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Review

Methylphenidate has nonlinear dose effects on cued response inhibition in adults but not adolescents

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ABSTRACT

Ongoing development of the dopamine system during adolescence may provide a partial mechanism for behavioral and psychiatric vulnerabilities. Despite early evidence for a hyperactive adolescent dopaminergic system, recent data suggest that adolescent dopamine may be functionally hypoactive compared to in adults. While this distinction has been established in response to dopaminergic drugs and natural rewards, little is known about age-related differences in cognitive efficacy of dopaminergic drugs. Using a recently established Cued Response Inhibition Task, we tested the effects of acute systemic methylphenidate, commonly known as Ritalin, on response inhibition and response initiation in adolescent and adults rats. First, we replicated previous data that adolescents are able to inhibit a response to a cue on par with adults, but are slower to produce a rewarded response after a stop cue. Next, we observed that methylphenidate modulated response inhibition in adult rats, with low dose (0.3 mg/kg) improving inhibition, and high dose (3 mg/kg) impairing performance. This dose-response pattern is commonly observed with psychostimulant cognitive modulation. In adolescents, however, methylphenidate had no effect on response inhibition at any dose. Latency of response initiation after the stop cue was not affected by methylphenidate in either adult or adolescent rats. These data establish that dose-response of a commonly prescribed psychostimulant medication is different in adolescents and adults. They further demonstrate that healthy adolescent response inhibition is not as sensitive to psychostimulants as in adults, supporting the idea that the dopamine system is hypoactive in adolescence.

This article is part of a Special Issue entitled SI: Adolescent plasticity.

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1. Introduction

Dopaminergic psychostimulants including methylphenidate (commonly known as Ritalin) are used to treat cognitive

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impairment caused by attention deficit hyperactivity disorder (ADHD) in adolescents and adults. These and other monoaminergic drugs alter cognition in a dose-dependent, nonlinear fashion (Robbins, 2005; Williams and Castner, 2006; Zahrt et al., 1997). This pattern is predicted by the Yerkes-Dodson law, which posits that the empirical relationship between arousal and performance often follows an inverted U-shape, with optimal levels of arousal improving cognition, and excessive arousal causing impairment (Yerkes and Dodson, 1908). Awareness of this trend has aided with determining clinically efficacious doses of drugs, and with understanding the nature of dopamine's role as a cognitive modulator. However, because the adolescent dopamine system is undergoing development, it is possible that this pattern of cognitive modulation does not apply to adolescent behavior (Ernst and Luciana, 2015; Simon and Moghaddam, 2015; Wong et al., 2013).

Despite increased dopamine receptor availability and baseline activity during adolescence (Andersen et al., 1997; Andersen et al., 2000; McCutcheon et al., 2012), accumulating evidence from rodent models suggests that adolescent functional dopamine activity is hypoactive compared to in adults. Adolescent putative dopamine neurons in the ventral tegmental area demonstrate reduced reward anticipatory activity compared to adults, as well as attenuated reward-evoked activation (Kim et al., 2016). In addition, amphetamine-evoked dopamine response in dorsal striatum, but not ventral striatum, is attenuated in adolescents (however, some stimulants may increase voltammetric dopamine signal in anesthetized animals (Matthews et al., 2013; Walker et al., 2010)). Finally, tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis, is less abundant in the adolescent dorsal striatum, while dopamine transporter levels are lower in adolescent dorsal and ventral striatum (Bondi et al., 2014; Matthews et al., 2013). These age-related contrasts in dopamine transmission are particularly relevant to current methods of psychiatric treatment, as psychostimulants are commonly prescribed to improve concentration and cognition in patients diagnosed with ADHD (Sahakian and Morein-Zamir, 2015).

