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The Effects of Housing Conditions and Methylphenidate on Two Volitional Inhibition Tasks

by

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ABSTRACT

The failure to withhold inappropriate behavior is a central component of most impulse control disorders, including Attention Deficit Hyperactivity Disorder (ADHD). The present study examined the effects of housing environment and methylphenidate (a drug often prescribed for ADHD) on the performance of rats in two response inhibition tasks: differential reinforcement of low rate (DRL) and fixed minimum interval (FMI). Both tasks required rats to wait a fixed amount of time (6 s) before emitting a reinforced response. The capacity to withhold the target response (volitional inhibition) and timing precision were estimated on the basis of performance in each of the tasks. Paradoxically, rats housed in a mildly enriched environment that included a conspecific displayed less volitional inhibition in both tasks compared to rats housed in an isolated environment. Enriched housing, however, increased timing precision. Acute administration of methylphenidate partially reversed the effects of enriched housing. Implications of these results in the assessment and treatment of ADHD-related impulsivity are discussed.

DEDICATION

This thesis is dedicated to Juniper and Joss.

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Introduction

Impulsivity is a critical component of several problem behaviors including substance abuse (Bechara, 2005; Perry & Carrol, 2008), personality disorders (Chapman, Leung and Lynch, 2008), and Attention Deficit Hyperactivity Disorder (ADHD) (Barkley, 1997). The behavioral methods used to measure impulsivity vary across clinical and experimental settings and may be measuring different processes only loosely associated with impulsivity. In fact, impulsivity encompasses multiple, functionally independent, psychological phenomena (Evenden, 1999; Arce & Santisteban, 2006; Fellows & Farah, 2005; Leshem & Glicksohn, 2007; Pattij & Vanderschuren, 2008; Winstanley, Eagle, & Robbins, 2006). The variety of impulsivity that is a main criterion of ADHD involves an inability to withhold prepotent responses (Barkley, 1997). Several behavioral phenomena are likely to be included even within this narrower definition, particularly when considering the sources of prepotency of the response to be withheld. For example, the kind of inhibitory effort required to hold a sneeze is unlikely to be the same as the effort required to avoid tasty but unhealthy food. More functionally, the factors involved in withholding an ongoing response are unlikely to be the same as those involved in withholding a tempting choice—the former comes after an action has been initiated or a decision has been made, whereas the latter precedes the action and involves the decision process itself. We use the term *volitional inhibition* to refer to the ability to withhold responses that, when emitted at the right time, have rewarding consequences, to differentiate it from other phenomena related to impulsivity and motor inhibition. Whereas

normal behavior is likely to involve non-clinical lapses in volitional inhibition, a more chronic deficit may characterize ADHD-related impulsivity. This paper aimed at isolating the components of volitional inhibition in Wistar rats, and at determining their sensitivity to two factors often related to impulsivity: housing conditions and the administration of methylphenidate hydrochloride (MPH).

Volitional inhibition is typically studied using Go/No-Go tasks, where subjects are asked to perform an action in the presence of a cue ("Go") but withhold it in the presence of a different cue ("No-Go") (Epstein et al., 2003; Tripp and Alsop, 1999, 2001). These tasks involve a conditional discrimination between stimuli, where discriminability is fallible. The most typical Go/No-Go tasks used with human participants are known as Continuous Performance Tests (CPTs), where subjects must report the presence of a target stimulus among stimuli presented sequentially (Klee & Garfinkle, 1983; Epstein et al 2003). Errors of commission—reporting the presence of the target when it was absent—are interpreted as indicative of low volitional inhibition.

The test of volitional inhibition most widely used in rodents is the 5-Choice Serial Reaction Time Task (5-CSRTT) (Robbins, 2002). In 5-CSRTT, a 0.5-s cue is presented in 1 of 5 possible locations; a nosepoke on the corresponding location is reinforced. Nosepokes produced before cue onset are punished with time-outs, and are indicative of impulsivity (Bari, Dalley & Robbins, 2008). A signal-detection analysis is readily applicable to 5-CSRTT performance: At any time, the rat must choose between nosepoking or engaging

in other behavior. Inaccuracy in memory favors a bias toward nosepoking, because it is the only behavior that is explicitly reinforced in 5-CSRTT. Thus, to the extent that behavior is insensitive to the cue but sensitive to reinforcement, premature (i.e., impulsive) nosepoking would be prevalent.

Other tasks may also be thought of as tests of volitional inhibition, such as the Differential Reinforcement of Low rates (DRL), the leverholding task (LHT, sometimes called Temporal Response Differentiation, or Differential Reinforcement of Response Duration), and the Fixed Consecutive Number (FCN) task. The signal to be detected in DRL is the minimum time that the animal has to wait between consecutive lever presses to obtain food (Sanabria & Killeen, 2008); in LHT, it is the minimum time that the animal has to hold down a lever to obtain food (Sanabria & Killeen, 2008); in FCN, it is the minimum number of consecutive lever presses before pressing another lever to collect food (Evenden & Meyerson, 1999) or to collect food and avoid electric shock (Evenden & Ko, 2005).

Go/No Go tasks like CPT and the 5-CSRTT may serve to evaluate differences in volitional inhibition between experimental and control groups. The construction of a quantitative model of volitional inhibition, however, requires more than the identification of qualitative differences; it requires precise estimation of model parameters. The estimation of impulsivity parameters hinges on the specification of mathematical relations between task-specific factors (e.g., salience of discriminative stimuli), inhibitory processes, and performance. Extant

inhibition assessment methods do not specify such relations. Moreover, the typical analysis of 5-CSRTT confounds overall rate of nosepoking (activity) with rate of premature nosepoking (impulsivity), because an increase in the former entails an increase in the latter and, because premature nosepokes preclude effective ones, it also entails a reduction in effective nosepokes. DRL, LHT, and FCN are also vulnerable to this kind of confound.

This study compared two behavioral methods of assessing volitional inhibition in rats: DRL and fixed minimal interval (FMI) (Mechner & Guevrekian, 1962). FMI is a variant of DRL where the initial response is qualitatively different from the terminal response that produces a reinforcer. The DRL procedure has been extensively investigated as a model of timing and inhibition (Orduña, Valencia-Torres & Bouzas, 2009; Sanabria & Killeen, 2008; Bardo, Cain & Bylica, 2006; Ferguson, Paule, Cada, Fogle, Gray & Berry, 2001; Kramer & Rilling, 1970), and it is commonly used to test the effects of pharmacological treatments on these dependent variables (e.g., Fowler, Pinkston & Vorontsova, 2009; Sable, Eubig, Powers, Wang & Schantz, 2009;Richards, Kabol & Seiden, 1993). FMI is a much less common procedure, but closely related variations have been conducted (Soffie & Lejeune, 1991; Morgan & Einon, 1975).

DRL and FMI performance were analyzed with a signal-detection approach in mind, using a target interval as the signal to be detected. Rats obtained sucrose rewards by starting a clock (not visible to them) and waiting at

least 6 s before stopping the clock; stopping the clock before 6 s had elapsed resulted in reward cancellation. This paradigm may be described in terms of a biased discrimination task: Rats had a continuous choice between stopping the clock and letting it continue to run. Whereas stopping the clock sometimes resulted in a reward, letting the clock run—by itself—never yielded a reward, it only increased the probability of a reward in the future. Thus, to the extent that passage of time was not well discriminated, rats had an incentive to stop the clock immediately. Because passage of time is a continuous variable, waiting times indicated exactly how much time justified a clock-stopping response. Moreover, the dispersion of waiting times was indicative of timing acumen, separately from volitional inhibition. These data could support inferences on model parameters based on extensively researched mathematical models relating timing, instrumental contingencies, instrumental behavior (Killeen and Fetterman, 1988; Machado, 1997), and, only recently, volitional inhibition (Sanabria and Killeen, 2008).

The proposed methods and analytical techniques were applied to assess the effects of housing conditions and MPH on volitional inhibition in rats. Prior manipulations of these variables have yielded mixed results. Rodents reared in isolation typically show poorer behavioral and cognitive performance relative to rats reared in a socially and physically enriched environment (Larsson, Winblad and Mohammed, 2002; Janus, Koperwas, Janus and Roder, 1995; Wright and Conrad, 2008). Rats reared in isolation are also more likely to self-administer amphetamines (Bardo, Klebaur, Valone and Deaton, 2001). Nonetheless, whereas

Perry, Stairs, and Bardo (2008) report that rats raised in isolation are more impulsive in a delay discounting choice task, Hellemans, Nobrega, and Olmstead (2005) report the opposite effect. More relevant to volitional inhibition, Dalley and colleagues (2002) report no differences in 5-CSRTT impulsivity between rats reared in isolated environments and in enriched environments. Isolated rats, however, produced more premature responses in a DRL procedure (Ough, Beatty & Khalili, 1972). In a 2-lever DRL, a variation of FMI in which pressing either one of two levers resets the clock, isolated rats made more initial and terminal lever presses than enriched rats, receiving fewer overall rewards (Morgan & Einon, 1975). A potential issue in all of these findings is that rodents reared in isolation, relative to those reared in enriched environments, are more active in open field tests (Amaral, Vargas, Hansel, Izquierdo & Souza, 2008; Smith, 1972), and lever press for food at higher rates (Rose, Love & Dell, 1985), even in the presence of free food (Coburn and Tarte, 1976). Additionally, isolated rats may be more sensitive to reinforcers than enriched animals (Rose, Love & Dell, 1985; Brenes, Rodriguez & Fornaguera, 2008).

