Published in final edited form as:

Nat Neurosci. 2010 April ; 13(4): 475–481. doi:10.1038/nn.2506.

Methylphenidate facilitates learning-induced amygdala plasticity

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Abstract

Although methylphenidate (Ritalin) has been used therapeutically for nearly 60 years, the mechanisms by which it acutely modifies behavioral performance are poorly understood. Here we combined intra-lateral amygdala *in vivo* pharmacology and *ex vivo* electrophysiology to show that acute administration of methylphenidate, as well as a selective dopamine transporter inhibitor, facilitated learning-induced strengthening of cortico-amygdala synapses through a postsynaptic increase in AMPA receptor-mediated currents, relative to those in saline-treated rats. Furthermore, local administration of methylphenidate in the lateral amygdala enhanced cue-reward learning through dopamine D1 receptor-dependent mechanisms and suppressed task-irrelevant behavior through D2 receptor-dependent mechanisms. These findings reveal critical and distinct roles for dopamine receptor subtypes in mediating methylphenidate-induced enhancements of neural transmission and learning performance.

Although methylphenidate (MPH) is primarily prescribed for the treatment of attention deficit hyperactivity disorder (ADHD)¹, the behavioral enhancements of MPH are not limited to those with ADHD, as MPH also improves task performance and decreases motor restlessness in the general population². ADHD is characterized by inattention, hyperactivity and impulsivity³ and has been linked to impaired learning performance in scholastic settings⁴. In recent decades, the diagnosis of ADHD and the prescription of MPH have markedly increased¹. MPH is a highly effective therapeutic agent for both those with ADHD and those without², improving scholastic performance in 70% of children and adults^{5,6}.

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Note: Supplementary information is available on the Nature Neuroscience website.

AUTHOR CONTRIBUTIONS

K.M.T. supervised experiments and performed all whole-cell recordings. K.M.T., A.B. and P.H.J. contributed to study design, results analysis, interpretation and manuscript writing. K.M.T., L.D.T., J.J.C. and E.F.H. surgically implanted guide cannulae, performed intra-LA drug infusions, conducted behavioral experiments, sectioned acute slice preparations and performed data entry and analyses. A.B. and P.H.J. provided mentorship and resources.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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What cellular and pharmacological mechanisms underlie acute MPH-induced enhancements of behavioral performance in the mammalian brain? Functional abnormalities of the basolateral amygdala (BLA), a brain region critical for learning the emotional and motivational significance of environmental stimuli^{7–12}, have been linked to ADHD¹³. To identify neural mechanisms underlying MPH effects on learning performance, we tested the effects of MPH in the lateral amygdala, where the relationship between the intrinsic microcircuitry and acute learning performance has been well characterized^{7,8}. The lateral amygdala is an early site of convergence for thalamic and cortical afferents carrying sensory information about environmental cues and primary reinforcers^{14,15} and is important for the acquisition and retrieval of stimulus-outcome memories^{16–18}. Furthermore, thalamo-amygdala synaptic strength predicts the success of cue-reward learning⁸, and memory consolidation is facilitated by infusions of MPH in the amygdala¹⁹ after training. Thus, the lateral amygdala brain region is well suited for studying the synaptic mechanisms by which MPH alters acquisition. Here we show that local administration of MPH facilitates performance on a sucrose self-administration task and facilitates learning-induced plasticity within a single training session.

RESULTS

Performance is modulated by MPH in the amygdala

To examine the acute effects of MPH on learning performance, we locally administered MPH into the lateral amygdala of rats (Supplementary Figs. 1 and 2), before training in a lateral amygdala-dependent cue-reward learning paradigm⁸ (Supplementary Figs. 2 and 3). After training, we collected brains for acute slice preparation and used *ex vivo* electrophysiological recording procedures to evaluate synaptic function (Supplementary Fig. 2).

