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Learning Experience Reverses Catecholaminergic Effects on Adaptive Behavior

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ABSTRACT

Background: Catecholamines are important for cognitive control and the ability to adapt behavior (e.g., after response errors). A prominent drug that modulates the catecholaminergic system is methylphenidate. On the basis of theoretical consideration, we propose that the effects of methylphenidate on behavioral adaptation depend on prior learning experience.
Methods: In a double-blind, randomized, placebo-controlled crossover study design, we examined the effect of methylphenidate (0.25 mg/kg) on post error behavioral adaptation processes in a group of n = 43 healthy young adults. Behavioral adaptation processes were examined in a working memory, modulated response selection task. The focus of the analysis was on order effects within the crossover study design to evaluate effects of prior learning/task experience.
Results: The effect of methylphenidate/placebo on post-error behavioral adaptation processes reverses depending on prior task experience. When there was no prior experience with the task, methylphenidate increased post-error slowing and thus intensified behavioral adaptation processes. However, when there was prior task experience, (i.e., when the placebo session was conducted first in the crossover design), methylphenidate even decreased post-error slowing and behavioral adaptation. Effect sizes were large and the power of the observed effects was higher than 95%.
Conclusions: The data suggest that catecholaminergic effects on cognitive control functions vary as a function of prior learning/task experience. The data establish a close link between learning/task familiarization and catecholaminergic effects for executive functions, which has not yet been studied, to our knowledge, but is of considerable clinical relevance. Theoretical implications are discussed.

Keywords: cognitive control, error, methylphenidate, dopamine, norepinephrine, behavioral adaptation

Introduction

The catecholaminergic system, including norepinephrine (NE) and dopamine (DA), is central for many cognitive processes, including cognitive control mechanisms (Robbins and Arnsten, 2009; Arnsten, 2011). Cognitive control is an umbrella term for functions necessary for goal-directed behavior and behavioral adjustments (Diamond, 2013). A central requirement for these behavioral adjustments is the ability to adapt behavior after errors (Falkenstein et al., 2000; Holroyd and Coles, 2002; Ridderinkhof et al., 2004; Ullsperger et al., 2014). From a neurobiological perspective, it is well-known that the DA system plays a central role in error monitoring (Holroyd and Coles, 2002; Beste et al., 2009; Willemssen et al., 2009; Ullsperger et al., 2014), and also the NE system has been shown to modulate error processing (Caetano et al., 2012; Warren and Holroyd, 2012; Colzato et al., 2013), suggesting that the catecholaminergic system is important for error-related behavioral adjustments.

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Significance Statement

The ability to adapt actions is central for goal-directed behavior. Pharmacological treatments (e.g., modulating the catecholaminergic system) aim to improve the ability to adapt behavior. However, study results are inconclusive. We modulated the catecholaminergic system with methylphenidate (MPH), which is commonly used in the treatment of various mental illnesses. We show that MPH does not always increase the ability to adapt behavior. Rather, the effect of MPH strongly depends on prior learning experience. MPH can even impair behavioral adaptation when prior learning experience is evident. The study establishes a close link between learning and catecholaminergic effects for executive functions, which has not yet been studied, to our knowledge, but is of considerable theoretical and clinical relevance.

A prominent drug that modulates the catecholaminergic system (i.e., DA and NE) is methylphenidate (MPH). MPH is a combined DA/NE transporter blocker and thus increases postsynaptic DA and NE levels (Volkow et al., 1999; Skirrow et al., 2015; Faraone, 2018). However, pharmacological studies examining error processing and modulating the catecholaminergic system using MPH revealed rather inconsistent results: Costa et al. (2013) reported stronger functional magnetic resonance imaging signals during erroneous response inhibition after 40 mg MPH administration in healthy participants, but these data were very variable and no changes in behavioral adaptation were observed. Similarly, Barnes et al. (2014) showed that the ERN was increased after 30 mg MPH administration in healthy participants, but there was no evidence for an MPH effect at the behavioral level. Other results in healthy subjects, however, revealed weaker error-related activity within the anterior cingulate cortex after 20 mg MPH administration compared with placebo along with a strong but very variable behavioral adaptation effect (Moeller et al., 2014). In clinical populations (i.e., children with attention deficit hyperactivity disorder), no effect of 15 mg MPH on post-error behavioral adaptation was found (Jonkman et al., 2007), and, again, electrophysiological correlates of error processes were modulated inconsistently. This heterogeneity of findings after MPH administration is also evident in other cognitive control domains (Linssen et al., 2014) and suggests that there are important unidentified factors determining the direction and magnitude of MPH-induced catecholaminergic effects on error monitoring and its neural correlates. It is important to identify these factors, since MPH is often used to treat cognitive control dysfunctions in neuropsychiatric disorders (Jonkman et al., 2007; Bluschke et al., 2018; Faraone, 2018).

