend effort are related to amplification of benefit-versus-cost information attended early in the decision process, whereas the effect of benefits is strengthened with higher synthesis capacity and by methylphenidate. These findings demonstrate that methylphenidate boosts the perceived benefits versus costs of cognitive effort by modulating striatal dopamine signaling.

Cognitive control is effortful, causing people to avoid demanding tasks (*1*) and to discount goals (*2*, *3*). Striatal dopamine invigorates physical action by mediating cost–benefit tradeoffs (*4*). In corticostriatal loops, dopamine has opponent effects on D1- and D2-expressing medium spiny neurons, which modulate sensitivity to the benefits versus the costs of actions (*5*). Given that similar mechanisms may govern cognitive action selection (*6*–*8*), we hypothesized that striatal dopamine could promote willingness to exert cognitive effort, enhancing attention, planning, and decision-making (*8*–*11*).

Converging evidence on cognitive motivation in Parkinson's disease (*12*–*15*) provides an initial basis for this conjecture. Moreover, catecholamine-enhancing psychostimulants alter cognitive effort in rodents (*10*) and humans (*16*). This raises the question of whether so-called "smart drugs" act by enhancing the willingness rather than the ability to exert cognitive control. Indeed, the dominant interpretation is that stimulants improve cognitive processing by direct cortical effects, noradrenaline transmission (*17*, *18*), and/or concomitant working memory improvements (*19*). We instead hypothesized that methylphenidate (a dopamine and noradrenaline reuptake blocker) boosts cognitive control by increasing striatal dopamine and, accordingly, sensitivity to the benefits versus costs of cognitive effort.

Fifty healthy, young adults (ages 18 to 43, 25 men) completed a cognitive effort–discounting paradigm (*2*) quantifying subjective effort costs as the amount of money required to make participants equally willing to perform a hard (N = 2, 3, 4) versus an easier (N = 1, 2) level of the N-back working memory task. We defined the subjective value of an offer to complete a harder task (N = 2 to 4) as the amount offered for the task minus subjective costs.

Subjective values decreased with N-back load, indicating rising subjective costs (Fig. 1A). Critically, greater willingness to expend cognitive effort correlated with higher dopamine synthesis capacity (measured using [^{18}F]DOPA positron emission tomography) in the caudate nucleus [independently defined (*20*); Fig. 1, A to C, and fig. S1]. A mixed-effects model confirmed that on placebo, subjective values increased with larger offer amounts (€4 versus €2 offers; $\beta = 0.022$, $P = 0.011$), smaller relative load ($\beta = -0.15$, $P = 8.9 \times 10^{-15}$), and higher

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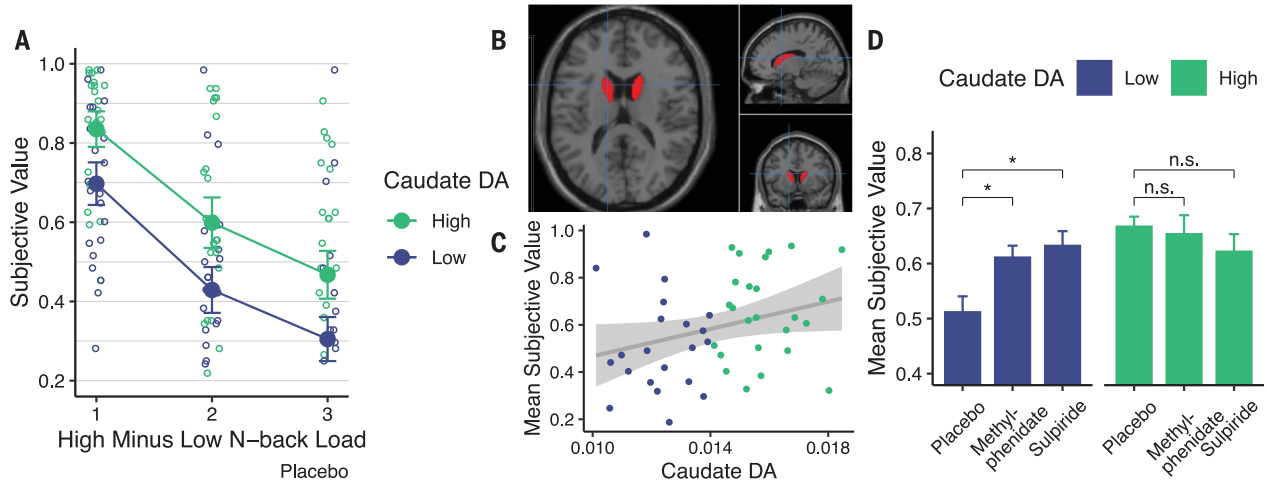

