Brief Communication

Stimulant drug effects on touchscreen automated paired-associates learning (PAL) in rats

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Here we tested in rats effects of the procognitive drugs modafinil and methylphenidate on post-acquisition performance in an object–location paired-associates learning (PAL) task. Modafinil (32; 64 mg/kg) was without effect, while higher (9 mg/kg) but not lower (4.5 mg/kg) doses of methylphenidate impaired PAL performance. Likewise, higher but not lower doses of amphetamine (0.4; 0.8 mg/kg) and MK-801 (0.08; 0.12 mg/kg) decreased PAL performance. Impaired PAL performance induced by methylphenidate, amphetamine, and MK801 most likely reflects compromised cognitive function, e.g., retrieval of learned paired associates. Our data suggest that stimulant drugs such as methylphenidate and modafinil might not facilitate performance in hippocampus-related cognitive tasks.

[Supplemental material is available for this article.]

Touchscreen equipped operant boxes represent a powerful tool to study cognition in rats. This methodology provides superior translational potential because a number of different cognitive tasks can be run that mirror touchscreen methods being part of the Cambridge Neuropsychological Test Automated Battery (CANTAB) used to test human subjects. For instance, the paired-associates learning task (PAL) allows to investigate learning of object–location associations in rodents and humans (Horner et al. 2013; Mar et al. 2013; Talpos and Steckler 2013; Josey and Brigman 2015). In rats, post-acquisition performance on the PAL task is sensitive to hippocampal dysfunction. For instance, intrahippocampal microinfusions of lidocaine or NMDA and AMPA receptor antagonists impaired PAL performance in animals that acquired the task before (Talpos et al. 2009). Likewise, in mice, post-acquisition intrahippocampal microinfusions of muscimol impaired PAL performance (Kim et al. 2015). In humans, PAL task performance is predictive of the conversion from mild cognitive dysfunction to Alzheimer's disease (Blackwell et al. 2004). Furthermore, in mild cognitive impairment, PAL performance was correlated with hippocampal volume (Keri et al. 2012).

To date, little is known about effects of procognitive drugs on PAL performance. The few available data show that, in mice, the cholinesterase inhibitor donezepil (0.3 mg/kg, i.p.) facilitated PAL performance (Bartko et al. 2011). In contrast, the effects of two other prominent procognitive drugs, methylphenidate and modafinil, in PAL have not been tested yet. Modafinil facilitated performance in a number of rodent cognitive tasks (Beracochea et al. 2001, 2002, 2003; Shuman et al. 2009), e.g., enhanced visual discrimination and visual sustained attention (Morgan et al. 2007). Likewise, methylphenidate improved acquisition and retention of spatial memory in maze tasks (Carmack et al. 2014). Both drugs seem to be used as cognitive enhancers for nonmedical purposes (McCabe et al. 2005). However, for both drugs, evidence in favor of cognitive enhancement in humans is mixed (Repantis et al. 2010). For instance, in healthy individuals, methylphenidate and modafinil did not improve PAL (Turner et al. 2003a; Muller et al. 2013).

Here we tested the effects of systemic methylphenidate and modafinil on post-acquisition PAL performance of rats. As both drugs failed to improve PAL performance in humans we hypothesize that they would not improve PAL performance in rats. For validation, we included the indirect dopamine agonist amphetamine and the NMDA receptor antagonist MK801, drugs with known effects on PAL performance (Talpos et al. 2014, 2015). Here we show that the higher but not lower doses of methylphenidate, amphetamine, and MK-801 impaired cognitive performance in the PAL task while modafinil at both doses tested was without effect.

All animal experiments were conducted according to the German law of animal protection and approved by the proper authorities. Male Lister Hooded rats (Charles River Laboratories, UK) were used weighting between 230 and 270 g at the beginning of the experiment. Details on housing conditions are given in the Supplemental Material. Operant boxes (Med Associates; 31.8 × 25.4 × 26.7 cm) were used with one end of the chamber equipped with a touch-sensitive, flat-screen LCD monitor equipped with an infrared sensor (see Supplemental Material for details on the touch screen box configuration). Animals were trained and tested on the dPAL task ("different paired-associate learning") according to a protocol by Talpos et al. (2009). In brief, the PAL task demands learning that a particular object, i.e., one out of three symbols, is only correct in a particular location, i.e., one out of three positions on the touchscreen. On a given trial, two symbols are displayed, one in its correct, another one in an incorrect position, and the rat has to respond to the symbol in the correct position (Supplemental Fig. S1). For details of the habituation, pretraining, and training protocol see Supplemental Material. Amphetamine (Sigma) was dissolved in saline (0.9% NaCl, Braun Melsungen), modafinil ((2-(diphenylmetyhl)sulfinyl)acetamide (Sequoia) was dissolved in 1% w/v methylcellulose (Sigma) in saline, methylphenidate (Sigma) was dissolved in saline, MK-801 was dissolved in saline. All drugs were administered i.p. 30 min prior behavioral testing. IP injections of respective vehicles served as controls. For all experiments, the same group of animals was used ($n = 6$). All experiments used a within-group design in which each rat

