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Methylphenidate enhances acquisition and retention of spatial memory

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HIGHLIGHTS

- 10 mg/kg MPH given pre-training enhances learning on the hidden platform version of the Morris water maze.
- 1 or 10 mg/kg MPH given pre-training enhances retention of spatial memory in the water maze.
- 10 mg/kg MPH given chronically before Pavlovian fear conditioning dramatically impairs long-term fear memory.

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ABSTRACT

Psychostimulants containing methylphenidate (MPH) are increasingly being used both on and off-label to enhance learning and memory. Still, almost no studies have investigated MPH's ability to specifically improve spatial or long-term memory. Here we examined the effect of training with 1 or 10 mg/kg MPH on hidden platform learning in the Morris water maze. 10 mg/kg MPH improved memory acquisition and retention, while 1 mg/kg MPH improved memory retention. Taken together with prior evidence that low, clinically relevant, doses of MPH (0.01–1 mg/kg MPH) enhance fear memory we conclude that MPH broadly enhances memory.

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1. Introduction

Psychostimulants containing methylphenidate (MPH) are used therapeutically to enhance cognition, improve executive function, promote wakefulness, and reduce impulsivity (for a review see [1]). Increasingly, MPH is being used both on and off-label to specifically improve long-term memory (LTM) [2–4]. Few studies, however, have examined MPH's ability to modulate spatial or long-term memory [5–7]. Rather, most research has focused on MPH-induced improvements in working memory, attention, and cognitive control [8–10].

Prior research in our laboratory has shown that low, clinically relevant doses of MPH (0.01–1 mg/kg) enhance LTM in Pavlovian fear conditioning, a leading model of memory in rats and mice [11–13]. In this paradigm animals learn to fear previously neutral tone and contextual stimuli following their pairing with an aversive foot-shock [12]. Both tone and contextual conditioning require the amygdala; contextual conditioning additionally requires the hippocampus [14,15]. While lower MPH doses enhanced fear memory, a relatively high dose (10 mg/kg) dramatically impaired fear memory [11]. Importantly, these memory-modulating effects were independent of any effects on locomotion, anxiety, or reinforcement [11].

Here we selected the doses of MPH that maximally enhanced (1 mg/kg) or impaired (10 mg/kg) fear memory acquisition [11] and assessed their effect on spatial memory using the well-established hidden platform version of the Morris water maze [16–18]. This hippocampal-dependent task requires subjects to use distal spatial cues to locate a fixed hidden platform in order to escape from a pool of opaque water [19–21]. In earlier work, we found that a much higher dose of the atypical psychostimulant modafinil [1] was necessary to enhance water maze acquisition (75 mg/kg) as compared to fear conditioning (0.75 mg/kg) [22].

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One possible explanation for the difference in dosing across fear conditioning and water maze is tolerance [23]. Unlike our earlier fear conditioning experiments where MPH or modafinil was given acutely [11,22], water maze training involves repeated stimulant injections. We examined this possibility by chronically administering 10 mg/kg MPH and then testing its effect on fear learning. Tolerance proved to be an unlikely explanation. We instead consider whether the difference in dosing is better explained by a difference in the level of arousal required for optimal performance on each task.

2. Materials and methods

2.1. Subjects

51 hybrid C57BL/6Jx129S1/SvlmJ mice (129B6; stock mice from the Jackson Laboratory, West Sacramento, CA) were used in approximately equal numbers of females ($n = 24$) and males ($n = 27$); treatment groups were balanced across sexes. Mice were 12 weeks old before testing and group housed (4–5 mice per cage) with continuous access to food and water. Mice were handled for 5 days (1 min/day) prior to experiments. The vivarium was maintained on a 14:10 h light:dark schedule and all testing was performed during the light phase of the cycle. Animal care and testing procedures were approved by the UCSD IACUC and were compliant with the NRC Guide.

2.2. Drugs

Methylphenidate HCl (MPH; Sigma–Aldrich) was dissolved in physiological 0.9% saline (vehicle) and administered in a dose of 1 or 10 mg/kg (salt weight). All saline and drug injections were administered intraperitoneally (i.p.) in a volume of 10 ml/kg.