Methylphenidate (MPH) is one of the most commonly prescribed drugs for treating ADHD (Setlik, Bond & Ho, 2009; Greenhill, Halperin & Abikoff, 1999). In humans, MPH has been widely shown to reduce impulsivity and other symptoms of ADHD (Sunohara, et Al., 1999; Pietras, Cherek, Lane, Tcheremissine & Steinberg, 2003). A variety of studies show decreased impulsivity in a stop signal reaction time task (Devito, et Al., 2009; Aron, Dowson, Sahakian & Robbins, 2003, Scheres et Al., 2003), as well as a delay

discounting task (Pietras, Cherek, Lane, Tcheremissine & Steinberg, 2003). In regards to volitional inhibition, Broyd et. Al (2005) demonstrated that MPH reduced the number of commission errors in children with ADHD, bringing them to the same level as non ADHD children. The replicability of this effect in animal models, however, has had mixed evidential support. Using delay-discounting tasks, Pitts and McKinney (2005) report that MPH decreases impulsivity in Sprague-Dawley rats, most noticeably at intermediate doses. However, Bizot and colleagues (2007) report these MPH-induced self-control improvements only in juvenile Wistar rats, not in adult Wistar, Spontaneously Hypertensive Rats (SHR, a widely used animal model of ADHD; Sagvolden, 2000), or Wistar-Kyoto rats (WKY, the conventional normotensive control of SHR). Perry and colleagues (2008) only report an MPH-induced reduction in delay-discounting impulsivity in isolated and not in socially reared rats.

More directly relevant to volitional inhibition, Evenden and Ko (2007) report that MPH (6 mg/kg) increased the number of long chains produced using the Fixed Consecutive Number (FCN) method with shock avoidance. The increase in long chains, however, did not result in improved response or chain efficiency scores, as measured by the total number of responses divided by the total number of un-shocked food deliveries, and the total number of chains divided by the total number of un-shocked food deliveries, respectively. This occurred because although animals increased the percentage of very long response chains, they also increased the percentage of very short response chains. Bizarro, Patel, Murtagh and Stolerman (2004) also report MPH-induced improvement of

volitional inhibition using 5-CSRTT (2, 5 and 10 mg/kg). In contrast, Navarra and colleagues (2008) report MPH-induced disruptions of volitional inhibition using 5-CSRTT at a dose of 5 mg/kg. Ferguson, Paule, Cada, Fogle, Gray and Berry (2007) report disrupted inhibition with MPH in DRL and LHT. To interpret these seemingly contradictory findings, it is important to consider the effect that MPH has on motivational and motoric responses, apart from inhibition. Heyman (1992) showed that at low doses (1.0 and 2.0 mg/kg), MPH increases response rates by increasing motivation to engage in the task. At a high dose (8 mg/kg) MPH affects motoric behavior by increasing maximal response rate.

Relative to these tests, there were two reasons to expect that the methods and analytical techniques presented in this paper would be more sensitive to changes in volitional inhibition. First, inferences were based on a more efficient use of performance data, examining the distribution of intervals produced and not just summary performance indices. This approach allowed further constraint on the Temporal Regulation model of volitional inhibition (Sanabria and Killeen, 2008). Second, performance of rats that were required to inhibit premature responses was compared with the performance of rats in a similar task, but that did not have a waiting requirement. This comparison differentiated effects on volitional inhibition from changes in activity and arousal, which were likely confounded in prior research.

Method

Subjects

Forty-eight male Wistar rats (Charles River, Laboratories, Hollister CA) served as subjects. Rats arrived to the laboratory on post-natal day (PND) 24. Rats had free access to food daily, and were housed on a 12/12 hrs light-dark cycle (dawn at 6 am) in translucent polycarbonate cases (260 mm wide by 460 mm deep by 210 mm high) covered with Sanichip bedding and wire lids. Other specific housing conditions (rats per cage, objects in cage) were part of the experimental manipulation and are explained in the procedure section.

Apparatus

Experimental sessions were conducted in ten MED Associates® modular test chambers (4 boxes were 305 mm long, 241 mm wide, and 210 mm high; 6 boxes were 305 mm long, 241 mm wide, and 292 mm high), each enclosed in a sound- and light-attenuating box equipped with a ventilating fan. The floor consisted of thin metal bars above a catch pan. The front and rear walls and the ceiling of the experimental chambers were made of clear plastic, with the front wall hinged and functioning as a door to the chamber. A square aperture (51 mm sides) located 15 mm above the floor and centered on an aluminum side panel on the right side of the chamber provided access to a receptacle (ENV-200-R2M) for 45 mg sugar flavored pellets (Dustless Precision pellets, product # F0042, Bio-Serv, Frenchtown, NJ). Each activation of a dispenser (ENV-203) delivered a single pellet. A retractable lever (ENV-112CM) was located on each side of the

food hopper. Only the lever closer to the chamber door, to the right of the hopper, was operative; the other lever remained retracted throughout the experiment. The center of the lever was 80 mm from the center of the food hopper, and 21 mm from the floor. Lever presses were recorded when a force of approximately 0.15 N was applied to the end of the lever. Three-color light stimuli (ENV 222M) were located directly above each retractable lever and could be illuminated yellow, green, and red. The ventilation fan mounted on the sound-attenuating chamber provided masking noise of approximately 60 dB. The test chambers could be dimly illuminated by a houselight located behind the left wall of the chamber. Experimental events were arranged via a Med-PC® interface connected to a PC controlled by Med-PC IV® software.

Procedure

Housing. Rats were separated into two different groups beginning post-natal day (PND) 25. Half of the rats were assigned to a mildly enriched environment (Group Paired) and half to an isolated environment (Group Single). The enriched environment involved housing 2 rats per cage with a PVC pipe and a crumpled up sheet of paper towel. The PVC pipe was moved and a new paper towel was provided at least once a week, when cages were changed for cleaning. The isolated environment involved housing a single rat per cage with no objects.

Experimental history. All rats were exposed to an autoshaping procedure from PND 35 to PND 86 using the same apparatus described in this report. The autoshaping procedure consisted of pairing either a 3 kHz tone or a right-lever

insertion with the probabilistic delivery of a food pellet (p = .1). Experience with one conditioning treatment or the other was counterbalanced across experimental groups.

Training sessions. Training sessions were conducted once daily, 7 days per week for each rat, starting on PND 89. Sessions started with a 5-min habituation period, where levers were retracted and the chamber was dark. Insertion of the right lever and the illumination of the houselight signaled the beginning of experimental conditions. Each session ended after 75 min or after a rat obtained 40 food pellets, whichever happened first.

Assignment to experimental conditions. Table 1 summarizes the design of the experiment. Rats were randomly arranged in pairs. Each pair of rats was randomly assigned to a *response sequence* condition, Lever or Head. The response requirement for the Lever group was a lever press followed by a head entry, and for the head group it was a head entry followed by a head entry. Each rat in each pair was randomly assigned to a different *task* condition, Waiting (WTN) or Yoked-control (YKC). Rats in a pair could be in the same or in different housing conditions, but were always in the same response sequence condition, and always in different task conditions. Response sequence and task conditions are described below in detail.

Waiting (WTN) condition. Rats in this task condition were required to either press a lever (Group WTN Lever) or remove their heads from the food hopper (Group WTN Head) to start a clock. While the clock was running, the 3-

color light stimuli above both levers were illuminated and the houselight was turned off. A head entry into the food hopper stopped the clock and terminated the lights for half of a second. The duration of the clock running constituted the *inter-response time (IRT)*. If the IRT was longer than a programmed target time, it counted as a *correct sequence*. Each correct sequence was reinforced with a food pellet on a variable-interval (VI) schedule that ran throughout the experimental session. Incorrect sequences were followed by a 2 s blackout. Target times and VI requirements were progressively increased to 6 and 60 s, respectively, as described in the "Shaping procedure and terminal schedule" section.

It is important to note that, for Group WTN Lever, lever presses did not stop the clock. Thus, a rat in this group could start the clock with a lever press and continue lever pressing while the clock was running; repeated lever presses had no programmed consequences. This is a potentially significant difference between the lever-press-head entry sequence and the differential reinforcement of low rates (DRL) schedule, where each lever press restarts the clock. Rats in Group WTN Head experienced contingencies more similar to DRL, because each clock-starting head-exit involved a clock-stopping head-entry, and thus repeated head-exits were impossible. For this group, lever presses had no programmed consequences.

Yoked-control (YKC) condition. Rats in this task condition obtained reinforcers by completing the same response sequence as their WTN partners, lever-press-then-head-entry (Group YKC Lever) or head-exit-then-head-entry

(Group YKC Head), but without having to wait the target time. Every reinforcer delivered to the WTN partner set up reinforcement for the YKC partner, which could be collected by completing the corresponding response sequence, regardless of how fast it was completed. Thus, rates of reinforcement were near equal for WTN and YKC partners. YKC rats, however, occasionally collected fewer reinforcers because WTN rats sometimes set up multiple reinforcers faster than YKC rats completed a single response sequence.

Shaping procedure and terminal schedule. Initially, the target time and the VI requirement for WTN rats were set to 0.5 and 2 s, respectively. The target time increased with each reinforcer by 1.25% across sessions until reaching 6 s, where it remained constant. After reaching the 6-s target time, the VI requirement was increased to 9, 13, 19, 28, 42, and 60 s, in daily succession. The schedule of reinforcement of correct sequences was then fixed at VI 60 s (intervals were drawn from a 12-item Fleshler-Hoffman distribution; Fleshler & Hoffman, 1962) for a minimum of 15 days, until stable performance was attained.