Rats that received intra-lateral amygdala (intra-LA) MPH before training, relative to those that received saline, earned a significantly higher ($P = 0.049$; Fig. 1) number of rewards per minute ('reward earning') but did not differ in overall motor activity (Supplementary Fig. 4). We used a behavioral index, 'task efficiency', defined as the number of rewards earned per cue presented⁸, to quantify the degree to which a rat had learned that the presentation of the cue indicated that sucrose was available. MPH-treated rats performed with a significantly higher task efficiency than saline-treated rats ($P = 0.012$; Fig. 1b). We also quantified the relative distribution of attention to goal-directed behavior using a behavioral index termed 'off-task behavior', defined as the number of inactive port entries per reward port entry. Because sucrose is delivered to the reward port, reward port entries reflect goal-oriented behavior, whereas inactive port entries reflect task-irrelevant behavior. MPH-treated rats showed ~50% less off-task behavior than saline controls ($P = 0.010$; Fig. 1d). Thus, the enhancement in reward earning seen by MPH rats relative to saline controls was due to a decrease in the amount of task-irrelevant behavior relative to goal-directed behavior, as well as an enhancement in the acquisition of the cue-reward association (Fig. 1a–d).

Distinct effects of NET and DAT inhibition

MPH targets multiple pharmacological targets, potently inhibiting both the norepinephrine transporter (NET) and the dopamine transporter (DAT). MPH has a higher binding affinity for the NET than for the DAT²⁰, and an increasingly prescribed alternative treatment for ADHD, atomoxetine (Strattera), preferentially targets the NET. Thus, we investigated the effects of intra-LA administration before training of nisoxetine (NXT), a highly selective NET inhibitor, on learning performance (Supplementary Fig. 5). Consistent with evidence that intra-BLA MPH enhances memory consolidation¹⁹, we found that although NXT dose-dependently enhanced memory retention, as measured by the behavioral index 'task accuracy' on a subsequent test session in the absence of any drug treatment ($P = 0.002$), there was no acute effect on learning performance relative to that of saline controls (Fig. 2). Task accuracy

quantifies the rat's ability to recognize that the absence of the cue indicates the absence of sucrose⁸ and is defined as the difference of the number of port entries in the presence of sucrose and the number of port entries in the absence of sucrose, normalized to the total port entry responses during the session.

Accumulating evidence suggests that MPH inhibition of the DAT²⁰ contributes to its therapeutic effects²¹. For example, subjects diagnosed with ADHD show significant increases in DAT density²² and presence of certain alleles of the *DAT1* (also known as *SLC6A3*) gene correlates with hyperactivity and impulsivity scores in subjects with ADHD²³. Furthermore, therapeutic doses of orally administered MPH in humans inhibit DAT function (50–75%) and increase extracellular dopamine^{24,25}. Because NET inhibition alone did not yield the same enhancements of acute task performance as did MPH, we hypothesized that the effects of MPH on learning occur by means of DAT inhibition. If so, then intra-LA infusions of the selective DAT blocker GBR-12909 (GBR)²⁶ should mimic the effects of MPH. In contrast to NXT treatment, GBR treatment resulted in a behavioral profile notably similar to that of MPH, with no differences observed between GBR and MPH groups. GBR-treated rats showed higher reward earning ($P = 0.013$) and task efficiency ($P = 0.002$), as well as less off-task behavior ($P = 0.006$), than saline-treated controls (Fig. 1a,b,d).

Thus, MPH inhibition of NET enhances memory retention, whereas MPH inhibition of DAT acutely enhances task performance. If increases in extracellular dopamine caused these enhancements in acute task performance, then dopamine receptor activation is likely to be required for acute MPH-induced performance enhancement.

Distinct contributions of D1 and D2 receptors to performance

To test this hypothesis, we performed intra-LA infusions of the potent dopamine D1 receptor (D1R) antagonist SCH-23390 (SCH). SCH-treated rats showed significantly lower reward earning ($P = 0.033$; Fig. 1a) and task accuracy (Fig. 1c) than did saline-treated rats. Impairments in reward earning and task accuracy indicate that D1R activation is necessary for general task performance and cue-reward learning. However, the ability to suppress task-irrelevant behavior, as measured by off-task behavior, was spared (Fig. 1d).