Fig. 1. Participants discounted offers as a function of cognitive load, dopamine synthesis capacity (DA), and drug. (**A**) Offers were discounted more for high- versus low-load levels and more by participants with below- versus above-median dopamine synthesis capacity. Circles show individual's indifference points. Filled circles show group mean ± SEM. (**B**) Caudate nucleus mask. Crosshairs indicate Montreal Neurological Institute (MNI) coordinates of [−14, 10, 16]. (**C**) Participant-averaged subjective values correlated with synthesis capacity on placebo (Spearman's $r = 0.32$, $P = 0.029$). (**D**) Methylphenidate [$t_{paired(22)} = 2.29$; $P = 0.032$] and sulpiride [$t_{paired(22)} = 2.36$; $P = 0.028$] increased subjective values for participants with low but not high synthesis capacity ($P \geq 0.021$ for both). Error bars indicate within-subject SEM.

dopamine synthesis capacity (β = 0.064; P = 0.022). These individual difference effects were selective to the caudate nucleus (figs. S1 and S2), consistent with human imaging studies on cognitive motivation (*7*, *21*, *22*). Although N-back performance decreased with load, dopamine effects on discounting could not be attributed to performance changes (see the supplementary results). Moreover, there were no drug effects on performance because drugs were administered after the N-back task.

If dopamine mediates cognitive effort, then it should be possible to increase motivation pharmacologically. Indeed, both methylphenidate and sulpiride increased subjective values for participants with low, but not high, dopamine synthesis capacity (Fig. 1D and fig. S2, B and C). A mixed-effects model revealed that both methylphenidate (β = −0.069, P = 0.0042) and sulpiride (β = −0.10, $P = 8.3 \times 10^{-4}$) interacted with dopamine synthesis capacity to increase subjective values. Neither drug showed main effects (both $P \geq 0.37$).

The converging effects of synthesis capacity and two separate drugs strongly implicate striatal dopamine. Methylphenidate blocks reuptake, increasing extracellular striatal dopamine tone (*23*), and can amplify transient dopamine signals (*24*). Sulpiride is a D2 receptor antagonist that at low doses can increase striatal dopamine release by binding to presynaptic autoreceptors, enhancing striatal reward signals and learning (*6*, *25*). Although sulpiride can block postsynaptic D2 receptors at higher doses (*26*), both drugs increase behavioral vigor [reaction times and saccade velocities; compare (*6*, *26*)], especially in participants with low dopamine synthesis capacity, corroborating that both drugs increase dopamine release (see the supplementary results).

To assess whether dopamine amplifies subjective benefits versus costs, we made a series of offers, in a second decision task, centered around participants' indifference points (Fig. 2A). To generate specific predictions, we simulated psychometric choice functions with a computational model of striatal dopamine effects on decision-making (*5*). With higher dopamine, the model predicts enhanced sensitivity to benefits and reduced sensitivity to costs. This manifests as a steeper choice function to the right of indifference, where the ratio of benefits to costs (of the high- versus low-effort option) is larger, but a shallower choice function to the left, where the benefits-to-costs ratio is smaller (Fig. 2B).