Crucially, all existing studies on MPH-related modulations in error monitoring used crossover study designs in which each participant was tested twice in a counterbalanced order. Just recently, it has been suggested that such crossover study designs may obscure MPH effects on some forms of cognitive control processes (Bensmann et al., 2019). The background is as follows. Increased DA/NE concentrations resulting from MPH administration have been shown to increase gain control (Servan-Schreiber et al., 1990; Adelhöfer et al., 2018; Bensmann et al., 2018; Beste et al., 2018). Gain control mechanisms reflect modulations in the signal-to-noise ratio in neural information processing (Servan-Schreiber et al., 1990; Li et al., 2001; Yousif et al., 2016; Ziegler et al., 2016) and high neural gain facilitates response control and selection processes (Aston-Jones and Cohen, 2005; Nieuwenhuis et al., 2005; Chmielewski et al., 2017; Mückschel et al., 2017; Adelhöfer et al., 2019). Importantly, gain control mechanisms are closely related to processes induced by learning and plasticity (Dosher and Lu, 1998; Gold et al., 1999). Such processes are likely to occur in crossover designs since measurements are repeated within participants. Bensmann et al. (2019) suggested that effects of MPH on cognitive control are modulated by prior task experience, because MPH effects and learning or task experience-related modulations seem to tap into identical or at least highly similar neural mechanisms. Specifically, Bensmann et al. (2019) suggested that these common neural principles refer to above-mentioned gain control mechanisms. Both catecholamines and learning seem to induce their effects by modulating gain control processes. Yet in addition to gain control considerations, some data seem to indicate that MPH effects in attention deficit hyperactivity disorder depend on task difficulty (Biehl et al., 2016). Task difficulty and learning effects are clearly interrelated since learning effects are particularly strong in more difficult tasks, and task difficulty reduces with increased task experience. Thus, also from that perspective there is ample reason to hypothesize that MPH effects are modulated by learning/task experience effects.

However, the aforementioned aspect focusing on gain control processes seems particularly relevant when it comes to error-related behavioral adaption, because theoretical concepts on error-related behavioral adaptation stress the role of DA-dependent reinforcement learning (Holroyd and Coles, 2002) and hence a system that is modulated by MPH. In line with a learning or familiarization-dependent modulation of error-processing mechanisms, previous research has shown that neurophysiological correlates of error monitoring are modulated by (prior) learning experience (Holroyd and Coles, 2002; Beaulieu et al., 2014). Thus, there is ample reason to hypothesize that the effects of MPH on error monitoring depend on prior experience with error-related behavioral adaptation processes in a specific task. If MPH effects and learning-related effects tap into identical neural mechanisms (Bensmann et al., 2019), it may be hypothesized that both effects add up (i.e., when MPH is administered in the second session) and post-error behavioral adaptation is better (stronger) compared with participants who take MPH in the first session. However, it needs to be considered that an inverted U-shape function has been described relating DA/NE concentrations and performance (Aston-Jones and Cohen, 2005; Cools and D'Esposito, 2011). According to that function, performance can decline once neural processes modulated by catecholamines are further modulated beyond an optimal point. It is therefore reasonable to hypothesize that post-error behavioral adjustment performance can also decline (i.e., there is a smaller post-error slowing [PES]) when MPH is administered in the second session and adds on prior task familiarization.

