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The Effect of Methylphenidate on Associative Learning Among Youth with Attention-Deficit/Hyperactivity Disorder

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THE EFFECT OF METHYLPHENIDATE ON ASSOCIATIVE LEARNING AMONG YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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To: Dean Michael R. Heithaus
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This dissertation, written by Amy R. Altszuler, and entitled The Effect of Methylphenidate on Associative Learning among Youth with Attention-Deficit/Hyperactivity Disorder, having been approved in respect to style and intellectual content, is referred to you for judgement.

We have read this dissertation and recommend that it be approved.

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ABSTRACT OF THE DISSERTATION

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Despite strong evidence supporting the short-term efficacy of interventions for youth with Attention-Deficit/Hyperactivity Disorder (ADHD), and despite the fact that the majority of youth with ADHD receive treatment for the disorder at some point over the course of childhood, the long-term prognosis for individuals with ADHD remains poor. One potential explanation for the gap between short-term efficacy and long-term outcomes is that the most common intervention for youth with ADHD, stimulant medication, paradoxically undermines children's abilities to learn from contingencies through their action on the dopaminergic system. The dynamic dopamine theory posits that by increasing levels of dopamine, stimulant medication enhances reward-based learning but prevents phasic dips in dopamine necessary for punishment-based learning to occur. The current study explored the hypothesis that stimulant medication undermines punishment-based learning among school-aged youth diagnosed with ADHD using an associative learning task. The study used a 4 (stimulant medication dose: placebo, low, moderate, high) x 2 (trial type: reward, punishment) x 2 (punishment condition: regular, enhanced) design to evaluate children's ability to learn stimuli-category associations following reward and punishment. On reward-based trials, participants earned points

following correct associations and received no feedback following incorrect associations. On punishment trials, participants lost points (20 in the regular condition, 100 in the enhanced condition) following incorrect associations and received no feedback following correct associations. Results indicated that there was no significant main effect of medication on children's associative learning. Rather, children demonstrated better overall performance in response to rewards regardless of medication condition. Children performed worse when they received the enhanced punishment condition, an effect that was moderated by higher doses of medication. Results indicate that other factors, aside from dopamine levels, likely contribute to associative learning among youth with ADHD. Specifically, the punishment to reward ratio is likely an important factor that should be considered when designing interventions for youth with ADHD.

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INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is a chronic neurodevelopmental disorder affecting approximately 10% of children and adolescents in the U.S. (Danielson, Bitsko, et al., 2018). The core symptoms of ADHD – inattention, hyperactivity, and impulsivity, lead to significant impairment across domains of daily life functioning, including home, school, and peer settings (Barkley, 2015; Fabiano et al., 2006). For the majority of individuals diagnosed with ADHD, symptoms continue to cause significant educational, financial, occupational and interpersonal problems in young adulthood (Altszuler et al., 2015; Barkley, Murphy, & Fischer, 2008; Gordon & Fabiano, 2019; Hechtman et al., 2016; Kuriyan et al., 2013), and for a subset of individuals ADHD develops into more serious impairments during adolescence and young adulthood, including substance abuse and criminality (Merrill et al., 2019; Molina & Pelham, 2014; Sibley et al., 2011). The prevalence and persistence of ADHD-related problems across several areas of functioning places a large economic burden on society, with recent cost estimates in the U.S. ranging from $143 - $266 billion annually (Doshi et al., 2012). Understanding how to best intervene with youth with ADHD to reduce life-long impairment associated with the disorder is therefore not only a matter of critical importance to individuals with ADHD and their families, but also a major public health concern.

Attention-Deficit/Hyperactivity Disorder remains a prevalent and costly problem despite decades of research supporting the significant acute benefits of interventions for the disorder, including stimulant medication, behavioral interventions (e.g., behavioral

parent training, behavioral classroom management) and their combination (Evans, Owens, & Bunford, 2014; Evans, Owens, Wymbs, & Ray, 2017; Fabiano et al., 2009; Macphee, Altszuler, Merrill, & Pelham, 2017; Pelham & Fabiano, 2008; Pliszka, 2007; Wolraich et al., 2011). Importantly, whereas stimulant medication is the most common of these treatments, with 90% of children with the disorder receiving stimulant treatment at some point in their lifetime (Danielson, Visser, Chronis-Tuscano, & DuPaul, 2018), no long-term benefits associated with stimulant medication has been documented in the literature. Stimulant effects are only apparent as long as the medication has a pharmacological effect (4 to 12 hours depending on the formulation; Pelham et al., 2001). Further, there do not appear to be any residual benefits associated with taking medication. In the Multimodal Treatment Study of ADHD (MTA), the largest longitudinal study of ADHD treatment to date, children who received stimulant medication outperformed those who received behavioral treatment alone at the initial 14-month assessment (MTA Cooperative Group, 1999), but by the 24-month assessment the benefit of medication over behavioral treatment decreased by 50% (MTA Cooperative Group, 2004) and by the 36-month assessment there was no measurable benefit of medication over behavioral intervention (Jensen, Arnold, Swanson, Vitiello, & Abikoff, 2007).

It is surprising that medication does not produce long-term benefits, as it has large acute effects on domains that would be expected to lead to improvements in long-term functioning, such as on-task behavior, compliance, and academic productivity (Chronis, Pelham, Gnagy, Roberts, & Aronoff, 2003; Fabiano et al., 2007; Greenhill, 2002; Kortekaas-Rijlaarsdam, Luman, Sonuga-Barke, & Oosterlaan, 2019; Pelham et al., 2014; Prasad et al., 2013). However, the effect of stimulants on areas of functioning in which

skill development is required is much more limited, including academic achievement (Barbaresi, Katusic, Colligan, Weaver, & Jacobsen, 2007; Massetti et al., 2008; Tamm et al., 2017), social functioning (Altszuler et al., 2017; Hoza et al., 2005; Pelham & Bender, 1982; Whalen & Henker, 1991) and parenting (Wells et al., 2006). These findings suggest that despite improving behavior and attention in the short-term, medication does not help children to develop the competencies needed (e.g., ability to learn academic concepts, social skills) to successfully navigate their schooling and interpersonal relationships, which are key predictors of long-term outcomes (Altszuler, Page, et al., 2015; Kuriyan et al., 2013; Molina et al., 2012).

The lack of stimulant effects in key domains and on long-term functioning provides clear rationale for the use of behavioral interventions (Altszuler, Macphee, et al., 2015; Macphee et al., 2017; Pelham, 2008). In contrast to medication, behavioral interventions target the development of skills by teaching the key adults in a child's life (e.g., parents, teachers) to reinforce appropriate behavior through the use of praise and rewards and to reduce inappropriate behavior through the use of punishments and privilege removal (Evans, Owens, & Bunford, 2014; Kaminski, Valle, Filene, & Boyle, 2008; Pelham & Fabiano, 2008). Behavioral interventions produce positive effects on behavior and attention that are similar in magnitude to those produced by stimulants (Fabiano et al., 2007; Pelham et al., 2016; Pelham et al., 2014), and parents prefer treatment plans that include behavioral intervention (Schatz et al., 2015; Waschbusch et al., 2011). The use of behavioral intervention as a stand-alone treatment remains quite low compared to medication (likely a result of costs and complexity associated with implementing quality behavioral intervention), but the use of behavioral interventions in

combination with stimulant medication has risen significantly in recent years (Danielson, Visser, et al., 2018), and is currently the most commonly recommended intervention by leading professional organizations (Pliszka, 2007; Wolraich et al., 2011).