Choice behavior supported model predictions. Simulated effects were mirrored by effects of dopamine synthesis capacity (Fig. 2C) and of methylphenidate and sulpiride versus placebo (Fig. 2D). Formally, high effort selection was sensitive to both benefits (offer amount differences; β = 2.30, $P = 1.2 \times 10^{-9}$)

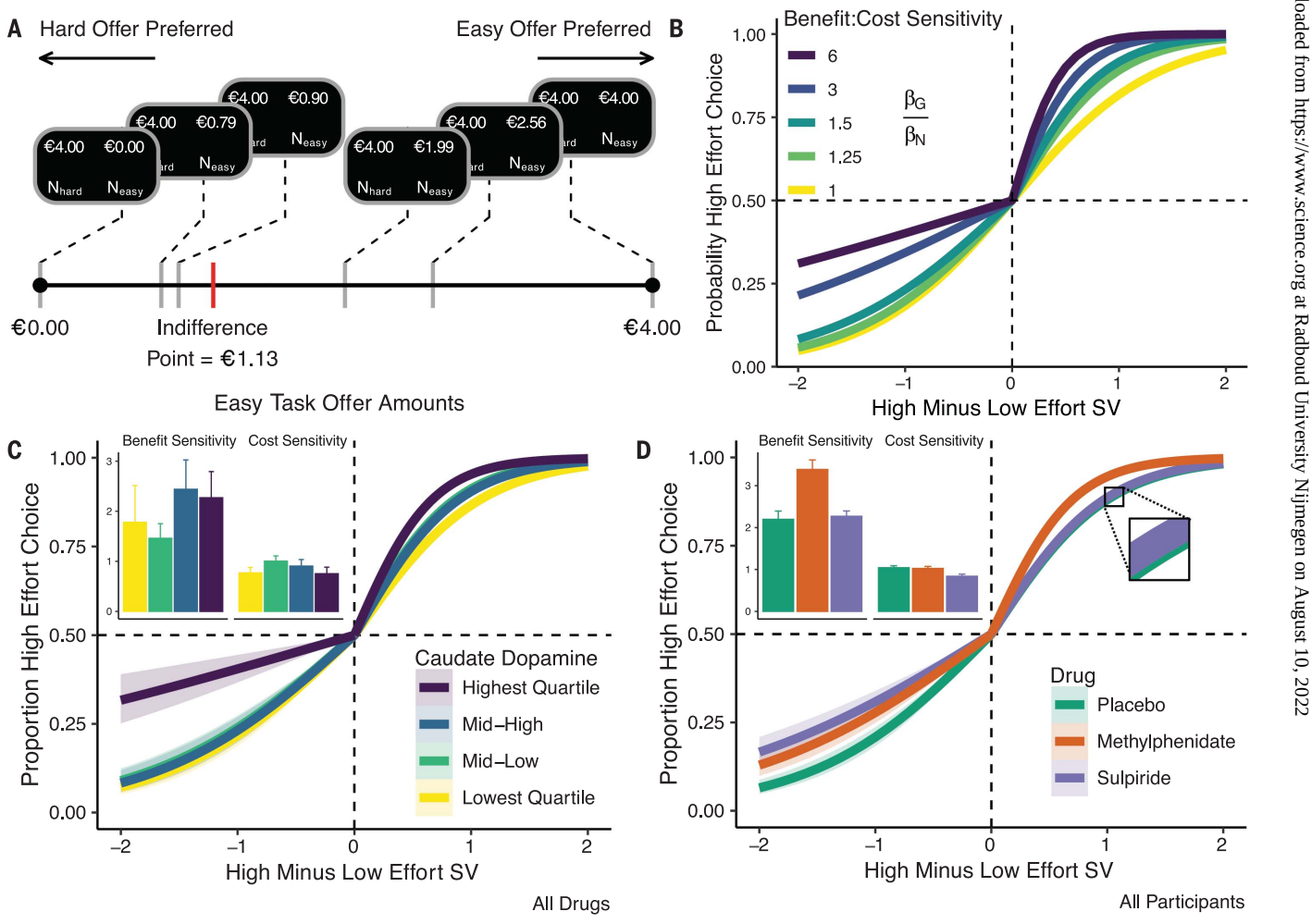

Fig. 2. Dopamine alters valuation by reweighting the benefits versus costs of cognitive work. (**A**) Low-effort (N_{easy}) offers were paired with a €4 offer for a high-effort N-back task (N_{hard}). (**B** to **D**) Simulated effects of dopamine on benefit-versus-cost sensitivity (B) are mirrored by empirical effects of dopamine synthesis capacity (C) and pharmacological agents (D). Mixed-effects logistic regression curves and 95% confidence intervals (CI) fit across all drugs for each synthesis capacity quartile (C) or all participants for each drug (D). SV, subjective value. Insets show the estimated effect of benefits and costs on choice across participants in each quartile ± SEM (C) and on each drug ± within-subject SEM (D).