MATERIALS AND METHODS

Participants and Power Considerations

To determine the sample size, an priori sensitivity (power) analysis was conducted using G*power (Faul et al., 2007). Previous data by our group analyzing order effects of MPH/placebo administration reported effect sizes η_p^2 of approximately .15

(Bensmann et al., 2019). However, having N of approximately 40 participants, even smaller interactive effects between MPH administration and prior task experience ($\eta_p^2 = .05$; i.e., 5% explained variance in the interaction) can be detected with a power of 95%. For the current study, we collected data from n = 42 healthy, young participants who took part in the study. Two participants were later excluded due to an accuracy of <50%. At random, 2 additional participants were excluded to maintain the same sample size per group, resulting in a sample of n = 38 participants included in the analysis (mean age 24.14; SD 3.09; range 19–31 years; 23 female). All participants were right-handed and had normal or corrected-to-normal vision. No participants reported regular drug intake or prior experience with MPH or had a history of psychiatric or neurological disorder. During the telephone interview, we used the screening questions from the Mini-DIPS (Margraf, 1994) to determine acute mental illnesses. If there was 1 positive screening answered question in the direction of a possible neuropsychiatric symptom/disorder, the participant was not further considered for the study. All participants provided written informed consent, and the institutional review board of TU Dresden approved the study.

MPH Administration

To investigate the interaction between task experience effects and MPH administration, we used a randomized, double-blind crossover design. That is, the experimenters and participants were blind to the order of MPH vs placebo administration. Each participant was randomly assigned to 1 of 2 groups. Every second participant who met the inclusion criteria during telephone screening was allotted the group who received MPH on the first appointment. One group started with MPH in the first session (placebo in the second session), the other group started with placebo in the first session (MPH in the second session). In each session, the participants performed the same task (see below). Between sessions there was a delay of 5 days and not more than 7 days. Participants received a single dose of MPH (0.25 mg/kg body weight). Since plasma levels of MPH peak 1 to 3 hours after oral administration (Challman and Lipsky, 2000; Rösler et al., 2009), the experiment began approximately 2 hours after MPH administration, which is in line with previous studies (Adelhöfer et al., 2018; Bensmann et al., 2019). Between the testing sessions, there was a delay of 5 days (no more than 7 days).

Task

Error-related behavioral adaptation is usually examined using flanker tasks. However, these tasks provoke errors related to action slips (i.e., inappropriate action impulses) and attentional lapses (Maier et al., 2011; van Driel et al., 2012), which need to be distinguished from failure of higher order cognitive processing (Pailing and Segalowitz, 2004; Hoffmann and Falkenstein, 2010; Hoffmann et al., 2014; Hoffmann and Beste, 2015). To examine the latter, we used a choice-response mental rotation task (Hoffmann et al., 2014) (see Figure 1).

It has been suggested that errors in mental rotation paradigms are predominantly errors from deliberation and less due to action slips (i.e., a lapse of attention) (Wascher et al., 1999; Maier et al., 2011; Plewan et al., 2016). To avoid modulating effects of sex, letter stimuli (F or R) were used because these do not evoke sex differences during mental rotation (Jansen-Osmann and Heil, 2007). The letter stimuli were rotated clockwise and counter-clockwise in a typical (nonmirrored) and a mirrored fashion (Heil et al., 1998; Heil, 2002; Beste et al., 2010). The rotation angles were 0°, 45°, 135°, 225°, or 315°. The letter stimuli were presented for 200 milliseconds. The task consisted of 640 trials, which were presented in 8 blocks of 80 trials each. The stimuli were presented in random order, and it was ensured that the same frequency of rotation angles and mirrored/nonmirrored letters was presented in each block. Whenever the stimulus was mirrored, the participants had to press the left response button, and when the stimulus was nonmirrored the participants pressed the right response button (i.e., CRTL keys on a standard QWERTZ-keyboard). The participants were instructed to respond as quickly and accurately as possible. To ensure a sufficiently high error rate, time pressure was applied. If the participants responded prior to the response deadline, a yellow "smiley" appeared on the screen. A red "frowney" appeared if the response to too slow. In the initial training block, this response deadline was 1000 ms. Importantly, the response deadline was