Recent trends supporting the combination of behavioral intervention and medications appear promising for improving long-term outcomes of youth with ADHD. When medication and behavioral interventions are combined, low doses of both modalities can achieve the same effects as high doses of either unimodal treatment (Fabiano et al., 2007; Pelham et al., 2014). Using low intensity treatments is likely more palatable than using high intensity interventions to parents and teachers (e.g., Coles et al., under review). Using low doses of medication reduces side effects (Fabiano et al., 2007; Pelham, Manos, et al., 2005), and low intensity behavioral interventions are less costly and take less parent and teacher time to implement (Page et al., 2016). Therefore, combined interventions, relative to unimodal treatment, may improve long-term adherence. Further, there is some evidence that combined intervention allows for both symptom reduction and skill development (Altszuler et al., 2017; Tamm et al., 2017), which should lead to better long-term outcomes. However, the mechanisms by which combined interventions achieve their effects is not well understood, and the literature documenting long-term effects of behavioral and combined interventions is limited.

Recent evidence collected in our laboratory suggests that stimulant medication may paradoxically undermine the effects of behavioral interventions, which may help explain why despite the large, acute effects of stimulant medication and combined interventions, and despite most individuals with ADHD receiving these interventions at some point during childhood, the long-term prognosis for individuals with ADHD

remains poor. Our laboratory recently completed a within-subjects crossover study in which children received intensive behavioral intervention combined with either stimulant medication or placebo for three weeks, and then received the opposite medication condition during the subsequent three weeks (Pelham at el., in preparation). Children who initiated treatment with combined intervention (i.e., stimulant medication plus intensive behavioral intervention) had twice as many negative verbalizations (i.e., talking back to adults, teasing peers) per day after medication was withdrawn compared to children who initiated treatment with placebo. The difference was observed despite the fact that children in the medication-first condition exhibited very low rates of negative verbalizations while taking medication. These results suggest that having medication onboard while participating in behavioral interventions reduces learning from behavioral contingencies. Post-hoc analyses of an earlier study conducted in our laboratory similarly suggest that the presence of medication interferes with response to intensive behavioral intervention (Chronis et al., 2004). Given the benefits associated with the use of combined interventions discussed above, understanding the mechanism by which stimulant medication may interfere with behavioral interventions is crucial for understanding how to improve long-term functioning among youth with ADHD.

The neurobiological literature suggests that stimulants may interfere with children's ability to learn from contingencies in their environment, such as those manipulated in behavioral interventions, through their action on the dopaminergic system (Frank, 2005). Stimulants increase tonic and phasic levels of the neurotransmitter dopamine (Schiffer et al., 2006; Volkow et al., 2001), functioning of which is depressed among individuals with ADHD (Ernst, Zametkin, Matochik, Jons, & Cohen, 1998;

Volkow et al., 2007; Volkow, Wang, & Baler, 2011). Dopaminergic function is central to creating behavior-consequence associations (Schultz, 1998) in that phasic activations of dopamine in response to rewards result in learned behavior-reward associations over time (Cohen, Haesler, Vong, Lowell, & Uchida, 2012; Fiorillo, Newsome, & Schultz, 2008), whereas phasic dips following punishment (Cohen et al., 2012; Ungless, Magill, & Bolam, 2004) result in learned avoidance of negative consequences (Frank, 2005). Stimulant medications increase levels of dopamine (Schiffer et al., 2006; Volkow et al., 2012; Volkow et al., 2001), which has been shown to enhance reward-based learning among adults with ADHD (e.g., Frank, Santamaria, O'Reilly, & Willcutt, 2007). However, by increasing dopamine levels, stimulant use may also prevent punishment-induced phasic dips in dopamine from reaching the level necessary to effectively shape behavior (Frank, 2005), an effect that has been consistently found among patients with Parkinson's Disease taking medication to increase dopamine levels (Bodi et al., 2009; Frank, O'Reilly, & Seeberger, 2004).

Stimulant-induced insensitivity to punishment learning has not yet been evaluated among youth with ADHD, but if supported, would have significant clinical implications. Interventions that include punishment-based components (e.g., reprimands, point or privilege loss) more effectively reduce disruptive behavior and increase academic productivity than those relying on reward-based strategies alone (Abramowitz, O'Leary, & Rosén, 1987; Acker & O'Leary, 1987; Rosen, O'Leary, Joyce, Conway, & Pfiffner, 1984), and have been found to result in better maintenance of on-task behavior (Sullivan & O'Leary, 1990). Therefore, if children fail to learn behavior-consequence associations while taking stimulant medication, they may face serious difficulties once stimulant

treatment is no longer active. The possibility that stimulant medication interferes with behavior-consequence associations is particularly worrisome given that the majority of individuals desist stimulant use during adolescence (McCarthy et al., 2009; Molina et al., 2009), a developmental period during which behavioral interventions are often less effective (Evans et al., 2014, 2017). Further, a recent study of treatment sequencing found that initiating treatment with stimulant medication reduces later uptake of behavioral intervention (Pelham et al., 2016). Therefore, failure to learn behavior-consequence associations during times of active stimulant use may result in youth with ADHD missing a critical window for developing the skills necessary for long-term success.

Research Objectives and Hypotheses

The current study aims to evaluate the impact of stimulant medication, specifically methylphenidate (MPH), on the ability of children with ADHD to learn from punishment and reward using a laboratory-based computer task. The first aim of the current study is to evaluate whether MPH impairs punishment-based learning on an associative learning task (Bodi et al., 2009). It is hypothesized that MPH will impair punishment-based learning as evidenced by lower accuracy on punishment-based learning trials compared to reward-based trials of the task when youth are taking MPH in contrast to similar performance across these trial types when taking a placebo. The second aim is to investigate whether the dose of MPH differentially impacts punishment-based learning by comparing accuracy on punishment-based and reward-based trials across MPH doses. It is hypothesized that the effect of MPH will be dose-dependent such that higher doses of MPH will impair punishment-based learning to a greater extent than will lower doses of MPH. The final aim is to evaluate whether the intensity of

punishment moderates the effect of MPH on punishment-based learning. It is hypothesized that the effect of MPH on punishment-based learning will be attenuated when punishment is intensified, as evidenced by increased accuracy on punishment-based trials of the associative learning task in an enhanced punishment condition relative to a regular punishment condition.

METHODOLOGY

Participants

Participants were 27 children between the ages of 7 and 12 (M = 8.72 years) diagnosed with *DSM-IV* ADHD-Combined subtype (ADHD-C) who were referred to clinical services at the Center for Children and Families (CCF) at FIU. Children were referred to the CCF by local professionals or schools, media advertisements, billboards, or parent self-referral. Participation was limited to children who met criteria for ADHD-C because models of dopamine dysfunction best account for the profile of impairment experienced by these individuals, rather than by children who meet criteria for the predominately inattentive or hyperactive/impulsive subtypes (Johansen, Sagvolden, Aase, & Russell, 2005). Sample characteristics are displayed in Table 1.