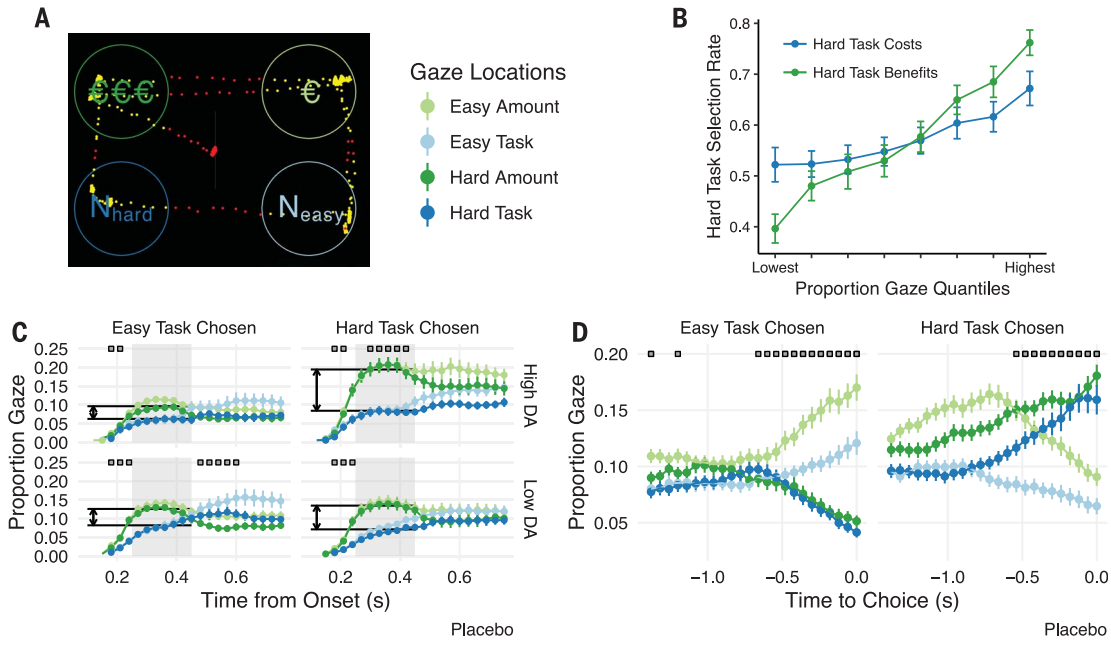

Fig. 3. Effect of gaze, value, and dopamine synthesis capacity on effort selection. (**A**) Participants decided between offers with costs (N-back load) and benefits (Euros) separated in space. Dots indicate gaze at (yellow) and away from (red) offers. (**B**) Proportion gaze at the high-effort offer predicted high-effort selection, and more so with gaze at benefits versus costs. (**C** and **D**) Proportional (cross-trial) gaze at the four information quadrants after offer onset and leading up to response. In (C), early gaze (250 to 450 ms after offer onset) is indicated by gray shading, and boxes indicate time points at which participants gazed reliably more at either benefits or cost information (paired *t* tests, $P < 0.05$). In (D), boxes indicate time points at which participants gazed reliably more at the selected offer (one-tailed paired *t* tests, $P < 0.05$). Error bars indicate ± SEM.

and costs (load differences; $\beta = -1.07$, $P = 2.2 \times 10^{-16}$). The effect of benefits increased with synthesis capacity ($\beta = 0.65$, $P = 0.0024$) and on methylphenidate ($\beta = 1.34$, $P = 0.0048$), whereas the effect of costs was attenuated on sulpiride ($\beta = 0.24$, $P = 0.036$). Participants also selected high-effort choices more often with higher dopamine synthesis capacity ($\beta = 1.02$, $P = 3.1 \times 10^{-4}$) and on methylphenidate ($\beta = 1.75$, $P = 0.0016$) versus placebo, but not reliably so for sulpiride ($\beta = 0.46$, $P = 0.12$). No other interactions or main effects were significant (all $P \geq 0.47$).