If MPH enhances task performance by increasing the activation of D1Rs, then infusion of MPH together with SCH (MPH+SCH) should attenuate MPH-induced enhancements. Rats given intra-LA infusions of MPH+SCH before training showed lower reward earning ($P = 0.013$) and task efficiency ($P = 0.042$) than those treated with MPH alone (Fig. 1a,b). However, there was no change in off-task behavior for MPH+SCH compared to the MPH, SCH or saline groups (Fig. 1d). Thus, learning the motivational significance of a reward-predictive cue requires D1R activation.

We next tested the role of D2 receptors (D2Rs) in mediating learning performance by infusing raclopride (RAC), a potent antagonist of D2Rs, before training into the lateral amygdala. Whereas RAC treatment did not change reward earning or task efficiency, there was significantly more off-task behavior ($P = 0.003$) relative to saline (Fig. 1d). This increase in off-task behavior was due not to a decrease in reward port entries but to a >40% increase in inactive port entries (Supplementary Figs. 6 and 7). Thus, D1R function is critical for cue-reward learning, whereas D2R function is critical for the suppression of task-irrelevant behavior.

If MPH exerts some behavioral effects by increasing the activation of D2Rs, then infusion of MPH together with RAC (MPH+RAC) should attenuate a subset of MPH-induced behavioral enhancements. Rats treated with MPH+RAC showed a task efficiency that was higher ($P = 0.023$) than that of saline controls but the same as that seen in rats treated with MPH alone

(Fig. 1b). Therefore, MPH affects task efficiency independently of D2R activation. In contrast to rats treated with MPH alone, rats treated with MPH+RAC did not show a difference in off-task behavior from that seen in saline controls (Fig. 1d). Although these specific behavioral aspects may be interrelated (Supplementary Figs. 8–10), these findings further support the hypothesis that acquisition of the cue-reward association and suppression of task-irrelevant behavior are mediated by distinct dopamine receptor subtypes.

MPH facilitates cortico-amygdala plasticity via dopamine

To test whether the MPH-induced enhancement in learning performance is related to changes in excitatory synaptic function, we performed whole-cell patch-clamp recordings within lateral amygdala slices after intra-LA infusions and training (Supplementary Fig. 2) in the same subjects whose behavioral data are presented in Figure 1. We measured the ratio of AMPA receptors (AMPA) to NMDA receptors (NMDAR) by stimulating thalamic (internal capsule) or cortical (external capsule) afferents to determine the effects of intra-LA administration of MPH, GBR, SCH and RAC on learning-induced glutamatergic synaptic plasticity. Notably, rats that received infusions of saline before training showed significantly higher thalamo-amygdala AMPAR/NMDAR than rats treated with saline in their home cage (not trained; $P = 0.05$). Treatment with SCH before training yielded significantly lower thalamo-amygdala AMPAR/NMDAR relative to saline treatment ($P = 0.008$; Fig. 3a,b), in addition to impairing cue-reward learning (Fig. 1c). Thus, D1R blockade may impair cue-reward learning by attenuating the learning-induced increases in thalamo-amygdala synaptic strength²⁷. No other treatment significantly altered synaptic strength in this pathway (Fig. 3b).

In contrast, rats treated before training with saline infusions did not show a difference in cortico-amygdala synaptic strength relative to saline home-cage rats (Fig. 3c), indicating that plasticity at these synapses is not required for learning this task. Only MPH ($P = 0.023$) and GBR ($P = 0.012$) groups showed learning-induced increases in cortico-amygdala synaptic strength relative to saline controls (Fig. 3c), suggesting that DAT blockade changes the inhibitory constraints on cortico-amygdala plasticity. The enhancement in cortico-amygdala AMPAR/NMDAR by MPH was reversed by co-infusion with either D1R (MPH+SCH; $P = 0.004$) or D2R antagonists (MPH+RAC; $P = 0.013$; Fig. 3c), indicating that this change in synaptic strength requires coactivation of these receptor subtypes.