Dependent Measures. Two variables were tracked daily: The mean number of sequences (correct and incorrect) completed by WTN and YKC rats, and the mean proportion of correct sequences completed by WTN rats. Ten experimental sessions were conducted after daily changes in each variable were deemed unsystematic. Data analysis was based on performance on these ten sessions. The main dependent measures were sequences per hour, proportion correct, and IRTs. Sequences per hour refer to the number of sequences

completed per hour, regardless of whether they were correct or incorrect. Proportion correct is the number of correct sequences divided by the total number of sequences.

MPH phase. Following the ten sessions used for data analysis (pre-MPH phase), daily experimental sessions continued. On Tuesdays and Fridays rats were injected with saline or methylphenidate hydrochloride (0.5, 2, or 8 mg/kg; Hawkins Pharmaceutical Group, Minneapolis, MN) 15 minutes before sessions. Two cycles of doses were conducted, with order of dose injected counterbalanced across groups following a Latin square design.

Statistical Analysis. For the pre-MPH phase of the experiment, sequences per hour and proportion correct were analyzed using a MANOVA with response sequence, housing and task as factors, and individual t-tests were used to test interaction effects. For the MPH phase, these same measures were analyzed using a MANOVA with response sequence, housing, task and drug as factors. The modeling procedure used for the distributions of IRTs is described in detail below.

Results – Pre-MPH

Figure 1 shows mean (±SEM) sequences per hour for each group of rats. The MANOVA revealed a significant interaction effect of response sequence (Lever vs. Head) and task (WTN vs. YKC) on sequence per hour ($F(1,7) = 14.4$, $p < 0.001$). Rats in the Head group completed sequences at a higher rate than those in the Lever group, but only if they did not have to wait (YKC condition, bottom panel) ($t(22) = 4.62$, $p < .001$).

Proportion of correct sequences is shown in Figure 2. This measure was sensitive to the interaction between task and housing condition ($F(1,7) = 4.6$, $p = .038$) and to the interaction between task and response sequence ($F(1,7) = 39.5$, $p < .001$). Figure 2 shows that when IRTs greater than 6 s were reinforced, Single rats and rats completing lever-head sequences produced a larger proportion of intervals above this threshold than Paired rats ($t(10) = -2.94$, $p < .05$) and rats completing head-head sequences ($t(10) = -2.27$, $p < .05$). Proportion correct for YKC animals is shown in the bottom. Although these animals did not actually make “correct” sequences because they were not required to wait, the measures are shown for comparison. For the YKC animals, the proportion of sequences that took more than 6 s to complete hovered at just about 4% across conditions, and there were no differences between housing or response sequence conditions.

Although sequences per hour and the proportion of correct sequences provide a global picture of the performance of rats across experimental groups, these measures neglect more subtle differences in the distribution of IRTs. Examining these distributions may reveal with more precision the sources of

variability in performance. The assessment methods reported below allow deriving timing parameters from the distribution of IRTs. Inferences on the mechanisms underlying waiting behavior may be drawn based on the Temporal Regulation model of volitional inhibition (Sanabria and Killeen, 2008) and on well known properties of timing performance (McGill and Gibbon, 1965; Killeen and Fetterman, 1988; Machado, 1997).

Model of Performance in a Volitional Inhibition Task

Clocked Bernoulli Modules. Prior research has shown that intervals between responses in both waiting and non-waiting conditions can be described by configurations of *clocked Bernoulli modules* (CBMs; Killeen, Hall, Reilly and Kettle, 2002; Sanabria and Killeen, 2008). A Bernoulli process is a series of trials that can have one of two outcomes, success or failure, which occur with probabilities π and $1 - \pi$. A CBM is a Bernoulli process with a specified inter-trial interval τ. A CBM may be illustrated by a flipping a coin every τ seconds; the coin has a success probability π; every success adds to a counter; when the count *n* exceeds criterion *N*, the process terminates (Figure 3). The mean time between consecutive successes is $c = \tau/\pi$; the mean duration between the beginning ("START") and the end ("STOP") of the process is *Nc*. When CBMs are applied to modeling behavior, IRTs are modeled as START-STOP intervals. To illustrate these computations and how they are applied to IRT modeling, consider an example in which the mean time between flips is 1 s and the probability of success is .5. In this example the mean time between consecutive successes is 1 s / .5 = 2 s. If a response were emitted after the first success, IRTs would be geometrically distributed with mean 1×2 s = 2 s. If a response were emitted after 3 successes, IRTs would be Erlang-distributed with mean 3×2 s = 6 s. Because the CBM is assumed to run very fast with both τ and π approaching zero, the geometric and Erlang distributions are pushed to their continuous limits, the exponential and gamma, respectively.

Substantial research (Brackney, Cheung, Neisewander & Sanabria, in press; Shull, Gaynor and Grimes, 2001; Shull & Grimes, 2003; Shull, Grimes & Bennett, 2004) suggests that the distribution of IRTs when reinforcement is not contingent on the time between responses is a mixture of two random distributions, one of short IRTs that are characteristic of subjects engaged in the reinforced task, and another of long IRTs that are characteristic of intervals between task engagements. The random processes that yield these distributions may be described as a mixture of 2 CBMs, each with different parameters τ and π, but both with $N = 1$ (Killeen et al, 2002). This is akin to choosing between two coins of different bias and then flipping it until a success is obtained. We hypothesized that this model would describe IRTs produced in the YKC task, because no particular IRT was differentially reinforced in this task.

Sanabria and Killeen (2008) suggested that the distribution of differentially reinforced IRTs could also be described as a mixture of 2 CBMs. One CBM outputs relatively short intervals of random duration, such that $N = 1$, generating what is often called the "DRL burst" (Richards, Sabol and Seiden, 1993), a rapid repetition of the instrumental response. The other CBM outputs IRTs according to the reinforcement contingency by using a criterion $N > 1$. We hypothesized that this mixture model would describe IRTs in the WTN Head group, with response bursts expressed as rapid head-exit-entry sequences. We also hypothesized that the CBM with $N > 1$ would describe the majority of IRTs in the WTN Lever group, because response bursts (CBM with $N = 1$) would be expressed as iterated lever presses.

Figure 4 shows how performance during a trial may be represented as a series of interlocking CBMs. Both CBMs in the YKC group are expected to operate with N close to or equal to 1, yielding two exponential distributions. Parameters p and $1 - p$ describe the proportion of IRTs that correspond to each exponential distribution. In the WTN group, CBM 1 is expected to have $N > 1$, yielding the gamma distribution of IRTs, and CBM 2 is expected to have N close to 1. In this case, p describes the proportion of inter-response times that are gamma distributed; the remaining IRTs are exponentially distributed.

Performance as a mixture of probability distributions. Because IRTs in the YKC task are hypothesized to be outputted by 2 CBMs with $N = 1$, this distribution may be characterized by a mixture of two exponential distributions:

$$I(t) = p\left(1 - e^{-(t-\delta)/E_1}\right) + (1-p)\left(1 - e^{-(t-\delta)/E_2}\right). \qquad 0 < \delta < t,\ E_1 < E_2 \quad (1)$$

$I(t)$ is the probability that a non-waiting interval will be shorter than t; δ represents the shortest interval that can be produced (e.g., the time it takes a rat to move from the lever to the hopper). This parameter was estimated using the shortest IRT that the rat produced. The proportion of short IRTs is denoted by p, and $1 - p$ is the proportion of the longer IRTs. E_1 and E_2 are the rate parameters of the exponential processes.

Similarly, the distribution of IRTs in the WTN group may be expressed as a mixture of two distributions: a gamma ($N > 1$) and an exponential ($N = 1$) distribution,

$$W(t) = p\ \gamma\left(N, c\ \right) + \left(1 - p\ \right)\left(1 - e^{-(t-\delta)/E_1}\right). \quad (2)$$

$W(t)$ is the probability that an IRT will be shorter than t; $\gamma(N, c)$ is a gamma distribution with shape parameter N and scale parameter c. Parameter p is the proportion of gamma-distributed IRTs, and is indicative of active engagement in "waiting" behavior. The mean IRT when the animal is engaged in waiting is expected to be close to the target time. Because response bursts in the WTN Lever condition are expected to be expressed in repetitive lever-presses, and not in repetitive lever-press-head-entry sequences, p is expected to be close to 1 in this condition.

Equations 1 and 2 are called *global models*. These two global models were compared along with two simpler versions of the models, the single exponential and the single gamma. The purpose of this comparison was to select the global model of IRTs that would be used for parameter estimation and inferential statistical analysis. The first step in our analysis was to determine which global model was more appropriate for each animal's IRT distribution. The second step consisted of determining the likelihood that model parameters N and c varied between Paired and Single rats, since these parameters were the primary indices used to measure inhibition and timing. The null hypothesis that parameters did not vary between Paired and Single rats was formulated as a model; the alternative hypothesis that parameters varied between Paired and Single rats was formulated as another model. To distinguish them from the global models, we call these models *comparison models*.

Selection of Global Models. Four global models, shown in Table 2, were compared to determine which best described IRT distributions. Equations 1 and 2

were compared along with the single-gamma and the single-exponential distributions. Global models were selected for each group using the corrected Akaike Information Criterion (AICc), (Anderson, 2008; Akaike, 1974). Each global model was fit to the data of each individual rat using the Maximum Likelihood Estimate (MLE) method. AICc balanced the goodness of fit of each model (its log-likelihood) against its number of free parameters; low AICc scores are indicative of high goodness of fit with few free parameters. Because absolute AICc scores are meaningless, they were re-scaled by subtracting from each AICc score the minimum AICc score across models under comparison; i.e., $\Delta_i = AICc_i - AICc_{MIN}$, where *i* indices the models under comparison (Burnham and Anderson, 2002). Thus, for the global model with the lowest AICc, $\Delta_i = 0$. A global model with $\Delta_i < 10$ was considered viable; it was selected for further analysis only if it had fewer free parameters than the global model with $\Delta_i = 0$, otherwise the latter was selected.

