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Acetylcholine and noradrenaline enhance foraging optimality in humans

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Foraging theory prescribes when optimal foragers should leave the current option for more rewarding alternatives. Actual foragers often exploit options longer than prescribed by the theory, but it is unclear how this foraging suboptimality arises. We investigated whether the upregulation of cholinergic, noradrenergic, and dopaminergic systems increases foraging optimality. In a double-blind, between-subject design, participants (N = 160) received placebo, the nicotinic acetylcholine receptor agonist *nicotine*, a noradrenaline reuptake inhibitor *reboxetine*, or a preferential dopamine reuptake inhibitor *methylphenidate*, and played the role of a farmer who collected milk from patches with different yield. Across all groups, participants on average overharvested. While methylphenidate had no effects on this bias, nicotine, and to some extent also reboxetine, significantly reduced deviation from foraging optimality, which resulted in better performance compared to placebo. Concurring with amplified goal-directedness and excluding heuristic explanations, nicotine independently also improved trial initiation and time perception. Our findings elucidate the neurochemical basis of behavioral flexibility and decision optimality and open unique perspectives on psychiatric disorders affecting these functions.

exploration | marginal value theorem | value-based decision-making | stay-or-switch | cognitive enhancers

Significance

Deciding when to say "stop" to the ongoing course of action is paramount for preserving mental health, ensuring the well-being of oneself and others, and managing resources in a sustainable fashion. And yet, cross-species studies converge in their portrayal of real-world decision-makers who are prone to the overstaying bias. We investigated whether and how cognitive enhancers can reduce this bias in a foraging context. We report that the pharmacological upregulation of cholinergic and noradrenergic systems enhances optimality in a common dilemma—staying with the status quo or leaving for more rewarding alternatives—and thereby suggest that acetylcholine and noradrenaline causally mediate foraging behavior in humans.

Decisions whether to continue consuming the currently available option or switch to a better alternative are paramount for adaptive behavior and mental health. Staying in toxic social environments, unrewarding jobs, or abusive relationships is detrimental for well-being but pervasive in today's societies (1, 2). In decision neuroscience, stay-or-leave dilemmas have been described using the foraging framework (3). In this framework, the decision-maker (or agent) sequentially samples spatially separated options, which gradually deplete when harvested (e.g., fulfilment from the current job or emotional satisfaction from the current relationship). For each option (commonly referred to as a *patch*), the agent must decide how long to exploit its depleting resources, before moving on to another patch in order to maximize gains and minimize search costs (4). Staying in the patch for too long reflects overexploitation of its resources and leads to slower-than-optimal reward accumulation. Conversely, systematically leaving patches too early (over-exploration) is inefficient because it incurs high travel costs without collecting much reward. The theoretically optimal solution for switch–stay dilemmas is provided by the marginal value theorem (MVT) (5). According to the theorem, the agent should search for a better option when the reward rate of the current option no longer exceeds the average reward rate of all alternative options. This theory has been used to successfully describe the foraging behavior of insects, fish, birds, nonhuman primates, and humans (6). However, deviations from optimality (particularly overstaying/overharvesting) are common as being optimal may be costly (i.e., require increased attention and cognitive effort, goal-directedness, working memory, or self-control) (7). It is crucial to recognize that these deviations can have significant ecological consequences, because overharvesting exacerbates the depletion of natural resources, leaving a negative impact on biodiversity and ecosystem function (8) and ultimately reducing social welfare (9). In light of the importance of these issues, it is surprising that it remains largely unknown how optimality and deviations from it are implemented biologically (6).

Various neurotransmitters underpin cognitive functions needed to implement stay-or-leave decisions (10). Particularly, one may expect dopamine, noradrenaline, and acetylcholine to play a role in enhancing foraging optimality. Earlier findings have linked these neurotransmitters to motivation- and attention-related processes, working memory, exertion of cognitive control, and behavioral flexibility (11–17), which makes them plausible candidates for underpinning the (sub)optimality of stay-or-leave decisions. As these

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neurotransmitters also play a role in attention-deficit/hyperactivity disorder (ADHD), anxiety disorder, depression, and schizophrenia, deciphering their relationship to foraging behavior has the potential to advance clinical research (10, 18). Indeed, the mentioned disorders, as well as pathological gambling (19), have been associated with impaired balancing of exploration and exploitation (20–24).

We designed a between-group, double-blind, placebo-controlled study to causally assess the role of upregulated dopaminergic, noradrenergic, and cholinergic systems on foraging optimality. Based on the role of dopamine in reward processing (11, 25, 26), effort exertion (27), and response vigour (28), and the putative requirement of these functions for calculating the optimal policy, dopamine has been hypothesized to be involved in foraging. First developed as a theoretical concept (29), this hypothesis has been so far empirically supported by two human studies (30, 31), which converged in causally linking increased levels of tonic dopamine to better estimation of the average reward rate. Consequently, we hypothesized that dopamine transporter blocker methylphenidate (20 mg) would increase sensitivity to the average reward rate (29, 31, 32) and thereby enhance foraging optimality. The tonic levels of noradrenaline in its primary source, the locus coeruleus, have been proposed to mediate the balance between focus and disengagement. According to adaptive gain theory, an increase from low to moderate noradrenaline levels should shift behavior from idleness to focused task engagement, accompanied by a reduction in decision noise, whereas a further increase to high levels should lead to distractibility and performance deterioration (33). Hence, we hypothesized that a moderate increase in noradrenaline induced by a low dose (4 mg) of the selective noradrenaline reuptake inhibitor reboxetine (34) should boost optimality and decrease noise in stay-or-leave decisions. Furthermore, multiple cross-species reports demonstrate cholinergic enhancement of attention, cognitive control, and sensitivity to reward (14, 15, 35–39). Accordingly, we hypothesized increased task engagement coupled with improved reward processing, which would manifest as increased optimality in stay-or-leave decisions, under a low dose (2 mg) of the nicotinic acetylcholine receptor agonist nicotine.

Results

Demographic and Psychometric Data. Drug groups did not differ from the placebo group in demographics (*SI Appendix*, section S5). There were also no differences in ADHD-like symptoms as measured by the Adult ADHD Self-Report Scale [ASRS (40)] and anxiety disposition as measured by the trait part of the State-Trait Anxiety Inventory [STAI-Y2 (41)].

Participants Adhered to MVT Principles but Overstayed. In our foraging task, participants (N = 160, 80 females, all drug groups combined) took on the role of a farmer and visited patches with cows to collect milk from. For each patch, participants had to decide for how long to reside based on three task components. These components were 1) current patch reward rate [i.e., amount of reward (low, medium, or high) harvested within a patch at any time point], 2) average farm/environment reward rate (poor environments had low average reward rate, i.e., many low-yield, few high-yield patches, whereas in rich environments the ratio was reversed), and 3) time cost for traveling between patches (Fig. 1 *A*–*C*). By optimizing the residency time within each patch, participants could maximize their overall gain. Participants were instructed about the environment-specific patch distributions prior to starting the task and could easily infer the environment richness from visual cues (see *Methods*). This reduced uncertainty and minimized the need to learn during the task (in contrast to explore-exploit dilemmas studied in multiarmed bandit tasks). Consequently, participants could optimize their strategy from the beginning of the task (*SI Appendix*, section S10).

According to the MVT, optimal residency times should vary as a function of both current and average reward rates and be specific for each patch–environment combination (Fig. 1*D*). To test whether this prescription was reflected in the behavior of our participants, we constructed a Bayesian hierarchical mixed-effects model that explained residency times with patch and environment types (*Methods*, Model M1). To account for previously reported effects of age and sex on foraging (3, 42, 43), we entered these covariates into the model. We also included the time participants took to enter a new patch (referred to as "initiation time"; below, we analyze initiation time separately; a model without the covariates fitted the data less well than a model with covariates: *Methods*) to account for potential trial- and participant-specific variation in response speed. As the travel time between patches was fixed (6 s), we did not consider it in any of our models. In line with the MVT, we observed that residency times were longer in higher-yield patches [$\beta_{high > low} = 1.25$, *95%CI* = (1.199, 1.304); $\beta_{high > medium} = 0.63$, *95%CI* = (0.576, 0.684)]. Also in line with the MVT, participants left patches in the poor environment later than in the rich environment [$\beta_{poor > rich} = 0.322$, *95%CI* = (0.245, 0.397); Fig. 2*A*]. Thus, participants learned that the next patch was more likely to be of low quality in the poor than the rich environment.

Another implication of MVT-optimal foraging is that the current reward rate at the moment of patch-leaving should be the same for all patch types within environments and differ only between environments. In agreement with this prescription, we found that current reward rates upon leaving were significantly higher in the rich compared to the poor environment [$\beta_{rich > poor} = 0.344$, *95%CI* = (0.263, 0.421), Fig. 2*B*]. Moreover, there was no difference in current reward rate upon leaving between medium- and low-yield patches [$\beta_{medium > low} = 0.0453$, *95%CI* = (−0.0341, 0.126)]. However, reward rates upon leaving were lower in the high-yield patches compared to both medium- [$\beta_{high > medium} = -0.224$, *95%CI* = (−0.303, −0.1549)] and low-yield patches [$\beta_{high > low} = -0.179$, *95%CI* = (−0.252, −0.1031)]. The patch-dependent difference was also present in the poor environment but only between high- and medium-rate patches [$\beta_{high > medium} = -0.0976$, *95%CI* = (−0.178, −0.0185); $\beta_{high > low} = -0.0476$, *95%CI* = (−0.125, 0.0275); $\beta_{medium > low} = -0.0502$, *95%CI* = (−0.0214, 0.121)]. These results converge with earlier findings (31) and indicate that human foragers comply with some aspects of the optimal policy prescribed by the MVT.

To interrogate the discrepancies between observed and MVT-prescribed foraging behavior, we calculated optimal residency times for each patch type conditioned on the environment (*SI Appendix*, section S8). We found that on average, participants showed absolute deviations from optimal foraging (|ΔFO| = 6.09s; $P < 0.001$, *t* test against 0, Fig. 2*C*), while signed analysis revealed that participants overstayed (*SI Appendix*, section S11). As one would expect, the degree of foraging suboptimality |ΔFO| negatively correlated with task earnings (*Pearson's r* = −0.82, $P < 0.001$, Fig. 2*D*). These findings confirm the well-established bias to suboptimally overstay in foraging tasks (31, 44).

Collectively, our results indicate that participants adjusted their residency times to the key task manipulations of patch and environment type (i.e., variations in current and average reward rates), tallying with the MVT principles. Moreover, participants showed an overstaying bias and thus deviated from the MVT-optimal policy, for all patch and environment types.

