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Modulation of methylphenidate effects on wheel running and acoustic startle by acute food deprivation in commercially and selectively bred rats

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ABSTRACT

Behavioral effects of the same dose of the same drug can vary in degree and direction between and within individuals. The present study examines behavioral base rates, feeding status, and dispositional differences as sources of inter- and intra-individual heterogeneity in drug response. Modulation of the effects of methylphenidate (MPD) on wheel running and acoustic startle by food deprivation was examined in three experiments. Freely fed or food deprived Harlan Sprague–Dawley rats (running study) or rats selectively bred for low (LoS) and high (HiS) saccharin intake (running and startle studies) were given MPD (10 mg/kg) or saline before testing. Overall drug effects and predictors of drug response were assessed. MPD increased running and startle amplitude and disrupted prepulse inhibition; systematic variation among rats of these effects and their modulation by food deprivation was observed. Deprivation-induced running predicted MPD's effect in Harlan SD and LoS rats. Observation of this relationship among commercial rats suggests that acute deprivation sensitivity has utility as a noninvasive marker for drug responses. Its observation in rats selected on a taste phenotype with known correlates points to fruitful avenues of research on stimulant drugs' mechanisms, especially in dopaminergic pathways, and may be relevant to their clinical usage.

1. Introduction

Methylphenidate (MPD) is a psychostimulant that increases catecholaminergic transmission through multiple mechanisms including reduced reuptake and enhanced presynaptic sequestration and release (Volz et al., 2008). Consistent with activity in distributed dopamine and norepinephrine pathways, MPD affects attention, emotion, motor activity, sleep, and eating, with effects in humans ranging from therapeutic to adverse, even at the same dose (Challman and Lipsky, 2000; Sonuga-Barke et al., 2009; Stein and McGough, 2008). This diversity of effects, coupled with widespread use of MPD by adolescents and adults (Johnston et al., 2007, 2009), makes the study of individual differences in MPD responses an interesting and important endeavor. The heterogeneity that is a bane to pharmacotherapy presents tractable questions for basic behavioral research with laboratory animals.

The present study combined experimental and correlational methods to examine sources of inter- and intra-individual variance in the behavioral effects of MPD in rats. Two modulators of MPD effects were of interest. The first was reduced food intake. Food deprivation enhances the rewarding and locomotor-activating effects of stimulant drugs, due in part to increased striatal and mesolimbic dopamine activity (Bell et al., 1997; Carr, 2007; Merrer and Stephens, 2006; Simpson, 1974). Food deprivation also directly increases wheel running (Epling and Pierce, 1996). A key question here was whether acute food deprivation is sufficient to produce these indirect and direct effects and, if so, whether they co-vary.

The second modulator of interest was risk reactivity. This construct was not manipulated experimentally. Rather, strong a priori inferences about it were made by comparing selectively bred Occidental Low- (LoS) and High- (HiS) Saccharin-Consuming rats. LoS and HiS rats differ on the selection phenotype of saccharin intake and on self-administration of ethanol and cocaine (LoS < HiS; Carroll et al., 2008; Dess et al., 1998, 2005). LoS rats cope less well with glucoprivation than do HiS rats (VanderWeele et al., 2002), which we have linked conceptually to other behaviors via the construct of risk reactivity (Dess et al., 2007). Risk reactivity manifests as species-typical responses to threat such as open-field defecation, nocturnality, and acoustic startle (LoS > HiS; Dess and Minor, 1996; Dess et al., 2000, 2007).

This pattern of correlates of the saccharin phenotype suggests that food deprivation will enhance stimulant effects more among LoS rats. Several studies have documented differences in stimulant self-administration in LoS and HiS rats (Carroll et al., 2008) but only one has examined a direct behavioral effect of acute stimulant treatment: Carroll et al. (2007) observed equivalent cocaine-elicited locomotor activity in male LoS and HiS rats. However, the rats were freely fed. The present study therefore provides the first test of the hypothesis that stimulant effects will be differentially modulated by food deprivation in the two lines.

MPD activates pathways involved in reward, attention, anxiety, locomotion, and stereotypies (Askenasy et al., 2007; Zhu et al., 2010),

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and many behavioral measures are sensitive to more than one process. Mindful of the limitations of any single measure, we selected two measures that are sensitive to stimulant treatment and distinguish LoS from HiS rats. The first was wheel running. Running in a familiar wheel is a bidirectionally sensitive measure that minimizes the conflict between novelty-induced exploration and anxiety that complicates interpretation of behavior in arenas and mazes (Bevins and Peterson, 2004; Cain et al., 2005; Li et al., 2010; Marriott, 1968; Stead et al., 2006). In a prior study, a small line difference in wheel running (LoS > HiS) was dramatically increased by food deprivation, a difference replicable across three deprivation/recovery episodes (Dess et al., 2000). That study involved females in 23-h sessions, so the present study with males in 2-h sessions provides information as to the robustness of that difference. More importantly, the present study bears on the question of whether individual differences that predispose more running, during either free feeding or deprivation, might mediate drug responses. Evidence from laboratory rodents is mixed: Among commercially bred rats, stimulants increase running more among more active rats (Ferreira et al., 2006; Irwin et al., 1958); in contrast, stimulants reduce running in mice selectively bred for high wheel running while increasing it in controls (Rhodes and Garland, 2003). Whether species, selection on a relevant phenotype, or other factors account for the "paradoxical" effect unique to the latter study is unclear. Also, animals in those studies were freely fed, leaving open the question of individual differences in the impact of deprivation are related to drug responses.

The second measure was acoustic startle. Startle amplitude is a reliable correlate of the saccharin phenotype (LoS > HiS; Dess et al., 2000; Gonzales et al., 2008). Unlike running, startle is a defensive reflex, not locomotor behavior, and is not reinforcing. It is, however, sensitive to attention and emotional state (Cook et al., 1991; Davis et al., 2008; Swerdlow et al., 2007), and individual differences in startle and inhibition of startle by a prepulse stimulus have been linked to dopamine function (Feifel, 1999; Swerdlow et al., 2001). Comparing results for startle to results for running provides clues as to whether the mechanisms of line differences in MPD effects are shared by running and startle pathways.