Evaluations of ADHD were made according to standard assessment procedures in the field (Pelham, Fabiano, & Massetti, 2005). Specifically, symptoms of ADHD, oppositional defiant disorder (ODD) and conduct disorder (CD), were assessed using the NIMH Diagnostic Interview Schedule for Children IV, computerized version (Shaffer, 2000), and parent and teacher ratings on the Disruptive Behavior Disorders Scale (DBD; Pelham, Gnagy, Greenslade, & Milich, 1992). Cross-situational impairment was assessed using parent and teacher ratings on the Impairment Rating Scale (IRS; Fabiano et al., 2006). Two doctoral level clinicians independently reviewed intake assessments to make diagnoses for each child who participated in the study. Twenty-four participants received a concurrent diagnosis of ODD and no participants were diagnosed with CD.

Children were excluded from the study on the basis of the following criteria: (1) a Full Scale IQ below 80 according to the Wechsler Abbreviated Scale of Intelligence,

Second Edition (WASI-II; Wechsler, 2011); (2) receiving psychotropic medication for conditions other than ADHD or active medical or psychiatric conditions that could be worsened by stimulants at the time of study enrollment; (3) documented intolerance to MPH medications; (4) concurrent diagnosis of *DSM-5* Autism Spectrum Disorder (ASD) as stimulants have been found to have reduced efficacy and tolerability in this population (Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, 2005); and (5) comorbid conditions requiring psychotropic medication or emergent treatment (e.g., mania, active suicidal ideation).

One participant withdrew from the study because of scheduling conflicts resulting from the parent's work schedule, partial data were collected and analyzed. All other participants completed the study.

Procedures

The study was approved by the Western Institutional Review Board (Protocol #: 20161191). Participants provided informed consent/assent prior to the implementation of study procedures. All children underwent an initial assessment to determine appropriateness for the study, which included an evaluation of ADHD, ODD and CD, a brief cognitive assessment, and a physical exam clearing participants to be prescribed stimulant medications.

Setting. The study was conducted within a Saturday Treatment Program (SatTP), an 8-week behavioral peer intervention for children with ADHD modeled after the Summer Treatment Program (Pelham et al., 2010). The SatTP was held for 3 hours on Saturday mornings and afternoons, and sessions were held approximately one week apart. Children were placed in 3 groups of 10 to 15, supervised by 5 to 7 paraprofessional counselors.

Counselors were supervised by an advanced doctoral student and a licensed clinical psychologist. Children participated in recreational activities (e.g., soccer drills and games) and cooperative learning activities. Staff members implemented a comprehensive behavior management system throughout the SatTP.

Design. The study used a 4 (medication: placebo; MPH: 0.15, 0.3, 0.6 mg/kg/dose) x 2 (trial type: reward, punishment) x 2 (task condition: regular punishment, enhanced punishment) within-subjects design to evaluate MPH and punishment manipulations on children's ability to learn associations from rewards and punishments. Study conditions were randomly assigned across the 8 days of the SatTP, such that each child received one condition per program day. Table 2 displays a sample study schedule for one participant.

Medication. Doses of MPH that most closely approximate 0.15, 0.3, and 0.6 mg/kg/dose and placebo were randomized by day over a total of the 8 days of the SatTP. The doses used in the current study represent standard dosing for low, moderate, and high doses of MPH respectively (Fabiano et al., 2007; Pelham et al., 2014; Pelham, Manos, et al., 2005). Order of medication condition was counter-balanced across participants. A portion of participants (n = 11), were participating in a concurrent medication study in which they were prescribed long-acting MPH on weekends, when study testing sessions were conducted. Ten of these children were prescribed OROS-MPH (Concerta) and one was prescribed Metadate CD. All other participants were prescribed immediate-release MPH. Long-acting and short-acting forms of MPH have been shown to have equivalent effects on children's attention, behavior, and productivity (Döpfner et al., 2004; Pelham et al., 2001; Swanson et al., 2004). Testing sessions were conducted within the time-course for the appropriate formulation of MPH.

Parents were provided dated blister packs containing medication capsules, sequenced according to the randomization schedule. Medication administration was confirmed by SatTP staff with parents at the start of each program day. Parents were also asked to return used blister packs as a check on medication adherence. Medication was delivered in a gelatin capsule so that participants, their parents, and staff members were not aware of medication condition. Adverse effects were monitored daily through parent and staff ratings on the Pittsburgh Side Effect Rating Scale (Pelham, 1993), a measure that has been routinely used in medication studies conducted within the STP (e.g., Pelham et al., 1999, 2001, 2005, 2014). No adverse events were reported during the study.

Task Procedures. One testing session was conducted per SatTP day. Task conditions were randomized by day and order was counter-balanced across participants. On four days, participants received the enhanced punishment condition and on four days participants received the regular punishment condition (Table 2). The computer task was administered individually to each child by a research assistant on a Dell laptop. The sessions were conducted in a quiet room and lasted approximately 15 minutes. Participants sat at a comfortable viewing distance from the laptop. Participants wore headphones and computer volume was kept at a standard level for all testing sessions.

Associative Learning Task. A modified version of a probabilistic learning task previously used by Bodi et al. (2009) to measure the impact of dopamine on associative learning among adults with Parkinson's Disease was used in the current study. The task measures participants' ability to learn stimuli-category associations through trial and error (see Table 3 for a description of the task structure). Stimuli were four kaleidoscopic

images, selected at random from a library of over 250 images (see Figure 1 for sample images). Unique images were presented during each testing session. Two of the four images presented during each testing session belonged to category "A" and the remaining two images belonged to category "B." One image from each category was associated with rewards (reward trials), such that participants earned points when they matched the image to the appropriate category. The remaining two images (one belonging to category "A" and one belonging to category "B") were associated with punishment (punishment trials), such that participants lost points when images were matched to the incorrect category. Punishment and reward trials were interspersed throughout each testing session. Two different punishment trial types were tested during unique testing sessions: regular and enhanced punishment (described in more detail below). Probabilistic feedback was provided across trial types, meaning that participants received accurate feedback on 80% of trials and inaccurate feedback on 20% of trials. Probabilistic feedback was introduced because pilot testing among youth ages 7-11 diagnosed with ADHD-C resulted in mean task performance above 80% across reward and punishment trial types, indicating potential ceiling effects (Altszuler, Macphee et al., 2016). Probabilistic feedback has been used in previous studies (Bodi et al., 2009; Frank et al., 2007; Mattfeld, Gluck, & Stark, 2011) to introduce variability in task performance and to prevent ceiling effects.