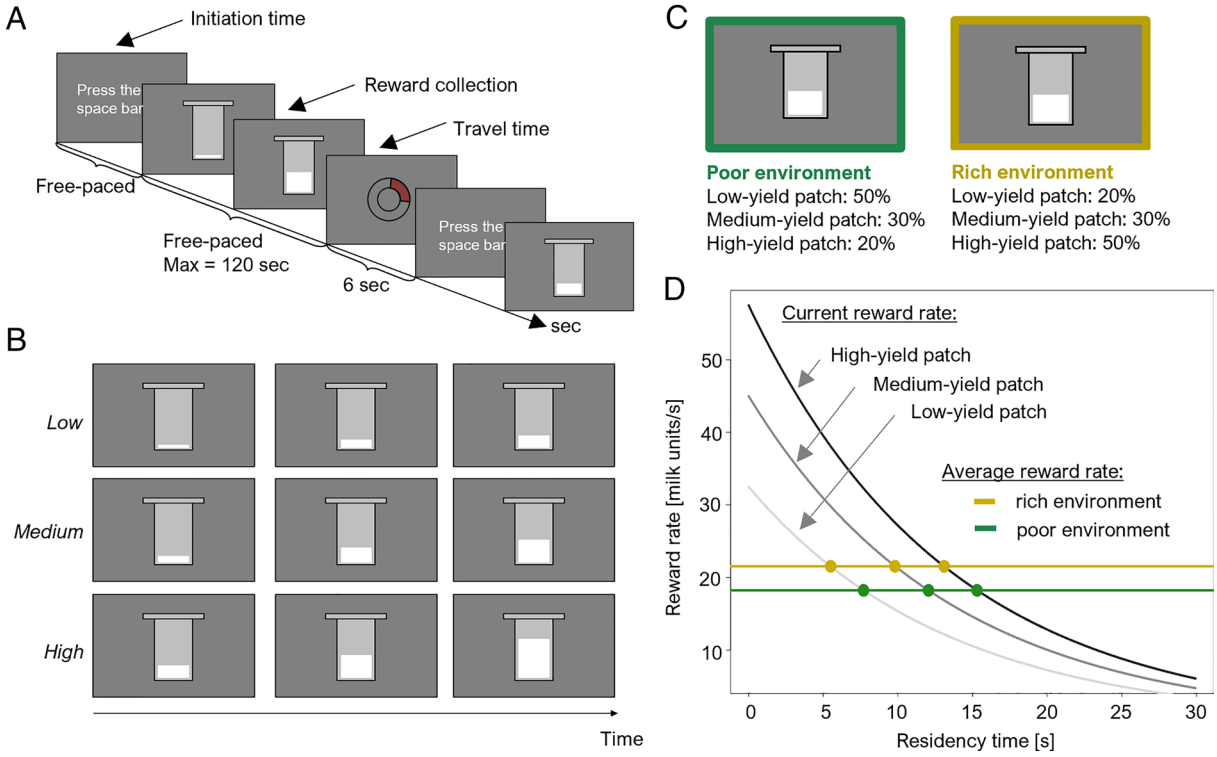

Fig. 1. Foraging task and optimality. (*A*) Example trial. Participants entered a patch full of cows and started collecting milk. They could stay in the patch for 120 s but were free to leave at any moment. Thus, they made stay-or-leave decisions with the aim of maximizing long-term reward. Upon leaving, they incurred a fixed travel cost of 6 s, during which no milk collection was possible, before initiating collection in the next patch. (*B*) Patch types (current reward rate). Each patch had one of three filling rates: low, medium, or high. These filling rates exponentially decreased with time. (*C*) Environment types (average reward rate). The rich and poor environments (indicated by frame color) differed in the proportion of the three patch types. (*D*) Optimal residency time as function of current and average reward rates. The horizontal lines illustrate the average reward rate for the two environments; the curves represent the current reward rates of the different patches. According to the MVT, the agent should leave the patch when the current reward rate equals or drops below the average reward rate. Accordingly, the optimal leaving time for each patch–environment pair is the intersection between patch curves and environment lines.

Cholinergic (and to Some Extent Noradrenergic) Stimulation Increases Optimality of Stay-or-Leave Decisions. After showing that foraging behavior was suboptimal, we asked whether our pharmacological interventions reduced the extent of suboptimality. First, we confirmed that drug administration was successful (*SI Appendix*, section S6). Next, we augmented our Bayesian hierarchical mixed-effects model (Model M1) by adding drug group as a fixed-effect factor and interactions (Model M2). The model again controlled for age, sex, and initiation times. Of note, all the results reported below remained significant when including weight, height, BMI, education, and delay between drug administration and task start as covariates (*SI Appendix*, section S13). The three dependent variables again were actual residency times, current reward rate upon leaving, and absolute deviation from foraging optimality.

First, we examined drug effects on residency times, i.e., stay duration within patches (Fig. 3*A*). Our mixed-effects model revealed significantly reduced residency times in the nicotine and reboxetine groups compared to the placebo group [$\beta_{nicotine > placebo}$ = −0.503, *95%CI* = (−0.829, −0.1833); $\beta_{reboxetine > placebo}$ = −0.342, *95%CI* = (−0.682, −0.0187)], with no effect of methylphenidate [$\beta_{methylphenidate > placebo}$ = −0.199, *95%CI* = (−0.543, 0.11)]. The drug effect was similarly present in all patch and environment types (*95%CI* of all interactions contained 0), providing no evidence that pharmacological interventions selectively affected particular patch- or environment-related reward rates. Thus, nicotine and reboxetine improved foraging (reduced residency times).

Second, we investigated drug effects on current reward rate upon leaving (Fig. 3*B*). Compared to the placebo group, participants in the nicotine and reboxetine groups left patches at significantly higher reward rates (closer to optimal) in both environments [$\beta_{nicotine > placebo}$ = 0.537, *95%CI* = (0.2073, 0.857); $\beta_{reboxetine > placebo}$ = 0.397, *95%CI* = (0.0749, 0.716)]. In contrast, there was no difference between placebo and methylphenidate groups [$\beta_{methylphenidate > placebo}$ = 0.198, *95%CI* = (−0.1349, 0.518)]. These findings suggest that nicotine and reboxetine enhanced sensitivity to the average reward rate. As the current reward rate decreased exponentially over time (Fig. 1*D*), it approached zero at longer residency times, potentially preventing detection of between-group differences. In contrast, we found clear differences of the nicotine and reboxetine groups to the placebo group, compatible with increased optimality.

Next, we directly examined whether the pharmacological interventions indeed brought participants closer to optimality (Fig. 3*C*). The nicotine group showed significantly reduced |ΔFO| compared to the placebo group [$\beta_{nicotine > placebo}$ = −0.449, *95%CI* = (−0.803, −0.1008)], whereas no effect was found for reboxetine and methylphenidate [$\beta_{reboxetine > placebo}$ = −0.301, *95%CI* = (−0.633, 0.0603); $\beta_{methylphenidate > placebo}$ = -0.153, *95%CI* = (−0.497, 0.1894)]. Thus, nicotine improved foraging optimality according to all three dependent variables, while reboxetine was associated only with reduced residency times and higher current reward rates at leaving.

Finally, we asked whether the pharmacological interventions reduced decision noise by assessing trial-by-trial variability in absolute deviation from foraging optimality. To this end, for each participant, we calculated the standard deviation of |ΔFO| over the first seven trials (the smallest number of trials per environment in the whole cohort) and used this metric as a dependent variable in a linear model with drug group, age, and sex as covariates. As predicted by adaptive gain theory, we found a significant reduction in intraindividual |ΔFO| variability for the reboxetine compared to the placebo group [$\beta_{reboxetine > placebo}$ = −0.807, *95%CI* = (−1.23, −0.381)].

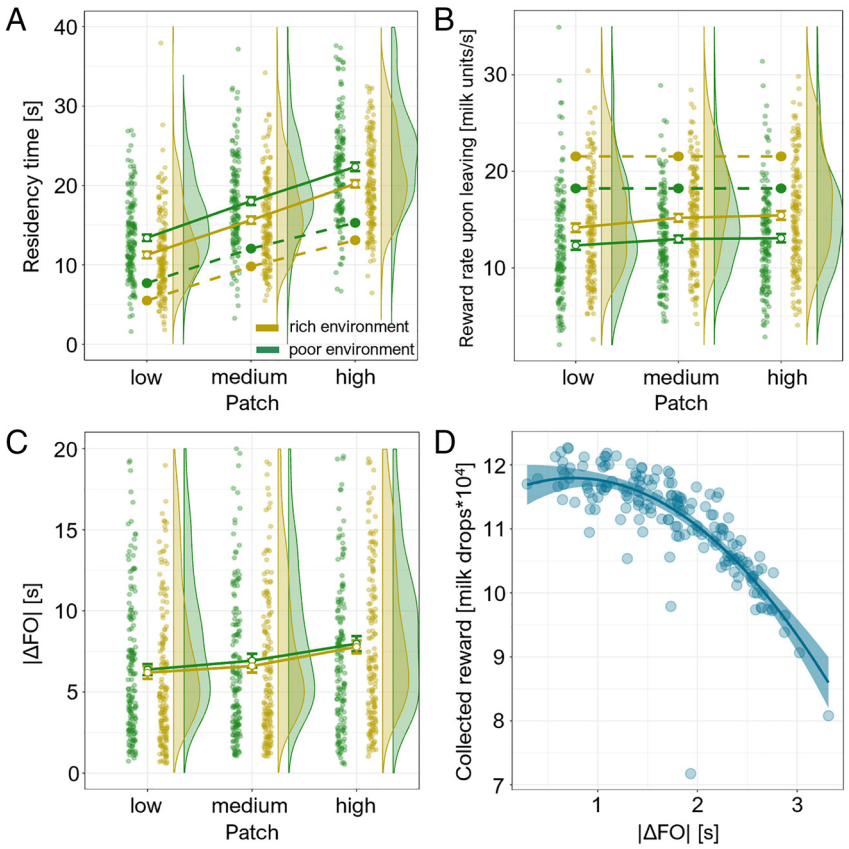

Fig. 2. Participants adhered partially to the prescriptions of the MVT. (*A*) Residency times varied as function of patch types and environments. As prescribed by the MVT, participants (N = 160, all drug groups combined) on average stayed longer in high-yield patches compared to low-yield patches and left patches in the rich environment earlier than in the poor environment. (*B*) Current reward rate upon leaving varied as function of environment. On average, participants (N = 160, all drug groups combined) left patches in the rich environment at a higher reward rate compared to the poor environment as prescribed by the MVT. (*C*) Absolute deviation from foraging optimality |ΔFO|. To optimize foraging, the MVT requires the agent to leave at |ΔFO| = 0s. On average, participants (N = 160, all drug groups combined) deviated from optimal leaving times prescribed by the MVT in all patches in both environments. In *A* and *B*, dashed lines denote optimal behavior. In *A*–*C*, solid lines depict observed behavior, with dots corresponding to the mean error bars indicating ± SEM; density plots represent the distribution of individual mean values. (*D*) Collected reward as function of degree of foraging suboptimality. Participants with higher deviation from the optimum collected less milk.