These results clearly implicate dopamine in choice, but they do not uncover how decision-making is altered. Dopamine could increase attention to benefits versus costs. Alternatively, it could alter the impact of these attributes on choice without affecting attention itself. We thus tracked eye gaze to quantify attention to attributes and how it interacted with dopamine. Proportion gaze at an offer (either costs or benefits) strongly predicted offer selection [Fig. 3B; $\beta = 0.30$, $P = 7.6 \times 10^{-6}$; cf. (*27*, *28*)]. However, gaze at benefits predicted steeper increases in hard task selection than gaze at costs (gaze by dimension interaction: $\beta = 0.41$, $P = 1.1 \times 10^{-5}$).

Gaze patterns implicated dopamine in enhancing the impact of attention to benefits versus costs on the decision to engage in cognitive effort. Early in a trial, participants fixated on benefits (of either offer) more than on costs, and this asymmetry was larger in trials in which they chose the high-effort option (choice effect: $\beta = 0.41$, $P = 0.0017$; Fig. 3C). Moreover, this effect was stronger in participants with higher dopamine synthesis capacity (choice by synthesis capacity interaction: $\beta = 0.37$, $P = 0.0045$; top versus bottom row, Fig. 3C). For those with lower synthesis capacity, methylphenidate strengthened this relationship (interaction between drug, synthesis capacity, and choice: $\beta = -0.36$, $P = 0.012$), although sulpiride did not ($\beta = -0.041$, $P = 0.78$). Drugs and synthesis capacity did not affect gaze patterns themselves ($P \geq 0.10$ for main effects), indicating that dopamine did not alter attention to benefits but rather strengthened the impact of attention to benefits versus costs on choice.

Gaze may correlate with choice because attention amplifies the perceived value of attended offers, causally biasing choice (*27*). Alternatively, reversing this causality, participants may simply look more at offers that they have already implicitly chosen (*28*). We found evidence for both: Early in a trial, attention influenced choice, whereas later, choice influenced attention. To address this, we fit drift diffusion models (*29*) in which cost and benefit information accumulate in a decision variable rising to a threshold. This variable is the instantaneous difference in the perceived value of the high- versus the low-valued offer. We considered "attention-biasing choice" models with multiplicative effects (i.e., gaze multiplies the effects of value information) and "choice-biasing attention" models in which gaze has a simple, additive effect (i.e., gaze correlates with choice but does not amplify value) (*28*). The best-fitting model [Fig. 4, A to C, and Eq. 1 (*30*)] included both additive and multiplicative effects (see the supplementary results).

We next considered the possibility that the gaze–value interactions changed dynamically across the trial. Indeed, ~775 ms before responding, participants began committing their gaze toward the to-be-chosen offer (Fig. 3D). Thus, whereas early gaze appears to influence choice formation (Fig. 3C), later gaze appears to reflect latent choices once formed. On this basis, we investigated whether early attention causally amplifies attended attributes (a multiplicative combination) whereas late gaze simply correlates with choice (additive; Fig. 4A). To test our hypothesis, we split trials according to when participants began committing their gaze to the to-be-chosen offer (the "bifurcation") for each participant and session and refit our model to gaze data from before or after this time point. The result supported our hypothesis. Multiplicative terms were reliably positive before bifurcation but near zero after bifurcation, with the opposite pattern for additive terms (Fig. 4, F and G). These results