Three experiments examined food deprivation and disposition as sources of variation in impacts of a single dose of MPD (10 mg/kg) on wheel running and startle. This MPD dose increases locomotor behavior robustly across measures, including wheel running (Askenasy et al., 2007; Marriott, 1968; Yang et al., 2010). It produces sensitization and tolerance less reliably than do, respectively, lower and higher doses (Askenasy et al., 2007) and is intermediate to the dose used in the two studies of MPD effects on startle in rats, which yielded typical stimulant effects (i.e. increased startle, impaired prepulse inhibition; Conti et al., 2006; Drolet et al., 2002). In Experiment 1, MPD's effect on running was measured in commercially bred rats (Harlan Sprague–Dawley) during free feeding and deprivation. A relatively stable baseline can be established for running, so each rat was tested with and without MPD in both feeding conditions. This design allowed examination of covariation at the individual level of MPD effects for evidence of rate dependency (Harris et al., 1978; Teicher et al., 2003). Experiment 2 replicated Experiment 1 with LoS and HiS rats. In Experiment 3, startle replaced running as the dependent measure. Startle habituates. Therefore, startle testing was limited to two sessions and line differences, but not individual differences among commercial rats or within lines, were examined.

2. Methods

2.1. Experiments 1 and 2

2.1.1. Rats

Male rats 65–90 days old were used. In Experiment 1, 13 Harlan Sprague–Dawley rats (Harlan Laboratories, San Diego, Inc) averaging 283 ± 5 g (mean ± SEM) were used. In Experiment 2, 20 HiS rats from eleven litters and 20 LoS rats from nine litters in Generations 32–33 began the study. One HiS rat was eliminated due to motor incoordination, and two LoS rats were eliminated due to procedural error, yielding final group sizes of 19 and 18. Bodyweight (412 ± 9 g) did not differ between lines. Rats were housed individually on a 12:12 h light:dark schedule (lights on at 0700). Purina 5001 Rodent Chow was available in home cages except as described below. Water was freely available in home cages.

2.1.2. Materials

Computerized running wheels (Model 86041, Lafayette Instruments, IN) were used. Methylphenidate (Sigma Aldrich, Inc; 10 mg/kg) or saline was injected i.p. at 1 ml/kg.

2.1.3. Procedure

Running sessions occurred between 0815 and 1245. Rats were transported in home cages from the vivarium to wheels in a separate room, then returned to the vivarium 2 h later. After daily 2-h training sessions (five in Exp. 1, five or six in Exp. 2), a series of four treatments differing with respect to drug and feeding status began (see Table 1). Two of the four running tests were preceded by a deprivation period (46 h with only 1 h of chow access at 23 h, after a 2-h running session). The running test occurred at the end of the deprivation period, and rats were returned to ad lib. feeding immediately afterwards. Rats were weighed and injected with MPD or saline 15 min before each test session.

Each rat was tested once in all four experimental conditions in one of four treatment orders. Orders were selected such that the two deprivation episodes (Saline/Deprived, MPD/Deprived) were either the first and third treatments or the second and fourth treatments, and the order of the two MPD conditions (MPD/Ad Lib., MPD/Deprived) was balanced. In the resulting Latin square, each treatment occurred once in each ordinal position, and the two MPD treatments occurred equally often with and without a prior deprivation episode (Saline/Deprived). Rats had 46 h of free feeding between deprivation and the next condition, 46 h between successive drug conditions, and one recovery running session between successive conditions. A single re-exposure to MPD at this dose using these temporal parameters should not cause appreciable sensitization or tolerance (Askenasy et al., 2007; Carroll et al., 2007; Wooters et al., 2006) and, in this

Table 1
Method summary for Experiments 1–3.

Experiments 1 and 2: Wheel running		
Conditions		
	Saline	MPD
Ad lib.	Saline/Ad lib.	MPD/Ad lib.
Deprived	Saline/Deprived	MPD/Deprived
Rats		Design
Experiment 1: Harlan Sprague–Dawley		Drug × Feeding (repeated measures)
Experiment 2: LoS, HiS		Drug × Feeding (repeated measures) × Line (between groups)
Experiment 3: Acoustic startle		
Conditions		
	Saline	MPD
Ad lib.	Saline/Ad lib.	MPD/Ad lib.
Deprived	Saline/Deprived	MPD/Deprived
Rats		Design
LoS, HiS		Drug (repeated measure) × Line × Feeding (between groups)

design, any such effects were not confounded with deprivation. In Experiment 2, lines and littermates (1–3 per litter) were balanced across treatment orders.

All procedures were approved by the Occidental College Institutional Animal Care and Use Committee, in accordance with the institution's federal Animal Welfare Assurance.

2.2. Experiment 3

2.2.1. Rats

Male HiS and LoS rats 65–90 days old from Generations 32–33 were maintained as described above. Twenty-four HiS rats from seven litters and 23 LoS rats from eight litters averaging 462 ± 9 g were used.

2.2.2. Materials

Acoustic startle testing was conducted in a startle chamber with a piezoelectric sensor and digital display of platform force in arbitrary units (SD Startle Pilot, San Diego Instruments, San Diego CA). It was housed in a sound-attenuating chamber with 60-dB ambient masking noise. The startle stimulus was a 40-ms, 95-dB white noise burst. The prepulse stimulus was a 40-ms, 65-dB white noise burst that preceded the startle stimulus by 100 ms. Methylphenidate (10 mg/kg) or saline was injected i.p. at 1 ml/kg. This dose disrupted prepulse inhibition in a preliminary study with ad lib. fed adult male LoS and HiS rats [$F(1,55) = 7.53$].

2.2.3. Procedure

Rats were assigned to a free-feeding or deprivation condition, with littermates balanced between conditions (1–2 littermates per condition). Each rat was tested once with MPD and once with saline. The saline and MPD tests were seven days apart, with drug treatment order balanced. The deprivation regime was the same as in Experiments 1 and 2.