We then confirmed these synaptic changes were learning induced rather than a result of acute drug exposure alone. Rats that received MPH or GBR infusions in their home cages did not show any increases relative to saline. In contrast, rats infused with MPH or GBR in their home cages were significantly lower in thalamo-amygdala ($P = 0.006$, $P = 0.049$, respectively) or cortico-amygdala synaptic strength ($P = 0.045$, $P = 0.012$, respectively) relative to rats that received MPH or GBR infusions before training (Fig. 3b,c).

Because a change in AMPAR/NMDAR ratio may reflect a change in either AMPAR- or NMDAR-mediated currents, we examined miniature excitatory postsynaptic currents (mEPSCs), which reflect spontaneously released vesicles of glutamate²⁸. A change in the amplitude of mEPSCs typically reflects a change in the number or function of postsynaptic AMPARs, whereas a change in the frequency of mEPSCs may reflect a change in the probability of release at the presynaptic terminal²⁸. We found that intra-LA MPH ($P = 0.012$), GBR ($P < 0.001$) or MPH+RAC ($P = 0.016$) infusions increased, while SCH infusions decreased ($P = 0.007$), mEPSC amplitude relative to saline infusions before training (Fig. 4a–c). mEPSC amplitude was not increased by home-cage MPH or GBR treatment relative to saline and was significantly lower than that of rats that received MPH or GBR before training (both $P < 0.001$; Fig. 4b). Co-infusion of MPH+SCH attenuated ($P < 0.001$), whereas MPH+RAC spared, MPH-induced facilitation of learning-induced increases in mEPSC amplitude (Fig. 4a–c). We observed no differences in frequency (Fig. 4a,d,e), suggesting that the change

in AMPAR/NMDAR was mediated postsynaptically²⁸. A lack of difference among groups for either cortico- or thalamo-amygdala afferents in paired-pulse ratio measurements (Supplementary Fig. 11), which reflect the probability of vesicle release²⁹, further supports the hypothesis that increases in both thalamo- and cortico-amygdala synaptic strength are mediated by postsynaptic increases in AMPAR currents. To confirm that D1R antagonism, rather than the associated impairment in learning performance, was the cause of the attenuation in mEPSC amplitude, we performed unilateral infusions of SCH before training to provide a within-subject control (Fig. 5).

To probe the relationship between these distinct aspects of behavior and the associated synaptic changes, we examined correlations among AMPAR/NMDAR, mEPSCs and task performance. Both cortico-amygdala and thalamo-amygdala AMPAR/NMDAR ratios were significantly correlated with reward earning and task efficiency (Supplementary Figs. 12 and 13). In contrast, only the cortico- amygdala AMPAR/NMDAR was inversely correlated with off-task behavior (Supplementary Fig. 14), suggesting that cortico-amygdala synapses may selectively modulate the ability to suppress task-irrelevant behavior, consistent with evidence linking ADHD to abnormal cortico- amygdala connectivity¹³. Studies in drug-naïve rats show correlations between learning and AMPAR/NMDAR ratios in thalamo-amygdala, but not cortico-amygdala synapses⁸, a result we replicated in saline-treated rats (Supplementary Fig. 15). Here the MPH and GBR groups were the only groups to show an increase in cortical AMPAR/NMDAR, and they heavily contributed to the correlation between cortical AMPAR/NMDAR and task efficiency. Additionally, mEPSC amplitude, but not frequency, was correlated with reward earning, task efficiency and off-task behavior (Supplementary Figs. 16–18), suggesting that postsynaptic AMPAR number or function predicts success in a cue-reward learning task.

