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A Novel Strategy for Dissecting Goal-Directed Action and Arousal Components of Motivated Behavior With a Progressive Hold-Down Task

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Motivation serves 2 important functions: It guides actions to be goal-directed, and it provides the energy and vigor required to perform the work necessary to meet those goals. Dissociating these 2 processes with existing behavioral assays has been a challenge. In this article, we report a novel experimental strategy to distinguish the 2 processes in mice. First, we characterize a novel motivation assay in which animals must hold down a lever for progressively longer intervals to earn each subsequent reward; we call this the progressive hold-down (PHD) task. We find that performance on the PHD task is sensitive to both food deprivation level and reward value. Next, we use a dose of methamphetamine (METH) 1.0 mg/kg, to evaluate behavior in both the progressive ratio (PR) and PHD tasks. Treatment with METH leads to more persistent lever pressing for food rewards in the PR. In the PHD task, we found that METH increased arousal, which leads to numerous bouts of hyperactive responding but neither increases nor impairs goal-directed action. The results demonstrate that these tools enable a more precise understanding of the underlying processes being altered in manipulations that alter motivated behavior.

Keywords: motivation, progressive ratio, progressive hold down, arousal, goal-directed action

Motivation drives us to execute actions and provides the vigor needed to overcome obstacles and achieve goals. Decades of research has led to the recognition that motivated behavior is complex, consisting of multiple interacting components that can be dissociated at both the behavioral and neural levels (Berridge & Robinson, 2003; Kelley, 2004; Salamone & Correa, 2002; Zhang et al., 2003). One long-recognized example is that motivation consists of both a goal-directed, directional component and an increased arousal, activational component (Duffy, 1957; Hebb, 1955; Salamone, 1988). Despite several recent advances in understanding the neurobiology of motivation (Gore et al., 2013; Trifilieff et al., 2013), most studies do not dissociate the directional and activational components of motivated behavior. Additionally, the progress that has been made studying goal-directed action selection (Kim et al., 2013; Kimchi & Laubach, 2009) and general arousal (Anaclet et al., 2009; Pfaff et al., 2012) has largely been made studying these processes in isolation. Thus, experimentally dissociating between goal-directed and activational processes remains a challenge. A more comprehensive understanding of motivation would be possible with a strategy of implementing behavioral assays that can detect changes in goal-directed behavior, alterations in arousal/response vigor, or changes in both of these processes.

The progressive ratio (PR) schedule is frequently used to assay motivation (Bradshaw & Killeen, 2012). In this task, subjects must increase the number of responses made to earn subsequent rewards. The point at which a subject quits working for rewards is called the breakpoint (BP) and serves as an index of motivation

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(Aberman et al., 1998; Hodos, 1961). Assays like the PR, however, do not clearly indicate which of the two processes of motivation are altered because they are not designed to distinguish increases in goal-directed responses from those arising as a consequence of enhanced arousal. For example, mice with reduced expression of the dopamine transporter (DAT-knockdown) have chronically elevated extracellular dopamine levels. These DAT-knockdown mice make more lever presses and reach higher BPs in a PR for food rewards (Cagniard et al., 2006) but also show increased locomotor activity in a novel environment (Zhuang et al., 2001). The higher BP could be the result of increased goal-directed action, increased arousal, or some interaction between the two processes.

The effects of psychostimulants, like amphetamines, represent another example of the challenge of measuring motivation. In a PR for food rewards, amphetamine increases subjects' BPs (Mayorga et al., 2000; Olausson et al., 2006) and also increases arousal across multiple measures, including locomotor activity (Hall et al., 2008; McNamara et al., 1993), wakefulness (Berridge, 2006), and the activity of neurons that promote arousal (Estabrooke et al., 2001). Numerous pharmacological and genetic manipulations can alter motivation in the PR and overall levels of locomotor activity in an open field test (see Figure 1). Developing a behavioral assay to separate these components would facilitate the neurobehavioral analysis of motivation, as well as have important practical implications for the treatment of motivational disorders. Impairments in motivation related to behavioral activation and the willingness to expend effort to accomplish goals are a clinically recognized problem for patients with schizophrenia and some affective disorders (Demyttenaere et al., 2005; Salamone et al., 2006; Stahl, 2002; Treadway & Zald, 2011; Tylee et al., 1999). Despite this awareness, at the present time no effective pharmacological interventions exist for these specific symptoms (Chase, 2011; Levy & Czernecki, 2006).

We here report a new strategy to differentiate behavior into goal-directed action and arousal. The strategy involves using the PR task along with a novel procedure that involves making a sustained response. Whereas increased goal-directed motivation increases responding in both tasks, hyperactivity would increase responding in the PR but make behavior much less efficient when a long-duration sustained response is required. We call this task the progressive hold-down (PHD) task because subjects are required