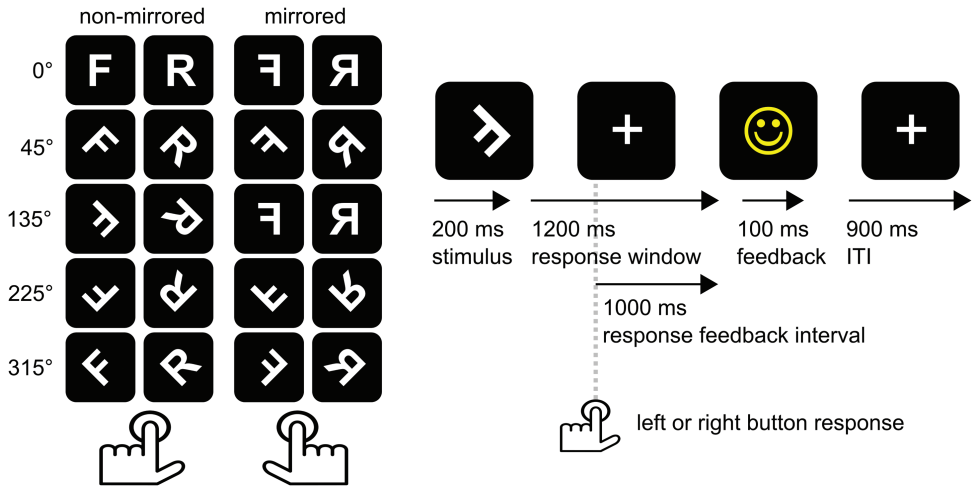

Figure 1. Presented letter stimuli (left) and stimulus timing (right). Letters ("F" or "R") were rotated at an angle of 0°, 45°, 135°, 225°, or 315°. Additionally, each letter was presented either mirrored or nonmirrored. The correct response button for nonmirrored and mirrored stimuli was randomized between participants. In each trial, the stimulus was presented for 200 milliseconds, followed by a 1200-millisecond response window. After a response of 1000 milliseconds or after the end of the response window, feedback was presented for 100 milliseconds. This was followed by an inter-trial interval of 900 milliseconds.

individually adjusted after each block to ensure that the error rate of each participant was consistently between 8% and 12% (Hoffmann et al., 2014). If the error rate in 1 block was <8%, the deadline was decreased by subtracting 1 SD of the reaction time (RT) of the previous block from the deadline of the previous block. If the error rate was >12%, 1 SD was added to the deadline of the previous block. The feedback stimulus was displayed for 100 milliseconds, followed by an inter-trial interval of 900 milliseconds. All trials with a correct button press during stimulus presentation or within the post-stimulus response window of 1200 milliseconds (i.e., within 1400 milliseconds from stimulus onset) were considered as correct trials. Pressing an incorrect button within 1400 milliseconds after stimulus onset was considered as error trial. Due to the focus on error processing, trials with a button press later than 1400 milliseconds after stimulus onset as well as trials without any response were considered as "misses" and excluded from further analysis. Before the experiment, the participants practiced the task for 80 trials.

Statistical Analyses

Mixed effects ANOVAs were used for the data analyses. The factor "drug sequence" (MPH first vs MPH second) was included as between-participant factor to account for the order in which the appointments were completed. The factor "substance" (placebo vs MPH) as well as "rotation angle" and "mirroring" were modelled as within-participant factors. Greenhouse-Geisser correction was applied when necessary. All post-hoc tests were Bonferroni-corrected. For all descriptive statistics, the mean and SEM are given as a measure of variability.

RESULTS

Regarding general task performance (the RTs), the mixed-effects ANOVA revealed a main effect of mirroring ($F[1,36]=36.6$; $P<.001$; $\eta^2p=.48$). Participants responded faster if the stimuli were not mirrored (413 milliseconds ±9) than in the nonmirrored condition (436 milliseconds ±9). The significant main effect of "rotation angle" ($F[1.42,51.26]=161.11$; $P<.001$; $\eta^2p=.82$) showed that RTs differed significantly between rotation angles (0°: 377 milliseconds ±7; 45°: 397 milliseconds ±8; 135°: 474 ms ±11; 225°: 478 milliseconds ±11; 315°: 396 milliseconds ±9). These RT differences were found between all rotation angles ($P<.001$) except between 45° and 315° as well as 135° and 225° ($P=1$). There was a significant interaction effect of substance × drug sequence ($F[1,39]=47.38$; $P<.001$; $\eta^2p=.57$). As previously mentioned, there was a significant interaction effect of substance × rotation angle × drug sequence ($F[1.9,68.42]=6$; $P=.005$; $\eta^2p=.14$). This interaction is shown below in Figure 2.

Post-hoc *t* tests comparing the RT difference between placebo and MPH condition separately for all rotation angles showed that in the placebo first group, participants responded faster on MPH than on placebo ($P<.005$), whereas participants responded slower on MPH compared with placebo in the MPH first group ($P<.003$). All other main effects and interaction were not significant ($P>.073$; $F<3.42$; Table 1).