Rats were briefly handled on the five days before startle testing began. Testing occurred between 1300 and 1500. Twenty minutes after injection of MPD or saline, a rat was placed in the startle chamber for a 3-min adaptation period, after which 30 trials (15 regular, 15 prepulse) occurred at 10 s intervals. Regular and prepulse trials were run in one of two quasi-random mirror-image orders. The chamber was swabbed between rats with 5% ammonium hydroxide.

3. Data analysis

3.1. Wheel running (Experiments 1 and 2)

Wheel running data (number of revolutions) were subjected to two kinds of analysis. Multivariate analyses of variance (MANOVA) were used to evaluate deprivation, drug, and, in Experiment 2, line effects. Whole-session data were examined in a MANOVA with feeding status, drug treatment, session time (successive 30-min intervals) and, in Experiment 2, line as variables (see Table 1). The highest order significant interactions were interpreted with pairwise contrasts, using Bonferroni-corrected p values.

Next, running was reanalyzed in a narrower time frame to permit comparison of MPD's effect on running to its effects on startle. In the startle study (Exp. 3), the injection–test interval was 5 min longer than in Experiments 1 and 2 (20 min, vs 15 min); startle trials began after a 3-min adaptation period and lasted 5 min. The comparable post-injection period in the running sessions, then, was Minutes 9–13. A MANOVA analyzed running during those minutes.

Pearson's r was used to evaluate relationships involving individual differences in drug response. Because MPD effects were significant in the first 30-min interval, those data were used. First, two correlations assessed the relationship between deprivation-induced hyperactivity and drug response in (a) the ad lib. condition and (b) the deprivation condition. *Deprivation-induced hyperactivity* (DIH) was defined as the difference between running after saline injection during deprivation vs free feeding. *Drug response* was defined as the difference between running in the MPD vs the saline condition; this value was calculated for each of the two feeding conditions. Then, Steiger's (1980) T_2 for dependent rs was used to compare the DIH/drug response correlation during free feeding to the DIH/drug response correlation during deprivation.

Comparing the relationship of DIH to drug response in the two feeding conditions via two correlations retains information about each condition, but ambiguity remains as to whether deprivation modulates drug response at the level of individuals. Intra-individual modulation of drug response by deprivation was indexed with a composite score for each rat: MPD response during free feeding was subtracted from MPD response during deprivation. This score is near 0 for rats who responded similarly to MPD in both conditions, positive when MPD increased running more (or reduced it less) during deprivation, and negative when MPD increased running less (or reduced it more) during deprivation. The correlation between this score and DIH was evaluated. In Experiment 2, Fisher's z for independent rs compared LoS to HiS rats, as a direct test of whether modulation of MPD's effect by deprivation differed between lines.

3.2. Acoustic startle (Experiment 3)

Challenges in quantifying prepulse inhibition have been discussed elsewhere (e.g. Sandner and Canal, 2007; Swerdlow et al., 2000a). Startle on prepulse trials usually is transformed to a measure of suppression relative to regular (non-prepulse) startle trials. Such transformations can vary artifactually as a function of regular startle amplitude. Absent consensus about how to manage this issue, we examined startle data in four stages. In Stage 1, startle values (15 of each trial type, averaged into five 3-trial blocks) were subjected to an omnibus MANOVA with line, drug, trial type, trial block, and feeding status as variables. Higher-order interactions involving trial type indicated that variables differentially affected startle on regular vs prepulse trials. Thus, in Stage 2, regular startle was examined using MANOVA, separately from prepulse inhibition.

The last two stages examined prepulse inhibition. In Stage 3, a data-driven approach was used to gauge the likelihood that effects were artifacts of regular startle amplitude. Prepulse trial data were transformed to percentage difference scores [PPI = (prepulse −regular)/regular, × 100, in each trial block]. These were used as the dependent variable in hierarchical regression in each drug condition in each trial block. To examine covariation between startle amplitude and PPI scores, regular startle was entered first. To test homogeneity of regression across groups, the group × regular startle interaction was entered after the group main effect. To test homogeneity of regression between drug conditions, βs for saline vs MPD were compared using T_2.

Finally, in Stage 4, PPI scores were subjected to a MANCOVA with line, drug, trial block, and, feeding status as variables. Regular startle amplitude in each trial block was used as a varying covariate. Contrasts on adjusted means were tested with Bonferroni-corrected p values.

For all analyses, test statistics significant at $\alpha = .05$ are reported.

4. Results

4.1. Experiment 1: running in Harlan Sprague–Dawley rats

Number of revolutions per 30-min interval is shown in Fig. 1. Rats ran more when given MPD, when food deprived, and early in the session. The drug effect was largest early in the session. A drug × feeding status × session time MANOVA yielded main effects of drug, $F(1,12) = 10.10$, feeding status, $F(1,12) = 40.51$, and session interval, $F(3,10) = 18.89$. The drug × session interval interaction also was

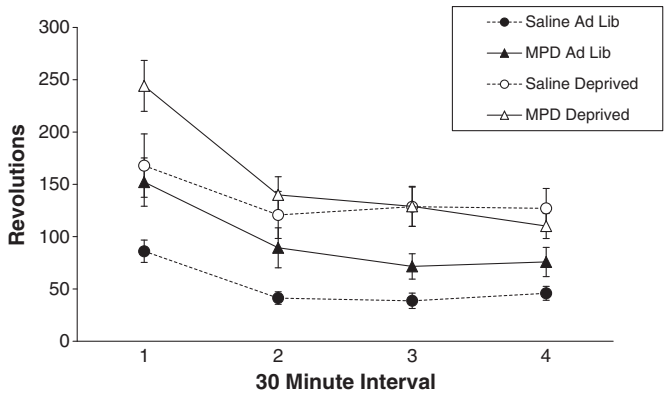

Fig. 1. Experiment 1: Wheel revolutions in successive 30-min intervals by Harlan SD rats while food deprived or fed ad lib., beginning 15 min after treatment with MPD or saline.

significant, $F(3,10) = 8.41$; contrasts showed that the MPD effect was significant only in the first 30 min. All other effects were additive. MPD and deprivation effects in Minutes 9–13 (not shown) were similar to results for the session overall. Rats ran more when given MPD, $F(1,12) = 22.11$, and when deprived, $F(1,12) = 15.94$, and running declined across minutes, $F(4,9) = 3.70$. MPD's effect was stable across this interval.