However, the nicotine and methylphenidate groups showed similar effects [$\beta_{nicotine > placebo} = -0.656$, $95\%CI = (-1.07, -0.232)$; $\beta_{methylphenidate > placebo} = -0.561$, $95\%CI = (-1, -0.162)$]. Thus, all three drugs decreased decision noise as measured by trial-by-trial variability in deviation from foraging optimality.

Little Evidence for Relation between Working Memory and Foraging Optimality. After showing that cholinergic and noradrenergic interventions reduced at least some aspects of foraging suboptimality, we assessed potential explanations for the effects. First, we checked whether intervention-induced changes in working-memory capacity explain differences in foraging optimality. In line with the well-established enhancing effect of methylphenidate on working memory (45), we found a within-subject improvement in working memory capacity measured with the Wechsler Digit Span task in the methylphenidate group but not in other drug groups. There were also no between-group differences after drug administration. Crucially, both levels of working memory capacity and changes in that capacity were unrelated to foraging optimality (*SI Appendix*, section S7). Thus, with our measures, we find little evidence for a relation between working memory and foraging optimality.

Nicotine and Methylphenidate Differentially Mediate the Focus of Attention during Foraging. To investigate whether drug administration modulated how attentive participants were during milk collection, we analyzed gaze data from the Foraging task (*SI Appendix*, section S15). We constructed several Bayesian hierarchical mixed-effects models to explain the effect of drugs on fixations of task-related stimuli while controlling for the effects of patch, environment, age, sex, and trial-specific residency times (as longer residency times allow for more and longer fixations).

We found an increase in the number of fixations within the bucket under nicotine compared to placebo, with no effect for methylphenidate and reboxetine [$\beta_{nicotine > placebo} = 0.323$, $95\%CI = (0.0632, 0.606)$; $\beta_{methylphenidate > placebo} = 0.255$, $95\%CI = (-0.0196, 0.518)$; $\beta_{reboxetine > placebo} = 0.164$, $95\%CI = (-0.1016, 0.447)$], suggesting a more attentive investigation of the current reward collection. Interestingly, the percentage of the bucket fixations relative to the total number of trial-specific fixations was unaffected in participants with nicotine (and reboxetine) compared to placebo [$\beta_{nicotine > placebo} = 0.157$, $95\%CI = (-0.0408, 0.344)$; $\beta_{reboxetine > placebo} = 0.165$, $95\%CI = (-0.0251, 0.363)$], suggesting that participants with nicotine also investigated other elements of the task layout (e.g., the frame symbolizing the environment). By contrast, this percentage was significantly increased (compared to placebo) in the methylphenidate group [$\beta_{methylphenidate > placebo} = 0.262$, $95\%CI = (0.0729, 0.457)$]. Relatedly, the methylphenidate group fixated the frame significantly less than the placebo group [$\beta_{methylphenidate > placebo} = -0.499$, $95\%CI = (-0.977, -0.0358)$; $\beta_{nicotine > placebo} = -0.206$, $95\%CI = (-0.681, 0.2604)$; $\beta_{reboxetine > placebo} = -0.335$, $95\%CI = (-0.816, 0.1291)$]. Thus, under methylphenidate,

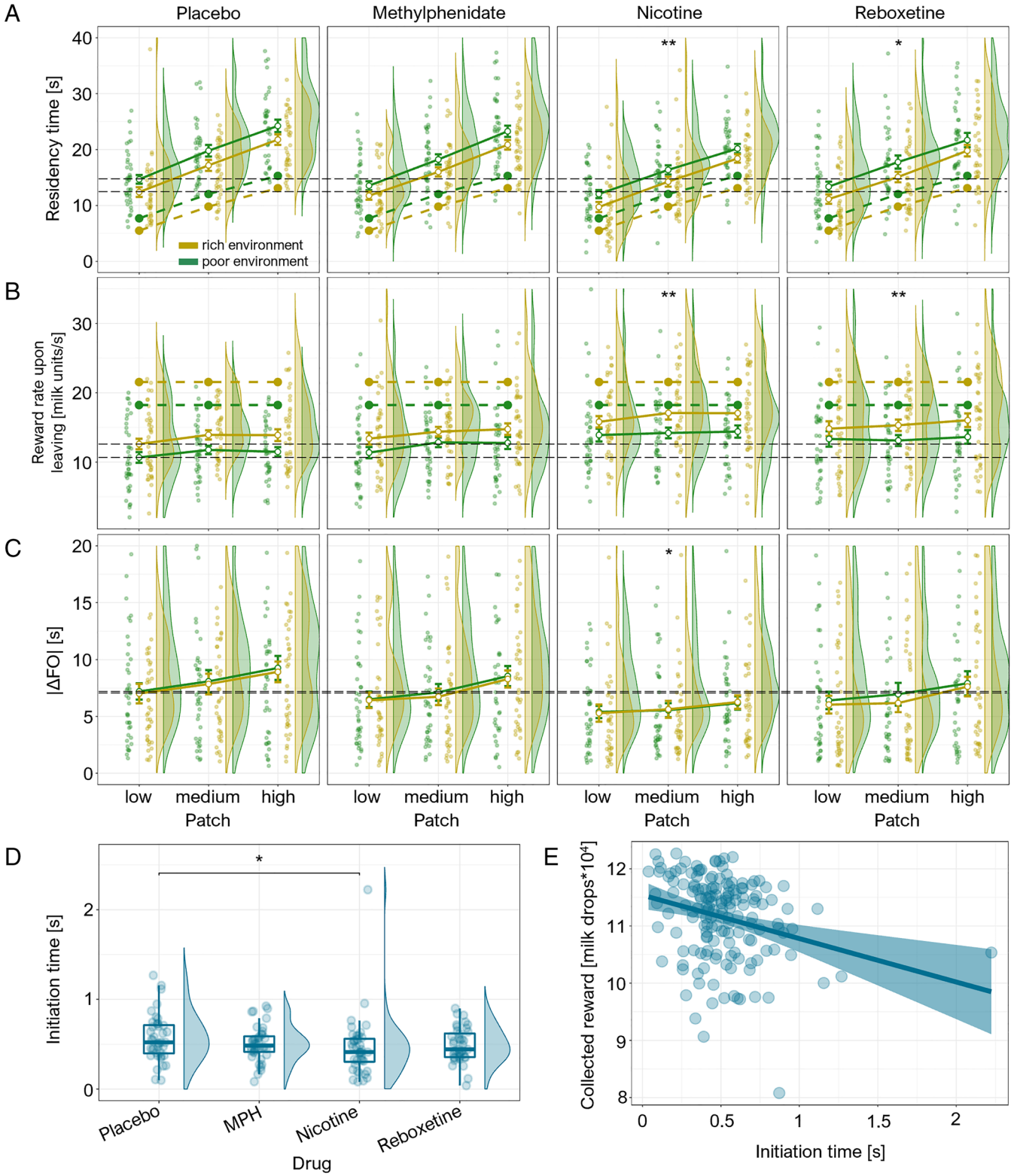

Fig. 3. Nicotine increases foraging optimality. (*A*) Residency times. Participants in the nicotine and reboxetine groups but not in the methylphenidate group left patches earlier compared to the placebo group. (*B*) Current reward rates upon leaving. Participants in the nicotine and reboxetine groups but not in the methylphenidate group left patches at higher reward rates compared to the placebo group. (*C*) Absolute deviation from foraging optimality |ΔFO|. Participants in the nicotine group but not in the other two drug groups deviated less from optimality than the placebo group. (*D*) Initiation times. Participants in the nicotine group initiated milk collection in new patches faster than the placebo group. (*E*) Performance as function of initiation times. The amount of collected reward negatively correlated with the time participants took to start the next trial. In (*A*–*C*), green and gold solid and dashed lines depict observed and optimal (when appropriate) values, respectively. Horizontal dashed lines indicate the average lowest points in each environment in the placebo group and facilitate visual comparisons with other groups. For individual data, each dot corresponds to the mean of one participant; errors bars indicate ± SEM. Stars indicate drug groups significantly differing from the placebo group. In (*D* and *E*), dots correspond to means of individual participants. In (*D*), density plots represent the distribution of individual mean values.

sustained focus on the trial-specific milk collection was accompanied by reduced attention to the information about the average reward rate of the environment.

Nicotine Increases Readiness to Initiate Trials. Rapidly entering a patch is essential for optimal foraging. By extension, earlier entries increase harvesting time, while later entries may prompt foragers to compensate by overstaying. In our task, participants could initiate milk collection any time after the message "Please press and hold the space bar" (Fig. 1*A*). On average, initiation times were short (0.5 s). Moreover, as one would expect, shorter initiation times increased task earnings (*Pearson's* r = −0.28, $P < 0.001$, Fig. 3*E*). A Bayesian linear model that accounted for drug group, age, and sex revealed significantly shorter initiation times in the nicotine group compared to the placebo group [$\beta_{nicotine > placebo}$ = −0.509, *95%CI* = (−0.941, −0.0591), Fig. 3*D*]. The other two drugs had no effect on initiation time [$\beta_{reboxetine > placebo}$ = −0.33, *95%CI* = (−0.762, 0.1212); $\beta_{methylphenidate > placebo}$ = −0.235, *95%CI* = (−0.690, 0.1976)]. Combined with the nicotine-related reduction in deviation from the optimal foraging policy, this finding reinforces the role of acetylcholine in optimizing rewards obtained through foraging.

As the initiation time prolongs travel time, it shifts the optimal point of leaving and could thereby contribute to overstaying suboptimality. To assess this possibility, we recalculated the optimal residency times separately for each participant, by adding the average individual initiation time to the 6 s of travel time fixed by the task design and refitted Model M2. This analysis confirmed the reduction in |ΔFO| under nicotine [$\beta_{nicotine > placebo}$ = −0.521, *95%CI* = (−0.853, −0.1803)], revealed a significant effect also for reboxetine [$\beta_{reboxetine > placebo}$ = −0.373, *95%CI* = (−0.704, −0.0122)], and no effect for methylphenidate [$\beta_{methylphenidate > placebo}$ = −0.191, *95%CI* = (−0.530, 0.1474)]. Thus, compared to placebo, participants under nicotine and reboxetine dynamically adapted their reward-earning strategy not only with respect to the inferred or externally provided task elements (i.e., environment and patch types) but also with respect to their own behavior.

Drug-Enhanced Optimality Is Unlikely to Result from Increased Impulsivity of Motor Responses. Could the accelerating effect of nicotine on residency and initiation times be explained by a simple increase in impulsive motor responses (46)? To test this possibility, we leveraged the data from a separate Time Perception task, which investigated how participants perceived the passage of time. Specifically, participants estimated how long it would take to fill a glass with juice up to an indicated level (*Methods* and *SI Appendix*, section S14). We designed the task such that its main features resembled those of the Foraging task: to start time estimation, participants pressed the space bar and then kept it pressed until they estimated the target level to be reached. Participants performed this task twice: once during screening (i.e., without any drug) and once in the main session (i.e., ON-drug).