Results – Models of Performance

Global Models. Of the 4 global models (Table 2), the AICc analysis favored the Gamma + Exp model in all cases (Table 3); therefore, this model was selected for subsequent analysis. Figure 5 shows fits of the Gamma + Exp model to the mean distribution of inter-response times. Curve fits show that this model provided an adequate description of the distributions. The curves through the data are fitted traces of the Gamma + Exp model.

The top of Figure 5 shows the WTN groups. Visible differences are apparent between the Head (left) and Lever (right) groups and between Paired (filled symbols, solid lines) and Single (unfilled symbols, dashed lines) rats. The most notable difference between Lever and Head was the high proportion of short IRTs in the Head group, a pattern not observed in the Lever group. This can be seen on the top-left panel of Figure 5 as the high limb in the leftmost part of the distribution.

Across housing groups, in both WTN Head and WTN Lever, the distribution for Single rats was shifted to the right relative to Paired rats, indicative of longer waiting times. Inter-response times were more dispersed in the Single than in the Paired group.

In the YKC group (bottom of Figure 5), very few IRTs were longer than 5 s. There was a difference between the Head and Lever group on the leftmost side of the distribution. For the Lever group, the probability of IRTs between 0 and .2 was equal to 0 (first point on the graph), whereas the Head group produced many IRTs in this range. Figure 5 does not reveal any systematic differences between housing conditions in the YKC group.

Parameter Estimation and Inferential Analysis. Parameters of the selected global models were estimated. Then, it was determined whether or not differences between groups justified the assignment of different parameter values across groups. From the assignment of different parameter values it was inferred that the component of the process indexed by the parameter was sensitive to the experimental manipulation. For instance, if a comparison between waiting

intervals in Paired and Single rats justified a smaller *N* for Paired rats, then it would be inferred that pair-housing shortened the criterial count in the volitional inhibition task.

The Gamma + Exp model served as the Global model used for the Comparison models. Four models were compared: one in which the mean of parameters *N* and *c* were held constant between rearing groups (Model *N* and *c* Same), one in which only the mean of parameter *N* was held constant (Model *N* Same), one in which only the mean of parameter *c* was held constant (Model *c* Same), and one in which the mean of both parameters varied between groups (Model *N* and *c* Vary). Δ_i was then used to select the best model between these four for each condition. Selection of one of the constrained models (Model *N* and *c* same, Model *N* Same, or Model *c* Same) would suggest that the mean parameter or parameters did not substantially differ between groups; selection of the unconstrained model would suggest the opposite.

Two indices, one of volitional inhibition (θ) and one of timing inaccuracy (*w*), were drawn from the estimates of *N* and *c* in WTN rats (Sanabria & Killeen, 2008). Inhibition refers to a bias for stopping the clock, either prematurely or conservatively, and timing inaccuracy is as a measure of discrimination of elapsed time. Index θ was computed as the mean waiting interval (*Nc*) divided by the target time (6 s); it provided an estimate of the threshold for action, with lower values indicating lower volitional inhibition. Index *w*, the Weber fraction (Gescheider, 1997), was computed as the standard deviation of waiting intervals

divided by the mean waiting interval (w = sqrt(1 / N)); lower values of w were indicative of poor temporal acumen.

Parameter Estimation. Table 4 shows the ΔAICc for each comparison model for each training group. The AICc analysis favored the comparison model that allowed N and c to vary between WTN Single and WTN Paired rats, and the model that allowed only N to vary between YKC Single and YKC Paired rats.

Table 5 shows that the criterial count (N) was visibly higher for Lever than for Head rats and at least twice as high for WTN than for YKC. The model selection procedure favored higher estimates of N for Paired than for Single rats. Although the criterial count for the YKC Paired group varied in the same direction, the estimates of N were much smaller, hovering around 1 in the YKC Head group. The time between counts, (c), was visibly higher for Head than for Lever rats and higher for YKC than for WTN rats. For WTN Single, the estimate of c that was practically double that of WTN Paired rats, but this estimate did not vary across housing conditions in the YKC group.

Figure 6 shows the derived indices of inhibition (response threshold or θ) and timing imprecision (Weber fraction or w). The left panel shows estimates for the Head group; the right panel shows estimates for the Lever group. Response thresholds (θ) indicate that Paired rats waited on average 1% longer than the target time, whereas Single rats waited 22% longer. There was no apparent difference in response inhibition between Head and Lever groups. The bottom panel shows estimates of w. The dispersion of IRTs was relatively smaller for

Paired rats in comparison to Single rats, as indexed by lower estimates of *w*.

Lever rats also appeared to have less dispersion than Head rats.

Discussion – Pre-MPH Phase

The pre-MPH phase of the experiment revealed that response sequence requirements (Lever vs. Head) and housing conditions (Paired vs. Single) produce differences in operant performance, and these differences depend on whether or not reinforcement is dependent on the time between responses.

Response Sequence. In the WTN group, there were no differences in sequences completed per hour, regardless of response sequence conditions. However, the YKC group (Figure 1, bottom) was sensitive to response sequence requirements. The observed effect may be due to a longer minimum duration required for responses initiated by a lever-press relative to those initiated by a head-exit. This difference in minimum IRT can be seen in Figure 5. Whereas the Head rats produced a high proportion of IRTs between 0 and 0.2 s, Lever rats did not produce such short intervals, as these rats could not physically complete a sequence in less than 0.2 s. The difference becomes intuitive if one considers the position of the rat relative to the food hopper at the beginning of a Lever sequence and at the beginning of a Head sequence. These differences did not occur in the WTN group because the 6-s target time required to earn reinforcers was well above the minimum IRT that the rat could produce.

The response sequence requirement affected the proportion of correct sequences produced in the WTN task, with the Lever group making more correct sequences. If this served as an index of inhibition, it would suggest that rats in the Lever group were more inhibited. There were no differences in the proportion of correct sequences between Lever and Head in the YKC groups. These animals

were not required to wait 6 s, so the proportion of correct sequences was very low. The modeling procedure was carried out in order to draw inferences on inhibition and timing on the basis of the entire distribution of IRTs. The Temporal Regulation model of response inhibition was robust in describing IRTs in both the Lever and Head procedural variations. In the WTN Head group, a large proportion of closely spaced, exponentially distributed IRTs were observed, in addition to the longer waiting intervals with a mean close to the target time. These quick, iterative responses are commonly referred to as the DRL burst (Rilling & Kramer, 1972). The FMI task was effective in eliminating the response burst component typically seen in waiting tasks. In this task, the mean waiting intervals were still close to the target time, but the exponentially distributed IRTs were spaced widely apart.

The higher proportion of correct sequences in the WTN group likely occurred because these animals did not produce as many quick, iterative responses. However, a lack of bursting does not necessarily mean that separating the terminal response from the initial response in the Lever group results in higher volitional inhibition. Because iterative responses in waiting tasks appear to be part of a motoric component of behavior separate from waiting, these responses should not be included when inferring levels of inhibition. The Temporal Regulation model separately captures IRTs that are independently distributed from those that are indicative of active engagement in waiting behavior. The measure of inhibition in this model, θ, only includes those waiting intervals. Timing accuracy was also inferred from the Temporal Regulation model as a measure of the

dispersion around the mean waiting interval. The observed better performance of rats in the Lever condition compared to the Head condition suggests that separating the initial response from the terminal response improves timing. In the typical waiting paradigm, two consecutive initial responses cannot be made before the criterion time has elapsed without restarting the clock. This was evident in the Head WTN task, where an intervening head entry resulted in a head exit that restarted the timer. Conversely, in the Lever sequence, the initial response of lever pressing could be performed repeatedly with no programmed consequences of restarting the clock. Repetitive lever pressing may have helped these animals discriminate time more accurately, by engaging in a task to move through behavioral states (Killeen & Fetteerman, 1988).

Housing. Housing conditions also substantially altered behavior in the present experiment. Although sequences per hour were similar regardless of housing, the proportion of correct sequences was significantly higher for Single rats in both the Head and Lever conditions.

Visual inspection of Figure 5 shows a horizontal displacement to the right in the waiting distributions of the Single animals; these animals produced a higher proportion of longer IRTs. Differences in response threshold θ, also supported the notion that Single rats waited substantially longer than Paired rats. This finding is consistent with some other studies showing decreased impulsivity in rats reared in isolation in a delay discounting task (Hellemans et al., 2005), and in a 5 CSRTT (Dalley et. Al), although these results were a non-significant trend. One potential explanation for the longer waiting intervals could be that Single animals are less

motivated, abandoning the task more frequently and resulting in longer waiting intervals. If this were the case, it would be expected that the median time to initiate the sequence would be higher for Single rats than for Paired rats (Wise,). However, inspection of the median latencies did not reveal any such effect (2.95 vs 4.1 for Single and Paired Head, and 4.1 vs 6.8 for Single and Paired Lever rats, respectively). In fact, it appears the Single rats actually had shorter latencies, indicating that, if anything, they were more motivated to begin the sequence.