Individual responses to MPD in the first 30-min interval varied from dramatic increases to reductions in running (range: +301 to −121 revolutions, vs saline). Correlations involving these values are shown in Table 2. During free feeding, MPD increased running more among rats who showed greater DIH. During deprivation, MPD increased running more among rats who showed less DIH and reduced running among rats with the highest DIH. Both correlations were significant, as was the difference between them, $T_2(10) = 11.57$. Examination of composite scores showed that DIH predicted the modulation of drug response by deprivation: MPD's facilitation of running was enhanced by deprivation among lower-DIH rats and was reduced or reversed by deprivation among higher-DIH rats.

Post hoc analyses assessed three third-variable accounts of these results. Data were taken from the first 30 min, during which MPD effects were significant. First, the role of asymmetrical order effects involving prior deprivation was assessed by repeating the MANOVA with deprivation sequence (Saline/Deprivation before vs after drug conditions) as a variable. No effects involving deprivation sequence were significant. Next, whether DIH/MPD response correlations could be explained in terms of baseline running was examined. Running on the last training day served as a measure of baseline running. It varied substantially (range: 44–237 revolutions). Correlations between DIH and indexes of drug response (MPD response during free feeding and deprivation, and the composite score) were reexamined in hierarchical regressions, with baseline running at the first step and DIH at the second step. After controlling for baseline running, all three relationships remained significant, respectively, $F(1,9) = 17.90$, 11.12, and 23.03 (see Table 2 for partial correlation coefficients). In addition, baseline running was uncorrelated with drug response during free feeding.

Weight loss also was considered. Rats lost about 11% of their bodyweight during deprivation, with little variation between individuals or deprivation episodes and no extreme weight loss. Due to differing treatment orders, an appropriate pre-deprivation bodyweight was available for both episodes for six rats, whose reduced bodyweight in the two episodes averaged, respectively, $88.2 \pm 0.5\%$ and $89.0 \pm 1.3\%$ (lowest 85.1%). Weight loss for all 13 rats in the second episode was similar ($89.5 \pm 0.6\%$, lowest 85.1%). After controlling for weight loss, DIH still predicted all three MPD response indexes, respectively, $F(1,10) = 16.13$, 5.46, and 32.01.

To summarize, MPD and deprivation effects are additive when means are compared (Fig. 1), but analysis of within-group variation reveals rate dependency of MPD effects, including "paradoxical" reduction in running by rats with high DIH (Table 2). Neither baseline running nor weight loss accounts for covariation of DIH and MPD responses. Rather, high DIH appears to be a marker for sensitivity to feeding status of pathways affected by MPD.

4.2. Experiment 2: running in LoS and HiS rats

Number of revolutions per 30-min interval is shown in Fig. 2. LoS and HiS rats ran more when food deprived and early in the session, and deprivation enhanced MPD's effect. A line × drug × feeding status × interval MANOVA yielded main effects of feeding status, $F(1,35) = 22.18$, and interval, $F(3,33) = 25.89$. The drug × feeding status × session time interaction also was significant, $F(3,33) = 3.45$; MPD-vs-saline contrasts showed that the drug effect was significant only in the first 30 min interval and only when the rats were food deprived. On this time scale, no effects involving line were significant.

Running in Minutes 9–13 are shown in Fig. 3. Deprivation increased running more in LoS than in HiS rats, as observed in females in 23-h sessions (Dess et al., 2000). Importantly for present

Table 2
Results from analyses of the relationships between running rates in different conditions in Experiments 1 and 2. All data are from the first 30 min of sessions, during which MPD effects were significant.

		Pearson's *r*	Partial correlation ($R_{xy.z}$) baseline running controlled		Partial correlation ($R_{xy.z}$) weight loss controlled	
Experiment 1	$df = 11$	DIH	$df = 10$	DIH		DIH
	MPD/Ad Lib.	0.76[c]	MPD/Ad Lib.	0.80[b]	MPD/Ad Lib.	0.79[b]
	MPD/Deprived	−0.63[ad]	MPD/Deprived	−0.64[bd]	MPD/Deprived	−0.59[ad]
	Composite score	−0.87[c]	Composite score	−0.90[c]	Composite score	−0.87[c]
Experiment 2						
LoS	$df = 16$		$df = 15$			
	MPD/Ad Lib.	−0.21	MPD/Ad Lib.	−0.26		
	MPD/Deprived	−0.44	MPD/Deprived	−0.58[ae]		
	Composite score	−0.52[ae]	Composite score	−0.71[bf]		
HiS	$df = 17$		$df = 16$			
	MPD/Ad Lib.	−0.16	MPD/Ad Lib.	−0.29		
	MPD/Deprived	0.20	MPD/Deprived	0.15		
	Composite score	0.30	Composite score	0.35		

[a] vs 0, $p < .05$.
[b] vs 0, $p < .01$.
[c] vs 0, $p < .001$.
[d] vs Ad Lib., $p < .05$.
[e] vs HiS, $p < .05$.
[f] vs HiS, $p < .001$.

