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Dopamine Antagonism Decreases Willingness to Expend Physical, But Not Cognitive, Effort: A Comparison of Two Rodent Cost/Benefit Decision-Making Tasks

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Successful decision making often requires weighing a given option's costs against its associated benefits, an ability that appears perturbed in virtually every severe mental illness. Animal models of such cost/benefit decision making overwhelmingly implicate mesolimbic dopamine in our willingness to exert effort for a larger reward. Until recently, however, animal models have invariably manipulated the degree of physical effort, whereas human studies of effort have primarily relied on cognitive costs. Dopamine's relationship to cognitive effort has not been directly examined, nor has the relationship between individuals' willingness to expend mental *versus* physical effort. It is therefore unclear whether willingness to work hard in one domain corresponds to willingness in the other. Here we utilize a rat cognitive effort task (rCET), wherein animals can choose to allocate greater visuospatial attention for a greater reward, and a previously established physical effort-discounting task (EDT) to examine dopaminergic and noradrenergic contributions to effort. The dopamine antagonists eticlopride and SCH23390 each decreased willingness to exert physical effort on the EDT; these drugs had no effect on willingness to exert mental effort for the rCET. Preference for the high effort option correlated across the two tasks, although this effect was transient. These results suggest that dopamine is only minimally involved in cost/benefit decision making with cognitive effort costs. The constructs of mental and physical effort may therefore comprise overlapping, but distinct, circuitry, and therapeutic interventions that prove efficacious in one effort domain may not be beneficial in another.
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INTRODUCTION

Critical decisions in life often require weighing a given option's costs against its associated benefits, and virtually every severe mental illness is associated with difficulties in such cost/benefit decision making (Caceda *et al*, 2014; Goschke, 2014). For one such cost, the effort to obtain a reward, a number of animal models have been developed: rats are given the option to climb a barrier in a T-maze in one task, or to make a higher number of responses on a lever in another, to obtain a larger food reward (Ghods-Sharifi *et al*, 2009; Salamone *et al*, 1994).

Overwhelmingly, these studies implicate mesolimbic dopamine in our willingness to exert effort (Salamone, 2009). Dopamine antagonism reliably decreases animals' choice of high-effort/high-reward (HR) options, whereas the psychostimulant amphetamine, which facilitates dopamine transmission, typically increases choice of HR options (Bardgett *et al*, 2009; Denk *et al*, 2005; Floresco *et al*, 2008). Dopaminergic projections to brain regions implicated in decision making also play a role in effortful choice (Cousins *et al*, 1996; Schweimer and Hauber, 2006).

Until recently, however, animal models have invariably manipulated the degree of *physical* effort, whereas human studies of effort have relied on *cognitive* costs (Kool *et al*, 2010; Naccache *et al*, 2005). Broadly, cognitive or mental effort costs are those that are nonphysical in nature, tax limited neurobiological resources, and are reflected in psychological constructs such as attention, response inhibition, and working memory; perhaps unsurprisingly, the underlying circuitry for cognitive *versus* physical effort appears in part distinct (Hosking *et al*, 2014; Schmidt *et al*, 2012). To account for the discrepancy in the literature, human studies have begun to incorporate physical costs in decision-making paradigms (Treadway *et al*, 2009) and have shown a similar involvement of dopamine in human decision making involving physical effort (Treadway *et al*, 2012; Wardle *et al*, 2011).

The converse approach, applying cognitive effort costs to animal models, allows for examination of mental effort in ways inaccessible to human studies. Our group has recently validated a rodent cognitive effort task (rCET), wherein animals can choose to allocate greater visuospatial attention for a greater reward, and shown that amphetamine's effects on the task are mediated by animals' individual sensitivity

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to the effort costs (Cocker *et al*, 2012). This finding is distinct from the physical effort literature, and although it may be dopaminergic in origin, amphetamine also facilitates transmission of other neuromodulators such as norepinephrine, serotonin, and acetylcholine (Mandel *et al*, 1994). To the best of our knowledge, dopamine's relationship to cognitive effort has not been directly examined, nor has the relationship between individuals' willingness to expend cognitive *versus* physical effort; it is unclear whether willingness to work hard in one domain corresponds to willingness in the other. These are important research questions, as effort costs in industrialized society are predominantly cognitive in nature, and thus societally relevant to novel therapeutic interventions.

The goal of this study was therefore twofold: to compare animals' behavior on the rCET to a well-established task of physical effort (Floresco *et al*, 2008), and to examine dopaminergic and noradrenergic contributions to cognitive *versus* physical effort.

MATERIALS AND METHODS

See Supplementary Methods for full details.

Subjects

Subjects were 55 male Long-Evans rats from Charles Rivers Laboratories (St Constant, QC, Canada), weighing 275–300 g at the beginning of the experiment, and food restricted to 14–16 g rat chow per day ($\sim$85% of free-feeding weight). Water was available *ad libitum*. Animals were pair housed in a climate-controlled colony room on a 12 h reverse light/dark cycle.

The Rat Cognitive Effort Task (rCET)

Figure 1a depicts the experimental timeline. The five-hole operant chambers and task procedures have been previously described (Cocker *et al*, 2012). Chambers were controlled by Med-PC software written by CAW (rCET) and Stan D Floresco (EDT). Briefly, animals were tested 4–5 days per week in 30 min sessions of no fixed trial limit. At the outset of training, the two levers were permanently designated to initiate either low-effort/low-reward (LR) or high-effort/high-reward (HR) trials, and these designations were evenly counterbalanced across subjects.

Figure 1b depicts the rCET trial structure. At the beginning of a trial, animals pressed one of the levers, thereby selecting a LR or HR trial. Following a 5-s intertrial interval (ITI), one of the five stimulus lights briefly illuminated, with a stimulus duration of 1.0 s for a LR trial and 0.2 s for a HR trial. Animals then had 5 s to nosepoke within the previously illuminated aperture (a correct response) for reward. Animals were rewarded with 1 sugar pellet for a correct LR trial and 2 sugar pellets for a correct HR trial. Upon delivery of reward, the tray light again illuminated to signal the opportunity to start the next trial.