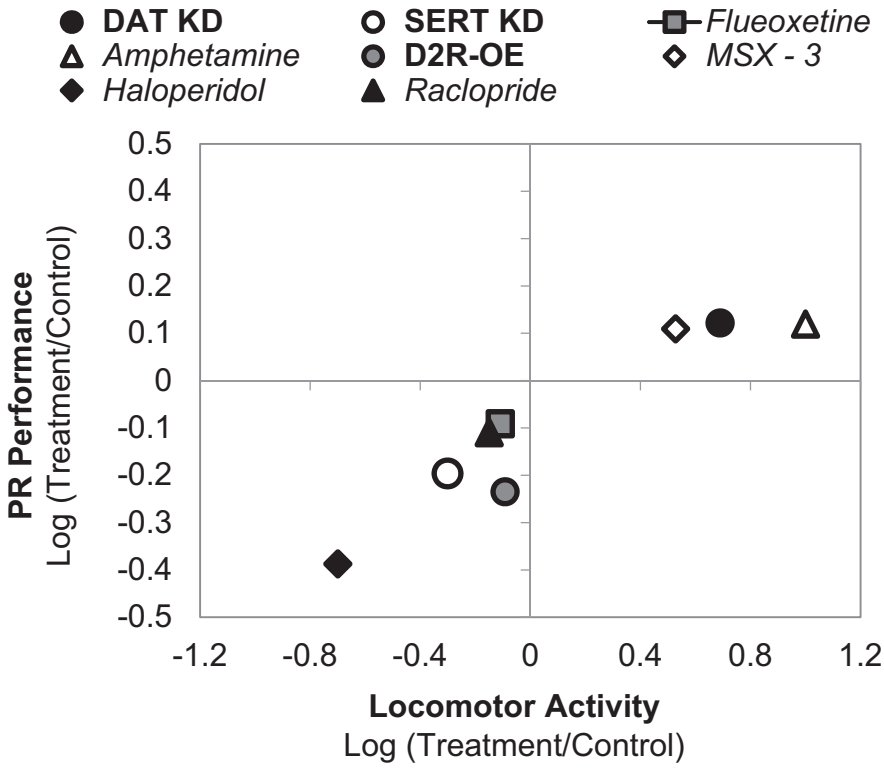

Figure 1. Relationship between progressive ratio (PR) performance and locomotor activity. Data for both PR performance and locomotor activity is expressed as a log ratio of treatment condition (transgenic or drug treated) divided by control condition (Wildtype or Vehicle), [e.g,. log (DAT KD PR performance/WT PR performance)]. **Bold = genetic manipulation**; *Italics = pharmacological manipulation*. Data for PR performance replotted from dopamine transporter knockdown (DAT KD; Cagniard et al., 2006), SERT KD (Sanders et al., 2007), Fluoxetine (Sanders et al., 2007), Amphetamine (Mayorga et al., 2000), D2R-OE (Simpson et al., 2011), Haloperidol (Aberman et al., 1998), Raclopride (Aberman et al., 1998), MSX-3 (Randall et al., 2012). Data for locomotor activity replotted from DAT KD (Zhuang et al., 2001), SERT KD (Sanders et al., 2007), Fluoxetine (Sanders et al., 2007), Amphetamine (Hall et al., 2008), D2R-OE (Kellendonk et al., 2006), Haloperidol (Simón et al., 2000), Raclopride (Simón et al., 2000), MSX-3 (Antoniou et al., 2005).

to hold a lever down for progressively longer durations to earn subsequent rewards. We first validate the PHD task as a measure of motivation by showing that it is sensitive to both levels of food deprivation and reward magnitude. Next, to evaluate the effectiveness of this strategy, we look at how performance on both PR and PHD task is affected by a dose of methamphetamine (METH; 1 mg/kg) that is known to induce hyperactivity. If METH increases goal-directed motivation, then performance on both PR and PHD should be enhanced; but if METH alters general arousal–hyperactivity then we would expect to see increased responding on the PR but impaired performance on the PHD task.

Method

Subjects

Subjects were C57BL/6J:129SvEvTac F1 hybrid female mice 120 days of age and weighing 24 g to 29 g at the start of the experiment. Mice were limited to 1.5 hr of food made available 1 hr after each behavioral testing session to motivate them to earn rewards of evaporated liquid milk. The one exception to this was when we ran the PHD task on a cohort of mice undergoing a restricted diet, during which mice received a set amount of food each day to be maintained at 85% of their ad lib body weight. Water was available ad libitum in home cages throughout the entire experiment, and subjects were maintained in a 12:12 light–dark schedule and tested during the light phase.

Separate groups of mice were used for the METH PR experiment (METH–PR, $n = 8$), the PHD under restricted feeding and reward magnitude experiments (PHD manipulations, $n = 12$), and the METH PHD experiment (METH–PHD, $n = 13$). All animal procedures were performed in accordance with Columbia University's animal care committee's regulations.

Apparatus

Experimental chambers (ENV-307w; Med Associates, St. Albans, VT) equipped with liquid dippers were used in the experiment. Unless otherwise noted, the apparatus was identical to that used by Drew and colleagues (2007). Two retractable levers were mounted on either side of a feeding trough, and a house light (Model 1820; Med Associates, St. Albans, VT) located at the top of the chamber was used to illuminate the chamber during the sessions. Rewards consisted of evaporated milk (.01 ml) delivered by raising a dipper located inside the feeder trough.

Behavioral Procedures

Subjects in the PHD experiments were trained to press levers for milk rewards using the procedure described by Drew and colleagues (2007). Once proficient at earning rewards on a continuous reinforcement schedule, subjects were then trained to hold the lever down.

Lever hold-down procedures. Subjects in all PHD experiments were exposed to two different hold-down procedures: variable interval hold down (VIH) and PHD. In both schedules, a required hold duration was assigned prior to the start of each trial. This was the duration of time the subject was required to hold the lever in the depressed position to receive a reward. An individual trial in either schedule followed a similar procedure: At the start of each trial, the house light was illuminated and a lever was extended. As soon as the mouse depressed the lever, a timer began counting how long the lever was in the depressed position. This timer stopped and was reset to 0.0s if the mouse ended the lever press before the required time was reached. If the lever was depressed as long as the required duration, the trial ended, and the subject received a reward. A tone (2 s) sounded and the house light was shut off to signal the presentation of the dipper (5 s).

VIH training. As in the PR experiment, all subjects were given initial lever press training, as described by Drew and colleagues (2007). Next, subjects were trained using the VIH task. At the beginning of each trial, the required hold duration was drawn randomly from a truncated exponential distribution. This hold requirement remained in place until the subject was reinforced for completing the trial, at which time the next trial's required hold duration was randomly determined. During the first session, the distribution of required hold durations had a mean of 0.5 s; (minimum = .01 s; maximum = 2.44 s). When a mouse earned 40 rewards on 3 consecutive days, the required hold durations for the subsequent session were drawn from an exponential distribution with a higher mean (1 s, 2 s, 3 s, 4 s, 5 s, 8 s, 10 s). Thus, during the final session of VIH training, subjects were required to hold down the lever for intervals that averaged 10 s but could be as long as 18.8 s.

Progressive hold-down testing. Once all mice earned 40 rewards on VIH-10 for 5 consecutive days, they moved on to the PHD task. In the PHD task, the first required hold duration was fixed, and the requirement for subsequent hold durations was increased by a multiplicative amount. We used a PHD schedule of (2.0 s $\times$ 1.13), meaning the first required hold duration was 2 s and was multiplied by 1.13 on each trial thereafter. Thus, the requirement in trial number (t) was ($2.0 \text{ s} \times 1.13^{t-1}$) such that the first four requirements were 2.00 s, 2.26 s, 2.55 s, and 2.88 s, and then 6.00 s for the 10th trial, 20.4 s for the 20th trial, and so forth. Sessions ended after 2 hr elapsed or following 15 min without a single lever press, whichever came first.