Differences in dopamine activity may also explain several key behavioral differences between adolescents and adults. For example, adolescents are more impulsive and exhibit enhanced sensation-seeking compared to adults (Adriani and Laviola, 2003; Arnett, 1994; Burton and Fletcher, 2012; Doremus-Fitzwater et al., 2010). Most of the classical dopamine-related behavioral tasks, however, involve long training periods, making them unfeasible for thorough pharmacological studies in adolescents. We have recently developed the Cue Response Inhibition Task (CRIT) to capture different elements of behavior using a design that can be acquired quickly enough to allow both baseline behavioral assessments and behavioral pharmacology during the brief adolescent window in rodent models (Simon et al., 2013b). During this task, rats learn to withhold a nose-poke response during a tone, then perform the response within a brief window after the tone to receive a pellet reinforcer. Thus, this task measures both ability to withhold a response (inability to withhold a response is also referred to as impulsive action), and ability to initiate a response quickly following a period of response inhibition. Adolescent rats are impaired in ability to quickly initiate a response, but are comparable to adults in cued response inhibition (Simon et al., 2013b).

Both response inhibition and response initiation are modulated by drugs that affect dopamine transmission (Bari and Robbins, 2013; Carli et al., 1985; Eagle et al., 2011). Thus, both of these behaviors as assessed with CRIT should be influenced by administration of a drug that enhances dopamine in the synapse. Here, we tested the effects of multiple doses of methylphenidate (*Ritalin*), a dopamine/norepinephrine transporter blocker commonly prescribed for ADHD, on cognitive measures assessed by CRIT in adolescent and adult rats. Because dopamine transmission is undergoing development during adolescence, we anticipated that methylphenidate would have a different pattern of cognitive efficacy in adolescence.

2. Results

2.1. Adolescent vs. Adult CRIT performance

All rats were trained in CRIT for 12 sessions. Data were compared between groups across the final three sessions of training. We first compared the ability to withhold a response during a cue, and found no difference in the ratio of correct to incorrect trials between adolescent and adult rats [$F(1,14)=1.84$, $p=.196$, Fig. 2A]. In addition, there were no differences between adults and adolescents in total correct responses ($F(1,14)=2.69$, $p=.123$), or in total premature responses during the cue ($F(1,14)=1.031$, $p=.327$). The amount of premature responses varied based on cue duration ($F(3,42)=48.287$), such that longer cues were associated with increased premature responses/impulsivity. There was no interaction between age and cue duration ($F(3,42)=.185$, $p=.906$), indicating that adult and adolescent groups were similarly sensitive to cue length.

As observed previously (Simon et al., 2013b), adolescent rats missed more trials than adults [$F(1,14)=5.999$, $p=.029$, Fig. 2B] and were slower to respond after the response inhibition cue than adults [$F(1,14)=14.371$, $p=.002$; Fig. 2B]. These effects were likely not related to gross differences in reward motivation between age groups, as there were no age-related differences in latency to collect food after delivery [$t(14)=.86$, $p=.40$] or total entries into the food trough [$t(14)=.08$, $p=.94$]. Rather, as expected, adolescent rats demonstrated an impaired ability to initiate a reward-directed response following response inhibition.

2.2. Effects of Methylphenidate on CRIT

After training, adult and adolescent rats were given one of three doses of methylphenidate (.3, 1.0, 3.0 mg/kg) or saline vehicle prior to CRIT (Fig. 1B). We first assessed the effects of methylphenidate on response inhibition. There was an age group X drug dose interaction, indicating that adult and adolescent rats were affected differently by methylphenidate [$F(3,45)=4.842$, $p=.005$; Fig. 3A]. There was no overall main effect of group [$F(1,15)=1.931$, $p=.185$]. Probing the interaction with individual repeated measures ANOVAs revealed an effect of methylphenidate dose on response inhibition in adults [$F(3,21)=5.442$, $p=.006$]. Specifically, high-dose (3.0 mg/kg) methylphenidate impaired performance relative to saline ($p=.024$), whereas low dose (0.3 mg/kg) methylphenidate caused a slight trend toward improved response inhibition ($p=.177$). Interestingly, there were no effects of dose in response inhibition observed in adolescent rats [$F(3,24)=.403$, $p=.752$; Fig. 3 A]. We then tested for the presence of a nonlinear relationship between dose and response inhibition using curve estimation analysis. We observed a significant quadratic relationship between drug dose and response inhibition performance in adults [$F(2,31)=3.95$, $p=.03$], but not in adolescents [$F(2,35)=.04$, $p=.96$]. Thus, methylphenidate had a dose dependent effect on adult response inhibition that resembled an inverted U curve, but had no influence on response inhibition in adolescents.