Trials went unrewarded for a number of reasons: if animals failed to make a lever response within 10 s (a choice omission); if animals nosepoked during the ITI (a premature response, an oft-reported measure of motor impulsivity; Robbins, 2002); if animals nosepoked in any aperture other than the one that was illuminated (an incorrect response); and if animals failed to nosepoke at the array within 5 s after stimulus-light illumination (a response omission). All such behaviors were punished with a 5-s time-out period, accompanied by illumination of the house light. During the time-out, new trials could not be initiated and thus reward could not be earned. Following the time-out, the house light extinguished and the tray light illuminated to signal that the rat could begin the next trial.

Behavioral Measurements for the rCET

Percent choice (rather than absolute number of choices) was used to determine preference for lever/trial type, in order to minimize the influence of variation in the number of trials completed. When baseline performance on the rCET was deemed statistically stable (ie, no effect of session on repeated-measures ANOVA for choice, accuracy, and premature responding over the last three sessions; see 'Data analysis' below), the mean choice of the HR option was 73%. Animals were grouped as 'workers' if they chose HR for $>$70% of trials ($n=40$) and as 'slackers' if they chose HR for $\leq$70% of trials ($n=15$). This subdivision was based on the mean split from the original rCET paper (Cocker *et al*, 2012). In the cohort of this particular study, the worker/slacker split happened to be more worker-lopsided than any previous cohort, but to maintain consistency in analyzing meaningful differences in the groups, we have fixed the worker/slacker distinction at 70%, as per the first cohort.

The following variables were also analyzed separately for LR and HR trials: percent accuracy, percent response omissions, percent premature responses, latency to choose between the LR and HR levers (lever choice latency), latency to correctly nosepoke in the illuminated aperture (correct latency), and latency to collect reward (collection latency). Failures to choose a lever at the beginning of the trial (choice omissions) and the total number of completed trials were also analyzed.

The (Physical) Effort-Discounting Task (EDT)

The cohort was divided in half once baseline behavior on the rCET had stabilized (30–35 free-choice sessions); 27 animals were switched to the EDT (workers: $n=20$; slackers: $n=7$), a physical effort decision-making task that has been well-described elsewhere (see, eg, Floresco *et al*, 2008), and is presented in Figure 1c. Within the EDT, animals received 40 free-choice trials per 32 min session, divided equally into four blocks.

New trials were presented every 40 s with illumination of the tray light, followed by the extension of the levers. Lever contingencies (LR or HR) were reversed from the rCET to avoid the confounding of perseverative responding from one task to the other. If animals responded on the LR lever, both levers retracted and the animal immediately received 2 sugar pellets; this cost (ie, a single lever press, FR1) remained constant for LR trials across the session. If animals responded on the HR lever, the LR lever retracted and animals were given 25 s to complete a higher number of presses for 4 sugar pellets. The HR costs increased across