2.3. Apparatus

2.3.1. Water maze

The water maze was 114 cm in diameter and 74 cm high. The water was made opaque with white tempera paint and heated to 23.5 °C using a built-in heater and thermostat. The maze was divided into four quadrants (Target Quadrant, TQ; Target Left, TL; Target Right, TR; Target Opposite, OP). Although the maze itself appeared isotropic, distal cues were placed around the room and included a door, a computer, and several posters. The white acrylic escape platform was an electromagnetically controlled Atlantis platform, 10 cm in diameter, covered with plastic mesh to provide a textured surface for the mice to grip. In the raised position the top of the platform was 1 cm below the surface of the water, available to the mouse. Location was tracked and scored using a computerized video tracking system connected to an overhead video camera (Water Maze, Med Associates).

2.3.2. Fear conditioning

Three to four mice were trained concurrently in individual conditioning chambers. Locomotor activity and freezing behaviour were recorded during conditioning and testing trials using the VideoFreeze system (Med Associates) as described previously [12,24].

2.4. Experimental procedures

2.4.1. Water maze

2.4.1.1. Acquisition. Mice were injected 30 min prior to each of 15 training days and were randomly assigned to groups by dose of MPH administered: 0 (saline control, $n = 10$), 1 ($n = 12$), or 10 mg/kg ($n = 10$). Each training day had 3 standard platform training trials and 1 variable interval (VI) platform probe trial.

For platform training trials the mouse was lowered into the pool facing the wall from one of four randomly assigned start locations. The trial lasted until the mouse found the hidden platform where it remained for 5 s. If the mouse did not find the platform in 60 s it was placed onto the platform for 5 s to provide reinforcement and exposure to the platform's location. Latency to the platform was measured as the time between the mouse leaving the starting location and climbing onto the platform. Swim speed was calculated as the average centimetres swam per second for the duration of the trial. Data were averaged for each day.

A single VI probe trial immediately followed the platform training trials each training day. The platform was unavailable for 10, 20, 30 or 40 s, after which it was raised. The intervals for the 15 training sessions were as follows: 10, 30, 20, 40, 40, 20, 30, 10, 40, 10, 30, 20, 40, 10, and 20 s. VI probe trials provide a more sensitive measure of spatial memory than no platform probe trials as they lead to more accurate and persistent searching at the platform location [17]. Additionally, VI trials can be used repeatedly because they are reinforcing and do not produce extinction [17,21]. Time spent in each quadrant was recorded.

No platform (NP) probe trials followed the training and VI probe trials on training days 5, 10, and 15 as a traditional measure of spatial learning. Mice were placed in the OP quadrant and the platform was unavailable for the entire 60 s trial. Time spent in each quadrant and platform crossings were recorded. Platform crossings were defined as the number of times a mouse swam across the exact location of the platform (10-cm diameter).

2.4.1.2. Retention. Mice were given off drug NP probe trials both one day (Day 16) and one week (Day 23) following training. Mice were placed in the OP quadrant and the trial lasted for 60 s with the platform unavailable for the entire trial. Time spent in each quadrant and platform crossings were recorded.

2.4.2. Fear conditioning

Mice were randomly assigned to groups by dose of MPH administered. Mice were injected with either 0 (saline control, $n = 9$) or 10 mg/kg MPH ($n = 7$) daily for 12 days before conditioning. On Day 13 mice were injected 30 min prior to the 10 min conditioning session. Drug treatment and sex were counterbalanced across conditioning chambers. Following a 3 min baseline period, mice received one tone-shock pairing in which a 30 s tone (2.8 kHz, 85 dBA) co-terminated with a 2 s scrambled, AC foot shook (0.75 mA, RMS) [12,24].

Seven days later mice were returned to the conditioning chambers without drug to assess context memory. Freezing was measured for 5 min. Twenty-four hours later mice were placed in an alternate context (modified along several dimensions [11,24]), also off drug, to assess tone fear. Tone testing consisted of a 2 min baseline followed by 3–30 s tone presentations (2.8 kHz, 85 dBA). Freezing behaviour was again recorded.

2.5. Statistical analyses

Data were entered into a multivariate analysis of variance (MANOVA) and the level of significance was set at $p \leq 0.05$. Post hoc comparisons were done with Fisher's protected least significant difference (unpaired tests) or paired two-tailed *t*-tests (paired tests). Three mice, one from each drug group, were excluded early in training for failing to perform the task (floating). Data from male and female mice were collapsed because there were no differences between the sexes on any measures (p values >0.3).