Next, we analyzed the effects of methylphenidate on ability to initiate an action after response inhibition. There were no age X dose interactions in either latency to respond after inhibition or omitted trials [latency: $F(3,45)=1.232$, $p=.309$; omissions: $F(3,45)=1.088$, $p=.364$; Fig. 3B-C], and no effects of drug treatment

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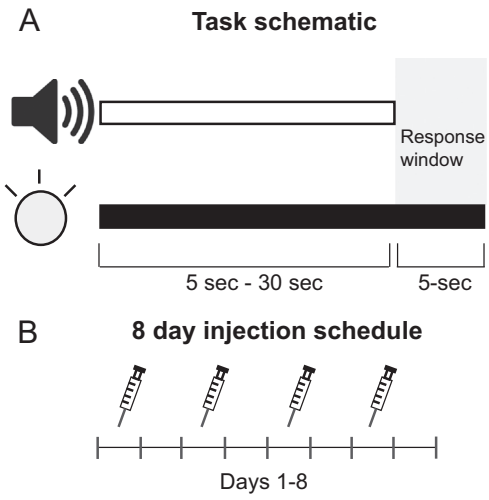

Fig. 1. Task Schematic A. Simplified schematic for Cued Response Inhibition Task. At the beginning of each trial, two cues are presented simultaneously: lighting of the response port, and a tone. The tone informs subjects to withhold a response into the lit port; responses during the tone are scored as failed trials and cause entry to the ITI. The tone lasts for 5, 10, 20, or 30 s (lengths determined pseudo-randomly). After termination of the tone, the port remains lit for 5 s. During this window, responses are rewarded. Critical measures of interest are: response inhibition ratio (correct: incorrect responses), latency to respond after tone termination, and omitted trials. B. After training, rats were given an 8-day methylphenidate injection schedule. Doses of .3, 1.0, 3.0 mg/kg methylphenidate or saline vehicle were administered on days 1, 3, 5, and 7, with drug-free sessions in between to allow washout and establish a consistent baseline.

for either measure [latency: $F(3,45)=.18$, $p=.91$; omissions: $F(3,45)=.094$, $p=.96$]. As observed before drug treatment, there were differences between adult and adolescent rats in both latency to respond after response inhibition ($p=.000$), and missed trials ($p=.033$) with saline vehicle (Fig. 3B-C). Finally, we observed that methylphenidate did not have any effects on latency to collect reward after a correct response for either age group, indicating no gross effects on overall motivation ($ps > .25$).

3. Discussion

Using the CRIT paradigm, we assessed the effects of acute systemic methylphenidate on response inhibition and initiation in adolescent and adult rats. Consistent with a previous report, (Simon et al., 2013b) there was no difference between adults and adolescents in signaled response inhibition, but adolescent rats had a longer latency to initiate a response after inhibition, and were more likely to fail to produce a timely response. Methylphenidate had an inverted U-like effect on cued response inhibition in adults, causing improvements at a low, clinically relevant dose (.3 mg/kg), and impairing performance at a high dose (3 mg/kg). Adolescent rats, however, were unaffected by any dose of methylphenidate. Response initiation was not affected by methylphenidate in either adolescent or adult rats.