The apparent reduced motivation and inhibition in Paired rats may be due to an elevated acute stress response to the experimental procedure in these rats. During the experimental session, the Paired animals were removed from their littermate to be placed into the operant chamber. The removal from the littermate may have elicited a stress response in these animals (Ferland & Schrader, 2010, Burman & Owen, 2008), possibly resulting in the reduced motivation and inhibition.

The longer waiting in Single animals was unlikely to be due to lower levels of activity, because yoked interval distributions were unaffected by housing conditions (Figure 5). Instead, the stress response induced by separation in Paired animals may have resulted in higher levels of arousal. Arousal is often linked in timing tasks with the speed of the pacemaker (Killeen & Fetterman, 1988), which is represented here by *c*, the time between counts in the hypothetical CBM 1 (Figure 4). Low arousal would imply high estimates of *c*, observed in group Single WTN, and high arousal by low estimates of *c*, observed in group Paired WTN. When waiting was not required (i.e. in the YKC animals), *c* was constant

between Paired and Single. It thus appears that reduced inhibition in Paired rats was facilitated by an increase in arousal induced by littermate separation stress.

Although other studies have suggested increased impulsivity in isolated rats (Perry et Al., 2008; Ough et Al., 1972), procedural details may explain the conflicted findings. The rats in the present experiment were run daily in operant chambers, and therefore they were handled daily. This is a necessity for obtaining stable data in most operant tasks. Holson, Scallet, Ali & Turner (1991) demonstrated that daily handling of isolated rodents decreased the "isolation stress" syndrome and brought these animals to the same activity level as their enriched counterparts, whether the social animals were handled or not. The daily handling in combination with the daily separation stress in the Paired rats may help to elucidate the present results.

Results—Methylphenidate Administration

Statistical Analysis. For the MPH phase of the experiment, a MANOVA was conducted to reveal the main effects of MPH and its interaction effects with housing, required response sequence, waiting task, and methylphenidate on each of the dependent measures from baseline. For the basic indices (sequences per hour and proportion correct), performance in no-injection sessions (those conducted a day before every injection session) was averaged with performance under saline injections and used as the baseline measure.

Most effects of housing and response sequence conditions observed during baseline were replicated. Figure 7 shows the mean (±SEM) values of sequences per hour. Head rats continued to complete sequences at a higher rate than Lever rats, particularly if waiting was not required ($F(1, 31) = 22.7$, $p < .001$) ($t(22) = 4.21$, $p < .001$). However, no significant effect of MPH on number of sequences completed per hour was observed.

Figure 8 shows the mean (±SEM) value of the proportion of correct sequences. Similar to baseline, Single and Lever rats were more likely to produce waiting intervals longer than 6 s than their Paired and Head counterparts (respectively, $F(1, 31) = 8.7$, $p = .004$; $F(1, 31) = 34.7$, $p < .001$) ($t(10) = -2.05$, $p = .06$); ($t(10) = -2.71$, $p < .05$), respectively. MPH had no effect on proportion of correct sequences.

Estimates of Temporal Regulation Parameters under MPH. Since the Gamma +Exp model best described IRTs in the pre-MPH phase of the

experiment, this model was used to estimate parameters at different doses of MPH. MLE and AIC were once again used select between comparison models. The models were tested in individual animals, and the best model for each group was determined. Four comparison models were tested: One in which both parameters *N* and *c* were constant across doses for every rat (Model *N* and *c* Same), one in which only *N* was constant across doses for every rat (Model *N* Same) one in which only *c* was constant across doses for every rat (Model *c* Same), and one in which all parameters varied for every rat (Model *N* and *c* Vary). For example, to test whether the parameter *N* was constant across doses (Model *N* Same), a single estimate of *N* was used for every MPH dose to fit the model to the data. This model has four fewer parameters than Model *N* and *c* Vary, because four estimates of *N* are constrained and do not vary. Then, the AICc value for Model *N* same was compared to the AICc values of the other three models. The model with the lowest $\Delta_{i,}$ or a Δ_i less than 10 with the fewest free parameters was chosen. To determine differences in parameters from baseline, 95% confidence intervals were calculated, indicating whether changes in parameters were different from zero.

Temporal Regulation Parameters under MPH. Table 6 shows the $\Delta_{i,}$ values for each group. For every group except Paired Head YKC, the best model was one in which both *N* and *c* varied across MPH doses. In group Paired Head YKC, the best model was one in which *N* was held constant across doses. Table 7 shows the mean (±SEM) parameter estimates of *N* and *c* for each group across

MPH doses. Values marked with an asterisk indicate that the value was significantly different from baseline, based on 95% confidence intervals.

As shown in Table 7, for both Paired WTN groups, MPH caused a significant decrease in *N* and increase in *c* from baseline at the highest dose (both groups) and at the 2 mg/kg dose (Paired WTN Lever). In the Single WTN Lever group, Saline, 0.5, and 8 mg/kg resulted in a decrease in *N*, and 8 mg/kg resulted in an increase in *c*. Some doses of MPH also changed *N* and *c* for Single YKC groups. In group Single YKC Head, *N* increased and *c* decreased at doses of 0.5 and 8 mg/kg. In group Single YKC Lever, *N* decreased and *c* increased after the Saline injection, and *N* also increased at 0.5 mg/kg MPH.

Figure 9 shows changes in mean (±SEM) derived measures of volitional inhibition (θ̣ and timing inaccuracy (*w*), as a function of MPH dose for each experimental condition. The x-axis shows each of the four doses of MPH, and the y-axis shows the log proportion change from baseline of each parameter value for each group. The log proportion change is calculated by dividing the MPH dose by the baseline value, and taking the log base 2 of that number. A positive value indicates that the mean measure increased at that dose, and a negative value indicates that the mean measure decreased at that dose. These measures are shown separately for each housing and response sequence conditions, but only in the WTN task as the YKC animals were not required to wait. The Head groups are shown on the left, and the Lever groups are shown on the right. Paired and Single groups are shown together on the graphs as black and gray bars, respectively.

Asterisks indicate that 95% confidence intervals drawn around the mean measure did not envelop zero.

The most noticeable difference in θ occurs in the Paired Head group at an 8 mg/kg dose. Although there appears to be a visible increase in θ, the effect was not significantly different from zero due to the high inter-subject variability. Significant changes in the inhibition metric occurred in the Paired Lever group, with a slight, decrease after the saline injection, and in the Single Lever group, with a decrease at 2 mg/kg MPH.

The effects of MPH on timing are shown in the bottom of Figure 9. The 8 mg/kg dose significantly increased the measure of dispersion, *w*, in the Paired Head group. This effect was also consistently observed in the Lever group. In the Single Lever group, doses of Saline and 0.5 and 8 mg/kg of MPH increased *w*. Doses of 2 and 8 mg/kg increased *w* in the Paired Lever group.

Discussion MPH

Overall, the MPH phase of the experiment replicated effects from baseline. Single rats had a higher proportion of correct sequences in comparison to Paired rats. Lever rats had a higher proportion correct in comparison to Head rats, and the effects of MPH depended on response sequence, housing and task conditions.

Similar to baseline, Paired rats had lower estimates of *c* and higher estimates of *N* (Table 6), in comparison to Single rats. This again suggest increased arousal in Paired rats, as arousal is indexed by the time between counts (*c*), with shorter times indicating higher levels of arousal. The highest dose of MPH tended to decrease *N* and increase *c* in both housing groups. It thus appears that methylphenidate worked to reduce arousal while shortening the criterial count in the WTN groups. Essentially, MPH appears to make Paired animals more similar to Single animals, and enhances the observed effects in Single animals. It is thus interesting that the highest dose of MPH reduced arousal in the highly aroused Paired rats.

Although a positive dose-dependent increase in volitional inhibition (θ) was observed in WTN rats, it was not statistically significant. This may be due to the high variability between animals, as well as the opposing changes of parameters within animals (i.e. decreases in *N* and increases in *c*). Timing accuracy, however, was substantially compromised by MPH, most notably in

Lever rats. MPH induced disruptions in timing have been observed previously (Mayorga, Popke, Fogle & Paule, 2000).

General Discussion

TLDR; The results of the present experiment suggest that response sequence requirements alter iterative responses and timing, but do not appear to affect volitional inhibition. Housing rats in a mildly enriched environment reduced volitional inhibition yet improved timing compared to rats that were single housed in a barren environment. Methylphenidate showed a slight trend in increasing volitional inhibition, but this effect was not significant. Timing, however, was substantially disrupted by MPH. These inferences on volitional inhibition effects were well described by the Gamma+ Exp model.

Volitional inhibition is one variety of impulsivity that may serve as an index for disorders associated with impulse control. Given the negative consequences that are often associated with impulsive behaviors, it is important to have robust and accurate measures of this construct. Tasks such as CPT and the 5-CSRTT provide useful yet qualitative indices of discrimination and inhibition. A necessary next step in understanding this variety of impulsivity is the use of methodological techniques and quantitative analyses that are sensitive to critical yet subtle effects of independent variables on behavioral measures of inhibition. The DRL and FMI procedures employed in the present experiment serve as useful methodological techniques for this assessment. Since CPT, 5 CSRTT, DRL and FMI are all used as measures of inhibition, it will be useful to examine the extent to which measures of inhibition taken from all of these tasks correlate with one another.

The methodological techniques in the present procedure allowed for inferences to be drawn on the entire distribution of IRTs. The Gamma + Exp provided an excellent fit of the distributions of IRTs in both DRL and FMI procedures. This model allowed for the extraction of inhibitory threshold and timing precision, separate from iterative responses.