Food Deprivation in the PHD Task

Subjects were tested on the PHD (2.0 s $\times$ 1.13) task under high- and low-motivational states through two different feeding conditions. In the high motivation condition, subject's daily access to food was restricted to maintain their bodyweight at either 85% of their ad libitum baseline bodyweights. In the low-motivation condition, subjects were given 24 hr access to home cage chow to allow them to maintain 100% of their baseline bodyweight. Subjects were tested on the PHD task in each condition for 3 consecutive days.

Reward Value in the PHD Task

Subjects were tested in the PHD (2.0 s $\times$ 1.13) schedule, and the reward consisted of a sucrose solution of different concentrations on different days (i.e., 5%, 10%, 20%, and 40% sucrose solutions). Subjects were first tested on consecutive days with the sucrose percentage changing in ascending order (5% to 10% to 20% to 40%) from day to day and were subsequently tested the following week on consecutive days with the sucrose percentage changing in a descending order (40% to 20% to 10% to 5%). Data was averaged over the 2 days of testing at each percentage. Sessions lasted 1 hr or until subjects failed to make a press for 15 min, whichever came first.

Progressive Ratio

Subjects in the METH PR experiment were trained to press levers for milk rewards using the procedure described by Drew and colleagues (2007). Once proficient at earning rewards, subjects were rewarded for pressing according to a variable interval (VI) schedule. In a VI schedule, no lever presses were reinforced until an uncertain interval had elapsed; the first press following this interval was reinforced. The duration of each interval was drawn randomly from an exponential distribution following reinforcement. Subjects were trained on VI-3 (mean interval duration of 3s) for 2 days, followed by VI-10 for 2 days, and VI-20 for 4 days before moving on to PR testing.

In PR testing the lever was extended at the start of the session. Once the mouse made a criterion number of lever presses, a reward was delivered. The criterion was set at four lever presses for the first trial and was multiplied by 1.18 thereafter and rounded to the nearest integer. This is subsequently denoted as PR (4×1.18). Thus, the requirement at trial (t) was ($4 \times 1.18^{r-1}$; i.e., 6 on Trial 5, 31 on Trial 15, 160 on Trial 25, and so forth). The session ended after 2 hr or after 3 min had elapsed without a lever press.

Subjects were tested in the PR following intraperitoneal (IP) injections of vehicle for 3 days to establish a behavioral baseline. Next, methamphetamine hydrochloride (Sigma Aldrich, St. Louis, Missouri) was dissolved in .9% saline and IP injected at 1.0 mg/kg in a volume of 0.01 ml/g prior to being tested on the PR schedule for 3 consecutive days. All injections were performed 20 min before the start of the behavioral session.

Methamphetamine in the PHD Task

Subjects were tested on the same PHD (2.0 s $\times$ 1.13) schedule used in the other experiments with one important difference: An inactive lever was extended in addition to the normal active lever at the start of each trial. This inactive lever was the lever opposite to that which each subject was trained to press, and responses made to it never yielded rewards. This lever was included to measure nongoal-directed hyperactive responses.

Subjects were tested on the PHD task and received IP injections of vehicle for 4 days followed by 4 days of 1.0 mg/kg of METH. The methamphetamine hydrochloride was prepared as described in the PR experiment. All injections were performed 20 min before the start of the behavioral session.

Data Analysis

All data were analyzed using two-tailed Student t tests without assuming equal variance or, where appropriate, repeated measure analysis of variance (ANOVA). In all experiments, data were averaged across all days of a specific treatment type (e.g., vehicle or METH) with the number of days provided in the figure legend. Planned comparisons are reported in the main text and significant post hoc analyses are reported in the figure legends.

Results

Measuring Motivation With the Progressive Hold Down Task

Baseline performance on the PHD task. We tested subjects in a PHD task under various conditions to characterize the PHD task as an assay of motivational behavior. Figure 2A shows performance from a representative session of one individual subject in the PHD task. Subjects were able to hold the lever down for longer durations, meeting the required hold duration set by the schedule on each trial. Successful presses (held long enough to meet the required duration) resulted in the delivery of a reward. Failed presses (those not held down long enough to meet the required hold duration for that trial) tended to occur toward the end of the session prior to the point when the subject stops pressing altogether.

Similar to behavior in the PR, the number of lever presses made in a PHD session is related to the number of rewards a subject earns (see Figure 2B), showing a significant positive correlation, $r(11) = 0.697$, $p < .05$. There is also a significant positive correlation between the session duration and the number of rewards a subject earns (see Figure 2C), $r(11) = 0.748$, $p < .05$. This implies that under baseline conditions the amount and the duration of goal-directed behavior in this task are related to how motivated a subject is to earn rewards, as has been demonstrated repeatedly for behavior in the PR.

Performance in the PHD task is modulated by level of food deprivation and reward value. To validate that the PHD task was sensitive to differences in motivation, we manipulated the level of two parameters known to alter motivated responding: level of food deprivation and reward value. In the deprivation experiment, subjects performed the PHD task under a high motivation condition (restricted feeding: subjects maintained at 85% of baseline body weight) and low motivation condition (ad lib feeding: subjects maintained at 100% baseline body weight). Food-deprived subjects made more lever presses, $t(11) = 7.037$, $p < .0001$ (see Figure 3A), continued working for longer durations (Vehicle $M = 62.8$ min $\pm$ 4.44; METH $M = 112.5$ min $\pm$ 2.49), $t(11) = 16.77$, $p < .0001$, and consequently earned more rewards, $t(11) = 9.826$, $p < .0001$ (see Figure 3B). To distinguish between hyperactive and goal-directed responding, we looked at two different measures of the lever-holding behavior. To estimate the amount of goal-directed responding, we calculated the mean duration of all of the holds that were greater than 2 s. We chose 2 s as the cutoff because it was the shortest duration requirement on the very first trial, and presses shorter than this could not possibly result in the goal. This measure is strongly correlated with the number of rewards subjects earn, $r(11) = 0.697$, $p < .05$. There was a significant increase in the mean of all holds greater than 2 s in the restricted feeding condition, $t(11) = 5.466$, $p = .0002$ (see Figure 3C), reflecting an increased amount of goal-directed behavior. To estimate the amount of hyperactive nongoal-directed responding a subject produced, we calculated the total number of presses made which were less than 2 s in duration. There was a small increase in the number of short <2 s presses made in the restricted feeding group compared with the ad lib feeding group, $t(11) = 2.562$, $p = .0264$ (see Figure 3D). Thus, food restriction leads to a large increase in goal-directed behavior and a small increase in rapid, hyperactive responding that does not earn rewards.