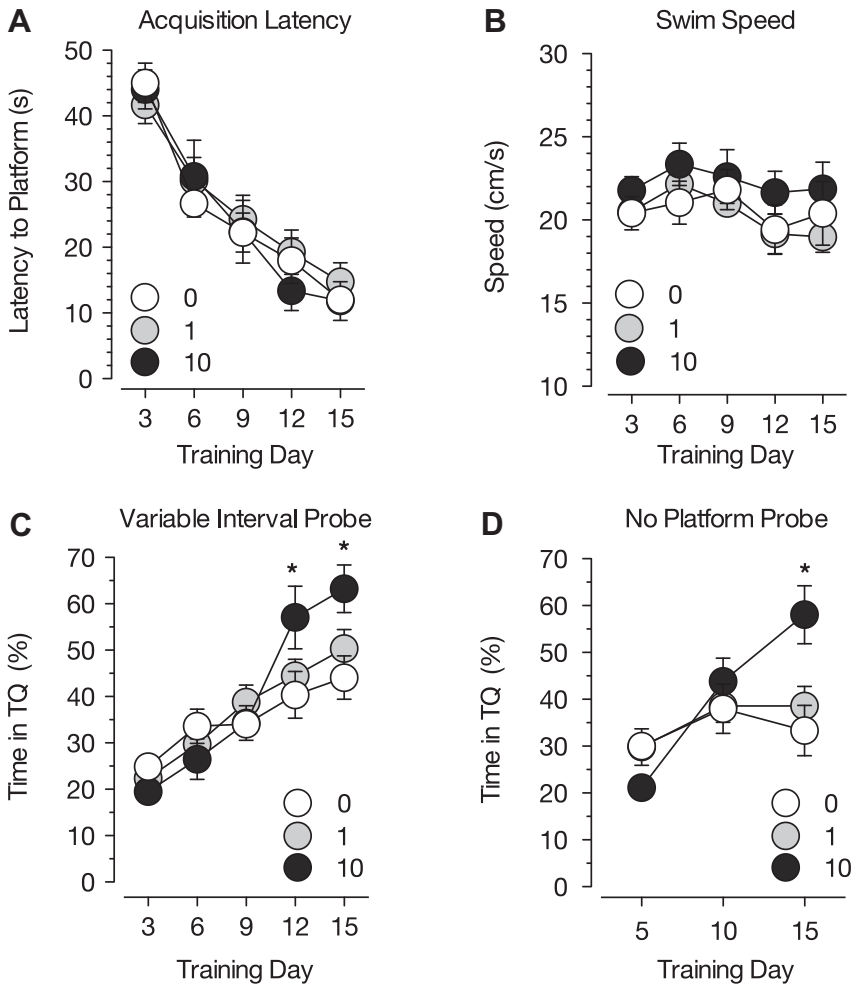

Fig. 1. Water maze acquisition. (A) Latency to find the platform across the 15 days of training presented in blocks of 3 days. Mice were given 0 (saline control, white circles), 1 (grey circles) or 10 mg/kg (black circles) MPH prior to each session. No group differences were found. (B) Average swim speed during the platform training trials did not differ between groups. (C) Time spent in the target quadrant (TQ) during variable interval probe trials. Mice trained with 10 mg/kg MPH spent more time in the TQ on Days 11–15 than saline controls. (D) Time spent in the TQ during no platform probe trials given on Days 5, 10, and 15. Mice trained with 10 mg/kg MPH spent more time in the TQ during the Day 15 trial than saline controls. Each point represents the mean ± 1 SEM. Starred (*) data points identify significant post hoc comparisons against the saline control group using Fisher's protected least significant difference tests following significant omnibus comparisons.

3. Results

3.1. Water maze

3.1.1. Water maze acquisition

3.1.1.1. Platform training trials. All groups learned the task over the 15 days of training (Days 1–15). For clarity, data are depicted in blocks of three training days (Fig. 1). Subjects took less time to find the platform on Day 15 versus Day 1 [0 mg/kg: $t(9) = 4.69$, $p = 0.001$; 1 mg/kg: $t(11) = 4.08$, $p = 0.002$; 10 mg/kg: $t(9) = 4.82$, $p = 0.001$] (Fig. 1A). Pre-training MPH had no effect on performance; no group differences were found in the latency to reach the platform [$F(2,29) = 0.15$, $p = 0.86$, *ns*] (Fig. 1A) or average swim speed [$F(2,29) = 1.04$, $p = 0.37$, *ns*] during platform training trials (Fig. 1B).