Each testing session consisted of 160 learning trials (40 trials/image) split into four consecutive testing blocks. The order of stimuli was counterbalanced across participants. Each testing session began with the presentation of one of the four images with the question "Is this an 'A' or a 'B'?" below the image, followed by the two possible categories. Stimuli were presented until the participant responded and trials were

separated by the presentation of a blank page for 1000 msec. Participants' point totals were displayed in the bottom right corner of the screen and were updated continuously depending on performance. On reward trials (Figure 1, Panel A), participants earned 20 points when the correct category was selected. To mimic feedback a child might receive from a parent or teacher (e.g., verbal praise, positive facial expression), point gain was associated with visual and audio feedback. Participants were presented with "+20" in green text, a happy face icon, and the "cha-ching" sound of a cash register. When the incorrect category was selected, participants did not receive any feedback or lose points. Across both punishment conditions (i.e., regular and enhanced), participants did not receive any feedback when the correct category was selected on punishment trials (Figure 1, Panels B and C). In the regular punishment condition, participants lost 20 points when the incorrect category was selected. Point loss was accompanied with visual and audio feedback, including "-20" presented in red text, a red sad face image, and a buzzer sound (Figure 1, Panel B). These punishments were intensified in the enhanced punishment condition such that participants lost 100 points, accompanied by "-100" presented in red text, a red angry face icon, and an airhorn sound (Figure 1, Panel C).

Prior to testing, task administrators provided participants with standardized instructions for completing the task. Participants were told they would be learning to match pictures to the correct letter. Category and trial types were explained to participants. Participants were also told that they would receive inaccurate feedback at times. Participants were instructed to keep as many points as possible and were shown all potential prizes for which points could be exchanged upon completion of the task. Participants were provided with one practice block prior to the first testing session to

ensure understanding of task procedures. During task administration, research assistants provided redirection if children engaged in off-task behavior and provided positive feedback for effort, but did not provide performance feedback. At the end of the task, children exchanged points for prizes, which ranged in point value depending on desirability.

Dependent Measure

Performance on the probabilistic learning task was analyzed as the dependent measure. Total correct categorizations out of total possible trials was calculated for each trial type (i.e., reward, punishment).

Analyses and Handling of Missing Data

Multilevel modeling (Hayes, 2006) was used to analyze the effect of study manipulations on task performance, with 128 observations per child (i.e., reward and punishment trial performance across 4 blocks per testing session, across 8 testing sessions). The model was fit for task performance on both trial types. Initial models indicated that the order of testing condition (e.g., condition received on day 5 versus day 8) and other potential covariates, including participant IQ, age, race, and ethnicity, failed to explain variance in task performance and were therefore dropped from the final model. Initial analyses also indicated that the interaction of block and study manipulations (i.e., punishment condition, medication dose) did not explain variance in task performance and those interactions were also dropped from model specification.

In the final model, trial performance was regressed on a random factor for child and several fixed effects: (a) medication dose (i.e., placebo, 0.15 mg/kg, 0.3 mg/kg, 0.6 mg/kg), (b) trial type (i.e., reward or punishment), (c) punishment condition (i.e., regular

or enhanced), (d) block, (e) the interaction of trial type and punishment condition, (f) the interaction of medication dose and trial type, (g) the interaction of medication dose and punishment condition, (h) the three-way interaction of medication, trial type, and punishment condition, and (i) the interaction of block and trial type. The effects testing study aims are (f) and (h). Effect (f) evaluates Aims 1 and 2: Does medication differentially impact learning from punishment compared to reward? Effect (h) evaluates Aim 3: Does dose of punishment moderate the effect of MPH on punishment learning? Multilevel models were conducted in SPSS 20.0. Where models indicated statistically significant effects, simple slope regressions (Preacher, Curran, & Bauer, 2006) were conducted using the reghelper package in *R*.

Overall, 13.4% of task performance data were missing as a result of participant absences (10.6%) or non-adherence to medication condition (2.8%). The multilevel modeling framework handles unbalanced observations on the outcome variable for data missing at random.

RESULTS

Table 4 displays raw means and standard deviations of task performance by trial type, punishment condition, and medication dose. Table 5 displays results of the multilevel model.

Learning Over Time

The effect of study manipulations on task performance was evaluated over the course of four blocks per testing session to assess learning over time. There was no significant direct effect of task block; however, there was a significant block by trial type interaction (p <0.05). As displayed in Figure 2, children's learning improved over time on punishment trials (Block 1 marginal mean= 0.52, Block 4 marginal mean= 0.59), whereas children's initial performance on reward trials was more accurate relative to punishment trials (Block 1 marginal mean=0.62) and remained consistent throughout testing (Block 4 marginal mean=0.64), t (1438) = 4.51, p <0.001.

Direct Effects of Study Manipulations

There was no significant direct effect of medication, nor any significant medication by trial type (i.e., reward, punishment) interactions. That is, medication did not improve children's associative learning on punishment- or reward-based learning trials.

There was a significant direct effect of trial type (p <0.001) such that children associated more stimuli with the correct categories on reward trials (marginal mean=0.62) compared to punishment trials (marginal mean=0.57). However, as mentioned above, there was a significant block by trial type interaction, such that this effect was no longer significant by block 4, t (328) = -0.48, p = 0.64.

There was a significant direct effect of punishment condition (p<0.01), such that children's task performance improved across trial types (i.e., reward and punishment) when they received the regular punishment condition (marginal mean=0.61) compared to the enhanced condition (marginal mean=0.58).

Interaction of Medication, Trial Type, and Punishment

The three-way interaction of medication, trial type, and punishment condition was significant for the moderate dose of MPH (p <0.01) and was trending towards significance for the high dose (p<0.10). Simple slopes regressions indicated that higher doses of medication (0.3 and 0.6 mg/kg MPH) had a differential effect on reward trial performance when participants received the enhanced punishment condition (Figure 3, Panel A). Specifically, in the enhanced punishment condition, participants performed significantly worse on reward trials when prescribed placebo (marginal mean= 0.55), t (1438) = 3.26, p < 0.01, and 0.15 mg/kg MPH (marginal mean= 0.58), t (1438) = 3.11, p < 0.01, compared to their performance when they received the regular punishment condition (placebo marginal mean= 0.64, 0.15 mg/kg marginal mean= 0.66). The same effect was not observed for punishment trials (Figure 3, Panel B).

DISCUSSION

The current study evaluated the impact of MPH on associative learning among youth with ADHD. The study measured the effect of four doses of MPH (i.e., placebo, low, moderate, and high) and two punishment conditions (i.e., regular and enhanced) on children's performance across reward- and punishment-based trial types on an associative learning task. Overall, results did not support hypotheses that stimulant medication interferes with children's punishment-based learning, and results indicated that this effect was not seen at any dose of medication. The study similarly did find support for intensifying punishment as a method for enhancing punishment-based learning. Across conditions, children performed only slightly above chance levels (averaging 62% accuracy on reward trials and 57% accuracy on punishment trials), indicating that the probabilistic nature of the task may have been too difficult to detect planned effects. Results did indicate that children demonstrated better overall performance when they were rewarded for correct responses relative to when they were punished for incorrect responses, regardless of medication status. Further, results indicated worse performance under more intensive punishment conditions, a finding that was attenuated by higher doses of medication. These findings, and their implications, are discussed in turn below.