Response Sequence

Although the waiting tasks employed in the present work quantified inhibition, small variations in these procedures resulted in visibly obvious differences in performance. The separation of the terminal response from the initial response in the Lever procedure resulted in a higher proportion of correct responses. However, the isolation of waiting behavior from performance revealed that rats in the FMI task were not actually more inhibited, instead they did not produce the burst of rapid iterative responses that was observed in DRL. Since the burst of iterative responses in DRL are likely the result of motivational and motor responses separate from waiting behavior, these short IRT should not considered in the calculation of inhibition. DRL, similar to the Head task in the present procedure, is used in many drug studies to measure the effects of pharmacological agents on timing and inhibition behavior (Bardo, Cain & Bylica, 2006; Fowler, Pinkston & Vorontsova, 2009; Sable, Eubig, Powers, Wang & Schantz, 2009). However, if inferences of inhibition are drawn from this task without separating out iterative responses, it may result in inaccurate estimations of inhibition. The optimal method for inferring inhibition involves modeling the distributions of IRTs and calculating θ. Proportion correct is a common dependent variable used

to measure timing performance on the task. Estimating inhibition parameters is better than using performance indices, because the latter conflate iterative responses with waiting behavior. Again, these two can be empirically separated—to some extent—using FMI, but the best way to do it is to isolate estimates of inhibition based on models grounded in theory.

Housing Conditions

Housing conditions significantly altered both inhibition and timing: rats raised in a mildly enriched environment exhibited greater volitional inhibition than rats raised in an enriched environment, but they were less accurate at timing. These differences were robust across response sequence conditions. Paired and social (i.e. 3 or more rats per cage) housing is a common method for rearing animals ( ). Many studies involving timing and impulsivity use this method (Balcells-Olivero, Richards, Seiden, 1997; Richards, Sabol & Seiden, 1993; Bizot et. Al, 2007;) whereas in other studies, animals are reared in isolated conditions (Bizarro et. Al, 2004; Navarro et al, 2008). Different rearing environments may be an important component in differential effects between studies [how?]. Deficits in impulsivity and timing are observed in children with ADHD (). The present results suggest that environmental factors may play a key role in these deficits, although in an unexpected direction. One potential implication of this research may involve factors that reduce separation stress in children. Power (1992) demonstrated that the mere presence of an adult in the experimental room improved inhibition and attention in children with ADHD. In future studies

involving rearing environment, it is important to consider the effects of increased stress due to littermate separation on behavior.

MPH

Although MPH appeared to produce a slight increase in volitional inhibition, this was a non-significant trend. The increase in *c* and decrease in *N* appeared to make the behavior of paired rats more similar to Single rats. The increase in *c* suggests that MPH may reduce arousal in a timing task. To determine if MPH significantly affects inhibition, procedural variations may be necessary. For example, Bizo et. Al (2007) only found a reduction in impulsivity after MPH administration in juvenile Wistar rats, but not in adult Wistar, SHR, or WKY rats, at a 3 mg/kg dose. The use of adolescent rats may serve as a better model for determining changes in inhibition. It may also be worthwhile to evaluate the effects of these drugs on an individual basis, taken baseline levels of activity into account.

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Table 1. Group assignment.

Housing	Response Sequence	
	Head	Lever
Paired	WTN (N = 5), YKC (N = 7)	WTN (N = 7), YKC (N = 5)
Single	WTN (N = 7), YKC (N = 5)	WTN (N = 5), YKC (N = 7)

Note. WTN is Waiting task condition, and YKC is Yoked-Control condition. Each WTN rat was paired with a YKC rat in the same response sequence condition but not necessarily in the same housing condition.

Table 2: Global models and the corresponding parameters and equations.

Model Name	Free Parameters	Equation
Exp	1	$I(t) = p\left(1 - e^{-(t-\delta)/E_1}\right)$
Exp + Exp	3	$I(t) = p\left(1 - e^{-(t-\delta)/E_1}\right) + (1-p)\left(1 - e^{-(t-\delta)/E_2}\right)$
Gamma	2	$W(t) = p\ \gamma(N, c\ )$
Gamma + Gamma + Exp	4	$W(t) = p\ \gamma(N, c\ ) + (1-p\ )\left(1 - e^{-(t-\delta)/E_1}\right)$

Table 3: ΔAIC analysis

	ΔAIC (WTN)	ΔAIC (YKC)
Exp	35916.27	65771.42
Exp + Exp	25250.05	1795.84
Gamma	20664.02	48327.41
Gamma + Exp	0	0

Table 4: Values of Δ_i for each group either under the constraint that the mean of parameters *N* and *c* were equal across rearing groups (*N* and *c* Same), only *N* was equal (*N* Same), only *c* was equal (*c* Same), or in the absence of any constraint (*N* and *c* Vary).

	Head WTN	Head YKC	Lever WTN	Lever YKC
$\boldsymbol{\Delta_i}$ *N* and *c* Same	760.5	30.0	187.7	56.4
$\boldsymbol{\Delta_i}$ *N* Same	27.6	18.0	135.0	55.8
$\boldsymbol{\Delta_i}$ *c* Same	748.6	0.0	98.4	0.0
$\boldsymbol{\Delta_i}$ *N* and *c* Vary	0.0	0.7	0.0	1.7

Table 5. Parameter estimates of *N* and *c* across groups in the pre-MPH phase.

	Head				Lever			
	Paired WTN	Single WTN	Paired YKC	Single YKC	Paired WTN	Single WTN	Paired YKC	Single YKC
N	6.19±1.07	4.12±1.40	1.20±0.17	1.00±0.0	11.95±1.69	7.63±1.75	5.07±2.72	2.81±0.69
c(s)	1.15±0.29	2.94±0.92	6.79±0.81	6.79±0.60	0.57±0.07	1.32±0.48	2.77±1.78	2.77±1.35

Table 6. Δi values of the best model of MPH effects on parameter values.

	Head				Lever			
	Paired WTN	Single WTN	Paired YKC	Single YKC	Paired WTN	Single WTN	Paired YKC	Single YKC
Δi All Same	2939.85	1285.29	128.65	615.29	820.9	566.23	621.61	2951.71
Δi N Same	366.19	649.49	0	77.46	119.76	224.91	178.97	285.23
Δi c Same	1504.94	1036.41	118.91	608.4	153.54	438.77	184.08	1612.98
Δi All Vary	0	0	1.32	0	0	0	0	0

Table 7. Parameter estimates for each group under doses of Saline and 0.5, 2, and 8 mg/kg MPH.

		Head				Lever			
	MPH dose mg/kg	Paired WTN	Single WTN	Paired YKC	Single YKC	Paired WTN	Single WTN	Paired YKC	Single YKC
N	S	5.33±1.3	3.41±0.81	1.1±0.05	1.08±0.07	9.98±1.24	*4.83±1.51	4.4±1.39	*2.02±.58
	0.5	6.25±1.58	3.6±0.41	1.1±0.05	*1.15±0.08	9.74±1.4	*3.98±0.29	3.54±0.72	*1.67±0.24
	2	5.64±1.07	4.39±0.57	1.1±0.05	1.32±0.18	*6.35±0.99	5.57±0.6	4.58±1.63	2.11±0.35
	8	*2.37±1.11	4.4±1.2	1.1±0.05	*1.45±0.09	*6.85±0.94	*3.47±0.85	3.27±0.92	3.27±0.98
c	S	1.48±0.4	3.67±1.09	7.92±1.28	7.66±1.77	0.62±0.08	5.22±3.76	0.22±0.12	*4.65±2.03
	0.5	1.47±0.45	2.46±0.34	6.41±0.95	*5.46±0.75	0.69±0.11	1.61±0.24	0.21±0.11	3.59±1.05
	2	1.59±0.62	2.05±0.37	7.15±0.92	10±5.3	*1.11±0.16	1.2±0.2	0.23±0.13	1.3±0.61
	8	*98.02±84.95	4.03±1.97	8.0±1.3	*0.17±0.03	*1.15±0.23	*3.06±0.72	0.25±0.14	5.01±3.2

*Confidence interval crossed zero.

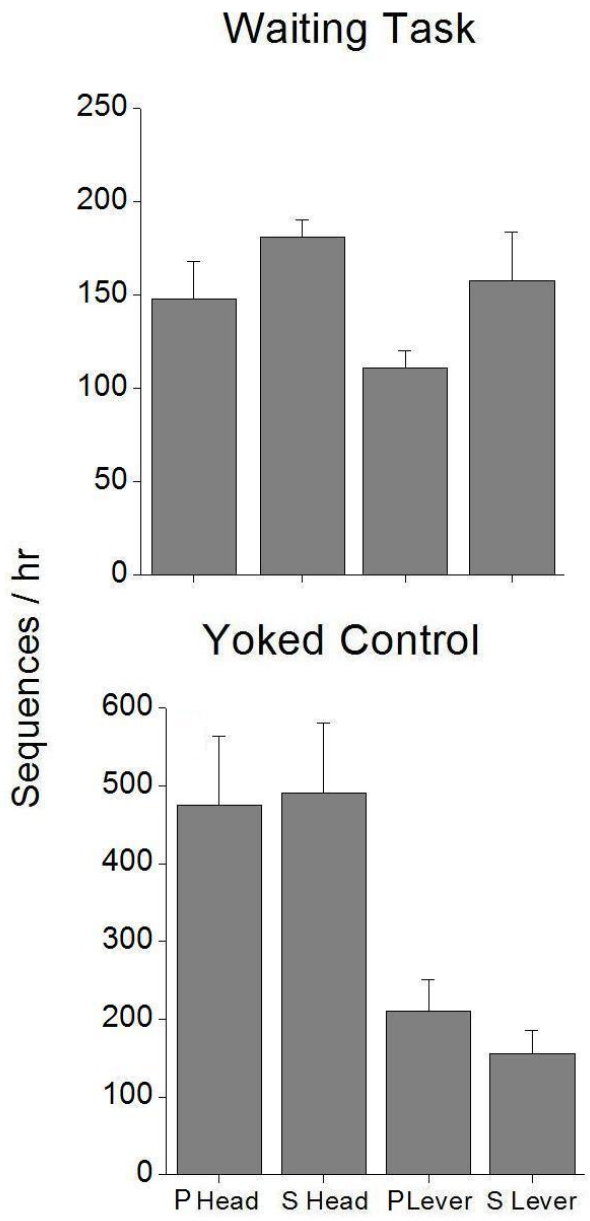

Figure 1. Response sequences completed per hour for WTN (top) and YKC (bottom) rats. Sequences per hour are compared across housing and response-sequence conditions.