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received all drugs and respective vehicle treatments with one treatment on one test day per week. Baseline training sessions without drug administration were conducted 4 d per week. The order of drug testing was as follows: amphetamine, methylphenidate, modafinil, MK-801. Drugs were administered using a within-subject cross-over design, i.e., half of the animals received drug or vehicle on the test day in week 1; this assignment was reversed on the test day in week 2. Percent correct, response latencies (time from symbol activation on the monitor to the response at the monitor), and magazine latencies (time from the response at the monitor until magazine entry) are given as means ± standard error of the mean (SEM). Data from each drug dose and respective vehicle control were subjected to a paired *t*-test.

Administration of the lower dose of amphetamine (0.4 mg/kg) tended to reduce the number of correct responses ($t_5 = 2.23$, $P = 0.07$), decreased response latencies ($t_5 = 3.24$, $P < 0.05$) but left unchanged magazine latencies ($t_5 = 0.90$, n.s.). In contrast, the higher dose of amphetamine (0.8 mg/kg) significantly reduced the number of correct responses ($t_5 = 2.87$, $P < 0.05$), but did not alter response latencies ($t_5 = 0.03$, n.s.) or magazine latencies ($t_5 = 1.63$, n.s.) (Fig. 1). No effect of amphetamine as well as all other drugs tested was ever seen on the number of trials completed, therefore, these data are not presented. Methylphenidate at 4.5 mg/kg did not change the number of correct responses ($t_5 = 0.16$, n.s.) and left unaffected response latencies ($t_5 = 1.49$, n.s.) and magazine latencies ($t_5 = 1.63$, n.s.) (Fig. 2). In contrast, methylphenidate at 9 mg/kg reduced the number of correct responses ($t_5 = 3.56$, $P < 0.05$) and decreased response latencies ($t_5 = 3.35$, $P < 0.05$) but not magazine latencies ($t_5 = 2.79$, n.s.) (Fig. 2). Modafinil at 32 mg/kg did not alter the number of correct responses ($t_5 = 1.48$, n.s.), response latencies ($t_5 = 0.05$, n.s.) and magazine latencies ($t_5 = 0.52$, n.s.). Likewise, modafinil at 64 mg/kg had no effects on the number of correct responses ($t_5 = 1.76$, n.s.), response latencies ($t_5 = 1.17$, n.s.) and magazine latencies ($t_5 = 0.06$, n.s.) (Fig. 3). Administration of the lower dose of MK-801 (0.8 mg/kg) did not alter the number of correct responses ($t_5 = 0.69$, n.s.), response latencies ($t_5 = 2.11$, n.s.), and magazine latencies ($t_5 = 1.73$, n.s.). However, the higher dose of MK-801 (1.2 mg/kg) reduced the number of correct responses ($t_5 = 2.61$, $P < 0.05$) but did not alter response latencies ($t_5 = 1.96$, n.s.) and magazine latencies ($t_5 = 0.52$, n.s.) (Supplemental Fig. S2).