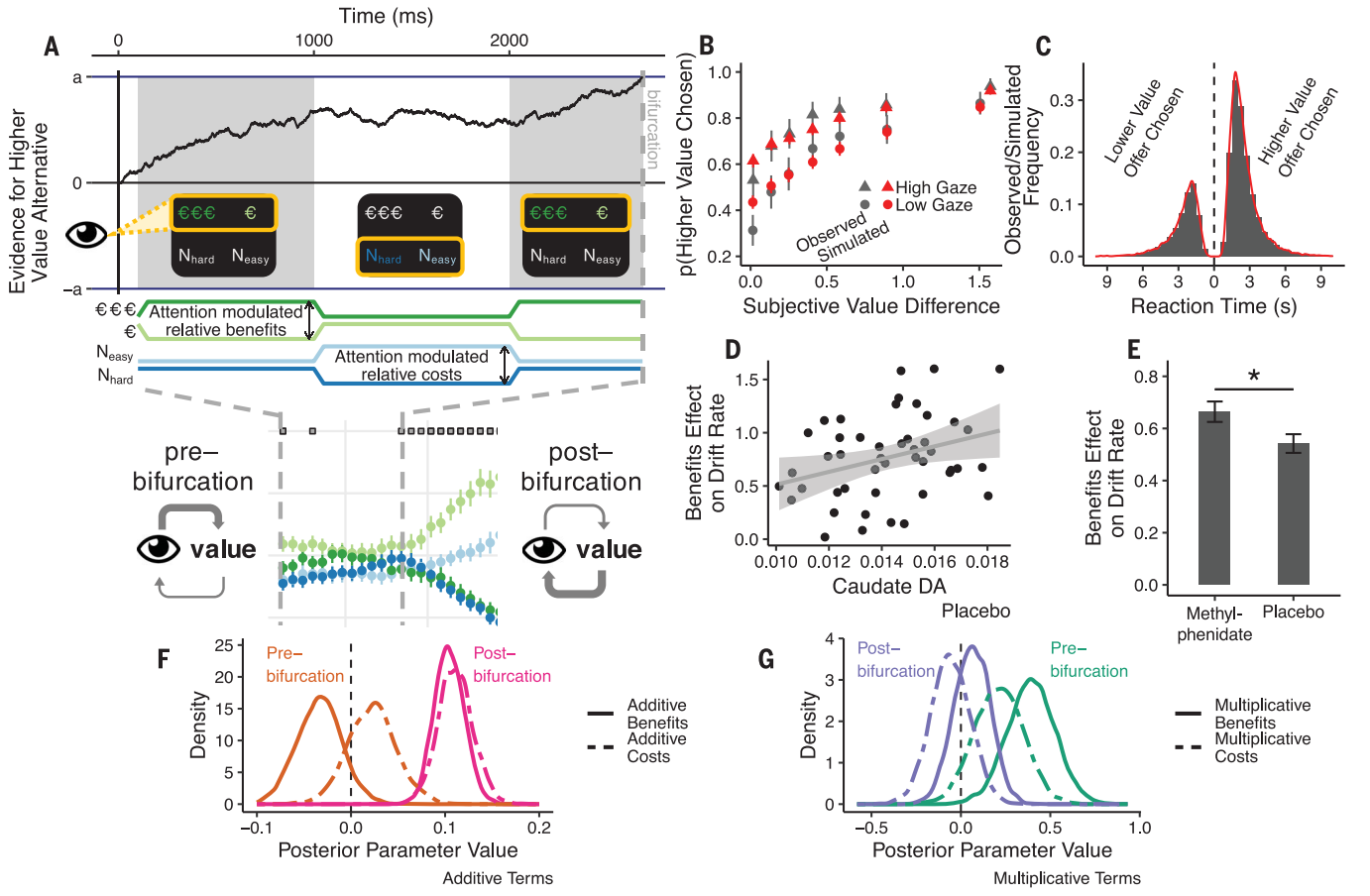

Fig. 4. Gaze dynamically biases and then reflects implicit choice. (**A**) Gaze attribute model. Early gaze amplified the effect of attended versus unattended attributes on choice during evidence accumulation to a decision threshold (a). Late gaze reflected the to-be-selected response. (**B** and **C**) Model simulations (red) predicted choice (gray) (B, split by median proportion gaze at the higher value offer) and reaction time (C) distributions. (**D**) Benefits effect on drift rate correlate with dopamine synthesis capacity (95% CI shown). (**E**) Methylphenidate enhances the benefit effect. (**F** and **G**) Posterior parameter densities from models fit alternately with pre- or postbifurcation gaze on placebo. (F) Additive benefit ($\beta_1 = -0.030$; $P = 0.076$) and cost ($\beta_2 = 0.020$; $P = 0.81$) gaze terms were approximately zero before bifurcation and reliably positive after bifurcation ($\beta_1 = 0.10$; $P < 2.2 \times 10^{-16}$ and $\beta_2 = 0.11$; $P = 0.0031$). (G) Multiplicative interaction terms reveal that the effects of benefits ($\beta_3 - \beta_5 = 0.40$; $P = 0.0024$) and costs (at trend level; $\beta_4 - \beta_6 = 0.12$; $P = 0.060$) were larger when fixating the respective attribute before bifurcation, whereas neither term was different from zero after bifurcation ($\beta_3 - \beta_5 = 0.07$; $P = 0.27$ and $\beta_4 - \beta_6 = -0.060$; $P = 0.70$). Error bars indicate ± SEM.

support the idea that although early attention appeared to amplify the effect of benefits versus costs, later gaze simply reflected a latent choice.

Finally, we tested whether the effects of dopamine on choice could be attributed to these dynamic decision processes. Indeed, both higher dopamine synthesis capacity [on placebo; Eq. 1 (*30*): $(\beta_3 + \beta_5)/2$; Pearson $r = 0.30$, $P = 0.039$; Fig. 4D] and methylphenidate [$t_{\text{paired},45} = 2.54$, $P = 0.015$; Fig. 4E] increased the effect of benefits on evidence accumulation. The corresponding effect of sulpiride on cost was not significant [Eq. 1 (*30*): $(\beta_4 + \beta_6)/2$; $t_{\text{paired},45} = -1.41$; $P = 0.17$; see the supplementary discussion]. We further found that methylphenidate amplified the effects of benefits on drift rate even when only modeling pre-bifurcation gaze [$t_{\text{paired},45} = 2.44$; $P = 0.019$) before the latent choice. Collectively, our results support that striatal dopamine enhances motivation for cognitive effort by amplifying the effects of benefits versus costs attended early in a decision.