The RT data suggest that the direction of the MPH/placebo effect was modulated depending on the test order. MPH led to slower RTs, relative to placebo, if MPH was administered in the second session. If MPH was administered in the first session, the accuracy was lower and the RTs faster. These effects were particularly visible at rotation angles of 135° and 225°. Since a speed-accuracy trade-off cannot be ruled out on that data, we calculated a composite score in which the RTs were relativized by the accuracy of the responses (i.e., RTs were divided by accuracy).

For the accuracy data, the ANOVA showed a significant main effect of mirroring ($F[1,36]=4.57$; $P=.039$; $\eta^2p=.11$). Participants responded more accurately in the mirrored condition (76% ±2) compared with the nonmirrored condition (78% ±2). There was a main effect of rotation ($F[1.46,52.66]=164.71$; $P<.001$; $\eta^2p=.82$). Accuracy differed significantly between rotation angles (all $P<.001$), except for 45° and 315° as well as for 135° and 225° (0°: 89% ±2; 45°: 87% ±2; 135°: 62% ±2; 225°: 61% ±2; 315°: 87% ±2). Additionally, there was a significant interaction effect of mirroring × rotation. Post-hoc *t* tests showed that accuracy differed significantly between the nonmirrored and mirrored condition for all rotation angles ($P<.01$), except for 315° ($P=.632$). All other main effects and interaction effects did not yield significance ($P>.3$; $F<1.23$). Therefore, there is no speed-accuracy trade-off.

The most important behavior parameter to analyze regarding error-monitoring processes is the PES. The PES was computed using the method proposed by Dutilh et al. (2012). The mean PES was 24.84 milliseconds (±3.99). The mixed-effects ANOVA revealed no main effect substance ($F[1,36]=.32$; $P=.576$), but an interaction substance × sequence group ($F[1,36]=18.89$; $P<.001$; $\eta^2_p=.344$), which is shown in Figure 3.

As can be seen in Figure 3, the degree of PES did not differ between sequence groups in the placebo condition ($t[36]=0.25$;

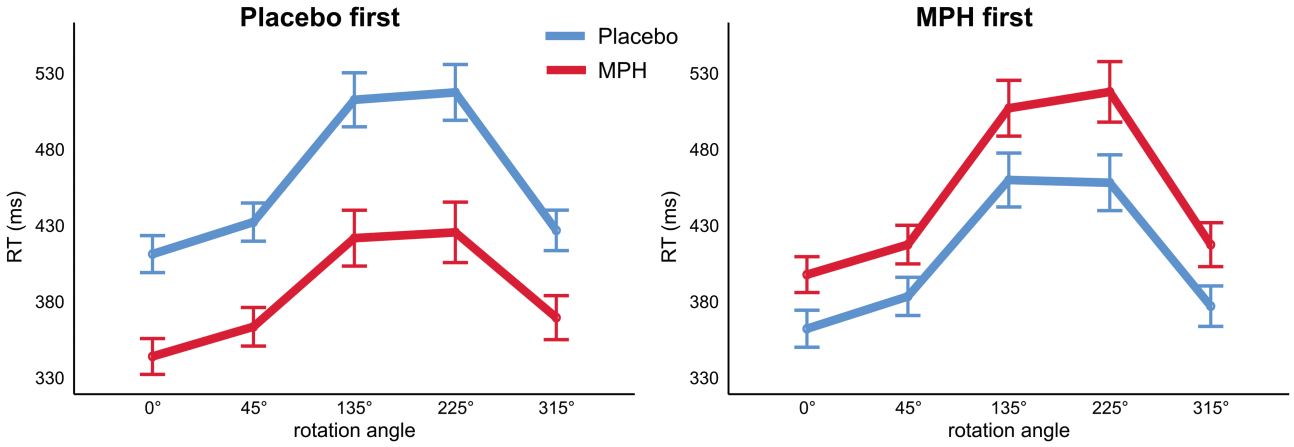

Figure 2. Interaction effect of substance × rotation angle × drug sequence for the accuracy data. The error bars denote the SEM.