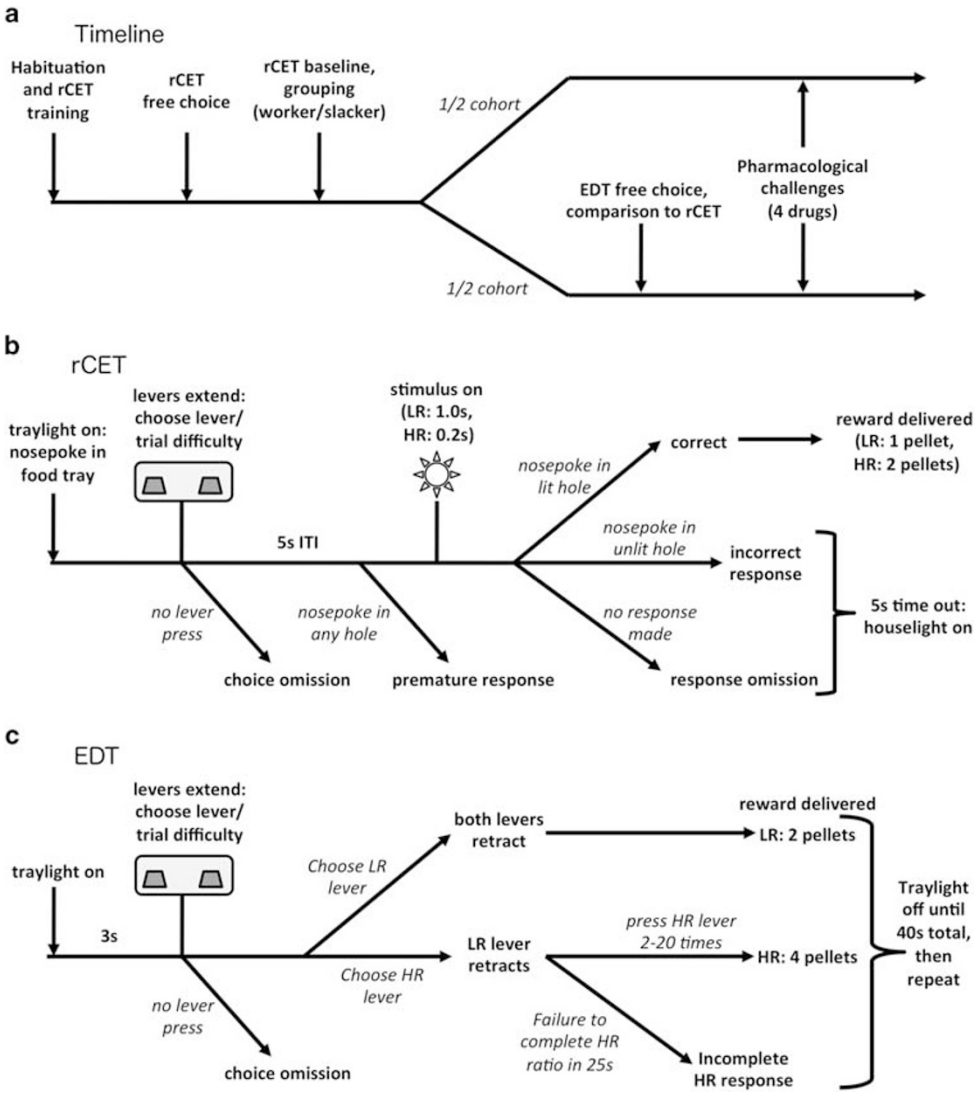

Figure 1 Experimental timeline and task schematics. (a) Timeline for the experiment. After establishing baseline behavior on the rat cognitive effort task (rCET), half of the cohort remained on the rCET and half were switched to the physical effort-discounting task (EDT). (b) Trial structure for the rCET. Trials began when the food tray light was illuminated. A nosepoke response in the food tray extinguished the light and extended the levers. Each lever was permanently designated to initiate either low-effort/low-reward (LR) or high-effort/high-reward (HR) trials. When animals pressed one of the levers, both levers retracted and a 5-s intertrial interval (ITI) began. Following the ITI, one of the five stimulus lights briefly illuminated, 1.0 s for a LR trial and 0.2 s for a HR trial. If animals nosepoked in the previously illuminated aperture within 5 s (a correct response), they were rewarded 1 sugar pellet for a LR trial and 2 sugar pellets for a HR trial. The food tray light then illuminated to signal the opportunity to start the next trial. A number of behaviors led to a 5-s time-out, signaled by house light illumination: failure to make a lever response (choice omission); failure to withhold responding during the ITI (premature response); nosepoke in an unlit hole following the stimulus (incorrect response); and failure to make a nosepoke response following the stimulus (response omission). Figure is reprinted with permission from Cocker *et al* (2012). (c) Trial structure for the EDT. New trials were presented every 40 s with illumination of the tray light, followed by the extension of the levers. If animals responded on the LR lever, both levers retracted and the animal immediately received 2 sugar pellets; this cost (ie, a single lever press, FR1) remained constant for LR trials across the session. If animals responded on the HR lever, the LR lever retracted and animals were given 25 s to complete a higher number of presses for 4 sugar pellets. The HR costs increased across the session, beginning with FR2 in the first block, followed by FR5, FR10, and FR20. Animals did not receive reward if they failed to make a lever response (choice omission) or if they failed to complete the required number of lever presses for a HR trial (incomplete HR response), although these occurred less than once per session per animal from the outset. Modified with permission from Floresco *et al* (2008).

the session, beginning with FR2 in the first block, followed by FR5, FR10, and FR20.

Animals did not receive reward if they did not make a choice within 25 s of lever insertion (choice omission) or if they failed to complete the required number of lever presses for a HR trial (incomplete HR response). As animals were experienced in lever pressing to obtain reward, choice omissions and incomplete HR responses occurred less than once per session per animal from the outset, and were virtually absent by the end of baseline EDT (15 sessions).

Behavioral Measurements for the EDT

Percent choice was used for LR or HR options/levers in each block. Average latency to complete HR choices (choice

latency), choice omissions, and incomplete HR responses were also measured.

Pharmacological Challenges

Upon stable baseline behavior in each respective task, drugs were administered in the following order: the dopamine D_2 antagonist eticlopride (0, 0.01, 0.03, and 0.06 mg/kg), dopamine D_1 antagonist SCH23390 (0, 0.001, 0.003, and 0.01 mg/kg), the α2-adrenergic receptor antagonist yohimbine (0, 1, 2, and 5 mg/kg), and the selective norepinephrine reuptake inhibitor atomoxetine (0, 0.1, 0.3, and 1.0 mg/kg). S(−)-Eticlopride hydrochloride, R(+)-SCH-23390 hydrochloride, and yohimbine hydrochloride were purchased from Sigma-Aldrich (Oakville, ON, Canada); tomoxetine hydrochloride was purchased from Tocris (Minneapolis, MN). Eticlopride, SCH23390, and atomoxetine were dissolved in 0.9% sterile saline, and yohimbine was dissolved in distilled water. All were prepared fresh daily and administered in a volume of 1 ml/kg via intraperitoneal injection, adhering to a digram-balanced Latin Square design (Cardinal and Aitken, 2006). The 3-day injection schedule started with a baseline session, followed by a drug or saline injection session, and then by a nontesting day. Injections for eticlopride, SCH23390, and yohimbine were administered 10 min before behavioral testing; atomoxetine injections were administered 30 min beforehand. Animals were given 1 week of drug-free testing between compounds to minimize carryover effects.

Data Analysis

All data were analyzed in SPSS (version 16.0; SPSS/IBM, Chicago, IL). All variables expressed as a percentage were arcsine transformed to minimize artificial ceiling effects (Zeeb *et al*, 2009). Data were analyzed using repeated-measures ANOVA with choice (two levels: LR or HR), session (three levels: baseline sessions 1–3), and dose (four levels: saline plus three drug doses) as within-subjects factors, and block (four levels: FR2, FR5, FR10, and FR20) was an additional within-subjects factor for the EDT. Group (two levels: worker or slacker) was used throughout the experiment as a between-subjects factor in all analyses. Groups proved stable across the experiment: at rCET baseline, all saline conditions for rCET drug challenges, and postdrug baseline, workers chose a significantly greater percentage of HR trials than slackers (group: all Fs >28.067, $p<0.001$). Any main effects of significance ($p<0.05$) were further analyzed via *post hoc* one-way ANOVA or paired-samples *t*-tests. Any *p*-values of >0.05 but <0.07 were reported as a statistical trend.

RESULTS

rCET: Eticlopride Administration

Following the acquisition of stable behavior on the rCET, half of the animals were switched to the EDT, whereas the other half ($n=28$) were given the following pharmacological challenges on the rCET.

Baseline behavior for the rCET has been previously discussed at length (Cocker *et al*, 2012; Hosking *et al*, 2014), and as such will only be cursorily addressed here. As per previous cohorts, animals chose HR trials more than LR trials following saline injection (saline only–choice: $F_{1,26}=13.461$, $p=0.001$), and workers chose a significantly higher proportion of HR trials than slackers (group: $F_{1,26}=40.814$, $p<0.001$). The dopamine D_2 receptor antagonist eticlopride had no effect on animals' choice (Figure 2a; dose: $F_{3,78}=1.222$, NS).