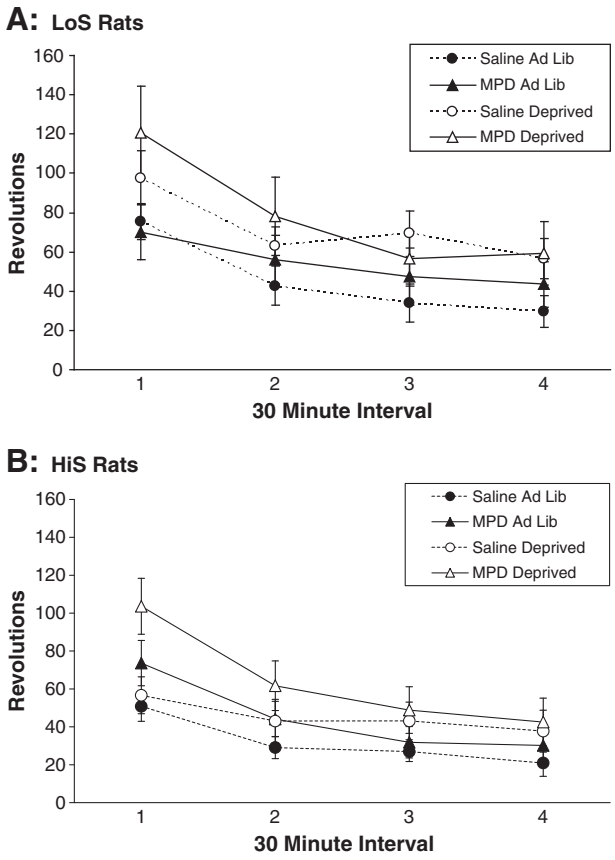

Fig. 2. Experiment 2: Wheel revolutions in successive 30-min intervals by LoS (upper panel) and HiS (lower panel) rats while food deprived or fed ad lib. after treatment with MPD or saline.

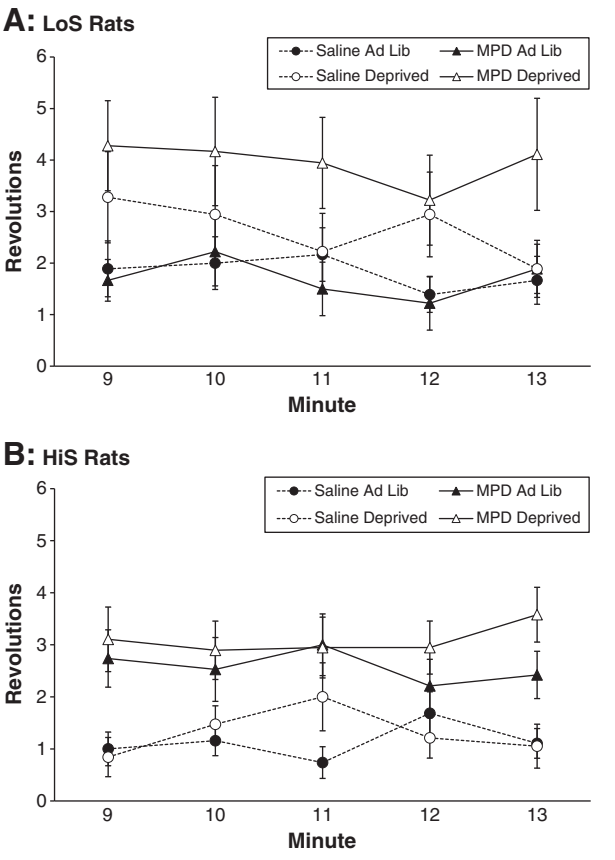

Fig. 3. Experiment 2: Wheel revolutions in Minutes 9–13 by LoS (upper panel) and HiS (lower panel) rats while food deprived or fed ad lib. after treatment with MPD or saline.

purposes, deprivation made MPD's effect more robust in LoS and less robust in HiS rats. A MANOVA yielded main effects of feeding status, $F(1,35) = 11.50$, and drug, $F(1,35) = 9.39$, and two interactions: line × feeding status, $F(1,35) = 4.59$, and line × feeding status × drug × minute, $F(4,32) = 3.00$. Contrasts showed that in LoS rats, MPD's effect was not significant in any minute during free feeding; during deprivation, it was significant in Minute 13 (and nearly so in Minute 11, $p = .06$). In HiS rats, MPD's effect was significant in Minutes 9, 10, 11, and 13 during free feeding and only in Minutes 9 and 13 (and nearly so in Minute 12, $p = .06$) during deprivation. Though subtle, the line difference in this interval is useful for comparison to results in the same post-injection interval for startle (Experiment 3).

MPD's effect on running in the first 30 min ranged from +315 to −113 among LoS and from +163 to −19 among HiS rats (revolutions after MPD vs saline). Correlations involving these values are shown in Table 2. Both lines trended toward an inverse relationship during free feeding, a trend strengthened somewhat by deprivation in LoS rats, but none of those correlations was significant. Analysis of the composite drug response score, however, reveals that deprivation modulated MPD response in LoS rats but not in HiS rats; the two correlations differed significantly, Fisher's $z = 2.48$. Repetition of correlational analyses for Minutes 9–13 showed the same pattern except that the inverse relationship between DIH and modulation of drug response by deprivation held in both LoS and HiS rats.

Post hoc analyses of data from the first 30 min show that, as in Experiment 1, MPD results cannot be explained in terms of deprivation sequence, baseline running, or weight loss. Repeating the MANOVA with deprivation sequence as a variable yielded no effects involving deprivation sequence. Average running on the last training day was less than in Harlan SD rats, as is typical for larger rats (Doerries, 1996). LoS rats ran slightly more than HiS rats (56 ± 7 vs 41 ± 6 revolutions, respectively). The line difference was not significant and the ranges were similar (range: 9–123 revolutions for LoS, 10–101 revolutions for HiS). Controlling for baseline running did not affect the pattern of results; in fact, the relationship between DIH and MPD response during deprivation strengthened among LoS rats such that the partial correlation coefficient differed significantly from both 0 [$F(1,15) = 7.57$] and the HiS rats' correlation, Fisher's $z = 2.19$. Baseline running was not correlated with drug response during free feeding in either line.

As in Experiment 1, rats lost about 11% of their bodyweight during deprivation, with little variability and no extreme weight loss. Weight loss was estimated from the nine rats in each line for which weight loss could be calculated for both deprivation episodes (LoS, 88.8 ± 0.5% and 89.8 ± 0.6%, lowest 86.0%; HiS, 88.9 ± 0.7% and 89.2 ± 0.7%, lowest 84.0%). This sample is too small for inferential tests; descriptively, though, the utility of DIH as a predictor of the composite score in this subset of rats changed little after controlling for weight loss ($R_{xy.z}$ = −0.50 vs −0.48 for LoS, 0.29 vs 0.44 for HiS).