To determine whether drug administration affected time estimation, we constructed a Bayesian hierarchical mixed-effects model that explained the numerical difference between the target time and participants' actual estimate by trial-specific filling rate, session (screening or main session), and drug group, while controlling for age, sex, and trial initiation time (Methods, Model M3). First, we found no difference between drug groups in the screening session as well as in the main session (all *95%CI* included 0, Fig. 4*A*). However, the model uncovered within-subject drug effects. Participants who received methylphenidate [$\beta_{Main > Screening}$ = 0.2333, *95%CI* = (0.093, 0.371)] or nicotine [$\beta_{Main > Screening}$ = 0.2287, *95%CI* = (0.095; 0.363)] in the main session underestimated target time significantly less when compared to themselves in the screening session whereas changes in the placebo and

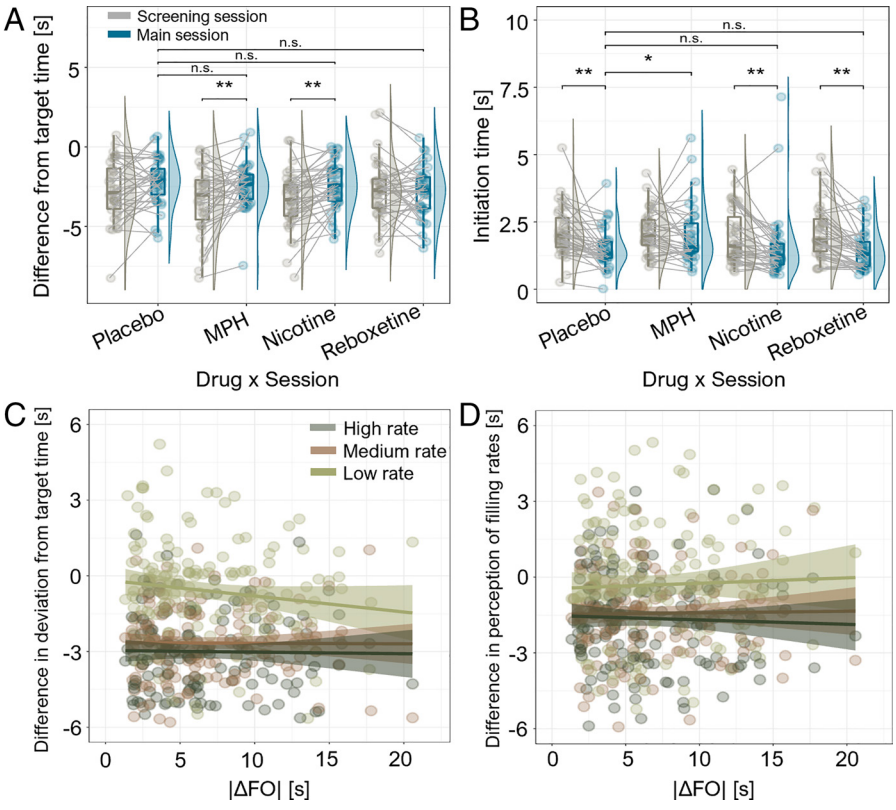

Fig. 4. Drug effects on time perception provide no explanation for drug effects on foraging optimality. (*A*) Methylphenidate and nicotine improve time perception within-subject. Compared to the screening session, participants who received methylphenidate or nicotine significantly improved their performance in the main session. There were no drug-related differences at the between-group level. (*B*) Nicotine does not affect trial-initiation time in Time Perception task. All groups except methylphenidate reduced their initiation times in the main session compared to the screening session, probably due to a learning effect. Unlike in the Foraging task, there were no significant differences associated with initiation times between the nicotine and placebo groups (and neither for reboxetine). In contrast to the Foraging Task, faster initiation provided no strategic advantage. (*C*) Foraging suboptimality unrelated to time perception. There was no correlation between individual deviations from foraging optimality and individual errors in time estimation. (*D*) Foraging suboptimality unrelated to perceived filling rates. There was no correlation between individual deviations from foraging optimality and individual differences in how participants perceived different filling rates in the Time Perception task. In (*A*–*D*), dots represent means of individual participants. In *A* and *B*, gray and blue colors indicate screening (OFF-drug) and main (ON-drug) sessions, respectively. In (*C* and *D*), each color corresponds to a different filling rate.

reboxetine groups did not reach significance (both *95%CI* included 0; Fig. 4*A*). Controlling for the magnitude of the target time did not affect these results (*SI Appendix*, section S14). Moreover, there were no significant effects of nicotine on initiation times for estimation, both within-subject and when compared to the placebo group (Fig. 4*B*; see also *SI Appendix*, section S14). Together, our data show that nicotine improved performance in both Foraging and Time Perception tasks. However, the two effects differed in directionality. In foraging, better performance was due to *shorter* residency and initiation times. By contrast, the improvement in the Time Perception task arose from *longer* response times. Thus, the findings from the Time Perception task rule out an impulsivity-based explanation of nicotine-induced improvement of performance in the Foraging task.

Drug-Enhanced Optimality Unlikely due to Effects on Time or Rate Perception. Next, we used the Time Perception task to test whether the nicotine effect on foraging reflects changes in the perception of time or filling rates. The filling rates in the Time Perception task matched those of the Foraging task. For each participant, we first assessed changes in time estimation accuracy by calculating between-session differences in average deviations from target time. We calculated differences separately for each filling rate and then entered them into the model (Model M3) to explain the variation in |ΔFO|. The effect of estimation accuracy on |ΔFO| was not significant, and the two variables were uncorrelated (Pearson's $r = -0.12$, $P = 0.13$, Fig. 4*C*). Moreover, a leave-one-out (LOO) procedure revealed that including estimation accuracy worsened the model fit compared to a model without it [ΔLOO = 1.5 ± 0.6; larger LOO-metrics (positive differences from initial model) indicate worse model fits]. We also assessed individual differences in rate perception by estimating the contrasts "low/medium/high filling rate >constant filling rate" for deviation from target time and then calculated the between-session difference in this metric. The measure was not correlated with the absolute deviation from foraging optimality (Pearson's $r = 0.001$, $P = 0.98$, Fig. 4*D*), did not explain |ΔFO| within the model, and worsened model fit (ΔLOO = 0.8 ± 0.7). These findings provide little evidence for a relation between foraging performance and accuracy in time estimation or rate perception. Moreover, drug effects on foraging optimality are unlikely to be explained by drug effects on these factors.

Discussion

Humans must frequently make foraging-like decisions: Stay with the status quo or switch to a better alternative. Optimizing such decisions balances costs (time and effort) with benefits. We show that cholinergic and noradrenergic systems causally contribute to optimizing stay-or-leave decisions in a dynamic foraging task.

The MVT (5) outlines a strategy for optimal resource management and provides a powerful framework to elucidate dynamics of individual and collective sustainable decision-making (47). Efficiency of resource consumption is thought to be one of the evolutionary drivers that shaped our brain, suggesting that foraging constitutes a default behavioral pattern (48). We find that our participants qualitatively followed prescriptions of the MVT in the lab, although they were not given any instructions to do so. Namely, they adapted their residency times to current patch and environment quality and often left different patch types within a given environment at the same reward rate. And yet, our participants overharvested their patches and thereby failed to quantitatively fulfil the core prescription of the theorem (49). Thus, our findings indicate that the pervasiveness of overharvesting is not limited to everyday life but arises also in tightly controlled lab conditions (1, 2, 30, 50, 51).

Our data provide unique insights into the neuromolecular basis of stay–leave dilemmas by showing that activation of the cholinergic system facilitates the optimal solution of such dilemmas. Most previous human studies used multiarmed bandit tasks (37, 52–54), which are conceptually different from foraging paradigms (55). The foraging framework complements the multiarmed bandit tasks by providing an ecologically valid framework, which closely mimics the structure of many real-life situations, where choice options (e.g., patches; flowers) with known rather than uncertain properties are encountered sequentially (e.g., mating partners; job positions) (56) rather than simultaneously. Furthermore, the rewards earned from these patches are not fluctuating randomly but diminish over time, similar to a finite resource in real life (57). This feature reflects real-world consequences of overharvesting such as deterioration of biodiversity and depletion of agricultural patches. Our data are compatible with the notion that the cholinergic system evolutionarily contributed to optimally solving naturalistic stay-or-leave dilemmas.

Previous pharmacological research on foraging in humans focused primarily on the role of dopamine (31, 32). Capitalizing on theoretical and empirical work, we hypothesized that also the cholinergic and the noradrenergic systems should contribute to task performance. Our hypotheses were largely confirmed. Both nicotine and reboxetine boosted foraging optimality by decreasing residency times and thus reducing the propensity of human agents to leave patches at suboptimally low reward rates. Thus, we establish unique causal links of acetylcholine and noradrenaline to solving stay-or-leave dilemmas. We next discuss these two findings in turn.

Participants in the nicotine group showed reduced overharvesting and left patches at higher current reward rates. These findings are compatible with a better integration of current and average reward rates into behavioral policy and thereby advance the existing knowledge on the cholinergic system. Nicotine has previously been shown to modulate reward sensitivity in multiple species (36, 37, 39, 58–60). We inform this body of research by suggesting that this effect may constitute the cholinergic contribution to optimizing foraging behavior. We note, however, that attribution of effects in complex behavioral tasks such as the present one is challenging and that an increase in reward sensitivity is only one possible explanation. Indeed, our drugs have effects also on other functions, such as sustained attention, effort sensitivity, or exertion of self-control (61), and some of these may also play roles in foraging (10). In line with this notion, additional gaze data revealed a more attentive examination of the current reward accumulation in the nicotine group compared to the placebo group, indicating a sustained focus on the task. Additionally, the finding that nicotine also accelerated trial initiation (but not general motor function) suggests that it facilitated the integration of multiple optimality-relevant task components to increase overall goal-directedness. This interpretation informs and extends research suggesting that cholinergic transmission in the prefrontal cortex underpins goal-directed behavior (17, 62). Moreover, as the arbitration between staying and leaving during foraging has been mainly associated with activity in the dorsal anterior cingulate cortex (63, 64), it is tempting to speculate that nicotine-induced increase in foraging optimality was at least partially due to its stimulating action on this brain region (65, 66). Finally, we note that increasing a neurotransmitter level may indirectly affect multiple neural circuits besides its primary target system (67) and future research is needed to decipher neuromodulatory effects in their full complexity.

In addition to increased goal directedness, several other explanations for the observed effects of nicotine are conceivable. First, nicotine-related decreases in residency and trial initiation times could be due to an increase in impulsive motor responses (68, 69). Contrary to this possibility, nicotine improved time estimation accuracy (70) in the Time Perception task by increasing response times. Moreover, between-session changes in time estimation accuracy were not associated with foraging behavior, excluding improvements in chronoception as a driver of foraging success in the nicotine group. We note that the task was designed specifically for this study and further investigation is needed to refine the interpretation of faster/slower response times arising here. For example, future studies may employ sequential sampling models to capture response times in this task (71).