Animals were more accurate (ie, demonstrated better performance) on LR *versus* HR trials (saline only–choice: $F_{1,26}=21.657$, $p<0.001$). As per previous cohorts, workers and slackers performed the rCET equally well (saline only–group/choice × group: all Fs <1.350, NS). This reiterates that choice preferences were not driven solely by individuals' ability to perform the task. Eticlopride had no effect on animals' accuracy (Figure 2b; dose/dose × group/choice × dose/choice × dose × group: all Fs <2.230, NS).

In general, premature responding was higher for HR *versus* LR trials (choice: $F_{1,26}=4.511$, $p=0.043$) but there were no differences in premature responding between workers and slackers (group/choice × group: all Fs <0.809, NS), indicating that choice preferences were not driven by individuals' motor impulsivity. Eticlopride had no effect on animals' rates of premature responding (Figure 2c; dose/dose × group/choice × dose/choice × dose × group: all Fs <1.489, NS).

Eticlopride also increased correct response latencies, response and choice omissions, and decreased the number of completed trials for all animals (see Supplementary Results for an exhaustive analysis).

rCET: SCH23390 Administration

The dopamine D_1 receptor antagonist SCH23390 had no effect on choice, accuracy, or premature responding for the rCET (Figure 2d–f; dose/dose × group/choice × dose/choice × dose × group: all Fs <2.132, NS). The drug did, however, increase choice latencies and response omissions, and decrease the number of completed trials (see Supplementary Results).

rCET: Yohimbine Administration

The α2-adrenergic receptor antagonist yohimbine did not affect animals' choice behavior (Figure 2g) or premature responding (Figure 2i; dose/dose × group: all Fs <0.978, NS). For all animals across both trial types, however, yohimbine dose-dependently decreased accuracy, an effect that achieved significance at the highest dose (Figure 2h; dose: $F_{3,78}=7.314$, $p=0.006$; dose × group/choice × dose/choice × dose × group: all Fs <2.276, NS; saline *vs* low-dose: $F_{1,26}=2.948$, NS; saline *vs* med-dose: $F_{1,26}=3.665$, $p=0.067$; saline *vs* high-dose: $F_{1,26}=13.640$, $p=0.001$). At low and intermediate doses, yohimbine had a speeding effect on all latencies, and it decreased response omissions and increased the number of completed trials, whereas at the highest dose it dramatically increased response and choice omissions and decreased trials (see Supplementary Results).

rCET: Atomoxetine Administration

Choice behavior, accuracy, and premature responses. The selective norepinephrine reuptake inhibitor atomoxetine