Lack of Main Effects of Medication

The lack of a significant main effect of MPH in the current study is surprising, given that stimulant medication has been shown to improve performance of youth with ADHD on a variety of laboratory tasks (e.g., Bubnik, Hawk, Pelham, Waxmonsky, & Rosch, 2015; Groen, Mulder, Wijers, Minderaa, & Althaus, 2009; Rosch et al., 2015; Strand et al., 2012). According to Frank's (2005) dynamic dopamine model, stimulant

medication would be expected to improve performance on reward-based trials as a result of increased dopamine levels, as has been observed with adults with Parkinson's Disease (Bodi et al., 2009; Frank, O'Reilly, & Seeberger, 2004) and adults with ADHD (Frank et al., 2007). Failure to find a stimulant effect on reward-based learning in the current study may have been caused by limited variability in reward-based trial performance over time. Across punishment conditions, block 4 learning on reward trials averaged approximately 58% accuracy when participants were unmedicated and ranged from 60-65% accuracy when participants were taking medication. In comparison, unmedicated adults with ADHD performed similarly low (approximately 60% accuracy) when learning from reward-based stimuli, but medication improved performance to approximately 75% accuracy on a similar task (Frank et al., 2007). The current study is the first to use such a probabilistic learning paradigm in children, and the lack of learning over time in response to rewards suggests that the task may have been too difficult for children to achieve over 65% accuracy on reward-based trials.

Following the dynamic dopamine model (Frank, 2005), stimulant medication would also be expected to impair punishment-based learning by blocking phasic dips in dopamine levels, an effect that was not observed in the current study. Frank and colleagues (2007) also failed to show that medication impaired punishment-based learning among individuals with ADHD, to which authors attributed to a floor effect as participants only demonstrated optimal responding to punishment-based stimuli about 60% of the time. A floor effect may also explain lack of findings in the current study as punishment-based learning averaged approximately 57% accuracy across conditions. However, learning from punishment did improve significantly over time, and whereas

medication status did not moderate learning rate in the current study, it is possible that additional learning opportunities may have produced sufficient variability in performance to detect a medication effect.

While task calibration appears to be a probable explanation for the failure of the current study to support Frank's dynamic dopamine model, it is also likely that factors other than stimulant-induced dopamine levels influenced reward- and punishment-based performance on the associative learning task. Other potential contributing factors are discussed below.

Differences in Punishment- and Reward-Based Learning

In the current study, children demonstrated higher overall performance when they were rewarded for correct responses compared to when they were punished for incorrect responses on the associative learning task. These results differ from findings in the behavioral intervention literature, which show that punishment-based strategies, including the loss of points and privileges, are more effective at shaping behavior than are reward-based strategies (Abramowitz et al., 1987; Acker & O'Leary, 1987; Pfiffner & O'Leary, 1987; Rosen et al., 1984). However, the relatively large initial difference in performance across punishment and reward trials observed in the current study (approximately 11 percentage points), decreased by more than half by the last block of the task and the difference between the two trial types was no longer statistically significant by block 4. That is, despite understanding reward-stimuli associations better at the outset, children demonstrated more learning over time in response to punishment stimuli, tempering conclusions that children with ADHD learn better from rewards. Given that the rate of punishment-based learning increased over time while reward-based

learning remained consistent, it is possible that accuracy on punishment-based stimuli would have continued to improve and perhaps match or surpass accuracy on reward-based stimuli with additional learning trials. However, as mentioned above, it is also possible that performance on reward trials was stilted by task difficulty. Adding additional learning opportunities and increasing the percentage of accurate feedback on future iterations of the task may help provide clarity regarding the effectiveness of punishment- and reward-based learning strategies for children with ADHD.

The differential rate of learning from punishment and reward observed in the current study is interesting, as the effect has not been found in studies using the same task with other populations (Bodi et al., 2009; Mattfeld et al., 2011), or in the behavioral intervention literature (Acker & O'Leary, 1987; Iwata & Bailey, 1974; Pfiffner & O'Leary, 1987; Rosen et al., 1984). The task experience, particularly the experience of receiving no feedback, may have contributed to the differential learning rate across trial types. When children correctly matched images to the appropriate category on reward trials, they received immediate feedback that they were correct. That is, they only had to make a "one-step" association that Image 1 equaled "A." In contrast, on punishment trials, children received feedback when they were incorrect, meaning they had to process that 1) Image 2 did not equal "B," and that 2) Image 2 therefore equaled "A." Relative to the one-step process of learning reward-stimuli associations, the two-step process of learning punishment-stimuli associations may have therefore placed greater working memory demands on children, an area that is quite impaired for children with ADHD (Kasper, Alderson, & Hudec, 2012). The no feedback condition likely added even greater working memory demands, as no feedback could either mean that children incorrectly

associated an image to a category on a reward trial or correctly associated an image to a category on a punishment trial, meaning that children had to remember 1) whether the image was associated with reward or punishment and 2) to which category the image belonged. Separating punishment and reward trials into different testing sessions may help reduce the cognitive load experienced by children when completing the task, allowing for greater clarification beyond the current study regarding the trial type from which children with ADHD learn best.

The probabilistic learning task used in the current study attempted to tease apart effects from rewards and punishments by associating feedback types to different images within a testing session. However, reward and cost components were still mixed in the current study such that point losses and gains contributed to the same total point bank, which participants exchanged for desirable prizes at the end of the session. The overall task experience therefore mirrored a token economy, in which children earn points for positive behavior and lose points for inappropriate behaviors, and points are then exchanged for privileges and rewards (Altszuler, Macphee, et al., 2015). While such procedures represent contingencies implemented as a part of good clinical practice for youth with ADHD (Evans et al., 2017), combining reward and punishment trials within a single testing session may have also contributed to difficulties teasing apart learning effects from reward versus cost strategies, as has been found in the behavioral intervention literature (Iwata & Bailey, 1974; Kaufman & O'Leary, 1972; McGoey & DuPaul, 2000). Further separating rewards and consequences into separate testing sessions may help address these limitations.

While it is unclear which strategy led to better learning in the current study, children did respond (albeit in different ways) to both reward- and punishment-based strategies. Findings related to reward- and punishment-based learning suggest that, consistent with common clinical recommendations, both reward- and punishment-based strategies should be used in the treatment of children with ADHD. Punishment and reward strategies are both widely recognized components of effective behavioral interventions for youth with ADHD and disruptive behavior problems (DuPaul, Eckert, & Vilardo, 2012; Kaminski et al., 2008), and all widely used behavioral parenting programs teach caregivers to use both positive reinforcement and punishment strategies, such as time out and privilege removal (e.g., Barkley, 2013; Cunningham et al., 1993; McMahon & Forehand, 2005).

Differences by Punishment Condition

It was hypothesized that intensifying punishment would lead to better learning, as doing so would lead to a larger phasic dip in dopamine (Schultz, 1998), counteracting the effect of stimulant-induced increases in dopamine. The current study is the first to evaluate the interaction of differing intensities of punishment and stimulant medication, and support was not found for this hypothesis. In contrast, participants performed worse overall when they received the enhanced punishment condition, which consisted of a loss of 100 points accompanied by an angry face and unpleasant sound, compared to when they received the regular punishment condition, which consisted of a loss of 20 points accompanied by a less aversive face and sound.