Our tasks by design depended on basic motor abilities, as participants had to actively use their fingers to respond. Hence, previously reported nicotine-related facilitation of motor responding could in principle explain a decrease in residency and especially trial-initiation times (72, 73). The absence of nicotine-related motor facilitation in the Time Perception task also excluded this possibility. Nicotine could have affected visual perception of patch-specific filling rates (74). Again, the lack of an association with foraging performance in the Time Perception task provided little support for this suggestion. Finally, as the main stimulus in our task was food-related (albeit implemented with an abstract representation of milk), our results could have been related to nicotine-induced reductions of appetite (75). This explanation seems unlikely because compared to placebo, the nicotine group collected more rather than less milk (i.e., spent relatively more time at high milk collection rates). Collectively, our control tasks and analyses rule out heuristic explanations of the observed effects of nicotine and reinforce the interpretation of an interplay with higher-level cognitive processes, extending the notion of nicotine as cognitive enhancer (76) to foraging contexts.

Nicotinic acetylcholine receptors are densely expressed (77) in midbrain dopamine neurons (which may enhance the addictive potential of nicotine (78)). The absence of methylphenidate effects in our study appears to favor a direct over a dopamine-mediated explanation of the nicotine effects. However, it is worth keeping in mind that nicotinic receptors up-regulate dopamine release predominantly in the ventral striatum (79, 80), while methylphenidate affects also prefrontal functions (81) and dopamine release, particularly in the dorsal striatum (82). Thus, it is conceivable that in our study nicotine affected behavior through local actions on dopamine. In agreement with this possibility, a recent human study showed a negative association between neuromelanin levels in the ventral tegmental area and the degree of overharvesting (83). As foraging-like decisions are frequent in our daily routines, experiencing the beneficial effects of nicotine on decision optimality may increase vulnerability to addiction (78). By extension, our findings provide a new perspective on the initiation and maintenance of smoking (37, 78).

Our findings also associated the noradrenergic system with foraging optimality. One influential account proposed that the noradrenergic system mediates exploration-exploitation trade-offs (33). Direct manipulation of noradrenaline tone with pharmacological interventions in humans, however, provided inconsistent results: some in favor (84), some against (53), and some finding no effect (52). The presently observed reboxetine-induced reduction in residency times and increase in current reward rate upon leaving provide a causal link to the optimal resolution of stay-or-leave dilemmas, which resemble exploitation–exploration dilemmas, thereby corroborating a role of noradrenaline in behavioral shifts as portrayed by adaptive gain theory.

Our reboxetine findings also inform reports of noradrenaline facilitating behavioral flexibility (85, 86) and of stimulation of rat locus coeruleus with designer receptor ligands causing rats to explore, i.e., leave all patches earlier than the control group (87). Note that the rats in the stimulation study disengaged from the task (worse performance), whereas our participants benefitted from noradrenergic stimulation. It is plausible to assume that direct stimulation of the locus coeruleus leads to high tonic noradrenaline levels, whereas our low dose of reboxetine (4 mg) elevates noradrenaline tone more moderately. Under this assumption, the previous animal and our human findings are both compatible with the inverted-U-shaped pattern of flexibility (moderate noradrenergic stimulation) and disengagement (strong noradrenergic stimulation) proposed by adaptive gain theory (33). We also found decreased decision noise under reboxetine, again in line with adaptive gain theory. Interestingly, this effect occurred in all drug groups [Levin et al. (88) and Nandam et al. (89) provide earlier reports of reduced responses variability under nicotine and methylphenidate in nonforaging situations, suggesting a more general mechanism of moderate increases in neurotransmitter levels]. Finally, we note that in our task, participants had full information about foraging-relevant parameters (e.g., environmental quality or travel time). Future studies could employ task designs, where environmental features must be inferred and learned (90) and thereby assess whether the foraging optimality-enhancing effects of cholinergic and noradrenergic stimulation extend to conditions of epistemic uncertainty (91).

Unlike nicotine and reboxetine, methylphenidate had little effect on foraging metrics. We note that methylphenidate may also increase noradrenaline, albeit to a lesser extent than reboxetine. As our data showed differential effects resulting from the independent upregulation of both systems, we discuss methylphenidate only with respect to its primary target. The absence of methylphenidate effects may seem surprising at first given prior reports of dopamine-related changes in foraging behavior (31). However, it is worth noting that the study of Le Heron et al. investigated elderly people (mean age 69, range 60 to 78 y), whereas our cohort was much younger (mean age 23, range 18 to 35 y). Age is associated with both increased overharvesting (42) and reduced dopamine activity (92). Thus, it is conceivable that the suboptimality in our methylphenidate group was too low or the dopamine activity too high for upregulation of the dopamine system to have an effect. Moreover, Le Heron et al. used the dopamine D2 receptor agonist cabergoline, which is more likely to affect striatal rather than prefrontal dopamine, due to imbalance in D1-D2 receptor expression between the striatum and the prefrontal cortex (93). In contrast, the dopamine transporter blocker methylphenidate results in increased stimulation of both D1 and D2 receptors (94, 95) and has been associated with increased dopamine levels in both the striatum and prefrontal cortex (96, 97). Thus, it is tempting to speculate that increased foraging optimality is underpinned primarily by the striatum (or the balance between prefrontal and striatal dopamine). Future recordings of neural data may address this issue.

We note that methylphenidate affected some aspects of behavior. Not only did it reduce decision noise and increase working memory capacity, but it also facilitated the viewing of information about current reward rate. Thus, methylphenidate appears to enhance attention to the most salient foreground stimulus (i.e., bucket filling up with milk), leaving fewer cognitive resources to process background task components (i.e., average reward rate and travel time) (96, 98, 99). Neglect of the average reward rate would explain why, contrary to our initial hypothesis, methylphenidate had little effect on foraging optimality. By extension, our

data enrich the existing literature (81, 100) with a foraging-related instance of methylphenidate concomitantly enhancing one cognitive function and worsening another.

Our study has limitations worth noting. First, we investigated behavioral and physiological effects but not neural mechanisms. Second, although we causally linked noradrenaline and acetylcholine to foraging optimality, we did so by upregulation only. Adding downregulation would provide a more complete picture of how the three neurotransmitters implement foraging. Moreover, while in our study low doses of reboxetine and nicotine led to cognitive and behavioral enhancement, inverted U-shaped effects have been reported for both drugs. Hence, future studies may want to investigate dose-dependent effects on foraging optimality. Finally, we note that we did not test for the effect of serotonin—a neuromodulator that has been associated with cognitive control and reward-guided behavior (101, 102). A practical limitation is that drugs commonly used in single-shot studies to increase the level of serotonin (e.g., the antidepressant citalopram) have a longer half-life ($t_{1/2}$) and a later peak (t_{max}) (103) compared to nicotine, reboxetine, and methylphenidate. This would have created a mismatch with the administration times of other drugs and further increased the duration of an already involved study. Moreover, the serotonin system is particularly complex (104), making it hard to interpret the effects of single-substance interventions. Future studies may therefore want to focus specifically on the role of serotonin in foraging behavior and combine serotonin reuptake inhibitors with specific serotonin receptor antagonists.

In conclusion, even though foraging-like decisions pervade our lives, our participants overharvested in a standard foraging paradigm. This bias was counteracted by nicotine and to some extent reboxetine. Our findings provide unique causal evidence for cholinergic and noradrenergic contributions to human foraging and suggest a set of putative molecular targets for enhancing optimality of decision-making in stay-or-leave dilemmas. Converging evidence from control analyses and control tasks suggests that nicotine increases goal-directedness. Our findings empower the research agenda on therapeutic approaches for psychiatric disorders such as depression, schizophrenia, anxiety, gambling, and obsessive-compulsive disorders, as well as ADHD, in which stay-or-leave decisions are known to be impaired (19–24). Moreover, they reveal that overharvesting and its reduction are under neuropharmacological control.

Methods

Participants. One hundred and sixty neurologically and psychiatrically healthy volunteers with normal or corrected-to-normal vision were recruited by the recruitment team of the Department of Economics at the University of Zurich. All participants provided written informed consent, both at screening and, if invited, at the main session in accordance with the Declaration of Helsinki. An initial sample of 302 volunteers took part in the screening session. Implementing a predefined set of inclusion and exclusion criteria (*SI Appendix*, sections S3 and S4), the sample participating in the main session had the following characteristics: mean age ± SD = 23.63 ± 3.65 y; 80 women, mean body mass index (BMI) ± SD = 22.61 ± 2.56 kg/m^2. Participants were randomly and double-blindly assigned to either the placebo or one of the three pharmacological intervention groups with 40 participants per group. During the main session, no participant experienced moderate or strong adverse drug effects, and none was excluded due to noncompliance with study rules.

Screening Session (OFF-Drug). First, participants performed a Time Perception task and subsequently filled out a set of questionnaires. Then, an electrocardiogram was acquired, and physiological parameters (blood pressure and heart rate) were measured for examination by a medical doctor. Finally, participants provided a urine test to ensure absence of traces of drugs of abuse, including cotinine. Participants were remunerated with a flat fee of 45 CHF for this 1-h session.

Main Session (ON-Drug). Participants fasted for 6 h and abstained from substances containing alcohol or caffeine for 12 h preceding the experiment. Upon their arrival to the lab, participants received a controlled breakfast. To monitor participant well-being, blood pressure and heart rate were measured three times during the 5-h session. Blood samples were taken twice to determine plasma levels of drugs and their metabolites. Saliva samples were collected three times to measure cortisol, which served as an index of arousal and stress (*SI Appendix*, section S1 for exact timing).

We used 20 mg methylphenidate, 4 mg reboxetine, and 2 mg nicotine to increase levels of dopamine, noradrenaline, and nicotine, respectively. For methylphenidate and reboxetine, they represent the lower end of the daily dosage range for achieving dopamine and noradrenaline transporter blockade and 2 mg nicotine is associated with minimal adverse effects (105–107). Each drug was administered orally–methylphenidate and reboxetine as a pill and nicotine as a chewing gum. Due to differences in pharmacokinetics of methylphenidate/reboxetine versus nicotine, and to ensure double-blinded conditions, all participants received two substances–first a pill and 1 h later a gum–but only one or neither was active. To minimize the chance that participants would guess which drug they received, gums in all four groups were covered with a few drops of tabasco sauce to mask their taste; all pills were tasteless and looked the same.

Foraging Task. The task was run in Psychtoolbox (108) and adopted from Le Heron et al. (31). In this task, participants took the role of a foraging farmer who collected milk from patches with cows. Each patch was visualized by a bucket, which was continuously filled with milk as long as the participant stayed in the patch.