To further examine the sensitivity of the PHD task to a subject's motivation to obtain rewards, we next tested subjects using sucrose solutions of different concentrations as the reward. Pilot studies showed that mice prefer sucrose solutions much less than evaporated milk so test session of 1 hr were used

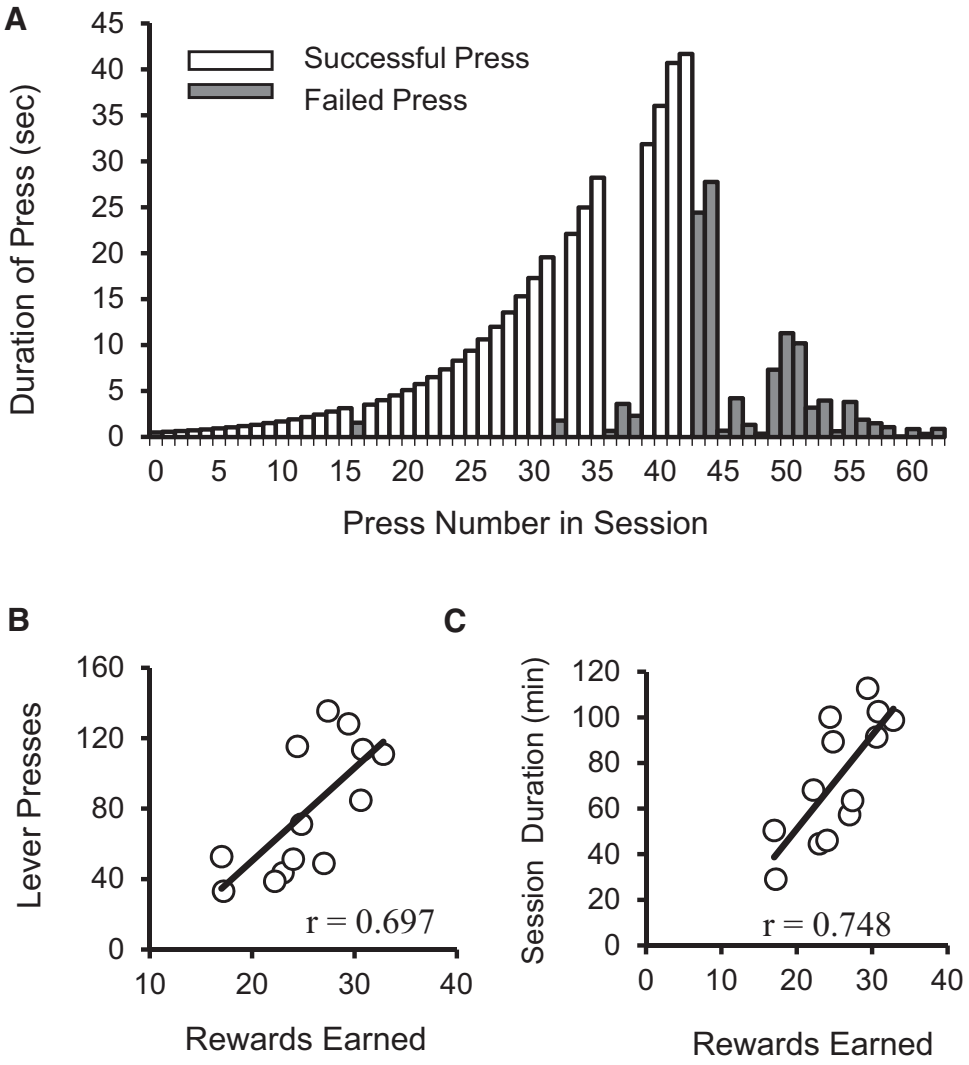

Figure 2. Characterization of baseline behavior in the progressive hold-down (PHD) task. (A) Representative performance of pressing for a single subject throughout a single PHD session. Shows both successful presses (white) and unsuccessful presses (gray). (B–C) There is a positive linear relationship between the number of presses made on the correct lever (B) and session duration (C) with the number of rewards earned. In (B–C), each point represents a single subject's average over 5 days of baseline progressive hold down testing.

in this experiment. Subjects were more motivated to work for the higher reward value as they made more lever presses for higher percentage sucrose solutions, $F(3, 27) = 6.47$, $p = .015$ (see Figure 4A), and earned more rewards, $F(3, 27) = 20.2$, $p < .001$ (see Figure 4B), as subjects made holds of significantly longer durations when they were working for higher sucrose concentrations.

We again used the mean hold times of all presses longer than 2 s to estimate goal-directedness and the number of presses less than 2 s to estimate hyperactivity or arousal. There was a significant effect of reward value on the amount of goal-directed behavior, $F(3, 27) = 14.98$, $p < .001$ (see Figure 4C), as the mean hold durations were longer for the higher sucrose concentrations. The reward value did not have a significant effect on the number of short presses (<2 s) made, $F(3, 27) = 0.612$, $p = .439$ (see Figure 4D).

Methamphetamine leads to greater persistence in the progressive ratio task. We tested mice using a PR schedule of reinforcement to determine whether METH would lead to an increase in performance similar to that reported for amphetamine in rats (Olausson et al., 2006; Poncelet et al., 1983; Mayorga et al., 2000) and in the DAT KD mouse (Cagniard et al., 2006). Figure 5A shows the progression of requirements in a PR (4×1.18), indicating the number of presses required to earn each reward. Treatment with METH led to a significant increase in the number or lever presses made, $t(7) = 4.538$, $p = .0027$ (see Figure 5B). Treatment with METH also caused subjects to continue working for longer durations before quitting (Vehicle $M = 109.0$ s $\pm$ 5.67,