Interestingly, the deterioration of learning in the enhanced punishment condition was driven nearly entirely by performance on reward trials, on which participants

performed approximately 4 percentage points worse in the enhanced condition. In contrast, there was little difference in punishment trial performance across the enhanced and regular punishment conditions. Learning deterioration in the enhanced punishment condition suggests that in the context of a more frustrating experience, children had more difficulty learning from reward-based stimuli. Children may have shown reduced performance on reward trials because performance on such trials was less meaningful in the enhanced punishment condition, as children only earned 20 points relative to losing 100 points. The fact that punishment condition influenced reward performance indicates that the overall task experience influenced children's ability to learn from rewards and punishments, providing additional support for separating punishment and reward testing sessions, as discussed above.

Children were able to maintain their performance on punishment trials (relative to reward trials) when they received the enhanced punishment condition, indicating that they were likely somewhat more motivated to avoid a large point loss. However, the presence of the enhanced punishment condition negatively impacted children's overall performance. It is likely (and was observed anecdotally), that children became more frustrated when they received the enhanced punishment condition. Overly strong punishments and criticisms, particularly relative to the strength of rewards, lead to increases in disruptive behavior and poorer behavioral outcomes (Musser, Karalunas, Dieckmann, Peris, & Nigg, 2017; Patterson, 2002). Children with ADHD are also more likely to give up in the face of frustration (Milich, 1994; Milich & Okazaki, 1991), which may have contributed to poorer performance on reward trials in the enhanced punishment condition relative to the regular punishment condition.

Medication, Punishment Condition, and Trial Type Interaction

As mentioned above, participants performed worse on reward trials when they received the enhanced punishment condition. However, deterioration of reward-based learning was attenuated by medication such that at moderate and high doses (0.3 – 0.6 mg/kg MPH), participants performed similarly across enhanced punishment (marginal means ranged from 63 – 66% accuracy) and regular punishment (marginal means ranged from 62 – 65% accuracy) conditions. In contrast, when participants were taking a placebo or a low dose (0.15 mg/kg MPH), they fared worse when they received the enhanced punishment (marginal means ranged from 55 – 58% accuracy) relative to when they received the regular punishment (marginal means ranged from 64 – 66% accuracy). These findings indicate that higher doses of medication helped offset the negative effects of the enhanced punishment condition on reward trial performance.

These findings are consistent with previous work examining the impact of stimulant medication on persistence among youth with ADHD. Previous work by Milich and colleagues (1991) demonstrated that children with ADHD performed the same on a solvable task when taking a moderate dose of medication (0.3 mg/kg MPH) relative to placebo. However, when given a frustrating task (a nonsense word search), children were much better able to persist when taking medication, and performed better on subsequent solvable puzzles, relative to their performance when taking placebo. Similarly, Pelham and colleagues (1997) found that a moderate dose (0.3 mg/kg MPH) improved persistence and reaction to failure among children with ADHD, and that research assistants (unaware of child medication status) rated children taking medication as putting forth more effort. Findings from the current study add to the literature that

medication provides a buffering effect when youth with ADHD are faced with frustrating situations.

Limitations

The current study was the first to evaluate stimulant-induced insensitivity to punishment-based learning among youth with ADHD and study limitations may help explain why support was not found for Frank's (2005) dynamic dopamine model among youth with ADHD. The current study was also the first to use the probabilistic learning task with children, and findings suggest that the task calibration used in the current study was likely too challenging for participants' developmental level. While learning did appear to occur from both trial types (as evidenced by better initial performance on reward trials and significantly improved learning over time on punishment trials), the highest accuracy achieved across conditions was 65%. Providing a higher percentage of accurate feedback will lead to better task performance (Altszuler, Macphee, et al., 2016), and might allow for detection of medication effects. It also appears that additional learning opportunities would have been helpful, particularly for punishment-based trials, as learning appeared to follow a linear trajectory and performance may have continued to improve with additional trials. As discussed previously, it is also possible that the differing cognitive loads posed by reward and punishment trials served as a confound, and that mixing punishment and reward trials in the same testing session influenced task performance. Limitations associated with the task development should be taken into account when designing future studies to evaluate the impact of stimulant medication on associative learning among youth with ADHD.

In addition to limitations associated with the task, the study sample was small and may have been underpowered to detect smaller effects. However, previous research indicates that medication should have relatively large effects on task performance (Bubnik et al., 2015; Rosch et al., 2015; Strand et al., 2012). Further, the use of a within-subjects design increases power and did allow for the detection of several significant effects in the current study. As with most studies conducted with youth with ADHD, the study sample was predominately male, and as with most studies conducted in South Florida, participants were predominately Hispanic/Latino. Study results may therefore lack generalizability.

Clinical Implications

The present study has several implications relevant to the treatment of children with ADHD. First, children learned from both reward- and punishment-based strategies, supporting current clinical recommendations to use both forms of behavior modification with youth with ADHD. Findings also highlight the importance of ensuring that reward and punishment-based strategies are balanced. When children lost more points than they earned, their performance was affected, likely due to frustration. Findings are in line with clinical recommendations to provide positive feedback at a higher frequency than negative redirections (Altszuler, Macphee, et al., 2015), because, as was seen in the current study, overly negative feedback results in worse behavior. Further, tasks that are too challenging may result in children giving up altogether (Milich et al., 1991; Milich & Okazaki, 1991). Consistent with past research, findings from the current study also indicate that stimulant medication improves performance among youth with ADHD when faced with frustrating or challenging tasks. These findings indicate that it can be helpful

to have medication onboard when children must face challenging or frustrating tasks. However, psychosocial interventions aimed at improving frustration management and teaching parents and teachers to set achievable goals for youth with ADHD have also been found to be effective (Kolko, Lindhiem, Hart, & Bukstein, 2014; Waxmonsky et al., 2016), and as discussed previously, interventions that teach skills are likely to lead to better long-term functioning.

Conclusions and Future Directions

Findings from the current study failed to support hypotheses that stimulant medication would impair punishment-based learning, and that enhanced punishment would attenuate these effects. One explanation for failure to find support for hypotheses is that the associative learning task used in the current study was not ideally calibrated to youth with ADHD. Due to this limitation, the hypothesis that medication interferes with punishment-based learning cannot be ruled out. Future work should continue to examine this hypothesis among youth with ADHD using suggested modifications to the current task to allow for more variability in task performance and to better isolate effects from reward- and punishment-based learning. Should support be found for this mechanism in a lab-based setting, it will be crucial to conduct studies in clinical settings to better understand how findings translate to clinical practice recommendations for youth with ADHD. Many factors influence contingency-based learning among youth with ADHD, and findings from the current study suggest that emotion regulation and working memory likely play a role. Future work should continue to explore how these variables impact children's response to behavioral interventions and stimulant medication. Lastly, many factors likely contribute to the gap between short-term efficacy and positive long-term

outcomes for youth with ADHD, including poor long-term adherence to treatment, reduced motivation to implement behavioral interventions following stimulant treatment, and lack of resources for/availability of chronic models of care for individuals with ADHD. More work targeting the development of long-term services for individuals with ADHD and engagement in such services is sorely needed to improve the long-term prognosis of these individuals.