The task manipulated two key variables of the MVT: current and average reward rates. The average reward rate of the environment was given by the proportion of patches with low, medium, and high current reward rate. The current reward rate is the reward provided by the current patch at any given time point t and followed:

$$\dot{g}(t) = A * e^{-0.075*t}, \quad [1]$$

where A is the scaling factor of the reward function, set to 32.5 in low, 45 in medium, and 57.5 in high-yield patches. The difference in the scaling factor ensured that the current milk collection rate differed between patches, so that for the same duration of stay, the amount of milk collected in the high-yield patch was clearly larger compared to the low-yield patch. The current reward rate decreased exponentially with time and reflected resource depletion.

At the beginning of the experiment, participants were presented with computer-based instructions, which familiarized them with different environment and patch types and introduced the travel cost. The instructions specified that in the rich environment (visualized by a golden frame around the bucket), 50% patches were high-yield, 30% medium-yield, and 20% low-yield. Conversely, the poor environment (framed in green) consisted of 20% high-yield patches, 30% medium-yield patches, and 50% low-yield patches. Giving participants full information eliminated the need to explore the environment to infer and learn its composition and allowed optimal foraging from the very first trial (109). Furthermore, the instructions mentioned that participants would forage in both environments for an equal amount of time (5 min) and never run out of patches. Finally, the instructions set the goal to collect as much milk as possible from both farms, as the total amount of collected milk would be converted into Swiss Francs at the end of the task. Crucially, participants were not given any information about the optimal behavior.

Comprehension of the task was assessed by three questions. In case of at least one wrong answer, the message "Please call the study investigator" was displayed. Participants then reviewed task instructions together with the study investigator. After correctly answering all comprehension questions, participants performed three practice trials, during which they familiarized themselves with the different patch types.

During the actual experiment, participants entered a new patch by pressing the space bar. As soon as they pressed, an empty bucket appeared in the middle of the screen and milk collection started. During milk collection, a colored frame

around the bucket indicated the quality of the environment participants were in. Conversely, participants had to infer the patch quality themselves by observing the rate of milk accumulation for every new patch. The bucket continued to fill as long as participants kept pressing the space bar, or 2 min elapsed (however, no participant reached the time limit). Upon key release, participants automatically left the patch and entered the travel phase, during which a clock ticked down the seconds and the total amount of milk collected so far was displayed on the screen. No milk collection was possible during travel time, which reflected the cost of exploration. After 6 s had elapsed, the message "Please press and hold the space bar" invited participants to enter a new patch and collect more milk. Participants were free to press the space bar at any moment after this cue, and the period between cue appearance and key press constituted the trial-specific initiation time. Participants spent 5 min in the first environment and were then informed by a 6-s message that "Now you will go to the other farm". In the new environment, the bucket was framed in a different color. Environment and patch orders were kept the same for all participants (*SI Appendix*, section S9).

Time Perception Task. Each trial comprised two phases. During the first phase, participants viewed a glass filling with juice at a trial-specific rate for ten seconds. During the second phase, an empty glass appeared, crossed by a horizontal line at a trial-specific height. Participants were instructed to press the space bar to fill the glass at the rate of the first phase. They released the space bar when they estimated the juice to have reached the horizontal line. Importantly, during the second phase participants did not see the juice filling the glass and had to rely only on their own estimation of elapsed time. Juice filling rates corresponded to the low, medium, and high milk filling rates from the Foraging task. Moreover, trials with a fourth, constant rather than decreasing, filling rate were included to provide a baseline for subsequent analysis.

Statistical Analysis. All statistical analyses were performed in *R4.0*. Bayesian hierarchical linear mixed-effects models were constructed using the package *brms* (110). To account for all possible effects, we first interrogated comprehensive models that included interactions between task-related within-subject factors, drug group, and session, when appropriate. For each model, all continuous variables were z-scored relative to the mean and SD of the whole cohort, and default uniform brms-priors were used. We fitted models with four chains of 3,000 iterations each (1,000 warm-up) and then inspected for convergence [all R-hat metrics should be smaller than 1.01 (111)]. Predictors were considered statistically significant if their 95% posterior credible intervals did not include zero. Model comparison was performed with a leave-one-out (LOO) procedure, with smaller LOO-metrics indicating better model fits (111).

Foraging Task. To determine whether participants conformed to core MVT prescriptions, i.e., whether their stay-or-leave decisions varied as function of both current and average reward rates, we constructed a Bayesian hierarchical linear mixed-effects model (Model M1). Patch and environment entered the model as categorical variables. The model also included regressors accounting for age and sex. Moreover, we controlled for initiation times with a square-root-transformed continuous regressor. Model comparison showed that the model with age, sex, and initiation times outperformed a model without these regressors ($\Delta LOO_{residency\ times} = -52.1 \pm 12.9$ and $\Delta LOO_{current\ reward\ rate} = -64.8 \pm 16.0$ in favor of the covariates-included-model). We also accounted for random effects by allowing the intercept to vary across participants with respect to patches and environments ($\Delta LOO_{residency\ times} = -470.6 \pm 34.9$ and $\Delta LOO_{current\ reward\ rate} = -448.6 \pm 39.5$ in favor of extended-random-effects-model when compared to subject-intercept-only-model). The full model assessed the effects of patch and environment on actual residency times and current patch reward rates at the moment of leave (together denoted with "dependent variable" in Model M1).

$$\begin{aligned} Dependent\ variable = {} & \beta_0 + \beta_1 Patch + \beta_2 Environment + \beta_3 Patch \\ & : Environment + \beta_4 Age + \beta_5 Sex + \beta_6 Initiation\ time + (1|Participant) \\ & + (1|Participant: Patch) + (1|Participant: Environment) \\ & + (1|Participant: Patch: Environment). \end{aligned} \quad [\mathbf{M\ 1}]$$

To assess the effects of the pharmacological interventions on foraging behavior, we first calculated deviation from foraging optimality (Eq. **2**). *Actual residency time*$_{n_{p,e}}$ was the residency time on trial *n* in patch *p* of environment *e*. *Optimal residency time*$_{p,e}$ corresponds to the optimal time at which the agent should leave patch *p* in environment *e* to maximize long-term net gain according to the MVT.

$$|\Delta FO| = \left| \left(Actual\ residency\ time_{n_{p,e}} - Optimal\ residency\ time_{p,e} \right) \right|. \quad [\mathbf{2}]$$

Negative deviations from optimality mean that, on average, the agent leaves patches earlier than prescribed by the MVT, i.e., a tendency to underharvest. Conversely, positive deviations from optimality indicate that the agent stays in patches longer than prescribed by the MVT, i.e., a tendency to overharvest. While the sign indicates differences in bias directionality, both tendencies lead to suboptimal reward collection. Consequently, in cases where an average decrease in signed deviation is driven by suboptimally short residency times, the interpretation of a putative drug effect is unclear: Should it be seen as reduced deviation or worsened performance? To prevent this unclarity, we focused on deviations from foraging optimality in absolute terms (|ΔFO|), which allowed us to interpret lower |ΔFO| values as reflecting behavior closer to optimal and thereby qualify drug effects unambiguously. Specifically, we augmented Model M1 by adding fixed-effect factors for drug group (Model M2). Applying the model on our three dependent variables (actual residency times, current reward rate upon leaving, and absolute deviation from optimal residency times) allowed us to test the primary hypotheses concerning drug effects:

$$\begin{aligned} Dependent\ variable = {} & \beta_0 + \beta_1 Patch + \beta_2 Environment + \beta_3 Drug + \\ & \beta_4 Patch: Environment + \beta_5 Patch: Drug + \beta_6 Environment: Drug + \\ & \beta_7 Patch: Environment: Drug + \beta_8 Age + \beta_9 Sex + \beta_{10} Initiation\ time + \\ & (1|Participant) + (1|Participant: Patch) + \\ & (1|Participant: Environment) + (1|Participant: Patch: Environment). \end{aligned} \quad [\mathbf{M\ 2}]$$

Initiation time and absolute deviation from foraging optimality were square-root-transformed, and all continuous variables were z-scored. High-yield patch, poor environment, female sex, and placebo group were set as baseline levels for corresponding factors. Post hoc contrasts were performed with functions *hypothesis()* and *emmeans()* from R-packages *brms* and *emmeans*, respectively (110, 112).

Time Perception Task. To assess the within- and between-subjects drug-induced changes in time estimation accuracy, we constructed a Bayesian hierarchical linear mixed-effects model (Model M3) where difference from the target time was explained by trial filling rate (corresponding to patch types from the Foraging task), session (Main or Screening), and drug group (placebo, methylphenidate, nicotine or reboxetine). Age, sex, and square-root-transformed initiation times were again used as control variables. We accounted for random effects by allowing the intercept to vary across participants with respect to the within-subject factors (filling rate and session).

$$\begin{aligned} Difference\ from\ target\ time = {} & \beta_0 + \beta_1 Patch + \beta_2 Session + \beta_3 Drug + \\ & \beta_4 Patch: Session + \beta_5 Patch: Drug + \beta_6 Session: Drug \\ & + \beta_7 Patch: Session: Drug + \beta_8 Age + \beta_9 Sex + \\ & \beta_{10} Initiation\ time + (1|Participant) + (1|Participant: Patch) + \\ & (1|Participant: Session) + (1|Participant: Patch: Session). \end{aligned} \quad [\mathbf{M\ 3}]$$

Gaze Data Acquisition. Gaze data were acquired using an EyeLink 1000 Plus eyetracker (SR Research). Before the task, a calibration routine was performed on nine screen locations and repeated until the maximum deviation from any location was less than 2°. Due to a technical issue, the sampling rates varied between 500, 1,000, and 2,000 Hz, although most participants in each group

were recorded at 1,000 Hz. To ensure consistency, the data were down- or upsampled to a rate of 1,000 Hz. Crucially, controlling for the acquisition frequency in our models did not change significance of the results.

After removing blinks, we extracted fixations identified with the EyeLink algorithm. Next, we identified the center of the screen for each individual by using the time periods when the fixation cross was displayed. We assessed the accuracy of the identification by manually checking the alignment between gaze position and key task features (bucket, milk, frame, collected reward, and clock). Twelve participants were excluded from the analyses due to insufficient data quality. Finally, we quantified the number of fixations within specific target zones (e.g., milk in the bucket or environment frame) and then assessed drug effects on these metrics by running a series of Bayesian hierarchical mixed-effect and general linear models. Detailed description of acquisition, preprocessing, and analysis of the gaze data is provided in *SI Appendix*, section S15.

Clinical Trial Registration

The study was registered on ClinicalTrials.gov (identifier: NCT 04384562).

Human Subjects

Participants gave informed written consent before participation. The study was approved by the Ethics Committee of the Canton of Zurich (study ID: 2020-00044).

Data, Materials, and Software Availability. All data as well as codes for experiment execution, data processing, analysis, and figure creation are available at GitHub (https://github.com/NickNeuro/Foraging_pharma_BEH) (113).