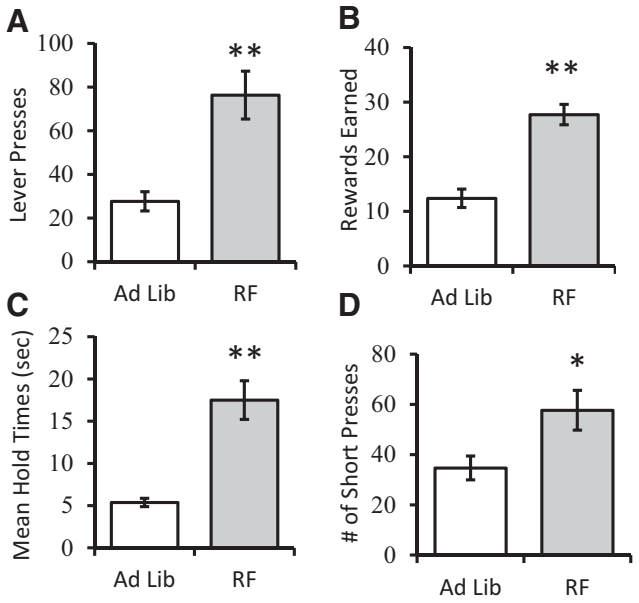

Figure 3. Food restriction effects on progressive hold-down (PHD) task performance. (A) Mean (± SEM) lever presses in the PHD task under ad lib and restricted feeding conditions. (B) Mean (± SEM) number of rewards earned in the PHD task under ad lib and restricted feeding conditions. (C) Mean (± SEM) duration (s) of all lever presses longer than 2 s under ad lib and restricted feeding conditions. (D) Mean (± SEM) number of lever presses made that were shorter than 2 s under ad lib and restricted feeding conditions. In (A–D), each point represents a subjects performance averaged over 3 days of ad lib and restricted feeding conditions. * $p < 0.5$. ** $p < .01$.

METH $M = 120.0$ s ± .001), $t(7) = 2.504$, $p = .047$. As a result of making more lever presses and continuing to work for longer durations before quitting, subjects earned significantly more rewards when given METH, as compared to vehicle (Vehicle: $M = 10.94$ presses/min ± 1.59; METH: $M = 16.08$ presses/min ± 2.21), $t(7) = 5.396$, $p = .0010$.

To analyze the effect that treatment with METH had on the rate or vigor of behavior in the PR, we looked at the response rate (presses per min) and the duration of each single response (time from the lever being pressed down to the time when it is let backup). METH led to an increase in the response rate, $t(7) = 3.084$, $p = .0177$ (see Figure 5D), as well as a shorter average response duration (Vehicle $M = 0.72$ s ± 0.05; METH $M = 0.53$s ± 0.05), $t(7) = 3.390$, $p = .0095$. Thus, METH responses were made more often, and each response was executed more quickly. Although both measures could indicate that METH may result in increased arousal or hyperactive responding, this cannot be definitively determined with the PR as every response counts toward the next reward and is considered goal directed. There was no significant difference in the number of missed rewards (i.e., rewards that the subject failed to collect) between vehicle and METH conditions (Vehicle $M = 0.54 \pm 0.19$; METH $M = 0.45 \pm 0.14$), $t(7) = 0.290$, $p = .779$, suggesting that METH treatment did not interfere with subjects motivation to collect the rewards.

Methamphetamine leads to inefficient performance in the PHD task. Having confirmed that the PHD task is sensitive to changes in a subject's motivational state, we next tested mice following treatment with METH to determine whether subjects would work harder and longer, as was shown in PR testing. Subjects were tested 20 min after receiving an IP injection of 1 mg/kg of METH, a dose known to induce a robust increase in activity (Hall et al., 2008). In addition, we included a nonreinforced "inactive lever" to provide a measure of activity that was not related to the goal of the task.

Figure 6A depicts the change in PHD task performance following administration of METH, using a representative press record of an individual subject during vehicle and METH treatment sessions. The number of lever presses made on the active lever was significantly higher on METH, $t(12) = 9.175$, $p < .0001$ (see Figure 6B). Treatment with METH also lead to a significant increase in how long subjects continued working (Vehicle $M = 62.8$ min ± 4.44; METH $M = 112.5$ min ± 2.49), $t(12) = 6.743$, $p < .0001$, as 75% of the sessions on METH went the full 2 hr compared with 11% during vehicle treatment. Despite increasing the number of presses on the active lever and the length of time that subjects continued pressing, mice did not earn significantly more rewards during the METH sessions, $t(12) = 1.647$, $p = .1254$ (see Figure 6C). Moreover, there was not a significant difference in the average hold duration of presses greater than 2 s, $t(12) = 0.4647$, $p = .6505$ (see Figure 6D), suggesting that METH treatment did not enhance goal-directed behavior.

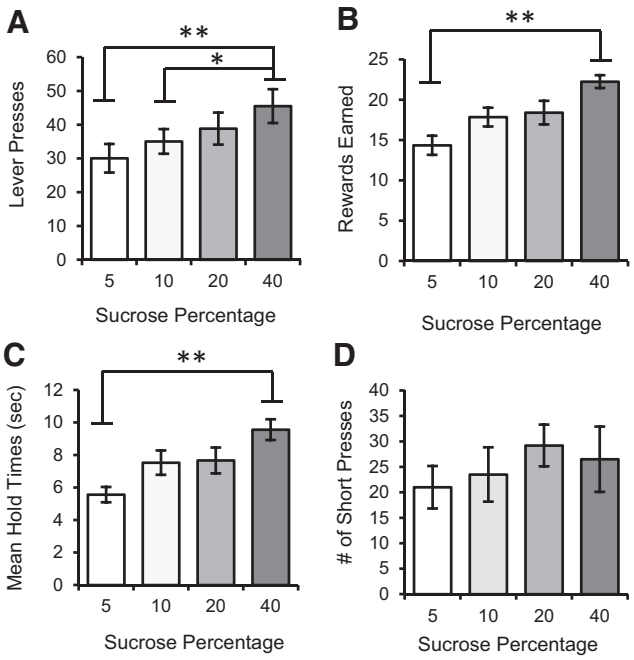

Figure 4. Reward value effects on progressive hold-down (PHD) task performance. (A) Mean (± SEM) number of lever presses for different sucrose concentrations in the PHD task; Tukey's HSD test. (B) Mean (± SEM) number of rewards earned for different sucrose concentrations in the PHD task; Tukey's HSD test. (C) Mean (± SEM) duration (s) of all lever presses longer than 2 s for different sucrose concentrations in the PHD task; Tukey's HSD test. (D) Mean (± SEM) number of lever presses made which were shorter than 2 s for different sucrose concentrations in the PHD task. In (A-D) each point represents a subjects performance averaged over 2 days of PHD testing at each sucrose concentration. ** $p < .01$.