Table 1. Comparison of Placebo and MPH Condition RTs for All Rotation Angles and Drug Sequence Groups

	Mean RT diff. (ms)	*df*	*T*	*P*	*d*
Placebo first					
0°	67.31	18	5.55	<.001	1.30
45°	68.84	18	6.25	<.001	1.44
135°	90.98	18	3.96	.005	.91
225°	92.07	18	4.08	.004	.94
315°	57.40	18	4.68	.001	1.08
MPH first					
0°	−35.59	18	−5.02	<.001	−1.24
45°	−34.07	18	−4.40	.002	−1.05
135°	−47.21	18	−4.20	.003	−.97
225°	−59.76	18	−5.29	<.001	−1.22
315°	−40.45	18	−4.83	.001	−1.14

Results of the Bonferroni-corrected *t* tests are given, including mean difference, degrees of freedom (df), T and P value as well as Cohen's d.

$P > .80$). However, in the MPH condition, the PES was larger when MPH was administered in the first session (36 milliseconds ± 6) compared with when MPH was administered in the second session (12 milliseconds ± 4) ($t[36] = -3.20$; $P = .003$). In the group in which placebo was administered in the first session (and MPH in the second session), the PES was even smaller after MPH administration than placebo administration ($t[18] = 2.28$; $P = .035$). In the group in which MPH was administered in the first session (and placebo in the second session), the PES was larger after MPH administration than placebo administration ($t[18] = 4.42$; $P < .001$). Taken together, the effect of MPH/placebo on post-error behavioral adaptation processes become reversed by prior task experience.

Discussion

In the current study, we examined the interplay of prior learning/task experience and effects of MPH on error-related behavioral adaptation processes and the associated neurophysiological mechanisms. If the order of the MPH/placebo session in the crossover design is not considered, no effect of MPH/placebo on post-error behavioral adaptation was detectable. The reason is that the data revealed that the effect of MPH/placebo on post-error behavioral adaptation processes is reversed depending on prior task experience. When there was no prior experience with the task, MPH increased PES and thus intensified behavioral adaptation processes. However, when there was prior task experience (i.e., when the placebo session was conducted first in the crossover design), MPH even decreased PES and behavioral adaptation. Thus, MPH effects on behavioral adaptation reverse depending on prior task experience.

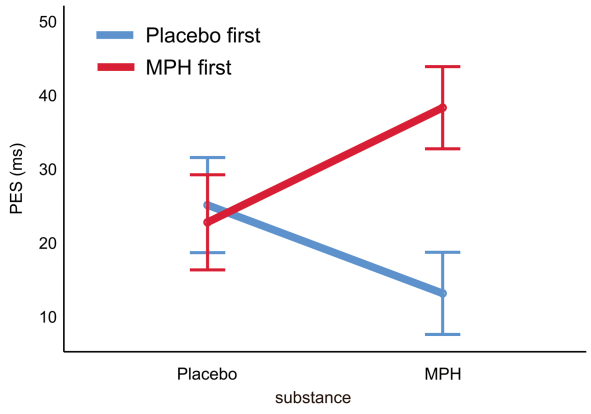

Figure 3. The mean post-error slowing (PES) effect is shown in milliseconds (ms) depending on task order and placebo/methylphenidate (MPH) condition. Error bars denote the standard error of the mean (SEM).

As previously mentioned, it has been suggested that MPH effects and learning-related modulations may tap into identical neural mechanisms (Bensmann et al., 2019) related to gain control. Both the DA and the NE system have been shown to increase gain control (Servan-Schreiber et al., 1990; Li et al., 2001; Adelhöfer et al., 2018; Bensmann et al., 2018). If MPH and learning-related modulations modulate identical neuronal processes, it is possible that the effects add up. One such additive effect could be that the effects of MPH and prior task experience (learning) are increased. Accordingly, performance could be better if only 1 of these modulating processes is effective. This, however, was not the case. The crucial aspect that needs to be considered is that for the DA and NE system (Aston-Jones and Cohen, 2005; Cools and D'Esposito, 2011), an inverted U-shape function has been described relating DA/NE concentrations and performance (see Figure 4A).