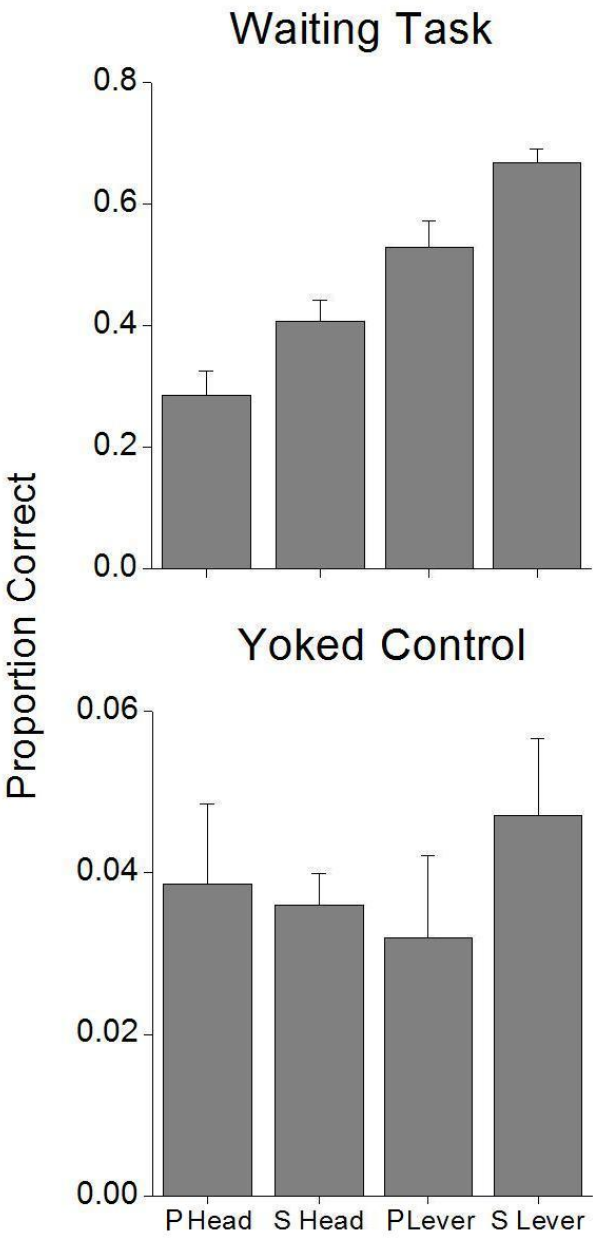

Figure 2. Proportion of correct responses completed by animals in the WTN task across housing and response sequence conditions.

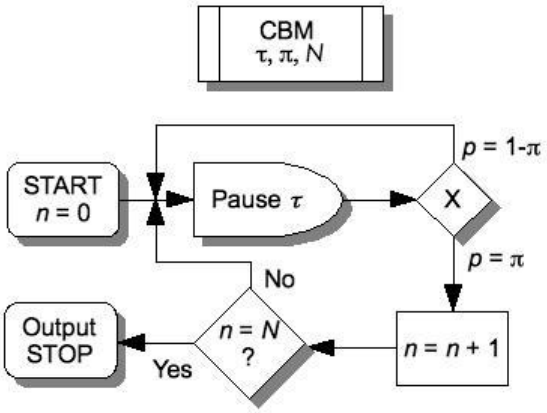

Figure 3: A clocked Bernoulli module (CBM). The time between coin flips is τ, the probability of incrementing a counter is π and the count criterion is *N*.

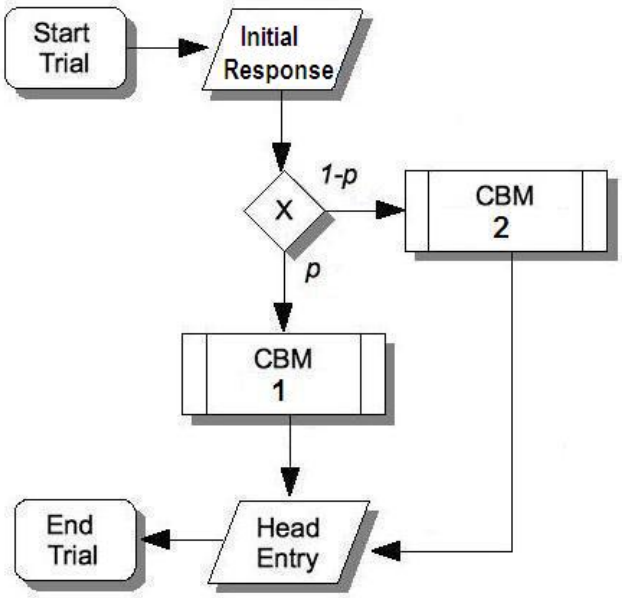

Figure 4: Series of interlocking CBMs representing performance during a trial.

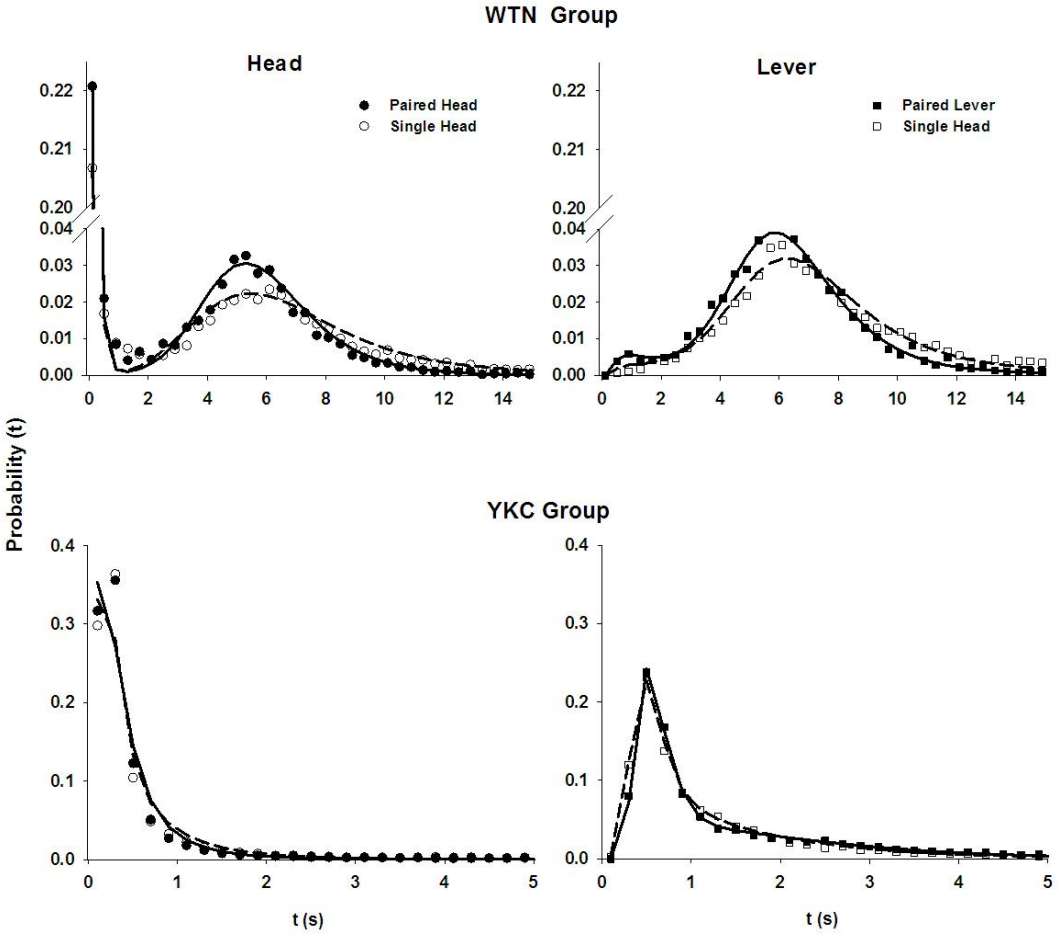

Figure 5. Probability density functions of IRTs fit with the Gamma + Exp model for each group.