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Table 1
Sample Characteristics

Age *M* (SD)	8.72 (1.70)
Gender (% Male)	77.8
Ethnicity (%)	
Hispanic	81.5
Non-Hispanic	14.8
Did not respond	3.7
Race (%)	
White	77.8
African American	14.8
Multi-racial	7.4
Highest Parental Education (%)	
Less than high school	3.7
High school or GED	14.8
Partial college	7.4
Associate's degree	14.8
Bachelor's degree	33.3
Graduate training or degree	25.9
Estimated Full-Scale IQ *M* (SD)	96.81 (13.02)
ODD Diagnosis (%)	88.9
CD Symptoms *M* (SD)	0.85 (0.91)

Note. n = 27

Table 2

Sample Participant Testing Schedule

Day	Medication	Punishment Condition
1	Placebo	Enhanced
2	0.3 mg/kg MPH	Regular
3	0.15 mg/kg MPH	Enhanced
4	Placebo	Regular
5	0.6 mg/kg MPH	Enhanced
6	0.15 mg/kg MPH	Regular
7	0.6 mg/kg MPH	Regular
8	0.3 mg/kg MPH	Enhanced

Note. MPH = Methylphenidate

Table 3

Task Structure by Trial Type and Punishment Condition

RP Condition	Probability "A" (%)	Probability "B" (%)	Trial Type
Image 1	80	20	Reward
Image 2	20	80	Reward
Image 3	80	20	Punishment (Regular)
Image 4	20	80	Punishment (Regular)
EP Condition	Probability "A" (%)	Probability "B" (%)	Trial Type
Image 1	80	20	Reward
Image 2	20	80	Reward
Image 3	80	20	Punishment (Enhanced)
Image 4	20	80	Punishment (Enhanced)

Note. RP = Regular Punishment, *EP* = Enhanced Punishment.

Table 4
Raw Means and Standard Deviations for Dependent Measures

Outcome	Punishment Condition	Placebo *M (SD)*	0.15 mg/kg MPH *M (SD)*	0.3 mg/kg MPH *M (SD)*	0.6 mg/kg MPH *M (SD)*
Reward trial performance	RP	0.59 (0.23)	0.62 (0.21)	0.63 (0.21)	0.64 (0.22)
	EP	0.55 (0.22)	0.58 (0.20)	0.64 (0.22)	0.63 (0.18)
Punishment trial performance	RP	0.56 (0.15)	0.58 (0.12)	0.57 (0.19)	0.57 (0.18)
	EP	0.57 (0.17)	0.57 (0.15)	0.56 (0.14)	0.56 (0.16)

Note. RP = Regular Punishment, *EP* = Enhanced Punishment. Models were conducted on estimated marginal means. Raw means and standard deviations are presented for ease of interpretation. Means represent the average percentage of correct stimuli-category associations per session.

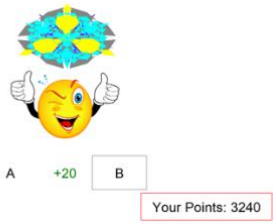
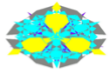
Table 5

Results of Multilevel Model for Task Performance

Term	Estimate	*SE*	t	*p*	95% CI
Intercept	0.62	0.03	22.13	<0.001	0.56, 0.67
Punishment Trial Type (vs. Reward)	-0.13	0.03	-4.04	<0.001	-0.19, -0.06
EP Condition (vs. RP)	-0.09	0.02	-3.26	<0.01	-0.13, -0.03
0.15 mg/kg MPH (vs. Placebo)	0.02	0.02	0.95	ns	-0.03, 0.07
0.3 mg/kg MPH (vs. Placebo)	-0.02	0.02	-0.74	ns	-0.07, 0.03
0.6 mg/kg MPH (vs. Placebo)	0.01	0.03	0.16	ns	-0.05, 0.05
Punishment Trial*EP Condition	0.09	0.03	2.66	<0.01	0.02, 0.16
Punishment Trial*0.15 mg/kg MPH	-0.01	0.03	-0.27	ns	-0.08, 0.06
Punishment Trial*0.3 mg/kg MPH	0.04	0.03	1.04	ns	-0.03, 0.10
Punishment Trial*0.6 mg/kg MPH	-0.01	0.04	-0.01	ns	-0.07, 0.07
EP Condition*0.15 mg/kg MPH	0.01	0.03	0.04	ns	-0.07, 0.07
EP Condition* 0.3 mg/kg MPH	0.11	0.03	3.17	<0.01	0.04, 0.18
EP Condition*0.6 mg/kg MPH	0.06	0.04	1.79	<0.10	-0.01, 0.13
Punishment Trial* EP Condition*0.15 mg/kg MPH	-0.01	0.05	-0.16	ns	-0.10, 0.09
Punishment Trial*EP Condition*0.3 mg/kg MPH	-0.13	0.05	-2.65	<0.01	-0.22, -0.03
Punishment Trial*EP Condition* 0.6 mg/kg MPH	-0.08	0.05	-1.72	<0.10	-0.18, 0.01
Block	0.01	0.01	1.09	ns	-0.01, 0.02
Punishment Trial*Block	0.02	0.01	2.42	<0.05	0.01, 0.03