3.1.1.2. Variable interval probe trials. Each day subjects were given one VI probe trial, on drug, following the 3 platform training trials. Subjects spent significantly more time in the TQ during the VI probe trial on Day 15 versus Day 1 [0 mg/kg: $t(9) = 2.78$, $p = 0.021$; 1 mg/kg: $t(11) = 6.16$, $p < 0.001$; 10 mg/kg: $t(9) = 7.27$, $p < 0.001$] (Fig. 1C). There was a significant day by group interaction for time spent in the TQ [$F(28,406) = 2.32$, $p < 0.001$] (Fig. 1C). The 10 mg/kg MPH group spent more time in the TQ on Days 11–15 than saline controls (p values <0.03). The saline control and 1 mg/kg MPH groups did not differ from one other (p value >0.3).

3.1.1.3. No platform probe trials. On Days 5, 10, and 15 subjects were given standard NP probe trials, on drug. Subjects spent significantly more time in the TQ on Day 15 versus Day 5 [0 mg/kg: $t(9) = 2.62$, $p = 0.03$; 1 mg/kg: $t(11) = 3.8$, $p = 0.003$; 10 mg/kg: $t(9) = 5.23$, $p = 0.001$] (Fig. 1D). There was a significant NP probe test day by group interaction for time spent in the TQ [$F(4,58) = 4.36$, $p = 0.004$] (Fig. 1D). Mice given 10 mg/kg MPH spent more time in the TQ during the Day 15 NP probe trial than the saline and 1 mg/kg MPH groups (p values <0.01), which did not differ from one another ($p > 0.4$).

3.1.2. Water maze retention

One day after training (Day 16) all mice were given a NP probe test, off drug. Fig. 2A depicts the percent time spent in each quadrant. To assess learning in each group paired two tailed t-tests between the time spent in the TQ versus the mean time spent in the other three quadrants were used. Mice trained with 1 mg/kg or 10 mg/kg MPH spent more time in the TQ than the other quadrants averaged, but saline controls did not: saline [$t(9) = 1.71$, $p = 0.12$], 1 mg/kg MPH [$t(11) = 4.30$, $p = 0.001$], 10 mg/kg MPH [$t(9) = 6.68$,