According to this Yerkes-Dodson relationship, increases in DA/NE neural transmission only lead to an improvement in performance up to a certain point. A further increase of DA/NE beyond this point leads to a deterioration of performance. This well explains the current data. Since gain control mechanisms are closely related to processes induced by learning and plasticity (Dosher and Lu, 1998; Gold et al., 1999), it is likely that prior task experience has already increased or adjusted task-related gain control mechanisms. If DA/NE concentrations are further increased by the MPH (Volkow et al., 1999; Skirrow et al., 2015; Faraone, 2018) and mechanisms that are essential for gain control are thus further strengthened (Servan-Schreiber et al., 1990; Li et al., 2001; Adelhöfer et al., 2018; Bensmann et al., 2018), this may lead to a reduction in the effectiveness of gain control due to Yerkes-Dodson principles. This suggests that gain control mechanisms may become altered. If MPH was given in the first session, task-familiarization processes have not yet become effective. Therefore, possible modulations in gain control processes are only due to the increase of catecholaminergic concentrations associated with MPH intake (Volkow et al., 1999; Skirrow et al., 2015; Adelhöfer et al., 2018; Faraone, 2018). Since no prior task familiarization is possible when MPH is already administered in the first session, the administration of MPH is uncritical, because MPH possibly does not induce an "overshoot" due to Yerkes-Dodson principles. Therefore, MPH administration leads to the expected improvement of post-error behavioral adaptation processes. The

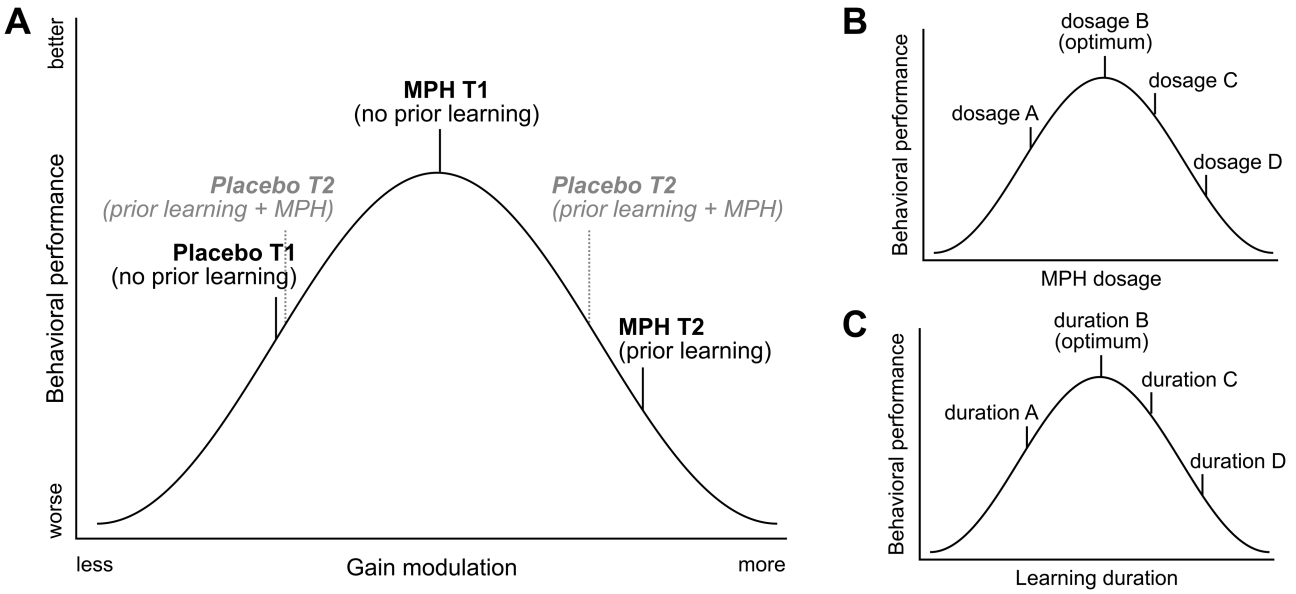

Figure 4. (A) Schematical illustration of the study's findings. The y-axis denotes behavioral performance (degree of post-error slowing [PES]). Along the inverted U-shape curve, the results of the different experimental conditions are delineated. Note that from the current study design it cannot be decided whether the condition in which placebo was administered at the second appointment can be located at the ascending or descending part of the inverted U-shape curve. (B) Conceptual illustration on the effects of a constant degree of learning/task familiarization combined with different methylphenidate (MPH) doses. (C) Conceptual illustration on the effects of a constant dose of MPH combined with a different degree of prior task experience.