MPH-induced enhancements require lateral amygdala dopamine

To test whether dopamine signaling in the amygdala is required for mediating MPH-induced behavioral enhancements, we systemically administered, using intraperitoneal (i.p.) injection, saline or a low dose of MPH along with intra-LA saline, SCH or RAC before training (Fig. 6 and Supplementary Fig. 19). Systemic MPH significantly increased reward earning and task efficiency, while reducing off-task behavior ($P = 0.037$, 0.008 and 0.04 , respectively; Fig. 6a,b,d), relative to systemic saline. Intra-LA SCH attenuated systemic MPH-induced enhancements in all behavioral measures tested, and these rats were impaired relative to rats treated with systemic saline in reward earning, task efficiency and task accuracy (Fig. 6a–c; $P = 0.013$, 0.001 and 0.042 , respectively).

In contrast, intra-LA RAC selectively attenuated MPH-induced reduction of off-task behavior (Fig. 6d; $P = 0.001$). Thus, D1R activation in the amygdala is necessary for mediating MPH-induced enhancements in cue-reward learning performance, and D2R activation in the amygdala is required for mediating MPH-induced reductions in off-task behavior. Therefore, dopamine signaling in the amygdala is critical in MPH-mediated learning performance enhancement.

DISCUSSION

Using a combination of *in vivo* pharmacology and *ex vivo* electrophysiology, we show that MPH enhances a lateral amygdala-dependent form of cue-reward learning and provide evidence suggesting that the learning enhancement depends upon dopaminergic modulation of excitatory synaptic plasticity within the lateral amygdala. These results extend previous findings that demonstrated an important role for dopamine within the lateral amygdala in the formation of both appetitive^{30–34} and aversive^{35–40} associations by identifying a potential mechanism whereby increases in dopamine in the amygdala modulate excitatory synaptic plasticity. Specifically, we found that MPH, and the dopamine uptake blocker GBR, enhanced

the AMPAR/NMDAR at cortico-amygdala synapses. We also found that different dopamine receptor subtypes contribute to distinct aspects of learning performance, such that cue-reward learning depends upon dopamine D1 receptor-dependent mechanisms, and the suppression of task-irrelevant behavior depends upon D2 receptor-dependent mechanisms. Together, these findings indicate a specific synaptic mechanism whereby MPH may enhance associative learning through actions in the lateral amygdala.

How does DAT blockade in the amygdala enhance learning performance? At basal dopamine levels, GABAergic activity keeps the firing rates of pyramidal neurons low, while D2Rs on pyramidal neurons influence the responsiveness of the cell by modulating input resistance⁴¹. When dopamine levels are elevated, spontaneous background inhibition from local interneurons increases^{42,43}, while feed-forward inhibition mediated by intercalated cell masses decreases owing to D1R activation^{27,43}. Thus, lateral amygdala pyramidal neurons will become less responsive to weaker, background inputs but much more responsive to stronger, coordinated excitatory inputs carrying sensory information^{39,44}. We hypothesize that by elevating extracellular dopamine²⁴, MPH or GBR release inhibitory constraints on cortico-amygdala plasticity and alter the responsiveness of amygdala neurons driving different aspects of behavior through mechanisms dependent on distinct D1 and D2 receptors. An extension of this hypothesis is that whereas elevated dopamine is required for cortico-amygdala potentiation, only basal levels of dopamine are required for thalamo-amygdala potentiation. Thus, at basal and elevated levels of dopamine, thalamo-amygdala synapses are readily potentiated with learning, but when dopamine receptors are antagonized, bringing the level of dopaminergic signaling below the basal level, potentiation in these synapses may be attenuated.

Therefore, we suggest that increased activation of dopamine receptors enhances the ability to acquire cue-reward associations and to suppress task-irrelevant behavior. Specifically, treatment with MPH or GBR enhances task efficiency, likely owing to the dopamine-induced increase in responsiveness to coordinated sensory inputs, and decreases off-task behavior, likely owing to the dopamine-induced decrease in pyramidal neuron responsiveness to weaker background inputs. In contrast, D1R antagonism by SCH attenuates cue-reward learning and the associated plasticity, which may reflect increases in the inhibition of lateral amygdala neurons by intercalated GABA neurons, which densely express D1Rs^{27,43}. In comparison, D2R inhibition selectively increases task-irrelevant behavior, in agreement with the notion that D2R antagonism facilitates the ability of weak excitation from task-irrelevant stimuli to drive neuronal excitation.