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30. $v_i \sim \beta_0 + \beta_1(g_{\text{BenA}} - g_{\text{BenB}}) + \beta_2(g_{\text{CostA}} - g_{\text{CostB}}) + \beta_3 g_{\text{Ben}}\Delta V_{\text{Ben}} + \beta_4 g_{\text{Cost}}\Delta V_{\text{Cost}} + \beta_5 g_{\text{Cost}}\Delta V_{\text{Ben}} + \beta_6 g_{\text{Ben}}\Delta V_{\text{Cost}}$ (Eq. 1), where

the rate at which participants accumulate evidence in favor of offer *A* versus *B* (v) on trial (*i*) is given by proportion gaze at benefits (g_{Ben}) and its interaction with the benefits of A versus B (ΔV_{Ben}), proportion gaze at costs (g_{Cost}) and its interaction with costs (ΔV_{Cost}), as well as additive contributions of gaze at offer A for both benefits ($g_{BenA} - g_{BenB}$) and costs ($g_{CostA} - g_{CostB}$).

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SUPPLEMENTARY MATERIALS

science.sciencemag.org/content/367/6484/1362/suppl/DC1
Materials and Methods
Supplementary Results
Figs. S1 to S5
Tables S1 to S7
References (*31*–*37*)

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Responsible use of psychostimulants

Psychostimulants have a place in the therapy of attentional disorders. However, they are also widely used off-label to enhance cognitive performance, and their mechanisms of action remain elusive. Westbrook *et al.* studied the effects of these drugs and concurrently measured striatal dopamine synthesis capacity in young, healthy participants (see the Perspective by Janes). They administered a placebo, methylphenidate (a dopamine and noradrenaline reuptake blocker), and sulpiride (a selective D2 receptor antagonist) while participants made explicit cost-benefit decisions about whether to engage in cognitive effort. Higher dopamine synthesis capacity in the caudate nucleus was associated with greater willingness to allocate cognitive effort. In addition, methylphenidate and sulpiride increased subjective values and motivation to work specifically for people with low dopamine synthesis capacity. Cognition-enhancing drugs may thus act at the motivational level rather than directly boosting cognition per se.

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