In summary, as in Harlan SD rats, food deprivation increased running in LoS and HiS rats, and unlike Harlan SD rats, MPD increased running only during deprivation. Within the post-injection interval matching startle testing (below), deprivation heightened MPD's effect in LoS rats and attenuated it in HiS rats. DIH robustly predicted modulation of drug response by deprivation among LoS rats, as it did among Harlan SD – but not HiS – rats.

4.3. Experiment 3: acoustic startle in LoS and HiS rats

In a preliminary omnibus MANOVA, no interactions of MPD treatment order with line, feeding status, or trial type were significant. Therefore, the MANOVA was repeated without order as a variable. It yielded main effects of line, $F(1,43) = 21.22$, drug, $F(1,43) = 57.97$, trial type, $F(1,43) = 112.09$, and trial block, $F(4,40) = 14.02$, and drug ×

feeding status, line × drug × feeding status, drug × trial type, and drug × trial type × feeding status interactions, $Fs(1,43) = 4.30$, 8.85, 4.61, and 4.00, respectively.

Due to interactions involving trial type, regular startle was analyzed separately from PPI. Regular startle is shown in Fig. 4. As expected, LoS rats startled more than HiS rats. MPD's effect was minimal among well fed rats. Deprivation enhanced MPD's elevation of startle, more so in LoS rats. A line × drug × feeding status × trial block MANOVA yielded main effects of line, $F(1,43) = 21.50$, drug, $F(1,43) = 22.45$, and block, $F(4,40) = 7.16$, and three interactions: drug × feeding status, $F(1,43) = 7.19$, line × drug × feeding status, $F(1,43) = 4.30$, and line × drug × feeding status × block, $F(4,40) = 3.62$. MPD vs saline contrasts for each group/condition in each trial block showed that for LoS rats, MPD elevated startle marginally in Block 1 ($p = .06$) among freely fed rats but increased startle in Blocks 2–5 among deprived rats. For HiS rats, MPD increased startle in Block 5 among ad lib. fed rats and in Blocks 1 and 5 among deprived rats.

Hierarchical regressions of regular startle on PPI showed that in every trial block in both drug conditions, β was negative (higher startle predicted stronger inhibition). Homogeneity of regression held in each trial block except for modest departure in Block 4 [among groups in the saline condition, $F(3,39) = 3.28$, and saline vs MPD, $T_2 = 2.09$]. Thus, use of regular startle as a varying covariate in analysis of PPI was reasonable (Hamilton, 1977).

A line × drug × feeding status × trial block MANCOVA on PPI yielded a main effect of drug, $F(1,42) = 34.46$, and block, $F(4,171) = 6.09$, and a line × feeding status × drug interaction, $F(1,42) = 5.65$. The trial block effect reflects less PPI in Block 1 than in other blocks. Because block did not interact with any other variable, marginal means (adjusted for the covariate) are shown in Fig. 5. A nonordinal interaction is apparent: Contrasts confirmed that deprivation increased disruption of PPI by MPD among LoS rats and blocked disruption among HiS rats.

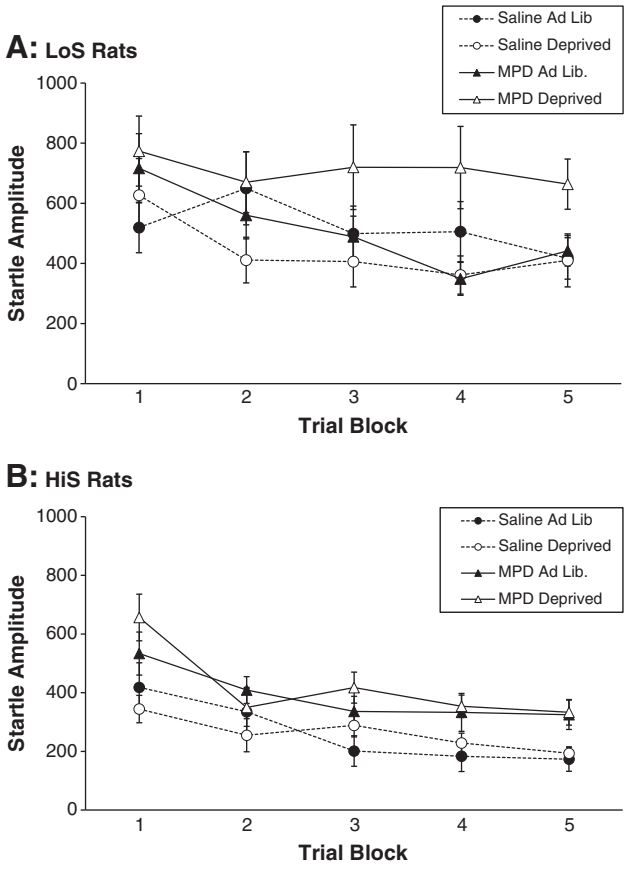

Fig. 4. Experiment 3: Acoustic startle magnitude on regular startle trials among LoS (upper panel) and HiS (upper panel) rats while food deprived or fed ad lib. after treatment with MPD or saline. Startle values for each trial type are averaged over 3-trial blocks.

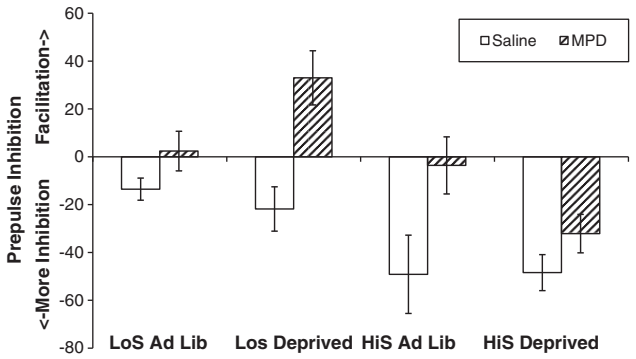

Fig. 5. Experiment 3: Prepulse inhibition scores among LoS and HiS rats while food deprived or fed ad lib. after treatment with MPD or saline in averaged over Blocks 1–5.