In conclusion, our findings suggest that MPH enhances learning performance through a dopamine-dependent mechanism by gating cortico-amygdala potentiation, facilitating cue-reward learning through a D1R-dependent mechanism and enhancing the ability to suppress task-irrelevant behavior through a D2R-dependent mechanism. Although NET inhibition did not acutely facilitate performance of our cue-reward learning task within the first exposure, the improvement in memory retention would likely contribute to behavioral enhancements observed across sessions. Furthermore, the NET may also act to clear dopamine from the extracellular space in brain regions with low DAT expression⁴⁵.

Although DAT inhibition enhances task performance during the initial training session, it is still unclear whether DAT inhibition enhances task acquisition, consolidation, expression or a combination of these processes. Future studies may determine whether these mechanisms of MPH action generalize to other brain regions involved in learning and attention or to other behavioral assays of cognitive performance.

METHODS

Methods and any associated references are available in the online version of the paper at <http://www.nature.com/natureneuroscience/>.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank H.L. Fields, G.D. Stuber, J.A. Rosenkranz and E.E. Steinberg for helpful comments; and A.C. Hollowell, S.L. Cho, S.J. Chang, L. Wang and F.W. Hopf for technical assistance. This research was supported by the State of California for Medical Research on Alcohol and Substance Abuse through the University of California at San Francisco (A.B. and P.H.J.), NIDA DA15096-01 (A.B.) and a Massachusetts Institute of Technology Peter J. Eloranta Summer Undergraduate Research Fellowship (L.D.T.).

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Figure 1.

MPH enhances task performance by altering different aspects of behavior through distinct D1 and D2 receptor-dependent mechanisms. **(a)** Intra-LA drug infusion alters reward earning ($F_{6,47} = 5.161$, $P < 0.001$). Relative to saline-treated rats, MPH and GBR groups earned significantly more rewards per minute, whereas SCH-treated rats earned a significantly fewer. MPH+SCH-treated, but not MPH+RAC-treated, rats earned significantly fewer than MPH-treated alone. **(b)** Task efficiency was altered by intra-LA drug infusion ($F_{6,47} = 3.886$, $P = 0.004$). Relative to saline, MPH, GBR and MPH+RAC-treated groups all showed significantly higher task efficiency. The MPH+SCH group, but not the MPH+RAC, showed lower task efficiency than the group treated with MPH alone. **(c)** Relative to saline, SCH-treated rats showed significantly lower task accuracy, and MPH+SCH-treated rats showed an attenuation of the enhancements induced by MPH alone, but MPH+RAC-treated rats did not differ from those treated with MPH alone ($F_{6,47} = 3.806$, $P = 0.019$). **(d)** Relative to the saline-treated group, MPH and GBR-treated groups showed significantly less off-task behavior, whereas RAC-treated rats showed significantly more ($F_{6,47} = 8.024$, $P < 0.001$). In **a–d**, numbers in bars indicate rats per group. All values are mean $\pm$ s.e.m. One-way analysis of variance followed by all-pairwise multiple comparison procedure (Fisher least significant difference method; $*P < 0.05$, $**P < 0.01$).

Figure 2.

Intra-LA NXT before training enhances memory retention but not acute task performance. Left column, performance on the initial training session; right column, performance during a 20-min memory retrieval test. No significant differences were observed during training, but NXT dose-dependently enhanced task accuracy ($F_{3,26} = 4.209$, $P = 0.002$) during a test session on the next day, on which no infusions were performed, suggesting that NET blockade may enhance memory retention in this task. Saline vehicle, $N = 8$; NXT 2 μg per side, $N = 6$; NXT 4 μg per side, $N = 7$; NXT 8 μg per side, $N = 6$. $**P < 0.01$.