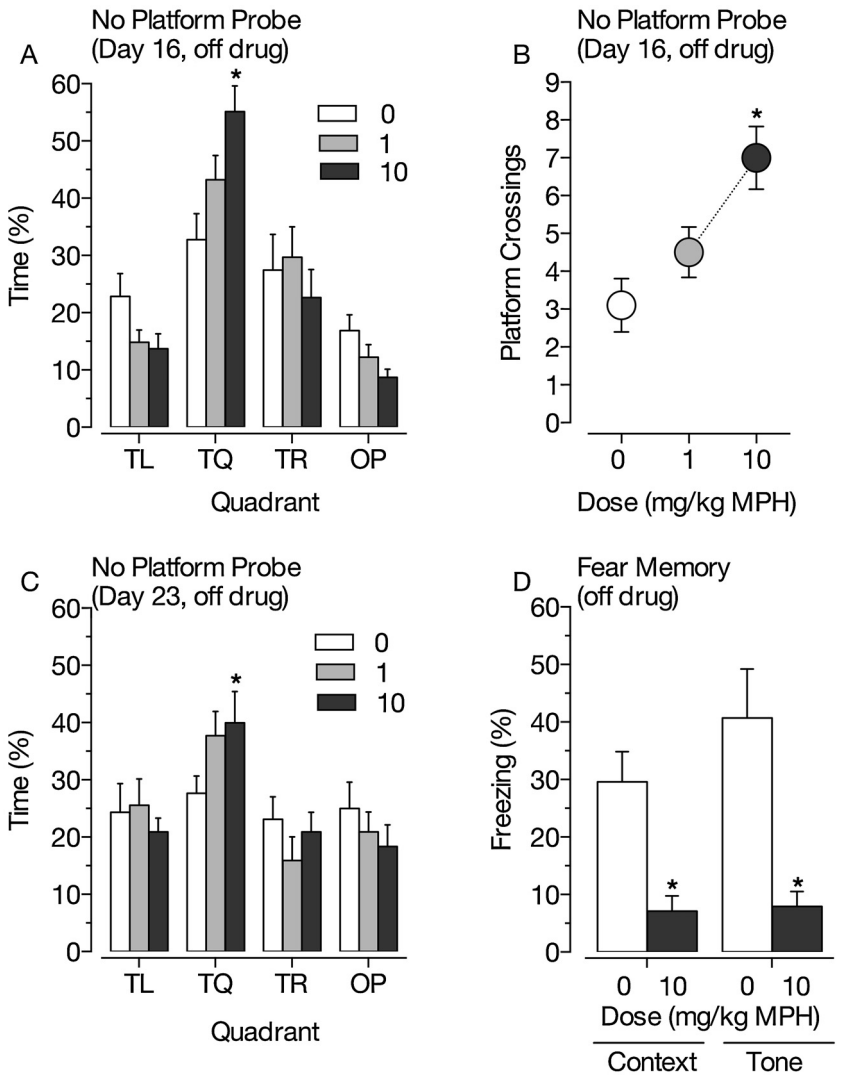

Fig. 2. Water maze retention. (A) Time spent in each quadrant during the off drug no platform probe trial conducted one-day post-training. Mice trained with 1 (grey bars) or 10 mg/kg (black bars) MPH, but not saline (0 mg/kg MPH, white bars), spent more time in the TQ than the other quadrants (TL: target left; TR: target right; OP: opposite). (B) Crossings over the exact platform location during the Day 16 NP probe trial. Mice trained with 10 mg/kg MPH crossed the platform location significantly more than saline controls. (C) Time spent in each quadrant during the off drug NP probe trial conducted one week after training. Mice trained with 1 or 10 mg/kg MPH, but not saline (0 mg/kg MPH), spent more time in the TQ than the other quadrants. Each point or bar represents the mean ± 1 SEM. (D) Pavlovian fear conditioning. Chronic dosing with 10 mg/kg MPH (black bars) prior to conditioning dramatically impaired long-term context (left) and tone fear memory (right) as compared to saline controls (0 mg/kg MPH, white bars). Each bar represents the mean ± 1 SEM average percent time freezing for the entire 5 min context test or the three 30-s tone presentations during the tone test. Starred (*) data points identify significant post hoc comparisons against the saline control group using Fisher's protected least significant difference tests following significant omnibus comparisons.

$p < 0.0001$]. This indicates that mice trained with MPH retained the location of the platform, while the saline control group had relatively weak memory. To determine whether the groups learned differently, we performed a MANOVA of time spent in the TQ and platform crossings. Significant group differences were found [Time in TQ: $F(2,29) = 5.98$, $p = 0.007$, Platform Crossings: $F(2,29) = 6.85$, $p = 0.004$]. Mice trained with 10 mg/kg MPH spent significantly more time in the TQ ($p = 0.002$; Fig. 2A) and crossed the platform location more times than the saline control group (p value <0.02; Fig. 2B). The saline control and 1 mg/kg MPH groups did not differ in terms of time spent in the TQ ($p = 0.1$) or platform crossings ($p = 0.18$).

One week after training (Day 23) mice were given a second off-drug NP probe test. Mice trained with 1 mg/kg or 10 mg/kg MPH spent more time in the TQ than the other quadrants averaged, though saline control mice did not: saline [$t(9) = 0.87$, $p = 0.45$], 1 mg/kg MPH [$t(11) = 2.98$, $p = 0.01$], 10 mg/kg MPH [$t(9) = 2.73$, $p = 0.02$] (Fig. 2C). Mice trained with 10 mg/kg MPH spent significantly more time in the TQ ($p < 0.01$; Fig. 2C) and crossed the platform location significantly more than the saline control group ($p < 0.03$; data not graphed). Thus, mice trained with MPH retained the location of the platform one-week post-training, while the saline control group did not.

3.2. Fear conditioning

10 mg/kg MPH enhanced spatial memory in the water maze. In previous work we found that acute administration of 1 mg/kg MPH enhanced and 10 mg/kg MPH impaired long-term fear memory [11]. It is possible that chronic administration of 10 mg/kg MPH produces tolerance [23], which might explain the different dose–response curves across the two tasks. To examine this possibility we gave 0 (saline control) or 10 mg/kg MPH once for each of

12 days prior to training and during fear conditioning, mimicking the water maze drug administration protocol.

3.2.1. Training

After 12 days of chronic dosing mice were given 0 or 10 mg/kg MPH 30 min prior to training in the conditioning chambers (Day 13). 10 mg/kg MPH significantly increased locomotor activity during the baseline period relative to saline controls (0 mg/kg: 177 ± 35.9, 10 mg/kg: 306.5 ± 40.7 arbitrary units) [$F(1,14) = 5.67$, $p = 0.03$] (data not graphed). The 2-s shock elicited a large increase in velocity, the unconditioned response, which did not differ between groups [$F(1,14) = 0.84$, $p = 0.38$] (data not graphed).