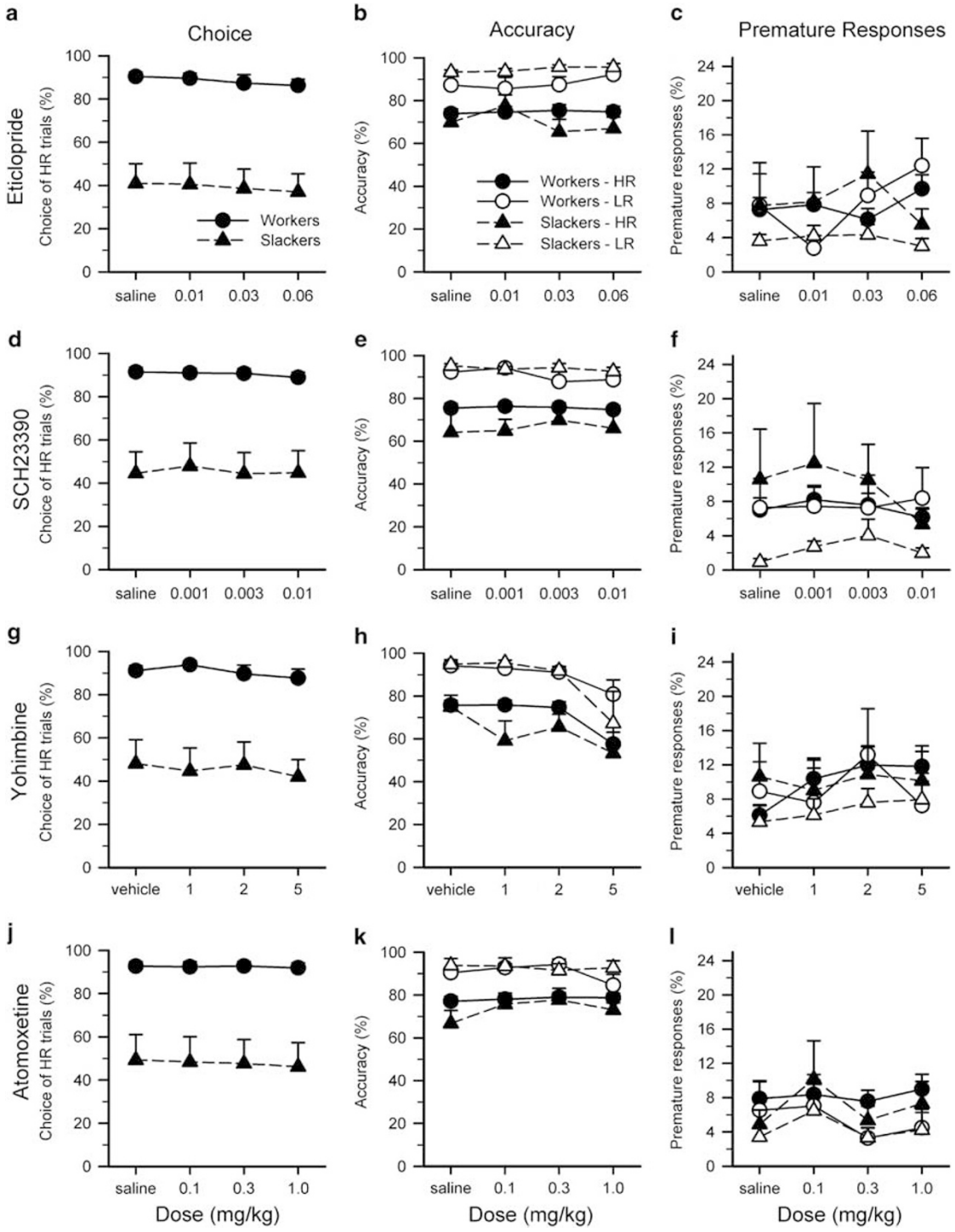

Figure 2 Dopamine and norepinephrine pharmacology on the rCET. (a–f) Neither the dopamine D_2-family receptor antagonist eticlopride nor the D_2-family receptor antagonist SCH23390 affected animals' choice, accuracy, or premature responding. (g–i) Although the α2-adrenergic receptor antagonist yohimbine did not affect animals' choice (g) or premature responding (i), it significantly decreased accuracy at the highest dose for all trial types. (j–l) The selective norepinephrine reuptake inhibitor atomoxetine had no effect on animals' choice (j) and premature responding (l) and virtually no effect on accuracy, with only a trend to decrease workers' performance on LR trials. Data are shown as the mean percent for each variable (± SEM).

had no effect on animals' choice (Figure 2j) and premature responding (Figure 2l; dose/dose × group/choice × dose/choice × dose × group: all Fs <1.680, NS) and virtually no effect on accuracy, with only a trend to decrease workers' performance on LR trials (Figure 2k; dose/dose × group/choice × dose: all Fs <2.172, NS; choice × dose × group: $F_{3,78} = 3.124$, $p = 0.031$; workers only–LR only–dose: $F_{3,57} = 3.141$, $p = 0.066$; workers only–HR only/slackers only–LR/HR–dose: all Fs <1.252, NS). Atomoxetine also increased choice latency and choice omissions, and

decreased the number of completed trials (see Supplementary Results).

EDT: Baseline Behavior and Comparison with rCET

As discussed above, half of the rats ($n = 27$) were switched from baseline rCET to the EDT before any drug challenges. Upon switching to the EDT, animals demonstrated high performance during the first three sessions, with less than one incomplete HR trial per animal per session, on average, and virtually zero choice omissions. Furthermore, although choice behavior was not yet stable (session: $F_{2,50} = 10.628$, $p = 0.001$), all animals demonstrated sensitivity to the physical effort costs: choice of HR decreased across blocks as the costs increased (Figure 3a; block: $F_{3,75} = 8.333$, $p = 0.001$; block × group: $F_{3,75} = 0.510$, NS). Remarkably, and despite reversing the lever/reward contingencies from the rCET to the EDT, the worker/slacker distinction held during these early sessions of the EDT: animals that had been deemed 'workers' for the rCET remained workers for the EDT, and it was similar for slackers (group: $F_{1,25} = 6.351$, $p = 0.018$). Baseline choice behavior on the rCET was linearly correlated with choice behavior on sessions 1–3 of the EDT (Figure 3b; adjusted $r^2 = 0.358$, $p = 0.001$).

However, upon reaching stability at sessions 13–15 (session/session × block/session × block × group: all Fs < 1.359, NS), the worker/slacker distinction was no longer valid for the EDT (Figure 3c; group: $F_{1,25} = 1.273$, NS), with no correlation to baseline behavior on the rCET (Figure 3d; adjusted $r^2 = 0.039$, NS), although animals were still sensitive to the increasing physical effort costs, overall (block: $F_{3,75} = 4.607$, $p = 0.005$).

EDT: Eticlopride Administration

Following the establishment of baseline behavior, four animals no longer sampled from both options/levers, instead pressing the LR lever exclusively. Because of the inflexibility of this behavior and the possibility of floor effects, drug challenge data from these animals were not included in analyses. Furthermore, one animal was removed from the study because of unexpected, unrelated health complications, leaving a total of 22 animals in this subgroup (workers: $n = 16$; slackers: $n = 6$).

The dopamine D_2 receptor antagonist eticlopride dose-dependently decreased all animals' choice of HR trials across all blocks (Figure 4a; dose: $F_{3,63} = 2.975$, $p = 0.038$; dose × group/dose × block/dose × block × group: all Fs < 1.395, NS; saline *vs* high-dose: $F_{1,21} = 3.900$, $p = 0.062$;