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1. C. E. Rusbult, J. M. Martz, Remaining in an abusive relationship: An investment model analysis of nonvoluntary dependence. *Pers. Soc. Psychol. Bull.* **21**, 558–571 (1995).
2. A. A. Buchko, C. Buscher, K. J. Buchko, Why do good employees stay in bad organizations? *Bus. Horiz.* **60**, 729–739 (2017).
3. K. Mehlhorn *et al.*, Unpacking the exploration–exploitation tradeoff: A synthesis of human and animal literatures. *Decision* **2**, 191–215 (2015).
4. D. W. Stephens, J. R. Krebs, *Foraging Theory* (Princeton University Press, 2019).
5. E. L. Charnov, Optimal foraging, the marginal value theorem. *Theor. Popul. Biol.* **9**, 129–136 (1976).
6. D. Mobbs, P. C. Trimmer, D. T. Blumstein, P. Dayan, Foraging for foundations in decision neuroscience: Insights from ethology. *Nat. Rev. Neurosci.* **19**, 419–427 (2018).
7. R. K. Kendall, A. M. Wikenheiser, Quitting while you're ahead: Patch foraging and temporal cognition. *Behav. Neurosci.* **136**, 467 (2022).
8. M. J. Novacek, E. E. Cleland, The current biodiversity extinction event: Scenarios for mitigation and recovery. *Proc. Natl. Acad. Sci. U.S.A.* **98**, 5466–5470 (2001).
9. A. Lampert, Over-exploitation of natural resources is followed by inevitable declines in economic growth and discount rate. *Nat. Commun.* **10**, 1–10 (2019).
10. D. L. Barack, M. L. Platt, "Engaging and exploring: Cortical circuits for adaptive foraging decisions" in *Impulsivity: How Time and Risk Influence Decision Making* (Springer International Publishing AG, 2017), **vol. 64**, pp. 163–199.
11. P. N. Tobler, C. D. Fiorillo, W. Schultz, Adaptive coding of reward value by dopamine neurons. *Science* **307**, 1642–1645 (2005).
12. R. Cools, Role of dopamine in the motivational and cognitive control of behavior. *Neuroscientist* **14**, 381–395 (2008).
13. S. J. Heishman, B. A. Kleykamp, E. G. Singleton, Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology* **210**, 453–469 (2010).
14. N. Petrovsky *et al.*, Nicotine differentially modulates antisaccade performance in healthy male non-smoking volunteers stratified for low and high accuracy. *Psychopharmacology* **221**, 27–38 (2012).
15. N. Petrovsky *et al.*, Nicotine enhances antisaccade performance in schizophrenia patients and healthy controls. *Int. J. Neuropsychopharmacol.* **16**, 1473–1481 (2013).
16. O. Borodovitsyna, M. Flamini, D. Chandler, Noradrenergic modulation of cognition in health and disease. *Neural. Plast.* **2017**, 1–14 (2017).
17. R. Cools, A. F. Arnsten, Neuromodulation of prefrontal cortex cognitive function in primates: The powerful roles of monoamines and acetylcholine. *Neuropsychopharmacology* **47**, 309–328 (2022).
18. M. A. Addicott, J. M. Pearson, M. M. Sweitzer, D. L. Barack, M. L. Platt, A primer on foraging and the explore/exploit trade-off for psychiatry research. *Neuropsychopharmacology* **42**, 1931–1939 (2017).
19. M. A. Addicott, J. M. Pearson, N. Kaiser, M. L. Platt, F. J. McClernon, Suboptimal foraging behavior: A new perspective on gambling. *Behav. Neurosci.* **129**, 656–665 (2015).
20. N. J. Blanco, A. R. Otto, W. T. Maddox, C. G. Beevers, B. C. Love, The influence of depression symptoms on exploratory decision-making. *Cognition* **129**, 563–568 (2013).
21. T. U. Hauser *et al.*, Role of the medial prefrontal cortex in impaired decision making in juvenile attention-deficit/hyperactivity disorder. *JAMA Psychiatry* **71**, 1165–1173 (2014).
22. F. Cathomas *et al.*, Increased random exploration in schizophrenia is associated with inflammation. *NPJ Schizophr.* **7**, 1–9 (2021).
23. K. C. Aberg, I. Toren, R. Paz, A neural and behavioral trade-off between value and uncertainty underlies exploratory decisions in normative anxiety. *Mol. Psychiatry* **27**, 1573–1587 (2022).
24. M. Dubois, T. U. Hauser, Value-free random exploration is linked to impulsivity. *Nat. Commun.* **13**, 1–17 (2022).
25. W. Schultz, P. Dayan, P. R. Montague, A neural substrate of prediction and reward. *Science* **275**, 1593–1599 (1997).
26. C. D. Fiorillo, P. N. Tobler, W. Schultz, Discrete coding of reward probability and uncertainty by dopamine neurons. *Science* **299**, 1898–1902 (2003).
27. J. D. Salamone, M. Correa, A. M. Farrar, E. J. Nunes, M. Pardo, Dopamine, behavioral economics, and effort. *Front. Behav. Neurosci.* **3**, 1–13 (2009).
28. U. Beierholm *et al.*, Dopamine modulates reward-related vigor. *Neuropsychopharmacology* **38**, 1495–1503 (2013).
29. Y. Niv, N. D. Daw, D. Joel, P. Dayan, Tonic dopamine: Opportunity costs and the control of response vigor. *Psychopharmacology* **191**, 507–520 (2007).
30. J. K. Lenow, S. M. Constantino, N. D. Daw, E. A. Phelps, Chronic and acute stress promote overexploitation in serial decision making. *J. Neurosci.* **37**, 5681–5689 (2017).
31. C. Le Heron *et al.*, Dopamine modulates dynamic decision-making during foraging. *J. Neurosci.* **40**, 5273–5282 (2020).
32. S. M. Constantino *et al.*, A neural mechanism for the opportunity cost of time. BioRxiv [Preprint] (2017). https://doi.org/10.1101/173443 (Accessed 15 March 2021).
33. G. Aston-Jones, J. D. Cohen, An integrative theory of locus coeruleus-norepinephrine function: Adaptive gain and optimal performance. *Annu. Rev. Neurosci.* **28**, 403–450 (2005).
34. P. Dostert, M. S. Benedetti, I. Poggesi, Review of the pharmacokinetics and metabolism of reboxetine, a selective noradrenaline reuptake inhibitor. *Eur. Neuropsychopharmacol.* **7**, S23–S35 (1997).
35. J. W. Young *et al.*, Nicotine improves sustained attention in mice: Evidence for involvement of the α 7 nicotinic acetylcholine receptor. *Neuropsychopharmacology* **29**, 891–900 (2004).
36. P. J. Kenny, A. Markou, Nicotine self-administration acutely activates brain reward systems and induces a long-lasting increase in reward sensitivity. *Neuropsychopharmacology* **31**, 1203–1211 (2006).
37. M. A. Addicott, J. M. Pearson, J. Wilson, M. L. Platt, F. J. McClernon, Smoking and the bandit: A preliminary study of smoker and nonsmoker differences in exploratory behavior measured with a multiarmed bandit task. *Exp. Clin. Psychopharmacol.* **21**, 66–73 (2013).
38. W. C. Fobbs, S. J. Mizumori, Cost-benefit decision circuitry: Proposed modulatory role for acetylcholine. *Prog. Mol. Biol. Transl. Sci.* **122**, 233–261 (2014).
39. M. Dongelmans *et al.*, Chronic nicotine increases midbrain dopamine neuron activity and biases individual strategies towards reduced exploration in mice. *Nat. Commun.* **12**, 1–15 (2021).
40. R. C. Kessler *et al.*, The world health organization adult ADHD self-report scale (ASRS): A short screening scale for use in the general population. *Psychol. Med.* **35**, 245–256 (2005).
41. C. D. Spielberger, State-trait anxiety inventory for adults (1983).
42. R. Mata, A. Wilke, U. Czienskowski, Cognitive aging and adaptive foraging behavior. *J. Gerontol. B Psychol. Sci. Soc. Sci.* **64**, 474–481 (2009).
43. D. R. Bach, M. Moutoussis, A. Bowler, R. J. Dolan, Predictors of risky foraging behaviour in healthy young people. *Nat. Hum. Behav.* **4**, 832–843 (2020).
44. S. M. Constantino, N. D. Daw, Learning the opportunity cost of time in a patch-foraging task. *Cogn. Affect. Behav. Neurosci.* **15**, 837–853 (2015).
45. A. M. Linssen, A. Sambeth, E. F. Vuurman, W. Riedel, Cognitive effects of methylphenidate in healthy volunteers: A review of single dose studies. *Int. J. Neuropsychopharmacol.* **17**, 961–977 (2014).
46. G. Edman, D. Schalling, S. Levander, Impulsivity and speed and errors in a reaction time task: A contribution to the construct validity of the concept of impulsivity. *Acta Psychol.* **53**, 1–8 (1983).
47. G. H. Davis, M. C. Crofoot, D. R. Farine, Using optimal foraging theory to infer how groups make collective decisions. *Trends Ecol. Evol.* **37**, 942–952 (2022).
48. A. J. Calhoun, B. Y. Hayden, The foraging brain. *Curr. Opin. Behav. Sci.* **5**, 24–31 (2015).
49. S. Hall-McMaster, F. Luyckx, Revisiting foraging approaches in neuroscience. *Cogn. Affect. Behav. Neurosci.* **19**, 225–230 (2019).