3.2.2. Testing

One week after training mice were returned to the conditioning context, off drug, to assess contextual memory. As compared to saline controls, chronic dosing with 10 mg/kg MPH prior to training dramatically impaired contextual memory [$F(1,14) = 10.20$, $p = 0.01$] (Fig. 2D, left). Twenty-four hours later tone memory was assessed, also off drug. Baseline locomotor activity in the alternate context did not differ between groups ($p > 0.2$). Mice chronically given 10 mg/kg MPH during training had significantly less tone memory than saline controls [$F(1,14) = 11.03$, $p = 0.005$] (Fig. 2D, right). Overall, these data suggest that the difference in dosing with regards to enhancing fear conditioning versus water maze memory cannot simply be explained by tolerance.

4. Discussion/conclusions

Here we demonstrate that mice given 10 mg/kg MPH pre-training learned the location of a fixed hidden platform faster than mice trained on saline or 1 mg/kg MPH (Fig. 1). Further, mice trained with either 1 or 10 mg/kg MPH retained the location of the platform both one day and one week post-training, while saline control mice did not (Fig. 2A–C). Together, these findings indicate that MPH dose-dependently enhances spatial learning and memory and that these effects persist when animals are tested off drug.

Interestingly, we observed different dose–response curves on fear conditioning and the water maze [11]. In the current study 10 mg/kg MPH optimally enhanced water maze learning; we previously found that 10 mg/kg MPH impaired fear memory [11]. Additionally, the 1 mg/kg dose of MPH that optimally enhanced fear learning [11] only modestly enhanced the retention of spatial memory in the water maze (Fig. 2C). It is important to note that this 1 mg/kg dose is the same as that typically prescribed therapeutically to humans (0.5–1 mg/kg) [13]. It is unclear how a dose of MPH in a mouse translates to a human dose [25] and unless specific evidence warrants otherwise, we have advocated using one-to-one dosing between humans and mice (see [1] and [11] for an extensive discussion).

Tolerance is one possible explanation for the different dose–response curves we observed across the two tasks [23]. In earlier work, a single injection of 10 mg/kg MPH was administered prior to fear conditioning [11], whereas water maze training involved injections of 10 mg/kg MPH for 15 days. Given that an enhancement in water maze learning was not seen until the 11th day of training (Fig. 1C), it is possible that subjects grew tolerant to the adverse behavioural effects seen with acute administration [23]. If this was the case then one might predict that mice given 10 mg/kg MPH chronically before fear conditioning would not have impaired fear memory. However, chronic dosing with 10 mg/kg MPH led to dramatically impaired fear memory when subjects were tested off drug (Fig. 2D). This decrement was independent of any effects on locomotion (see [11] for a discussion).

Instead, these dosing differences likely reflect different levels of arousal required for each task or differential action on the neural substrates for each task. It has been widely hypothesized that cognitive tasks have different optimal levels of arousal [26–28]. Often, high levels of arousal/activation are associated with impaired performance, while moderate arousal/activation is associated with the best performance [1]. Consistent with the present study, we previously found that a much higher dose of modafinil, an atypical psychostimulant [1], was required to enhance water maze learning (75 mg/kg) in comparison to the dose required to enhance fear learning (0.75 mg/kg) [22]. Thus, our results suggest that fear conditioning and the water maze themselves may produce different levels of arousal/activation or may require different amounts of monoamine activation for optimal learning [29–31]. We have argued that psychostimulant dose can be viewed as a proxy for the level of arousal/activation in animal models [1]. One may speculate that the water maze requires a greater level of activation than fear conditioning for optimal performance, which shifts the MPH dose–response curve to the right [22]. Still, we would expect that very high doses of MPH would impair water maze performance.

Nonetheless, 10 mg/kg MPH produced a compelling long-term enhancement of spatial learning that persisted when subjects were tested off-drug. Taken together with evidence that MPH (0.01–1 mg/kg) can enhance fear memory [11], it is clear that MPH produces a broad improvement in associative memory. We suggest that psychostimulant-induced memory enhancement should be the standard with which novel nootropics are compared. Indeed, although many novel cognitive enhancers are being developed, it remains to be seen if they will be definitively more effective and/or safe than the classical psychostimulants.

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