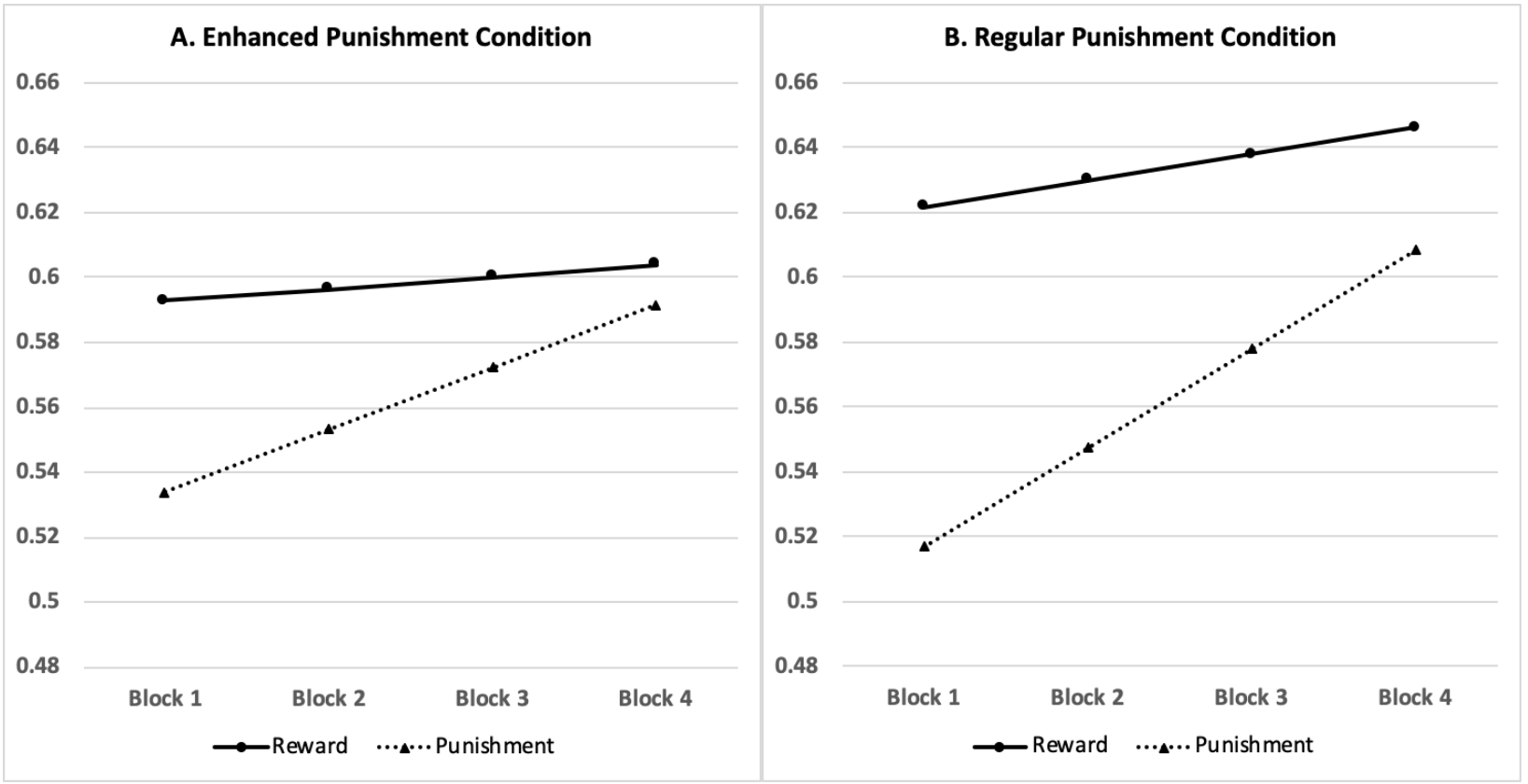
Note. SE = standard error. *EP* = Enhanced Punishment. *RP* = Regular Punishment. All binary variables were coded as dummy variables (e.g., Punishment Trial = 0, Reward Trial = 1).

Figure 1
Task Feedback by Trial Type and Punishment Condition

	a. Reward	**b. Regular Punishment**	**c. Enhanced Punishment**
Correct Selection			
Incorrect Selection			

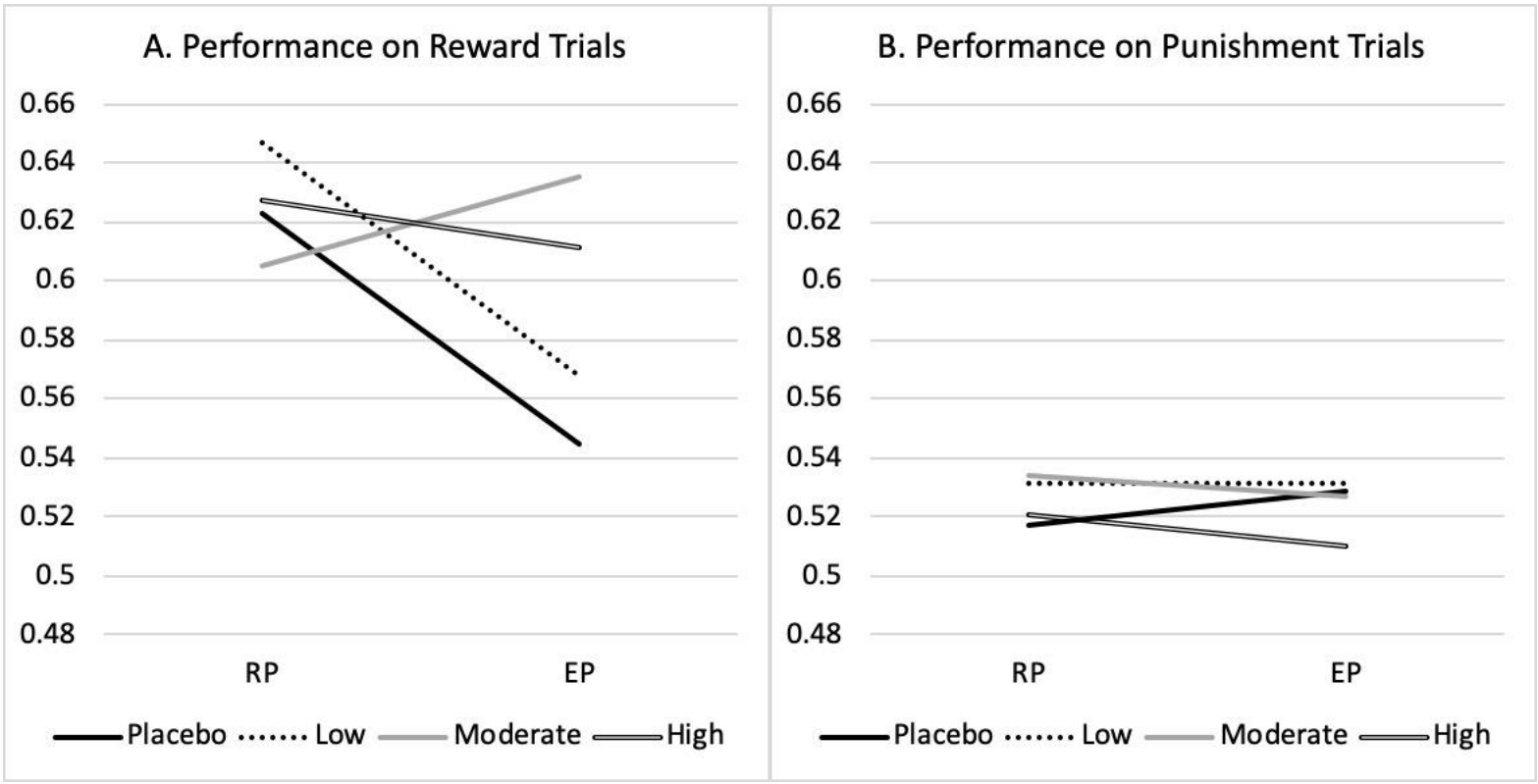
Note. Accurate feedback is depicted for demonstration purposes. Sample image for Reward and Regular Punishment trials belonged to Category "B." Sample image for Enhanced Punishment trials belonged to Category "A."

Figure 2
Task Learning by Punishment Condition and Trial Type



Note. Task performance is measured by the percentage of correct stimuli-category associations per testing session.

Figure 3
Task Performance by Trial Type, Punishment Condition, and Medication Dose



Note. RP = Regular Punishment. *EP* = Enhanced Punishment. Task performance is measured by the percentage of correct stimuli-category associations per testing session.

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