5. Discussion

Well-known stimulant effects including increased running and startle amplitude and disrupted prepulse inhibition were observed, validating the protocols and dose selection. These findings add to the two other studies of MPD effects on startle modulation in rats (Conti et al., 2006; Drolet et al., 2002), an empirical database that remains sparse compared to those for amphetamine and apomorphine. Three kinds of variation in stimulant effects reported previously – enhancement by food deprivation (Carr, 2007), strain differences (Bell et al., 2003; Drolet et al., 2002; Swerdlow et al., 2007, 2008; Varty and Higgins, 1994), and rate dependency (Belke and Dunbar, 2001; Belke et al., 2005; Harris et al., 1978) – were observed. The present study extends the literature by linking these variations in ways that are practically useful and point to new research avenues.

5.1. Strain differences in MPD's effect on wheel running

Group-aggregated analyses show that MPD increases running in Harlan SD, LoS, and HiS rats. MPD is equally effective regardless of feeding status in Harlan SD rats. In contrast, MPD increases running among LoS and HiS rats only when food deprived. The difference could be due to intrinsic strain or rearing differences. Alternatively, basal metabolic status could be key (Carr, 2007): Freely fed LoS and HiS rats may be too large/fatty to respond to MPD, and deprivation functionally increases MPD's potency by generating a metabolic state more similar to smaller, leaner Harlan SD rats. Either way, a practical implication is that the expression of (sub)strain differences in MPD's effects on running will vary depending on animals' nutritional status (Cabib et al., 2000; Kanarek et al., 2005).

With respect to intragroup heterogeneity, strain differences again depend on feeding status. During free feeding, Harlan SD rats were distinguished from both LoS and HiS rats by a strong positive correlation between DIH and MPD response. This difference, like the freely fed Harlan SD rats' greater group-wise MPD response, could be due to the Harlan SD rats' being leaner and/or more active. Relationships during deprivation, however, are less easily explained. Rats in all three (sub)strains lost about 11% of their bodyweight, so relative weight reduction cannot explain differences. Relative to Harlan SD rats, both LoS and HiS lines were 45% heavier and ran half as much at the end of training. Yet, Harlan SD and LoS rats, despite their size/weight and activity differences, had in common that MPD's facilitation of running during deprivation was greater in individuals for whom deprivation alone elicited little hyperactivity. That relationship was not observed among HiS rats, though they were comparable to LoS rats in bodyweight and baseline running. These deprivation-contingent

relationships also cannot be easily explained in terms of regression to the mean or ceiling/floor effects. For instance, saline-treated deprived LoS rats ran about as much as did saline-treated freely feeding Harlan SD, and yet MPD responses in those conditions bore opposite relationships to DIH in the two strains.

What, then, might account for the inverse relationship of DIH to MPD responses in deprived Harlan SD and LoS rats? Wheel running reflects multiple processes – reward, arousal, locomotor activation – that are sensitive to stimulant drugs, food deprivation, and stimulant enhancement by deprivation (Berridge, 2006; Carr, 2007). Moreover, running is not just an *effect* — it also is a *cause*. For example, running is rewarding; as such, it can reinforce itself or other behaviors and substitute for drug self-administration (Belke, 1996; Cosgrove et al., 2002). Consequently, individual differences in MPD responses could be rooted in anything from congenital events to interplay between feeding status and running history or current rate. The roles of individual differences in momentary states generated by deprivation vs neuroregulatory processes for which those states are a proxy remain to be determined.

Meanwhile, we tentatively suggest a proximate mechanism for the inverse relationship between DIH and modulation of MPD response by food deprivation in Harlan SD and LoS rats. It is based on evidence that deprivation reduces extracellular dopamine in reward pathways and facilitates dopamine release in response to salient incentives (Carr, 2007). Key variance may be in the degree to which deprivation reduces extracellular dopamine. The resulting reward deficit could be redressed by running, with rats with a larger deficit running more. MPD, however, synergistically increases dopamine availability by blocking reuptake and enhancing running-induced dopamine release. At some point, the rewardingness of increased dopamine transmission diminishes, and aversive effects recruit (Guzman and Ettenberg, 2007). Rats can titrate dopamine transmission around some optimal level by running more or less, depending on MPD treatment. Consistent with this reward-titration idea, Belke and colleagues reported rate-dependent effects of stimulants on lever pressing reinforced by the opportunity to run in food-deprived rats. Amphetamine or cocaine increased lever pressing during low-rate periods and decreased lever pressing during high-rate periods (Belke and Dunbar, 2001; Belke et al., 2005). If running is itself an operant response on which dopamine-mediated reward is based, the rate dependency in Harlan SD and LoS animals follows. Our focus on reward rather than nonspecific locomotor activation is supported by Larson and Carroll's (2005) observation among food-deprived rats that high wheel-runners self-administer more cocaine than low wheel-runners, with no difference on cocaine-induced ambulation in a maze. Moreover, more anxiety predicts greater sensitivity to cocaine's aversive effects (Bush and Vaccarino, 2007), consistent with suppressed running after MPD among LoS rats expressing high DIH. This explanation can be tested in future research using behavioral and pharmacological tools that allow the rewarding, aversive, and locomotor-activating effects of MPD to be dissociated.

On a practical note, these results should be useful to investigators who want to control for or study rate dependency. Post-experimental tests of saccharin intake or deprivation sensitivity could be added to current protocols. Such added-on tests can increase statistical sensitivity to experimental manipulations and yield substantive information about individual differences for relatively little additional time or expense, without interfering with results of primary interest.

5.2. Saccharin phenotype as a marker for MPD's effects on acoustic startle

Food deprivation enhances MPD's facilitation of acoustic startle amplitude and disruption of PPI more among LoS rats than HiS rats. This line difference also was expressed in wheel running during the same post-injection interval. Observing this line difference in both running and startle adds to the list of measures by which LoS rats exhibit heightened responsiveness to metabolic threats (Dess et al., 2007). Differential responsiveness to MPD treatment in such distinct contexts and response systems implicates more than reinforcement in the line differences. It points to one or more pathways by which the salience, or behavioral imperative, of diverse stimuli and situations is gauged. Good candidates are pathways involving the nucleus accumbens core (Cadoni et al., 2003; Swerdlow et al., 2007), anterior insula (Paulus and Stein, 2006; Plailly et al., 2007) and ventral tegmental area (Gifkins et al., 2002).