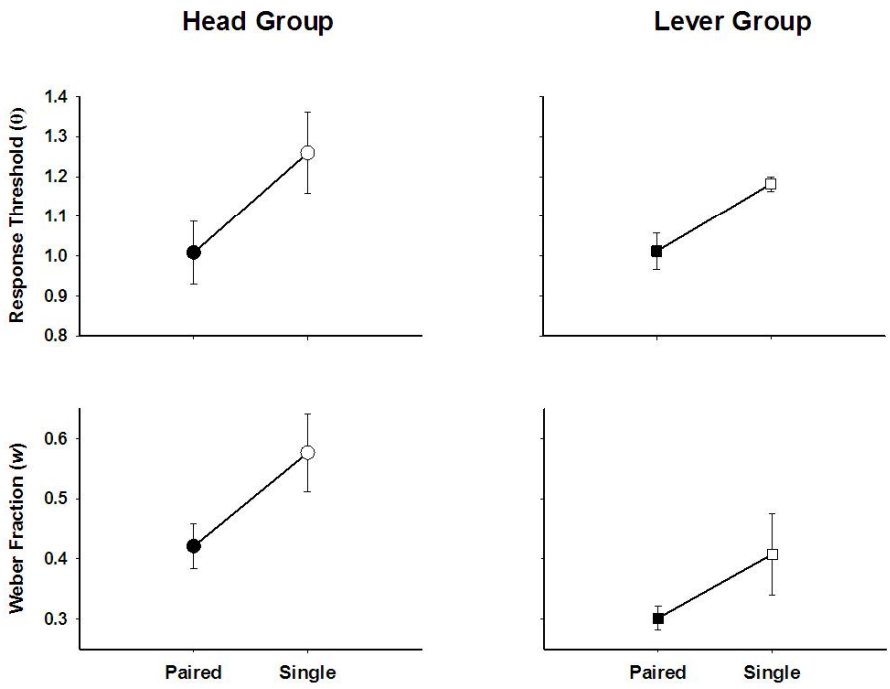

Figure 6: Estimates of θ and *w* across rearing groups in each response sequence conditions.

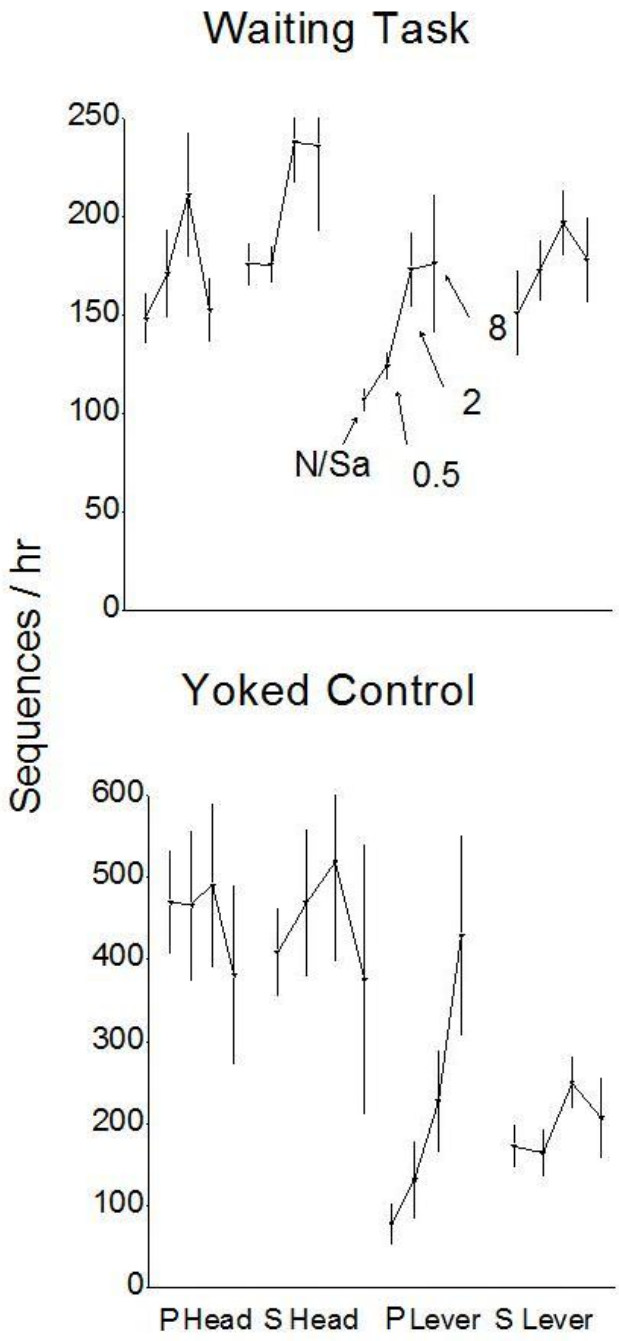

Figure 7. Sequences per hour completed by each group under the four doses of MPH.

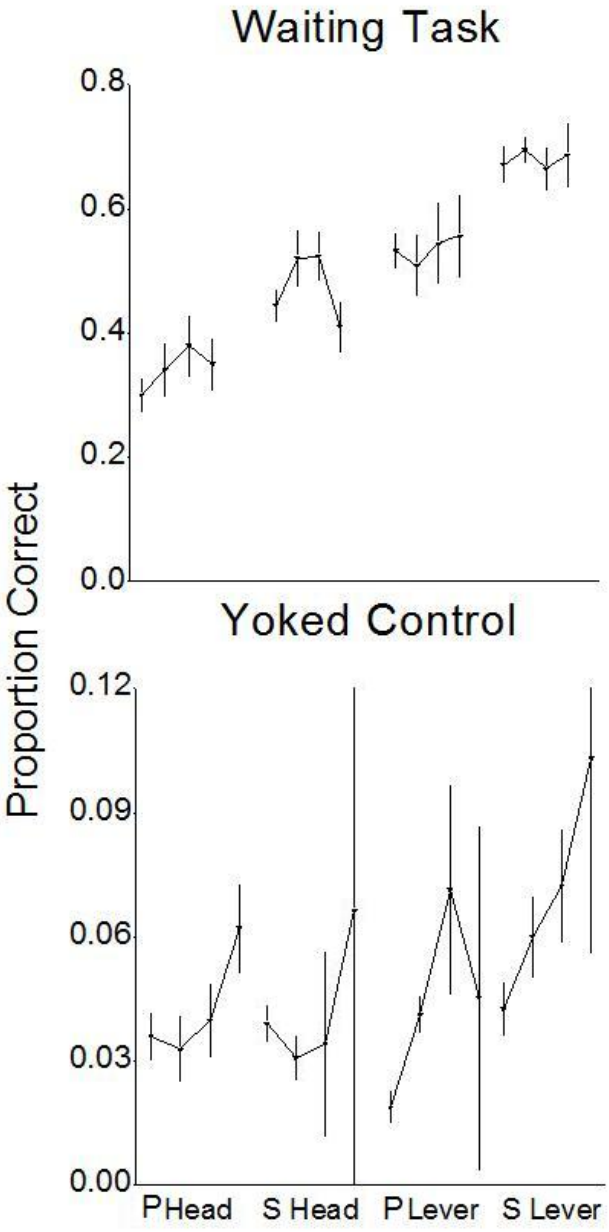

Figure 8. Proportion of correct sequences in each group under the four doses of MPH.

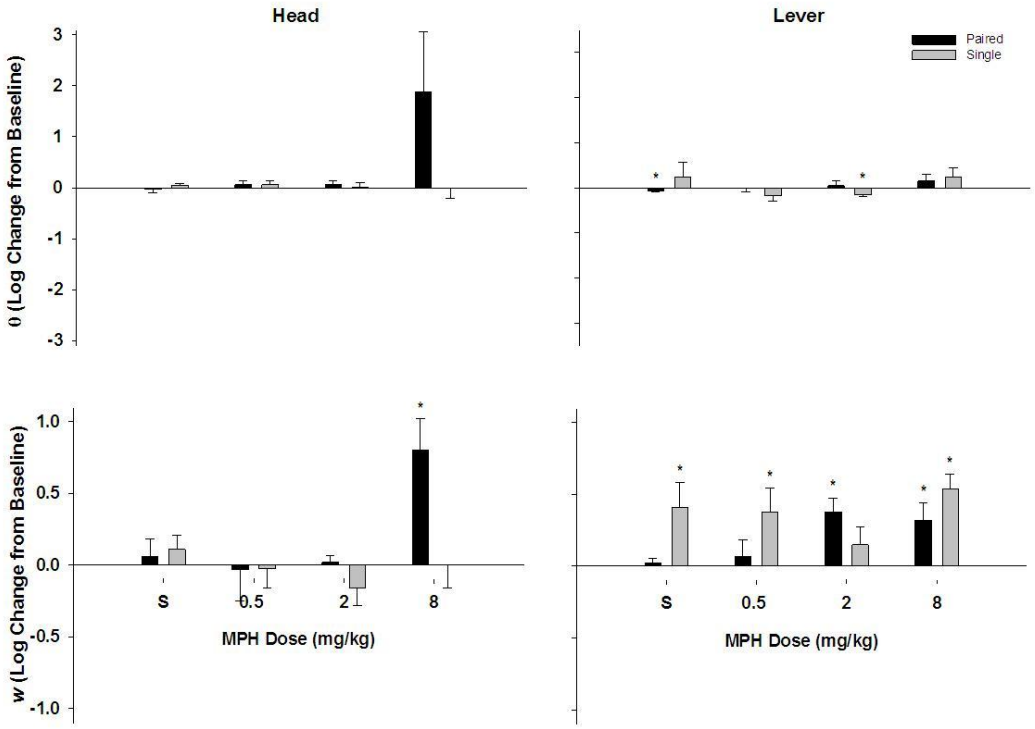

Figure 9. Log proportion changes in θ and *w* across each dose of MPH.