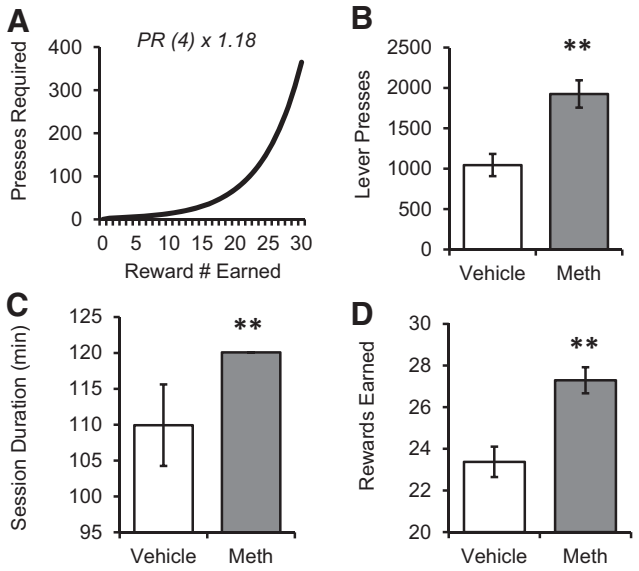

Figure 5. Methamphetamine (METH) increases responding in a progressive ratio (PR). (A) Relationship between number of presses required and reward number for the PR 4 × 1.18 schedule. (B) Mean (± SEM) number of lever presses in the PR. (C) Mean (± SEM) number of rewards earned in the PR. (D) Mean (± SEM) session duration (min) in the PR. For (B–D), each point represents a single subject's performance averaged over 4 days of vehicle or METH treatment. ** $p < .01$.

During baseline vehicle treatment there was a significant positive relationship between the number of lever presses made on the active lever and the number of rewards earned, $r(12) = 0.585$, $p < .05$ (see Figure 6E). During METH treatment, however, there was a nonsignificant negative relationship between the number of lever presses made and the number of rewards earned, $r(12) = -0.395$, $p > .10$ (see Figure 6F), as there was a significant increase in the total number of failed press attempts on the correct lever (Vehicle $M = 30.9 \pm 1.77$; METH $M = 167.26 \pm 10.2$), $t(12) = 10.16$, $p < 0.001$. This is evident from the distribution of the duration of unsuccessful press attempts (see Figure 6G), there was a significant increase in the number of presses made which were shorter than 2 s in duration during METH treatment, $t(12) = 6.903$, $p < .0001$ (see Figure 6H), suggestive of an increase in hyperactive responding.

Behavioral Changes in Progressive Hold-Down Task Induced by Methamphetamine Are the Result of Increased Arousal

We next analyzed how the increase in hyperactive presses following METH treatment affected various measures of performance in the PHD task. Treatment with METH led to a significant increase in the rate of lever pressing (Vehicle: $M = 1.18$ responses/min $\pm$ 0.08; METH: $M = 2.10 \pm 0.15$), $t(12) = 6.503$, $p < .0001$. We computed each subject's efficiency, defined as the proportion of lever presses made that were rewarded, from the first press to the last rewarded press. Following METH treatment, there was a significant decrease in the efficiency of responding, $t(12) = 10.55$, $p < .0001$ (see Figure 7A). This decrease in efficiency can be seen from the beginning of the session, as there is a decrease in efficiency at every single hold requirement (see Figure 7B). Additionally, as a consequence of the increased hyperactive responding on METH, it took subjects longer to complete each hold requirement, even the short ones at the very beginning of the session (see Figure 7C). Thus, METH appears to increase arousal and hyperactive responding at the expense of efficient, goal-directed action.

We additionally looked at the number of lever presses made on the inactive lever as this is thought to measure hyperactive nongoal-directed responding. Although the average number of inactive presses was higher during METH treatment (Vehicle $M = 11.46 \pm 7.4$; METH $M = 35.46 \pm 20.7$), this measure was strongly skewed such that most subjects made few presses on the inactive lever and a few subjects made many. A Mann–Whitney test of a difference in the medians did not detect a significantly difference in the number of inactive lever presses made, $U(12) = 52.50$, $p = .106$. Further evidence that METH did not increase goal-directed action comes from the within session pattern of responding on the inactive lever. As can be seen in Figure 7(D–E), the number of presses on the inactive lever did not begin to increase until there was a rise in the number of failed press attempts on the active lever in both vehicle (see Figure 7D) and METH (see Figure 7E) conditions. Previous studies suggest that when subjects are no longer rewarded for goal-directed action (e.g., during extinction), behavior becomes more variable, and subjects make responses that were not previously reinforced (Rick et al., 2006; Neuringer et al., 2001; Antonitis, 1951). Our data show that subjects wait to switch to the inactive lever only after they have exceeded a certain number of failed goal-directed attempts. It is interesting to note that there was no difference in the number of failed, long goal-directed attempts between vehicle and METH, $t(12) = 0.1779$, $p = .8617$ (Figure 7F), which further suggests that METH does not change goal-directed motivation because subjects are not treating the short hyperactive responses in the same way they treat failed goal-directed attempts.

Discussion

Motivation has long been known to consist of several underlying processes, two important ones being a directional process, steering behavior toward a specific goal, and an activation process, providing energy and vigor to behavior by increasing arousal. Our novel experimental strategy elucidates which of these two processes is altered by evaluating subjects in both the PR and the novel PHD task. In the PHD task, we demonstrate that established motivation manipulations of food deprivation and reward value lead to an increase in goal-directed behavior, but have little effect on hyperactive nonrewarded responding. To test the efficacy of our novel strategy, we use a dose of a drug known to increase overall levels of general locomotor activity (1.0 mg/kg of METH) as a tool to compare the behavioral profiles of mice when tested on the PR and PHD task. In the PR, treatment with METH leads to increases in the number or responses and amount of time subjects continue working in the task. In the PHD task, treatment with METH leads to a large increase in responding, making overall performance less efficient but neither increases nor impairs goal-directed motivation. As elaborated in the following paragraphs, the results of the current experiment demonstrate the efficacy of using the PR and PHD tasks jointly to differentiate the components of motivation.