Neurochemical substrates of line differences may include a ubiquitous mechanism key to signaling and regulating cellular energy status, such as adenosine (Minor and Hunter, 2002). With respect to dopaminergic mechanisms, research from other laboratories provides guidance. At an interstimulus interval comparable to the one used in the present study, Sprague–Dawley rats show more PPI disruption than Long–Evans or Brown Norway rats, and D2 activation has been implicated in the strain difference (Swerdlow et al., 2008; Weber et al., 2008). Also, D1 rather than D2 activation appears to account for a difference in PPI disruptability between Sprague–Dawley rats from different suppliers (Harlan Inc. > Bantan Kingman Inc.; Swerdlow et al., 2000a, 2000b). Given the Sprague–Dawley derivation of the LoS and HiS lines and the use of Harlan SD rats for outbreeding in our colony (Carroll et al., 2008), it seems likely that Harlan SD rats would show PPI disruption by MPD in this startle preparation. More intriguing conjectures are that D1 receptors would mediate any differences among the substrains in PPI disruptability and, whether through the same or another mechanism, that DIH would predict the modulation of PPI disruption by food deprivation in Harlan SD and LoS rats — but not HiS rats.

Positive PPI scores indicate enhancement of startle by the prepulse stimulus (prepulse facilitation), a phenomenon usually observed only at a shorter or longer interstimulus interval than the interval used here (100 ms; Mansbach and Geyer, 1991; Reijmers and Peeters, 1994). Ketamine creates exceptions, causing prepulse facilitation at intermediate interstimulus intervals (De Bruin et al., 1999; Imre et al., 2006). The group mean for deprived LoS rats given MPD was positive even before covariate adjustment, consistent with prepulse facilitation. However, most of the rats startled less on prepulse trials than on regular trials. These results underscore the challenge of quantifying and interpreting prepulse inhibition. Whether PPI disruption by MPD in deprived LoS rats reflects impaired sensorimotor gating and/or a separate facilitatory process (De Bruin et al., 1999; Imre et al., 2006; Qu et al., 2009; Yee et al., 2004) remains to be determined.

In striking contrast to results for LoS rats, PPI disruption by MPD was eliminated by deprivation among HiS rats. This finding is intriguing in light of HiS rats' greater impulsivity (vs LoS rats; Anker et al., 2008; Perry et al., 2007). HiS rats showed robust PPI after saline injection in both feeding conditions (see also Dess et al., 2005), so at least by this measure, they do not comprise an inattention model. However, the resistance to MPD's disruptive effect conferred by deprivation only in HiS rats may be relevant to the study of mechanisms by which MPD can improve or impair cognitive function (Blondeau and Dellu-Hagedorn, 2007; Hawk et al., 2003).

These findings complement previous documentation of rat strain and supplier differences in PPI disruption by stimulant drugs (Swerdlow et al., 2007, 2008; Weber et al., 2008) and extend that literature to include modulation by feeding status and prediction of effects by a phenotype linked to cocaine and ethanol self-administration, preference for ethanol-paired flavors, and ethanol withdrawal severity (Carroll et al., 2008; Dess et al., 2005). These data should be useful to others using startle as an investigative tool, particularly with respect to selection of strain and supplier and feeding status during drug administration. The LoS and HiS lines have been cryopreserved at the federally funded Rat Research & Resource Center (Columbia, MO), making them an option for further study by other investigators.

5.3. Parametric considerations

Deprivation and drug parameters were held constant in this study in interests of keeping its complexity manageable. Metabolic status and its correlates (e.g. adiposity, circadian activity patterns) are sensitive to the pattern, chronicity, and severity of restricted access to food. However, some effects of food deprivation recruit quickly, persist, and are robust across diverse deprivation protocols (e.g. Davidson et al., 1992; Marinkovic et al., 2007), so how sensitive the effects reported here would be to parametric variation of food access is an open question.

Average MPD effects in all three strains of rats comported to well known stimulant effects, providing a foundation from which to ask whether the novel findings generalize to other doses or drugs. Strain differences sometimes hold across stimulant doses (e.g. Swerdlow et al., 2001) and sometimes they do not (Bell et al., 2003). Similarly, some traits expressed in response to one stimulant are expressed differently, or not at all, to another (e.g. Cain et al., 2009 vs Wooters et al., 2006; Rhodes and Garland, 2003; also see Arnold, 2000). Direct comparison of MPD at several doses to other stimulants would be informative.

5.4. Broader implications

These results invite inquiry into how taste phenotypes and/or food deprivation sensitivity may relate to MPD's therapeutic and side effects. Stimulants are the drug treatment of choice for Attention Deficit Hyperactivity Disorder (ADHD; Kollins, 2008). Variability among individuals is a continuing challenge in pharmacotherapy (Stein and McGough, 2008), and taste shows promise as a noninvasive peripheral marker for central adenosine and monoamine function (DeMet et al., 1989; Heath et al., 2006). Anxiety, commonly comorbid with ADHD (Jarrett and Ollendick, 2008; Ollendick et al., 2008), predicts response to MPD on some measures (Bedard and Tannock, 2008; Goez et al., 2007; Tannock et al., 1995; Urman et al., 1995). While MPD treatment is not generally contraindicated by anxiety (Garcia et al., 2009; Ollendick et al., 2008), identifying the anxious individuals who are most likely to benefit from MPD treatment or to suffer fewer adverse effects would be helpful.

Chronically or phasically reduced food intake frequently accompanies ADHD, either due to a comorbid eating disorder (Biederman et al., 2007; Quinn, 2008) or as a side effect of MPD treatment (Graham and Coghill, 2008). Children with the 9-repeat dopamine transporter (DAT1) allele experience more appetite suppression and lower overall efficacy during MPD treatment than do other children (Davis et al. 2007; Stein et al. 2005). Like experimental restriction of feeding, leptin-induced weight loss enhances stimulant effects, raising the possibility that endogenous anorexia and weight loss can affect MPD responses (Carr, 2007). Thus, experimental food deprivation, including acute deprivation, has potential as a means of assessing whether anorexia's behavior-activating effects moderate MPD efficacy.

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