Non-linear modulation of motivated behavior by dopamine receptor activation has been observed throughout the literature. Behavioral flexibility, working memory, and attention are all improved with optimal dopamine increase, and impaired with excessive dopamine (Berridge and Arnsten, 2013; Robbins, 2005). A similar pattern has been observed with response inhibition. Response inhibition measured via the stop signal reaction time task (SSRT) in humans was improved by acute methylphenidate (Nandam et al., 2011), and low dose methylphenidate reduced impulsivity in specific subgroups of rats (Eagle et al., 2007; Puumala et al., 1996). Conversely, higher doses of methylphenidate, or amphetamine, administration (which exerts greater effects on dopamine than methylphenidate), impaired response inhibition (Baarendse and Vanderschuren, 2012; Navarra et al., 2008; Pattij et al., 2007). The current study complements these findings to observe a non-linear influence of methylphenidate on response inhibition in a single group of adult rats. In contrast, this traditionally observed non-linear dose-response impact of methylphenidate was absent in adolescents, as the drug was ineffective as a cognitive modulator of response inhibition. This suggests that healthy adolescents may be less sensitive to some of the cognitive-enhancing effects of low dose methylphenidate at the same time as being protected from the adverse effects of the higher doses of the drug.

Psychostimulant drugs such as methylphenidate, commonly known as Ritalin, are used to treat cognitive deficits and hyperactivity in adolescents and adults with attention deficit hyperactivity disorder (ADHD). The alleviation of impulsive action (the inability to adequately inhibit a prepotent response) could be a particularly useful drug effect, as excessive impulsivity promotes drug abuse and other maladaptive behaviors (Anker et al., 2009; Dalley et al., 2007; Farrington, 1995; Garavan and Stout, 2005). A concern has been that chronic exposure to psychostimulants may have long-lasting consequences on brain function and dopamine

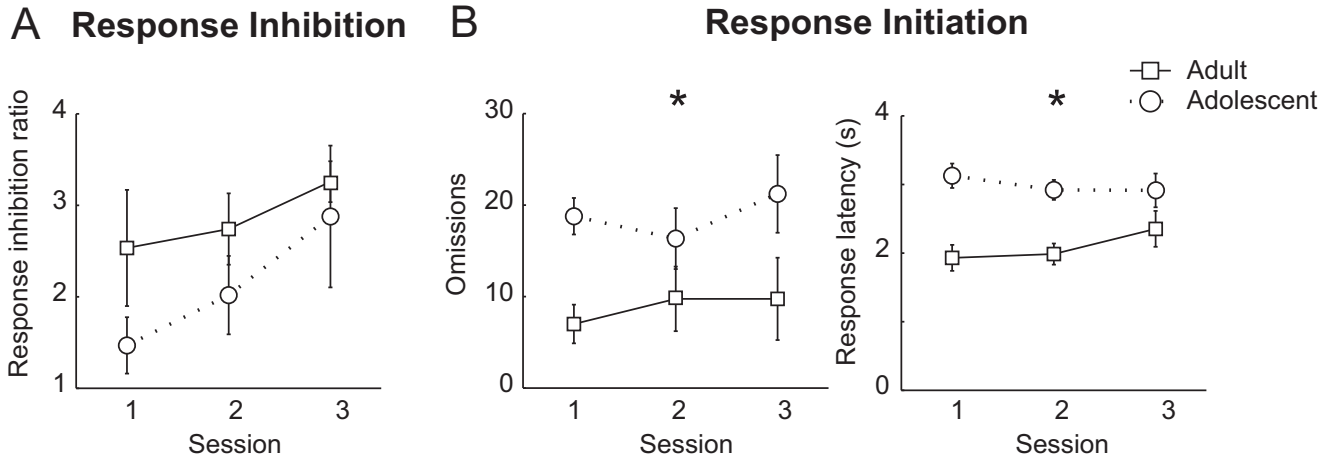

Fig. 2. Adolescents demonstrate similar response inhibition to adults, but reduced ability to initiate a prompt response after response inhibition A. There were no significant differences in response inhibition between adult and adolescent rats over the final three sessions of training ($p=.2$). B. Adolescents had more omitted trials than adults, indicating a reduced ability to respond within the time window following response inhibition (left). Adolescents also had a longer latency to respond following termination of the response inhibition tone compared to adults (right).