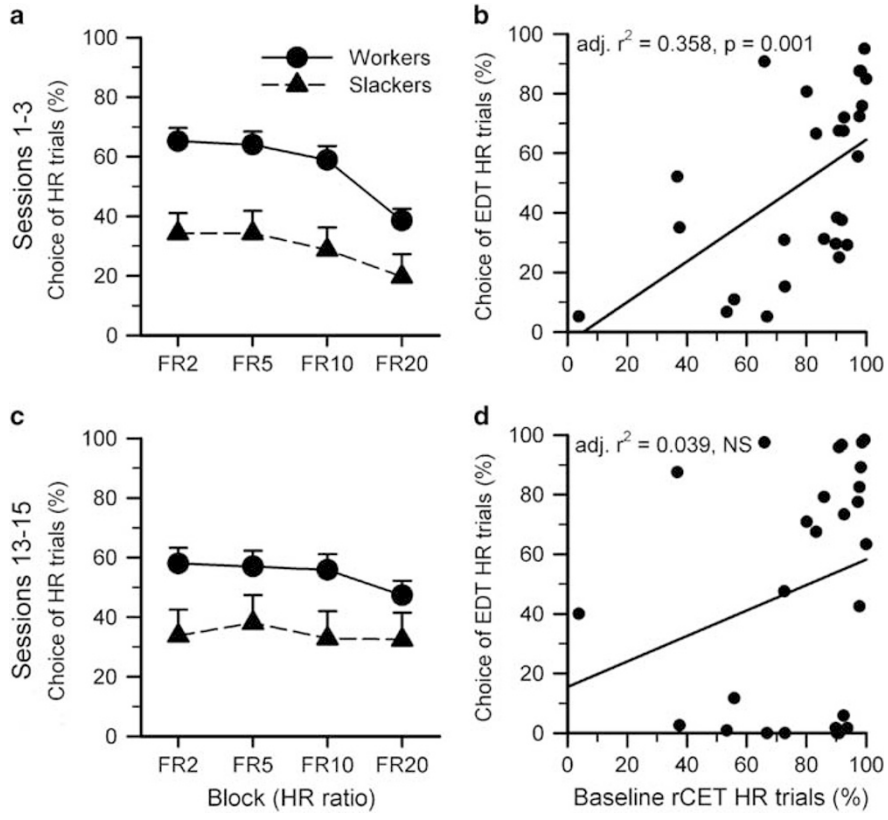

Figure 3 Baseline behavior on the EDT *versus* rCET. (a) During the first three sessions, all animals demonstrated sensitivity to the physical effort costs: choice of HR decreased across blocks as the costs increased. Remarkably, and despite reversing the lever/reward contingencies from the rCET to the EDT, the worker/slacker distinction held during these early sessions of the EDT: animals that had been deemed 'workers' for the rCET remained workers for the EDT, and it was similar for slackers. (b) Baseline choice behavior on the rCET was linearly correlated with choice behavior on sessions 1–3 of the EDT. (c) However, upon reaching stability at sessions 13–15, the worker/slacker distinction was no longer valid for the EDT, although animals were still sensitive to the increasing physical effort costs, overall. (d) No correlation to baseline behavior on the rCET was observed for sessions 13–15. Data (a, c) are shown as the mean percent (± SEM).

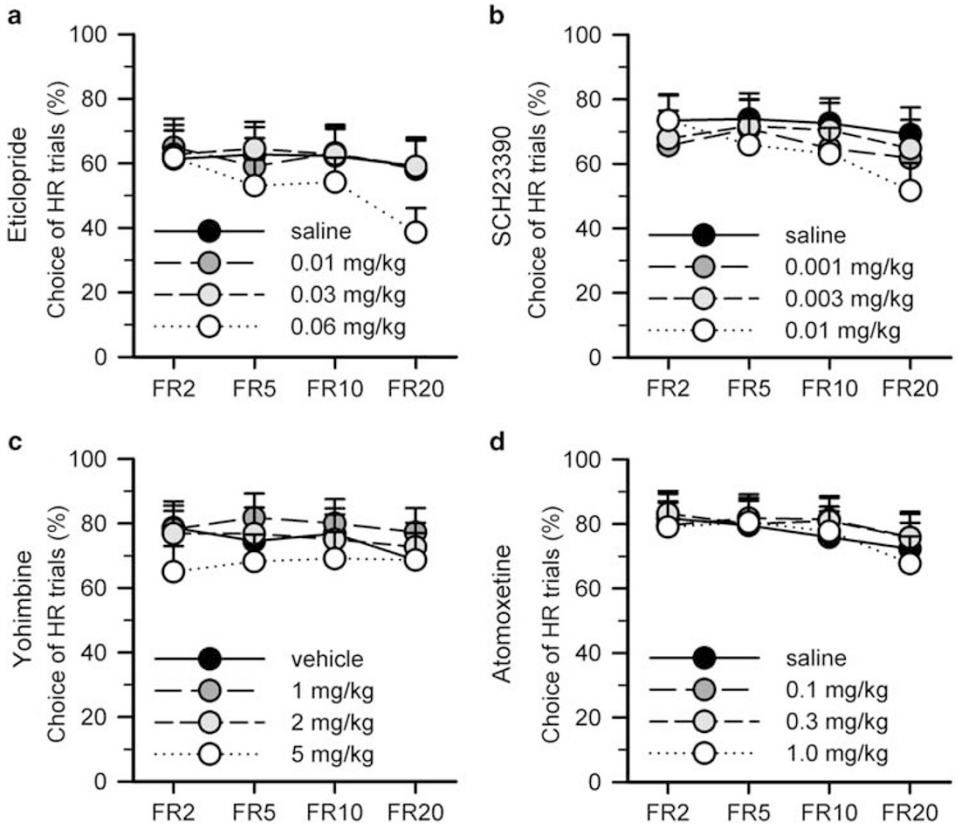

Figure 4 Dopamine and norepinephrine pharmacology on the EDT. (a) Eticlopride dose-dependently decreased all animals' choice of HR trials across all blocks. (b) SCH23390 decreased choice of HR at the highest effort block. (c) Yohimbine appeared to have some minor effects on choice behavior, decreasing choice of the HR lever during the first two blocks, but this effect was not robust. (d) Atomoxetine did not affect choice on the EDT. Data are shown as the mean percent for each variable (± SEM).

saline *vs* low/saline *vs* med-dose: all Fs <0.293, NS). Eticlopride also increased the latency to complete HR trials and very modestly increased the number of choice omissions (see Supplementary Results).

EDT: SCH23390 Administration

The dopamine D_1 receptor antagonist SCH23390 decreased HR choice at the highest effort block (Figure 4b; dose × block: $F_{3,63}=3.316$, $p=0.009$; FR20 only–dose: $F_{3,63}=5.165$, $p=0.003$; FR2/FR5/FR10 only–dose: all Fs <1.783, NS; dose/dose × group/dose × block × group: all Fs <1.986, NS). SCH23390 also very modestly increased HR choice latencies and choice omissions (see Supplementary Results).

EDT: Yohimbine Administration

The α2-adrenergic receptor antagonist yohimbine appeared to have some minor effects on choice behavior, decreasing choice of the HR lever during the first two blocks, but this effect was not robust, as evidenced by the lack of a dose × block effect (Figure 4c; dose: $F_{3,60}=2.506$, $p=0.067$; dose × group/dose × block/dose × block × group: all Fs <1.641, NS; FR2 only–dose: $F_{3,60}=3.570$, $p=0.019$; FR5 only–dose: $F_{3,60}=3.150$, $p=0.031$; FR10/FR20 only–dose: 1.434, NS). Yohimbine also lengthened the latency to complete HR trials for each block (see Supplementary Results).