data thus show that there is an optimal area in which post-error behavioral adaptation processes are particularly effective. The above line of arguments is based on a relationship between gain control principles and the inverted U-shape function describing the interrelation of catecholaminergic concentrations and performance (see Figure 4A). Corroborating this, also other studies on response selection show these processes are affected by gain modulation principles (Adelhöfer et al., 2018; Bensmann et al., 2018). Moreover, previous data from a genetic association study (Colzato et al., 2013) suggest that post-error behavioral adaptation follows principles of an inverted U-shape function describing the interrelation of catecholaminergic concentrations and performance. This genetic association study, as well as other pharmacological studies administering norepiphrinergic drugs, suggests that the effect of noradrenergic drugs on post-error behavioral adaptation is modulated in opposite directions, depending on the baseline level of NE activity (Luksys et al., 2009; de Rover et al., 2012; Colzato et al., 2013). The reported lack of behavioral effects of MPH administration in previous studies (Jonkman et al., 2007; Costa et al., 2013; Barnes et al., 2014) may be due to multiple reasons. First, the studies did not examine task order effects, and also the enrolled study samples were smaller, making it difficult to examine such effects. Moreover, it is also possible that (genetically) determined baseline levels in catecholaminergic concentrations are important to consider (Colzato et al., 2013) and may modulate the effects. The same applies to the administered dosage of drugs. Future studies shall investigate the interplay of drug dosage, genetically determined catecholaminergic concentrations, and processes of task-familiarization on cognitive control. Another particular important aspect to consider is the dosage of MPH administered. As outlined in the introduction, previous studies in healthy participants used vastly differing dosages (between 20 and 40 mg) and the pattern of effects was also very heterogenous. None of these studies examined learning/task familiarization effects in their study design. For future studies, it will be important to manipulate the dosage and examine whether various doses also modulate the degree of learning effects as observed in the current study. In the current study, a dose of 0.25 mg/kg bodyweight was chosen because previous findings by our group showed that conflict-related behavioral adjustments, known to reveal close conceptual links to error processes (Yeung et al., 2004; Ullsperger et al., 2014), are modulated by a dose of 0.25 mg/kg in healthy participants of similar age (Adelhöfer et al., 2018). Yet it is important to note that the dose chosen in the current study was one-half the dose of the study by Bensmann et al. (2019), which first reported learning-dependent modulations of MPH effects. Crucially, the finding that learning-dependent modulations were also observed with 0.25 mg/kg suggests that learning effects are very powerful to push a catecholaminergic modulation of cognitive control functions out of an "optimal window" (cf. inverted U-shape curve) and thereby decrease cognitive functions. It is conceivable that MPH dose and learning effects reflect interchangeable mechanisms to modulate cognitive control processes (see Figure 4B–C). On the one hand, it is possible that different degrees of learning experience modulate MPH effects. Keeping the MPH dose constant, it is possible that small amounts of learning do not invert MPH effects. However, when learning experience is strong, it may invert MPH effects (Figure 4B). Yet it is also possible that a constant amount of learning/task experience has a different effect depending on MPH dose. It is possible that the same amount of learning/task experience does not invert the MPH effect, if MPH is administered at very low doses. With increasing MPH dose, learning is more likely to invert the effects of MPH (Figure 4C). It remains to be investigated whether there is a linear dependency between the amount of learning/task experience and MPH dose.

However, it has to be considered that the observed modulation of MPH effects depending on prior task experience may reflect a special case of the investigated cognitive control function. From a theoretical perspective, post-error behavioral adaption processes have been framed in reinforcement learning

frameworks (Holroyd and Coles, 2002), which model post-error behavioral adaptation processes referring to learning mechanisms. Consequently, neurophysiological correlates of error monitoring have been shown to be affected by learning experience (Holroyd and Coles, 2002; Beaulieu et al., 2014). It is possible that this makes error processing particularly prone to effects of task familiarization processes that modulate MPH effects in the current study. Thus, it is possible that a modulation of MPH effects is only evident when cognitive functions are examined that show a close relation to learning and plasticity mechanisms. If this requirement is not met, modulation of MPH effects depending on prior task experience is expectable.

In summary, we provide evidence that effects of MPH on the ability to adapt behavior after response errors reverses as a function of prior task experience. When there was no prior experience with the task, MPH increased PES and thus intensified behavioral adaptation processes. However, when there was prior task experience, that is, when the placebo session was conducted first in the crossover design, MPH even decreased PES and behavioral adaptation. The data suggest that catecholaminergic effects on cognitive control functions vary as a function of prior learning/task experience. Thus, the data establish a close link between learning and catecholaminergic effects for executive functions.

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Interest Statement

None.

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