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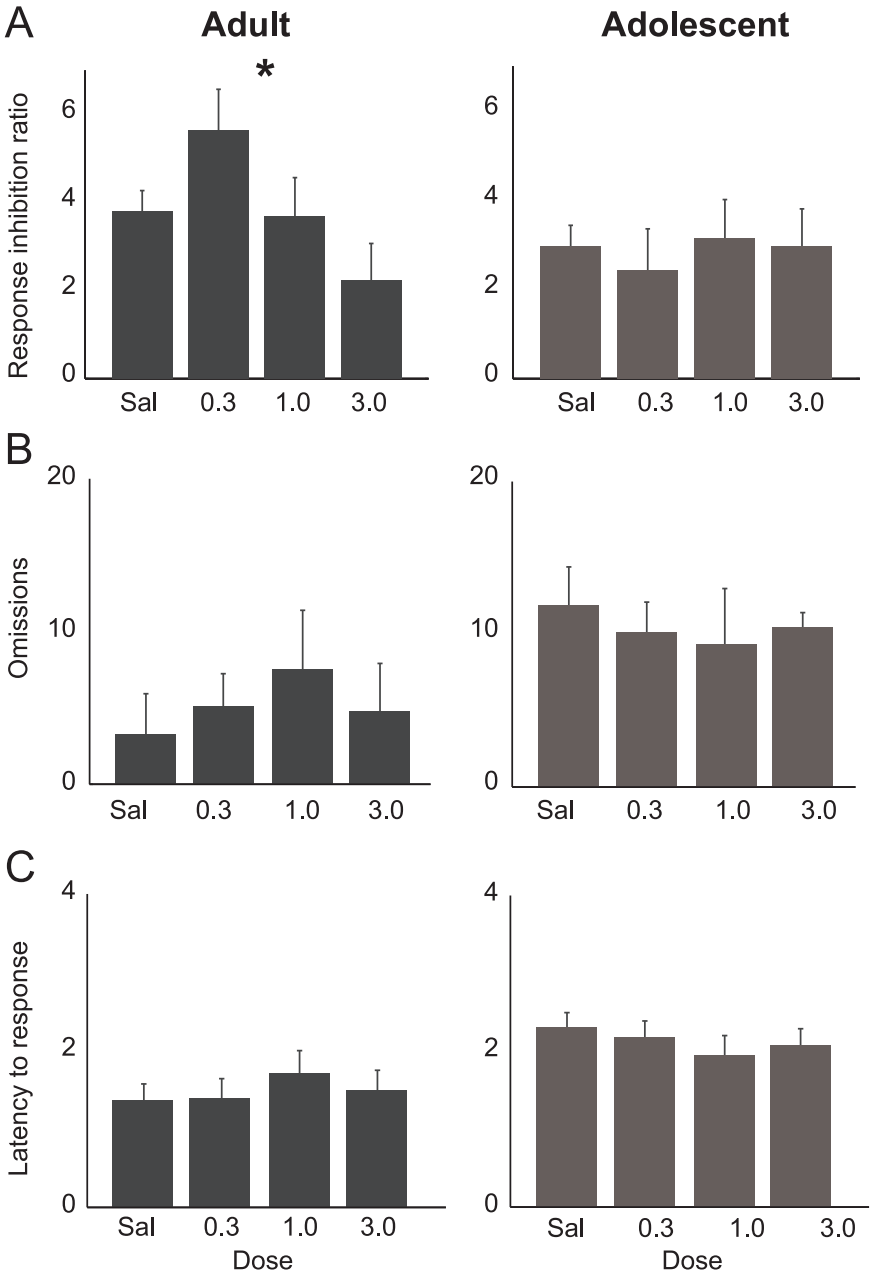