50. J. E. Duffy, Why biodiversity is important to the functioning of real-world ecosystems. *Front. Ecol. Environ.* **7**, 437–444 (2009).
51. S. Brownlee *et al.*, Evidence for overuse of medical services around the world. *Lancet* **390**, 156–168 (2017).
52. M. Jepma, E. T. Te Beek, E.-J. Wagenmakers, J. Van Gerven, S. Nieuwenhuis, The role of the noradrenergic system in the exploration-exploitation trade-off: A pharmacological study. *Front. Hum. Neurosci.* **4**, 1–13 (2010).
53. C. M. Warren *et al.*, The effect of atomoxetine on random and directed exploration in humans. *PLoS One* **12**, e0176034 (2017).
54. K. Chakroun, D. Mathar, A. Wiehler, F. Ganzer, J. Peters, Dopaminergic modulation of the exploration/exploitation trade-off in human decision-making. *Elife* **9**, e51260 (2020).
55. B. von Helversen, R. Mata, G. R. Samanez-Larkin, A. Wilke, Foraging, exploration, or search? On the (lack of) convergent validity between three behavioral paradigms. *Evol. Behav. Sci.* **12**, 152–162 (2018).
56. A. Kacelnik, M. Vasconcelos, T. Monteiro, J. Aw, Darwin's "tug-of-war" vs. starlings'"horse-racing": How adaptations for sequential encounters drive simultaneous choice. *Behav. Ecol. Sociobiol.* **65**, 547–558 (2011).
57. R. Dietz, D. O'Neill, *Enough is Enough: Building a Sustainable Economy in a World of Finite Resources* (Routledge, 2013).
58. R. S. Barr, D. A. Pizzagalli, M. A. Culhane, D. C. Goff, A. E. Evins, A single dose of nicotine enhances reward responsiveness in nonsmokers: Implications for development of dependence. *Biol. Psychiatry* **63**, 1061–1065 (2008).
59. J. Peters *et al.*, Lower ventral striatal activation during reward anticipation in adolescent smokers. *Am. J. Psychiatry* **168**, 540–549 (2011).
60. E. Lesage *et al.*, Neural signatures of cognitive flexibility and reward sensitivity following nicotinic receptor stimulation in dependent smokers: A randomized trial. *JAMA Psychiatry* **74**, 632–640 (2017).
61. Y.-L. Boureau, P. Sokol-Hessner, N. D. Daw, Deciding how to decide: Self-control and meta-decision making. *Trends Cogn. Sci.* **19**, 700–710 (2015).
62. T. Wallace, D. Bertrand, Importance of the nicotinic acetylcholine receptor system in the prefrontal cortex. *Biochem. Pharmacol.* **85**, 1713–1720 (2013).
63. N. Kolling, T. E. Behrens, R. B. Mars, M. F. Rushworth, Neural mechanisms of foraging. *Science* **336**, 95–98 (2012).
64. A. Shenhav, M. A. Straccia, J. D. Cohen, M. M. Botvinick, Anterior cingulate engagement in a foraging context reflects choice difficulty, not foraging value. *Nat. Neurosci.* **17**, 1249–1254 (2014).
65. V. Kumari *et al.*, Cognitive effects of nicotine in humans: An fMRI study. *Neuroimage* **19**, 1002–1013 (2003).
66. L. E. Hong *et al.*, Association of nicotine addiction and nicotine's actions with separate cingulate cortex functional circuits. *Arch. Gen. Psychiatry* **66**, 431–441 (2009).
67. M. Husain, M. A. Mehta, Cognitive enhancement by drugs in health and disease. *Trends Cogn. Sci.* **15**, 28–36 (2011).
68. A. S. Potter, D. J. Bucci, P. A. Newhouse, Manipulation of nicotinic acetylcholine receptors differentially affects behavioral inhibition in human subjects with and without disordered baseline impulsivity. *Psychopharmacology* **220**, 331–340 (2012).
69. J. G. Hosking, F. C. Lam, C. A. Winstanley, Nicotine increases impulsivity and decreases willingness to exert cognitive effort despite improving attention in "slacker" rats: Insights into cholinergic regulation of cost/benefit decision making. *PLoS One* **9**, e111580 (2014).
70. S. C. Hinton, W. H. Meck, Increasing the speed of an internal clock: The effects of nicotine on interval timing. *Drug Dev. Res.* **38**, 204–211 (1996).
71. B. U. Forstmann, R. Ratcliff, E.-J. Wagenmakers, Sequential sampling models in cognitive neuroscience: Advantages, applications, and extensions. *Annu. Rev. Psychol.* **67**, 641–666 (2016).
72. K. A. Perkins *et al.*, Chronic and acute tolerance to subjective, behavioral and cardiovascular effects of nicotine in humans. *J. Pharmacol. Exp. Ther.* **270**, 628–638 (1994).
73. O. Tucha, K. W. Lange, Effects of nicotine chewing gum on a real-life motor task: A kinematic analysis of handwriting movements in smokers and non-smokers. *Psychopharmacology* **173**, 49–56 (2004).
74. T. P. Fernandes, N. L. Almeida, G. M. Silva, N. A. Santos, Nicotine gum enhances visual processing in healthy nonsmokers. *Brain Imaging Behav.* **15**, 2593–2605 (2021).
75. A. Schwartz, N. Bellissimo, Nicotine and energy balance: A review examining the effect of nicotine on hormonal appetite regulation and energy expenditure. *Appetite* **164**, 105260 (2021).
76. D. M. Warburton, Nicotine as a cognitive enhancer. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **16**, 181–192 (1992).
77. C. Gotti, F. Clementi, Neuronal nicotinic receptors: From structure to pathology. *Prog. Neurobiol.* **74**, 363–396 (2004).
78. G. Valentine, M. Sofuoglu, Cognitive effects of nicotine: Recent progress. *Curr. Neuropharmacol.* **16**, 403–414 (2018).
79. J. Grenhoff, G. Aston-Jones, T. Svensson, Nicotinic effects on the firing pattern of midbrain dopamine neurons. *Acta Physiol. Scand.* **128**, 351–358 (1986).
80. G. Mereu *et al.*, Preferential stimulation of ventral tegmental area dopaminergic neurons by nicotine. *Eur. J. Pharmacol.* **141**, 395–399 (1987).
81. S. J. Fallon, M. E. van der Schaaf, N. Ter Huurne, R. Cools, The neurocognitive cost of enhancing cognition with methylphenidate: Improved distractor resistance but impaired updating. *J. Cogn. Neurosci.* **29**, 652–663 (2017).
82. R. M. Birn *et al.*, Changes in endogenous dopamine induced by methylphenidate predict functional connectivity in nonhuman primates. *J. Neurosci.* **39**, 1436–1444 (2019).
83. C. M. Raio *et al.*, Suboptimal foraging decisions and involvement of the ventral tegmental area in human opioid addiction. bioRxiv [Preprint] (2022). https://doi.org/10.1101/2022.03.24.485654 (Accessed 28 March 2022).
84. M. Dubois *et al.*, Human complex exploration strategies are enriched by noradrenaline-modulated heuristics. *Elife* **10**, e59907 (2021).
85. E. Seu, A. Lang, R. J. Rivera, J. D. Jentsch, Inhibition of the norepinephrine transporter improves behavioral flexibility in rats and monkeys. *Psychopharmacology* **202**, 505–519 (2009).
86. C. I. Jahn *et al.*, Dual contributions of noradrenaline to behavioural flexibility and motivation. *Psychopharmacology* **235**, 2687–2702 (2018).
87. G. A. Kane *et al.*, Increased locus coeruleus tonic activity causes disengagement from a patch-foraging task. *Cogn. Affect. Behav. Neurosci.* **17**, 1073–1083 (2017).
88. E. D. Levin *et al.*, Transdermal nicotine effects on attention. *Psychopharmacology* **140**, 135–141 (1998).
89. L. S. Nandam *et al.*, Methylphenidate but not atomoxetine or citalopram modulates inhibitory control and response time variability. *Biol. Psychiatry* **69**, 902–904 (2011).
90. D. L. Barack, A. Bakkour, D. Shohamy, C. D. Salzman, Visuospatial information foraging describes search behavior in learning latent environmental features. *Sci. Rep.* **13**, 1126 (2023).
91. A. J. Yu, P. Dayan, Uncertainty, neuromodulation, and attention. *Neuron* **46**, 681–692 (2005).
92. T. M. Hess, A. M. Freund, P. N. Tobler, Effort mobilization and healthy aging. *J. Gerontol. B Psychol. Sci. Soc. Sci.* **76**, S135–S144 (2021).
93. N. L. Jenni, J. D. Larkin, S. B. Floresco, Prefrontal dopamine D1 and D2 receptors regulate dissociable aspects of decision making via distinct ventral striatal and amygdalar circuits. *J. Neurosci.* **37**, 6200–6213 (2017).
94. N. D. Volkow *et al.*, Effects of methylphenidate on regional brain glucose metabolism in humans: Relationship to dopamine D2 receptors. *Am. J. Psychiatry* **154**, 50–55 (1997).
95. K. M. Tye *et al.*, Methylphenidate facilitates learning-induced amygdala plasticity. *Nat. Neurosci.* **13**, 475–481 (2010).
96. N. D. Volkow, G.-J. Wang, J. S. Fowler, Y.-S. Ding, Imaging the effects of methylphenidate on brain dopamine: New model on its therapeutic actions for attention-deficit/hyperactivity disorder. *Biol. Psychiatry* **57**, 1410–1415 (2005).
97. C. W. Berridge *et al.*, Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. *Biol. Psychiatry* **60**, 1111–1120 (2006).
98. N. D. Volkow *et al.*, Evidence that methylphenidate enhances the saliency of a mathematical task by increasing dopamine in the human brain. *Am. J. Psychiatry* **161**, 1173–1180 (2004).
99. C. F. Zink, G. Pagnoni, J. Chappelow, M. Martin-Skurski, G. S. Berns, Human striatal activation reflects degree of stimulus saliency. *Neuroimage* **29**, 977–983 (2006).
100. N. Ter Huurne *et al.*, Methylphenidate alters selective attention by amplifying salience. *Psychopharmacology* **232**, 4317–4323 (2015).
101. R. Cools, A. C. Roberts, T. W. Robbins, Serotoninergic regulation of emotional and behavioural control processes. *Trends Cogn. Sci.* **12**, 31–40 (2008).
102. P. Dayan, Q. J. Huys, Serotonin in affective control. *Annu. Rev. Neurosci.* **32**, 95–126 (2009).
103. P. Kragh-Sørensen, K. F. Overø, O. L. Petersen, K. Jensen, W. Parnas, The kinetics of citalopram: Single and multiple dose studies in man. *Acta Pharmacol. Toxicol.* **48**, 53–60 (1981).
104. B. Jacobs, C. Fornal, "Serotonin and behavior: A general hypothesis" in *Psychopharmacology: The Fourth Generation of Progress* (Raven Press New York, 1995), pp. 461–469.
105. N. Herrera *et al.*, Nicotine gum, 2 and 4 mg, for nicotine dependence: A double-blind placebo-controlled trial within a behavior modification support program. *Chest* **108**, 447–451 (1995).
106. K. J. Holm, C. M. Spencer, Reboxetine. *CNS Drugs* **12**, 65–83 (1999).
107. K. A. Lyseng-Williamson, G. M. Keating, Extended-release methylphenidate (Ritalin® LA). *Drugs* **62**, 2251–2259 (2002).
108. D. H. Brainard, The psychophysics toolbox. *Spat. Vis.* **10**, 433–436 (1997).
109. Z. P. Kilpatrick, J. D. Davidson, A. El Hady, Uncertainty drives deviations in normative foraging decision strategies. *J. R. Soc. Interface* **18**, 20210337 (2021).
110. P.-C. Bürkner, brms: An R package for Bayesian multilevel models using Stan. *J. Stat. Softw.* **80**, 1–28 (2017).
111. A. Vehtari, A. Gelman, J. Gabry, Practical Bayesian model evaluation using leave-one-out cross-validation and WAIC. *Stat. Comput.* **27**, 1413–1432 (2017).
112. R. V. Lenth, emmeans: Estimated Marginal Means, aka Least-Squares Means (R package version 1.7.4-1., (2022). https://CRAN.R-project.org/package=emmeans.
113. N. Sidorenko, Foraging_pharma_BEH. GitHub https://github.com/NickNeuro/Foraging_pharma_BEH/tree/main/Data_for_analysis (Accessed 11 August 2023).