EDT: Atomoxetine Administration

The selective norepinephrine reuptake inhibitor atomoxetine had no effect on any behavioral measures of the EDT (Figure 4d; dose/dose × group/dose × block/dose × block × group: all Fs <2.909, NS).

DISCUSSION

Here we show for the first time that antagonism of either D_1-family or D_2-family dopamine receptors, as well as norepinephrine facilitation, had no discernible effect on animals' willingness to expend mental effort. Although these drugs had observable effects on other behavioral measures (eg, increased latencies, decreased trials), dopamine antagonism did not decrease choice of HR options, in contrast with observations in physical effort paradigms (Bardgett *et al*, 2009; Nunes *et al*, 2010). Indeed, here we show that both D_1-family and D_2-family antagonism, as well as the pharmacological stressor yohimbine, decreased choice of HR on a previously established task of physical effort, the EDT; these data are novel, as previous pharmacological EDT studies have only utilized the nonspecific dopamine

antagonist flupenthixol (Floresco *et al*, 2008) and, to the best of our knowledge, norepinephrine has not been independently manipulated on any animal model of effort-based decision making. In addition to the pharmacological challenges, a transient correlation was demonstrated between choice on the two tasks. As such, willingness to expend physical effort does appear to be at least partially associated with willingness to expend cognitive effort. However, unlike choices based on physical effort costs, decision making with respect to this particular form of cognitive effort is not dopamine dependent.

One alternative possibility is that the rCET does not adequately model effort-based cost/benefit decision making. For example, animals' 'decisions' on the rCET may reflect a simpler behavioral strategy, such as matching law (Herrnstein, 1970), that instead is primarily driven by the probability of reward (ie, animals' accuracy) rather than effort. In a previous study, however, effort costs were removed entirely and reward probability was instead yoked to experimental animals' percent accuracy; in this control task, animals' choice differed significantly from their experimental counterparts, thereby demonstrating that decision making on the rCET is uniquely influenced by the cognitive effort cost (Cocker *et al*, 2012). A similar possibility is that animals' choice on the rCET is based on a habitual, or 'model-free', rather than a goal-directed, 'model-based' strategy (Rangel *et al*, 2008). This appears unlikely, however, as reward devaluation via acute and chronic satiation decreases all animals' choice of the high-effort/HR option (Cocker *et al*, 2012). Alternatively, the effort expenditure required in HR *versus* LR trials may not be large enough to recruit neural circuits involved in differential effort cost calculations. However, rCET accuracy/performance for LR trials is significantly higher than for HR, suggesting that a 1.0-s stimulus is much easier to correctly identify than a brief 0.2-s stimulus. In addition, some experimental manipulations that affect physical effort decision-making paradigms also affect choice on the rCET, suggesting not only overlap in the neural loci involved but also some conceptual unity across the subtypes of effort-based choice (Hosking *et al*, 2014). Taken together, the rCET therefore appears to successfully model decision making with differing mental effort costs.

Nevertheless, disparities in the response to drug challenges across cognitive *versus* physical effort tasks may reflect differences in task design rather than differences in effort costs *per se*. These task differences were not trivial: trials were of no fixed limit and self-initiated in the 30 min sessions of rCET, whereas all EDT sessions had 48 computer-initiated trials within 32 min; effort costs remained fixed within each rCET session, whereas HR options became costlier across blocks in the EDT; animals were rewarded 1 *versus* 2 sugar pellets for LR *versus* HR on the rCET, whereas they were rewarded with 2 *versus* 4 pellets on the EDT. Contrast effects may thus explain why a substantial number of animals switched to preferences toward EDT LR, contrary to most physical effort studies: animals could now receive the previous rCET HR reward (2 pellets) for very little effort on the EDT LR option. Furthermore, the EDT is a simpler task, with virtually guaranteed receipt of reward and no uncertainty associated with each option, and as such it may be easier to classify options as preferred *versus* nonpreferred. However, it is unlikely that these task differences can fully explain the differential drug effects. Animals completed three times as many trials for the rCET *versus* the EDT, suggesting greater total effort expenditure per session; if dopamine antagonism were to affect all forms of effort equally, then one would expect a greater attenuation of rCET HR than EDT HR. In fact, the opposite is observed. Furthermore, the current doses fall near those established in previous decision-making studies (St Onge and Floresco, 2009; Zeeb *et al*, 2009) and affect other behavioral measures in both tasks. It is thus parsimonious to conclude that dopamine antagonism decreased choice of HR on the EDT and not the rCET because dopamine function is related to decision making with physical, but not these cognitive, effort costs at baseline.

As regard the possibility that individual differences are unique for cognitive (and not physical) effort, we believe this unlikely. First, one of us (Floresco) has had the opportunity to observe a sizable number of animals performing the EDT; across these many cohorts, behavioral differences are readily observable in some individuals but do not appear to explain the experimental effects reported in previous papers. Second, individual differences are observed in other decision-making tasks if the options are appropriately framed or titrated (Randall *et al*, 2012; Winstanley *et al*, 2010; Zeeb *et al*, 2010). The difficulty of the rCET is such that it consistently provides a spectrum of choice behaviors; when the effort component is removed from the task, as it was in a yoked-control task in the original rCET study (Cocker *et al*, 2012), the individual differences disappear. Altogether, this suggests that individual differences are not a uniquely cognitive effort phenomenon, but rather the result of the options' specific costs and benefits. One can imagine the design of a physical effort task wherein the options are set so that more variability in choice behavior is observed. Critically, larger sample sizes are needed if these are to be taken into account in interpreting experimental outcomes, and that has not been consistently undertaken in the field, but may be partially addressed with meta-analysis.