Fig. 3. Methylphenidate modulates response inhibition in adults but not in adolescents A. In adults, methylphenidate had dose dependent effects on response inhibition. Low dose methylphenidate (.3 mg/kg) caused a trend toward increased ability to withhold a response, mid dose (1 mg/kg) did not alter behavior, and high dose (3 mg/kg) impaired the ability to withhold a response. There were no effects of any dose methylphenidate in adolescents. A drug X age interaction revealed that the age groups statistically responded differently to methylphenidate. Note that, as in Fig. 2A, there were no baseline differences between age groups in response inhibition under saline treatment. B. Methylphenidate had no effects on omitted trials in either adults or adolescents. Note that, as in Fig. 2B, an age-related difference in omissions was evident in rats treated with saline (sal). C. Methylphenidate did not affect latency to respond after the response inhibition tone. Adolescents showed increased response latency compared to adults with saline treatment, as in Fig. 2B.

transmission (Adriani et al., 2012; Harvey et al., 2011). Interestingly, adolescents appear to be protected from some, but vulnerable to other, long term adverse effects of psychostimulants compared to adults (Harvey et al., 2009; Kerstetter and Kantak, 2007; Torres-Reveron and Dow-Edwards, 2005). This age-related difference may be attributed, in part, to the current finding that methylphenidate has a diminished effect in healthy adolescents.

Our findings are consistent with reduced behavioral sensitivity to enhanced dopamine transmission in adolescents (Matthews et al., 2013; Yang et al., 2011). These results also fit particularly well with observations of reduced levels of dopamine transporter in adolescent compared to adult striatum, as reduced baseline transporter availability would attenuate the effects of transporter blockade by methylphenidate (Matthews et al., 2013; Tarazi et al., 1998). It should be noted that methylphenidate does not act solely on dopamine, but also increases norepinephrine (NE) transmission by blocking reuptake. Thus, age-related differences in behavioral sensitivity to methylphenidate may be, in part, related to altered NE responsivity in adolescents. Increasing NE activity through agonists or reuptake inhibitors has been shown to reduce impulsive action/improve response inhibition in rodents and humans (Chamberlain et al., 2007; Eagle et al., 2008a; Fernando et al., 2012; Humby et al., 2013; Liu et al., 2015; Robinson et al., 2008). Furthermore, systemic blockade of NE reuptake causes a substantial increase in extracellular NE in the prefrontal cortex, (Bymaster et al., 2002), a region strongly implicated in response

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inhibition (Bari and Robbins, 2013; Donnelly et al., 2014; Loos et al., 2010; Simon et al., 2013a). While little is known about adolescent sensitivity to NE compared to adults with respect to impulsivity, current research is beginning to shed light on developmental differences in NE function. NE transporter levels in prefrontal cortex are higher in adolescence compared to early adulthood, suggesting reduced baseline NE function during adolescence (Bradshaw et al., 2016). Additionally, neurons in the adolescent locus coeruleus, the primary site of norepinephrine synthesis, respond differently to social stressors than in adults (Bingham et al., 2011; Zitnik et al., 2015).

Several brain regions that contribute to behavioral inhibition differ functionally between adults and adolescents. Orbitofrontal cortex, proposed to be a critical component of response inhibition circuitry (Bari et al., 2011; Eagle et al., 2008b), responds differently to reward-related events in adolescents compared to adults, and produces a highly variable, "noisy" signal during adolescence (Galvan et al., 2006; Sturman and Moghaddam, 2011). In addition, dorsal and ventral striatum, both of which play a role in response inhibition (Agnoli and Carli, 2012; Basar et al., 2010; Dalley et al., 2007; Eagle et al., 2011; Ghahremani et al., 2012; Simon et al., 2013a), undergo substantial development throughout adolescence (Geier et al., 2010; Matthews et al., 2013; Robinson et al., 2011). Dorsal striatum, in particular, demonstrates profound age-related differences in neural processing during reward seeking behavior (Sturman and Moghaddam, 2012). Although these developmental differences are not sufficient to produce visible effects on impulsivity as measured by the current task, differences in sensitivity to methylphenidate within these regions (such as the lack of sensitivity to amphetamine observed in adolescent dorsal striatum (Matthews et al., 2013)) may be related to adolescent insulation against methylphenidate's cognitive effects. Development of other structures critical for response inhibition, such as the subthalamic nucleus (Aron and Poldrack, 2006; Uslaner and Robinson, 2006), remains to be elucidated.