Figure 3.

Inhibition of the dopamine transporter gates cortico-amygdala synaptic potentiation. **(a)** Representative traces of AMPAR/NMDAR ratios evoked from thalamic and cortical afferents for each group. **(b,c)** AMPAR/NMDAR ratios evoked from thalamic ($F_{8,62} = 3.471$, $P = 0.003$) or cortical ($F_{8,59} = 3.557$, $P = 0.002$) afferents for each drug-treatment group after training were significantly altered. Inset shows rats treated with saline, MPH and GBR that were returned to their home cages in lieu of training. Numbers in bars indicate the number of cells per group. **(b)** SCH-treated rats show a significant decrease in thalamo-amygdala AMPAR/NMDAR. **(c)** MPH and GBR groups show significant increases in cortico-amygdala AMPAR/NMDAR. * $P < 0.05$, ** $P < 0.01$.

Figure 4.

Dopamine modulates learning-induced increases in mEPSC amplitude but not frequency. **(a)** Sample mEPSCs from each drug-treatment group. **(b)** Mean mEPSC amplitude for each group varied ($F_{8,113} = 10.177$, $P < 0.001$) with treatment. MPH, GBR and MPH+RAC groups had higher, whereas SCH-treated rats had lower, mEPSC amplitude than did saline controls. Inset: saline-, MPH- and GBR-treated home-cage controls. **(c)** Cumulative probability plot of mEPSC amplitude for representative cells from each group; 1 pA bins. **(d)** No significant change in mEPSC frequency of any groups relative to saline ($F_{8,113} = 0.202$, $P = 0.990$). **(e)** Cumulative probability plot of mEPSC frequency; 20-ms bins. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Figure 5.

D1R antagonism in the lateral amygdala attenuates learning-induced synaptic changes. **(a–h)** Rats given, before training, bilateral infusions of SCH compared with rats given unilateral infusions of SCH and contralateral infusions of saline. **(a)** Unilateral infusion of SCH and saline significantly decreased reward earning ($F_{2,19} = 5.107$, $P = 0.018$) relative to bilateral saline infusion ($P = 0.009$) and did not differ from bilateral SCH. **(b–d)** Rats treated with unilateral SCH and saline infusions did not show significant differences from rats treated with bilateral saline in task efficiency, task accuracy or off-task behavior. **(f,h)** Unilateral infusions of SCH and saline provide a within-subjects ($N = 6$ rats; $n = 11$ cells from saline-treated side; $n = 9$ cells from SCH-treated side) comparison of the effects of D1 receptor antagonism on learning-induced plasticity. **(e–h)** For both between-subjects and within-subjects comparisons, treatment with SCH significantly attenuated learning-induced increases in mEPSC amplitude ($*P < 0.05$, $**P < 0.01$, $***P < 0.001$, Student's t -test) relative to saline **(e,f)**, with no change in mEPSC frequency **(g,h)**.

Figure 6.

Dopamine signaling in the amygdala is necessary for mediating enhancements of learning performance induced by systemic administration of MPH. Behavioral measures of four groups of rats treated before training with (1) i.p. saline and intra-LA saline ($N = 8$ rats), (2) i.p. MPH and intra-LA saline ($N = 8$ rats), (3) i.p. MPH and intra-LA SCH ($N = 7$ rats) and (4) i.p. MPH and intra-LA RAC ($N = 9$ rats). (**a–c**) Intra-LA infusion of SCH significantly attenuated, whereas RAC spared, enhancements induced by systemic MPH in reward earning ($F_{3,31} = 8.568$, $P < 0.001$), task efficiency ($F_{3,31} = 20.194$, $P < 0.001$) and task accuracy ($F_{3,31} = 6.004$, $P = 0.003$). (**d**) Intra-LA infusion of RAC or SCH significantly attenuated reductions induced by systemic MPH in off-task behavior ($F_{3,31} = 4.48$, $P = 0.011$). In **a–d**, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.