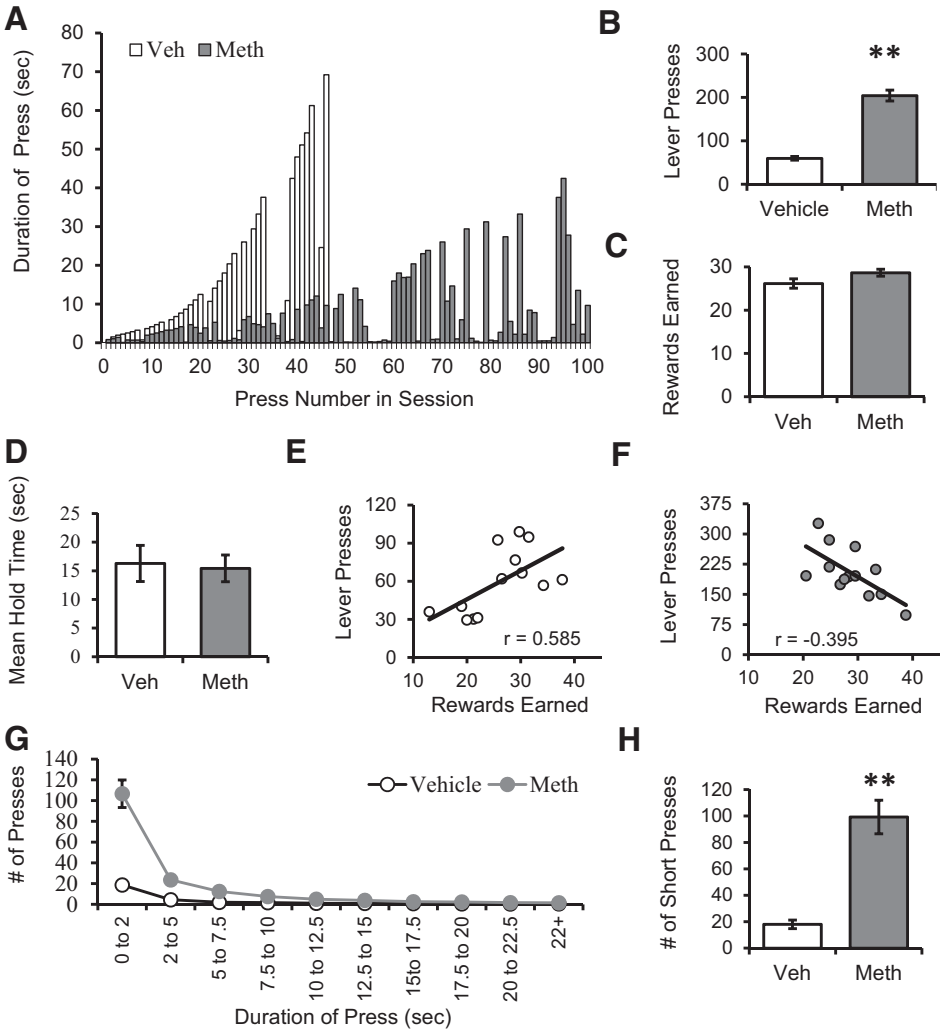

Figure 6. Methamphetamine (METH) increases amount lever pressing in the progressive hold-down (PHD) task. (A) Shows a representative press record of the first 100 presses for a single subject tested on the PHD task following treatment with vehicle (white) and METH (grey). (B) Mean (± SEM) number of lever presses on the correct lever. (C) Mean (± SEM), number of rewards earned. (D) Mean (± SEM) duration (s) of all lever presses longer than 2 s. (E–F) There is a significant positive relationship between the number of presses and the number of rewards earned during vehicle treatment (E), whereas there is a negative relationship between these measures during METH treatment (F). (G) Shows the distribution of the durations of unsuccessful holds, Mean (± SEM). (G) Mean (± SEM) number of lever presses made which were shorter than 2 s. In (B–E, G), each point represents a single subject's performance averaged across 4 days of each treatment condition. ** $p < .01$.

The PHD Task Measures Both Goal-Directed Behavior and Hyperactive Responding

One of the main reasons that the PR has become a popular measure of motivated behavior is that the number of lever presses made and the amount of time spent working are directly related to the number of rewards earned, giving the task substantial face validity (Bradshaw & Killeen, 2012). Under baseline conditions in the PHD task, the number of presses subjects make and the amount of time they spend working are also strongly positively correlated with the number of rewards earned. The main distinction between the PR and PHD tasks, however, is that these three measures are not always proxies for one another. In the PHD task, if a subject keeps prolonging the duration of their lever presses, then the relationships will remain. If, however, subjects make presses of a short duration, as one would expect in the case of high arousal or hyperactivity, this dilutes the relationship between the number of presses made, the amount of time spent working, and the number of rewards earned.

We found the PHD task to be sensitive to both changes in goal-directed responding as well as high arousal hyperactive responding by examining the effects of manipulating the value of rewards in two different ways. First, we tested mice on a restricted diet, in which they are more motivated to earn food rewards. Second, we increased the value of the rewards that could be earned in the task. We show that being on a restricted