In summary, consistent with previous findings of dopamine hyposensitivity in adolescents, we find that doses of methylphenidate, which modulate response inhibition in adults, do not affect adolescents. Reduced efficacy of methylphenidate in healthy adolescents may potentially account for this drug's effectiveness and low side effect profile in treating impulsivity and cognitive deficits of ADHD. More importantly, this study establishes that dose-response profile of commonly prescribed psychiatric medications may be entirely different in adolescents compared to adults.

4. Experimental procedures

4.1. Subjects

Male adolescent (aged P28-P49, n=9) and adult (aged P60+, n=8) Sprague Dawley rats were used for this experiment. All subjects were pair-housed with a similarly aged animal on a 12 h reverse dark/light cycle (lights on at 7 p.m.). All rats were handled, habituated to operant boxes and sucrose pellets (45 mg, Bioserve, Frenchtown, NJ), and mildly food restricted before behavioral training. Adolescents were fed 5 g/cage (2 subjects per cage) on day 1 and 8 g/cage on day 2, followed by daily maintenance of 10 g/cage. This schedule has previously been demonstrated to allow weight gain while inducing sufficient motivation to perform CRIT and other instrumental tasks (Simon et al., 2013b; Sturman et al., 2010). Adults were maintained at approximately 90% of their free feeding weight.

4.2. Behavior

The Conditioned Response Inhibition Task (CRIT) was described previously in detail in Simon et al. (2013b). In brief, adolescent and adult rats were acclimated to pellet delivery with a 30 min magazine training session. Rats were then trained to perform a single nose-poke into a lit port to earn a pellet. After shaping, rats were trained in CRIT. Each trial began with illumination of the nose-poke port (previously associated with reward-seeking) and presentation of a tone. This tone signaled that reward was not available; when the tone ceased, a nose-poke into the lit port once again elicited reward delivery. To prevent subjects from predicting the length of the response inhibitory period/tone, the duration of this cue was variable (pseudorandomly selected length of 5, 10, 20, or 30 s). After the tone, the nosepoke port only remained illuminated for 5 s, after which reward was no longer available. After either reward delivery or 5 s without a response, there was a 10–12 s intertrial interval. Each session lasted 60 min, and rats were trained in this task for 12 consecutive sessions prior to treatment. Trials in which rats responded during the port cue after the response inhibiting tone were scored as correct, and trials with a response during the tone were incorrect. Trials in which rats failed to respond during the 5 s response period after the tone were scored as omissions.

4.3. Drugs

Following training, behavior was tested during a 7-day drug regimen. Three doses of methylphenidate (.3, 1, and 3 mg/kg) or saline vehicle were administered on days 1, 3, 5, and 7, with drug-free baseline sessions on days 2, 4, 6, and 8 (Fig. 1B). Doses within this range have been previously shown to modulate dopamine and behavior while still maintaining cognitive task performance (Andrzejewski et al., 2014; Fernando et al., 2012; Urban et al., 2012). All drugs were administered 15 min before testing.

4.4. Data analysis

The measures of interest during CRIT were response inhibition ratio (correct/incorrect trials), total omissions, and latency to respond after the tone. Performance was compared via mixed ANOVA during the final three days of training, with age group as the between factor and session as the within factor. During drug treatment, behavior was analyzed using an age X drug dose ANOVA. Differences between individual doses were determined using repeated measure contrasts. Due to a technical issue, one adolescent rat was removed from all pre-drug analyses.

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