Considerable attention has been paid to dopaminergic signaling underlying the satisfaction or subversion of expectation, with dopaminergic signals shifting from rewards themselves to their predictive cues as the association is learned (Schultz *et al*, 1997). Such prediction errors also appear useful in the encoding of subjective value for a given option, thus guiding individuals' choice preferences during the learning and updating of contingencies (Lak *et al*, 2014). When such contingencies are well learned and fixed, as is the case for the rCET, dopamine's error-prediction signaling may be of less utility (Kilpatrick *et al*, 2000; Murray *et al*, 2012; Wickens *et al*, 2003). Of course, dopamine also plays a critical role in the generation, maintenance, and cessation of motor behavior via its influence on basal ganglia output (Freeze *et al*, 2013); perturbations of the dopamine system can tremendously and adversely impact individuals' motor functioning and quality of life (Claassen *et al*, 2011). Although researchers have long separated dopamine's reward and motor aspects into 'ventral' and 'dorsal' anatomical components, respectively, it is likely that these reward and motor facets are more functionally and anatomically integrated than previously suggested (Kravitz *et al*, 2012). Put another way, reward

learning and motor learning appear by necessity interconnected. It should perhaps be no surprise, then, that dopamine function is necessary for selecting, initiating, and maintaining behaviors with a larger motor component, that is higher physical effort, in order to obtain a larger reward (Salamone *et al*, 2009). Although D_1-family antagonism (via SCH23390) seemingly resulted in a more statistically robust decrease in choice at FR20, a very similar pattern was observed following D_2-family antagonism (via eticlopride), with no dose × block or dose × block × group interaction; however, reporting eticlopride's effect at FR20 was not statistically justified.

As is the case for the rCET, however, options that vary only by their cognitive effort requirements place equivalent demands on the motor component of dopaminergic signaling. Indeed, researchers have known for some time that mental and physical effort differ in their systemic catecholamine profiles (Fibiger *et al*, 1984) and in their lasting effects on subsequent task performance (Smit *et al*, 2005). Critically, at least one study has dissociated regions in humans that process different types of effort costs, with physical effort exertion encoded by motor cortex, and cognitive effort exertion encoded by dorsolateral prefrontal and inferior parietal cortices (Schmidt *et al*, 2012), targets of future rCET studies. Although dopamine likely plays a role in learning the contingencies of rCET, and thus in guiding goal-directed behavior during training, its contribution at baseline (when task parameters are extremely familiar and fixed) appears only necessary insofar as to elicit food-seeking behavior and successfully navigate the operant chamber. Such an interpretation explains why general motor impairments were observed during dopamine antagonism without any concomitant changes to rCET choice.

In contrast to the null effects observed here with dopamine antagonists, systemic amphetamine caused workers to 'slack off' and slackers to 'work harder' on the rCET (Cocker *et al*, 2012). Although amphetamine has powerful effects on the DA system, this psychostimulant also potentiates other monoamine neuromodulators, including norepinephrine (Robertson *et al*, 2009). Noradrenergic drugs are also administered as a treatment for ADHD, in which attentional deficits are prominent, and given the attentional core of the rCET, we predicted norepinephrine would contribute to behavior on this task. However, atomoxetine—a selective norepinephrine reuptake inhibitor—did not affect choice behavior, nor did the α2-adrenergic receptor antagonist yohimbine, suggesting the noradrenergic contribution to amphetamine's effects, and rCET performance in general, is weak.

Unlike a number of studies using the 5-choice serial reaction-time task (5CSRTT), no change in premature responding was observed on the rCET following administration of either noradrenergic compound, despite the similarities in trial structure between the two tasks (Navarra *et al*, 2008; Robinson *et al*, 2008; Sun *et al*, 2010). Norepinephrine has been postulated to play a role in decision making with effort costs (Malecek and Poldrack, 2013); although putative damage to noradrenergic fibers may have contributed to previous results demonstrating dopamine's role in effort (see, eg, Schweimer *et al*, 2005), to the best of our knowledge, norepinephrine has not been directly manipulated on any animal model of effort-based decision making. As regard the current lack of effects, it may relate to the rapid and continuous flow of events in the 5CSRTT: the response the animal makes to collect reward instantly begins the next trial, encouraging a constant cycle of activity that may facilitate premature responding and loss of stimulus control (Robbins, 2002). In contrast, such behavioral momentum is checked at the start of each rCET trial, as the animal must signal its preference for a hard or easy trial via a lever-press response before spinning around and facing the array again. This choice point may act as something of a brake in an otherwise iterative motor sequence, thereby decreasing impulsivity; certainly, premature responses are less frequent in the rCET (Robbins, 2002), although this could also arise from more extensive training. Whether this additional step also renders premature responding insensitive to noradrenergic manipulation, by limiting impulsive responses that result from cyclical responding, remains an intriguing possibility that may be worthy of further investigation.

In addition to increasing monoamine transmission, amphetamine also potentiates acetylcholine transmission across the cortex (Day *et al*, 1994), an effect independent of dopaminergic efflux at the basal forebrain (Arnold *et al*, 2001). Sustained attention increases prefrontal cortical cholinergic tone (Passetti *et al*, 2000), and strategies to reduce this cognitive effort also reduce prefrontal cortical acetylcholine (Dalley *et al*, 2001). A number of studies suggest that whereas norepinephrine signaling accompanies unexpected uncertainty (where contingencies are changed or reversed without warning to the individual), acetylcholine signaling accompanies expected uncertainty (where probabilities are known by the individual, as in the case of animals' accuracy on the rCET; Robbins and Roberts, 2007; Yu and Dayan, 2005). Acetylcholine therefore remains a strong candidate for neuromodulatory influence over decision making with cognitive effort costs.

Regardless of whether these costs are mental or physical, higher effort demands induce a negative emotional reaction (Morsella *et al*, 2011) and, all other things being equal, individuals will avoid the option with higher effort (Kool *et al*, 2010; Walton *et al*, 2002). Furthermore, many of our day-to-day tasks involve a combination of physical and mental effort; at least one human effort study deliberately incorporated a combination of both costs, and suggested that physical and mental effort share common neuroanatomical nodes, such as the ventral striatum (Schmidt *et al*, 2012). It seems appropriate, then, to consider both mental and physical to be 'effort'. With overlapping but distinct neurobiological underpinnings, however, therapeutic interventions may need to be specific in their targeting; drugs that prove efficacious in one effort domain may not be beneficial in another.

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