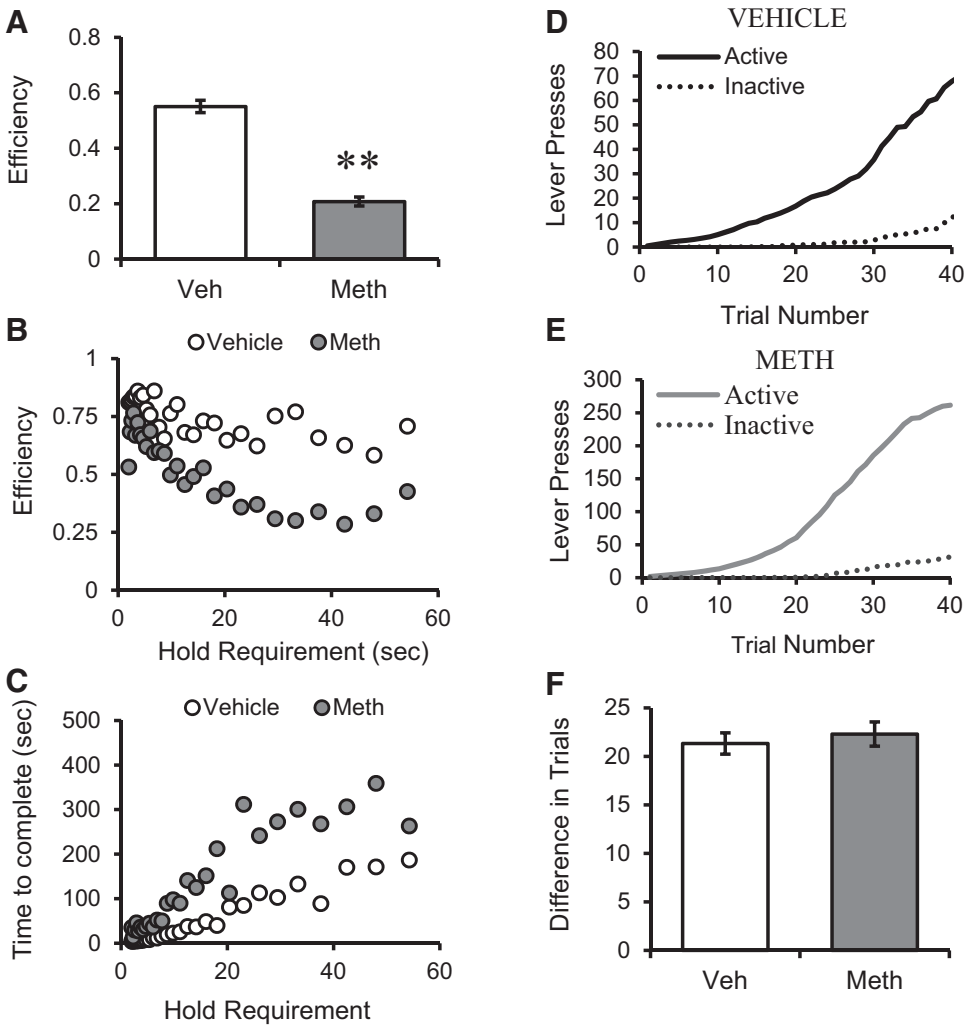

Figure 7. Methamphetamine (METH) increases hyperactive responses in the progressive hold-down (PHD) task. (A) The mean (± SEM) efficiency (proportion of successful responses on the active lever until the last rewarded press). (B) Mean efficiency as a function of the required hold duration (s) in the PHD session. (C) Mean time (s) it takes subjects to complete a required hold duration (s). (D–E) The mean cumulative number of failed presses on the active and inactive lever as a function of the trial number during vehicle (D) and METH (E) treatment. (F) The mean (± SEM) difference in the number of trials between the first failed press on the active lever and the first press on the inactive lever. In (A, F), each point represents a single subject's performance averaged across the 4 days of each treatment condition. In (B–C), each point represents the treatment condition average of all subjects at each given hold requirement. In (D–E), each point represents the treatment condition average of all subjects for each trial number. ** $p < .01$.

diet resulted in increased rewards earned, amount of lever pressing, and time spent working. It is important to note that this manipulation also led to a large increase in the maximal hold durations, as would be expected with increased amounts of goal-directed behavior in this task. There was a small increase in the number of short duration responses made, but this is not surprising as food deprived subjects do show elevated levels of arousal compared with ad lib maintained subjects (Harrison & Archer, 1987; Heiderstadt et al., 2000). Similarly, subjects are sensitive to the value of the reward, and subjects made more presses and held the lever down longer for higher concentrations of a sucrose reward. Increasing reward value did not, however, lead to an increase in the amount of short duration (hyperactive) responses made. Thus, performance in the PHD task reflects the goal-directed motivation of subjects.

We further demonstrated the sensitivity of PHD task to changes in general arousal–hyperactivity by examining the effects of a dose of METH known to increase this aspect of motivation. Administration of METH in PR led to an increased number of lever presses, number of rewards earned, and total duration of time spent working for food rewards. However, the effect of METH on PHD performance suggests that the increases observed in the PR are driven mainly by the activational process of motivation rather than the directional process. As in the PR, METH led to a greater

number of responses, but the main increase in behavior seen with METH was with presses of short durations (<2 s), which led to inefficient PHD performance. In contrast to PR results, METH did not result in subjects earning an increased number of rewards in the PHD task. These results are consistent with several studies documenting METH's ability to increase arousal across a variety of behavioral measures (Cruickshank & Dyer, 2009; Estabrooke et al., 2001; Hart et al., 2008) and suggests that this dose of METH does not lead to increased goal-directed motivation.

Please note that this study was not intended to be a comprehensive examination of the psychopharmacology of methamphetamine. Rather, it is intended to be a demonstration of the additional nuanced information one can gain by using the PHD in conjunction with the PR. We only examined one dose that we knew would increase general activity. Thus, whether and how amphetamines might affect motivation at different doses is a remaining question that future studies could address.

Implications for Studying the Neurobiology of Motivation

The present results indicate that we cannot rely on any single behavioral assay to study complex behavioral processes like motivation. An increase in responding on the PR may reflect increased goal-directed motivation in studies that employed a wide range of techniques, including behavioral manipulations (Barr & Phillips, 1999; Bowman & Brown, 1998; Ferguson & Paule, 1997; Hodos, 1961; Hodos, & Kalman, 1963), pharmacological manipulations (Aberman et al., 1998; Randall, 2012; Simpson et al., 2011), and genetic manipulations (Cagniard et al., 2006; Drew et al., 2007; Gore & Zweifel, 2013; Sanders et al., 2007; Trifilieff et al., 2013). The current results suggest that these different manipulations may affect motivated behavior by affecting different underlying processes.

Use of both the PR and the PHD tasks allows understanding of how drug or genetic manipulations influence the processes underlying motivated behavior and reduces the risk drawing incorrect conclusions based on a single assay. By understanding the results of manipulations across these two tasks, a deeper understanding can be achieved. For example, if either improved or impaired performance occurred in both tasks it would strongly suggest an increase or decrease in goal-directed motivation, respectively. In contrast, increased performance in the PR and impaired or unaltered performance in the PHD task (as demonstrated with METH) is indicative of increased arousal or hyperkinesia. Moreover, no difference in PR and an increase in PHD might reflect intact goal-directed motivation and impaired arousal, whereas a decrease in PR performance and an increase in PHD performance may reflect psychomotor slowing or bradykinesia, either of which would facilitate holding behavior but disrupt continuous and fluid initiation of the behaviors required for success in the PR.

Finally, we note that improvements in the ability to measure complex behavior in laboratory animals may have a large impact on the development of new treatments for psychiatric disease. Impaired goal-directed motivation or apathy is a problematic symptom common to several psychiatric diseases, including schizophrenia (Kiang, Christensen, Remington, & Kapur, 2003; Roth, Flashman, Saykin, McAllister, & Vidaver 2004; Faerden et al., 2009) and some affective disorders (Feil, Razani, Boone, & Lesser, 2003; Marin, Razani, Boone, & Lesser, 2003). There are, however, currently no effective treatments for this aspect of impaired motivation (Chase, 2011; Levy & Czernecki, 2006), representing a major gap in the current treatment repertoire. The methods developed here enable the identification of mechanisms and factors that specifically enhance goal-directed responding in preclinical research.

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