Here we show that amphetamine at 0.8 mg/kg markedly reduced correct choices but not response and magazine latencies. Likewise, Talpos et al. (2014) revealed that amphetamine (0.5, 0.75 mg/kg) significantly reduced correct choices in PAL without influencing response latencies. The findings by Talpos et al. (2014) and our findings imply that impaired choice accuracy seen here may not be secondary to amphetamine-induced behavioral activation or enhanced impulsivity (Cole and Robbins 1987), effects that might have altered response or magazine latencies. Of note, in a touchscreen-based complex visual discrimination task that, by using morphed stimulus pairs, involved increasing levels of perceptual demands, amphetamine dose-dependently impaired choice accuracy (Talpos et al. 2012). Of note, there was no dose × perceptual complexity interaction. The failure to detect such an interaction strongly suggests that amphetamine did not compromise visual discrimination. Collectively, these findings indicate that the effects of amphetamine in the PAL task used here may not reflect disrupted visual discrimination. Alternatively, amphetamine could have interfered with memory retrieval, however, the few available studies in humans and laboratory animals gave mixed results. For instance, in rats tested in a radial maze task, amphetamine (0.25; 0.5 mg/kg) facilitated retrieval of spatial information (Sara and Deweer 1982). In contrast, in humans, moderate doses of amphetamine that enhanced memory encoding and consolidation, increased retrieval errors in an episodic memory task involving picture stimuli (Ballard et al. 2014). Thus, it appears that, depending on the type of information, acute amphetamine can impair or facilitate retrieval. Remarkably, chronic amphetamine user's display pronounced impairments in CANTAB including PAL that can persist after several years of drug abstinence and may reflect neuropathology in frontal and temporal cortices (Ersche et al. 2006). It is well known that amphetamine can increase extracellular catecholamines in many brain areas including the hippocampus (Kuczenski and Segal 1997; Borgkvist et al. 2012). Remarkably, glucocorticoids, by promoting the release and/or blocking the reuptake of noradrenaline, can impair retrieval of hippocampus-dependent

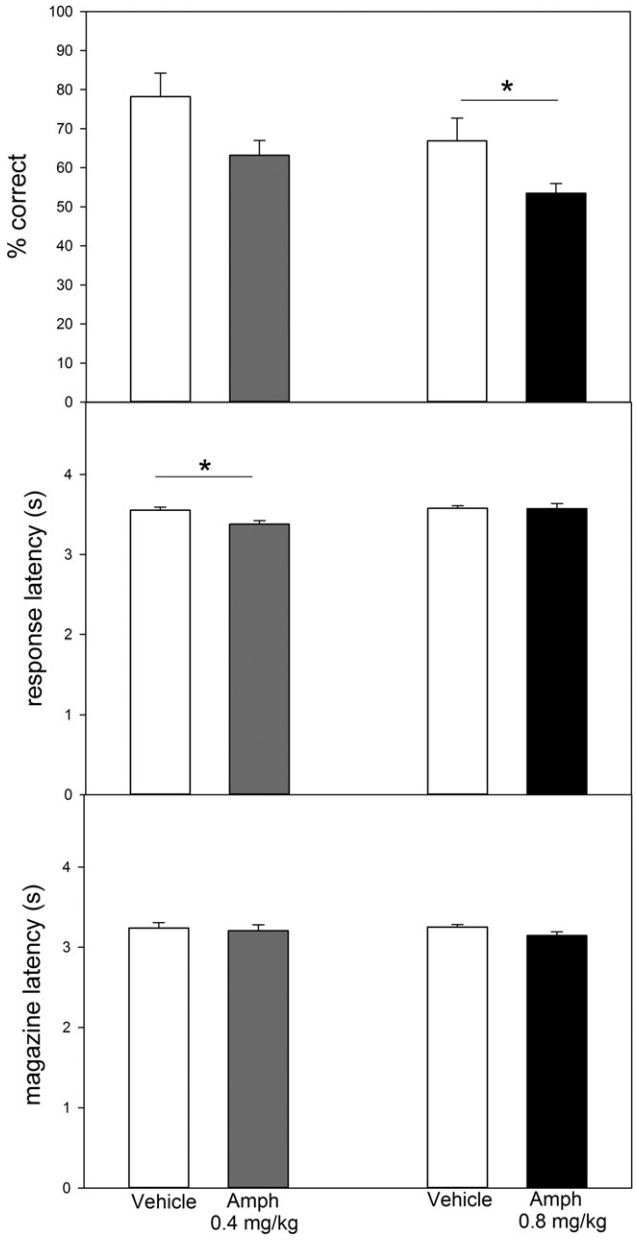

Figure 1. Effects of amphetamine (0.4, 0.8 mg/kg) on PAL performance. Percent correct responses, response latencies and magazine latencies are given as means ± SEM. The lower drug dose tended to reduce % correct responses ($P = 0.07$, *t*-test), while the higher dose significantly decreased % correct responses ((*) $P < 0.05$, paired *t*-test). No other significant effects were detected.

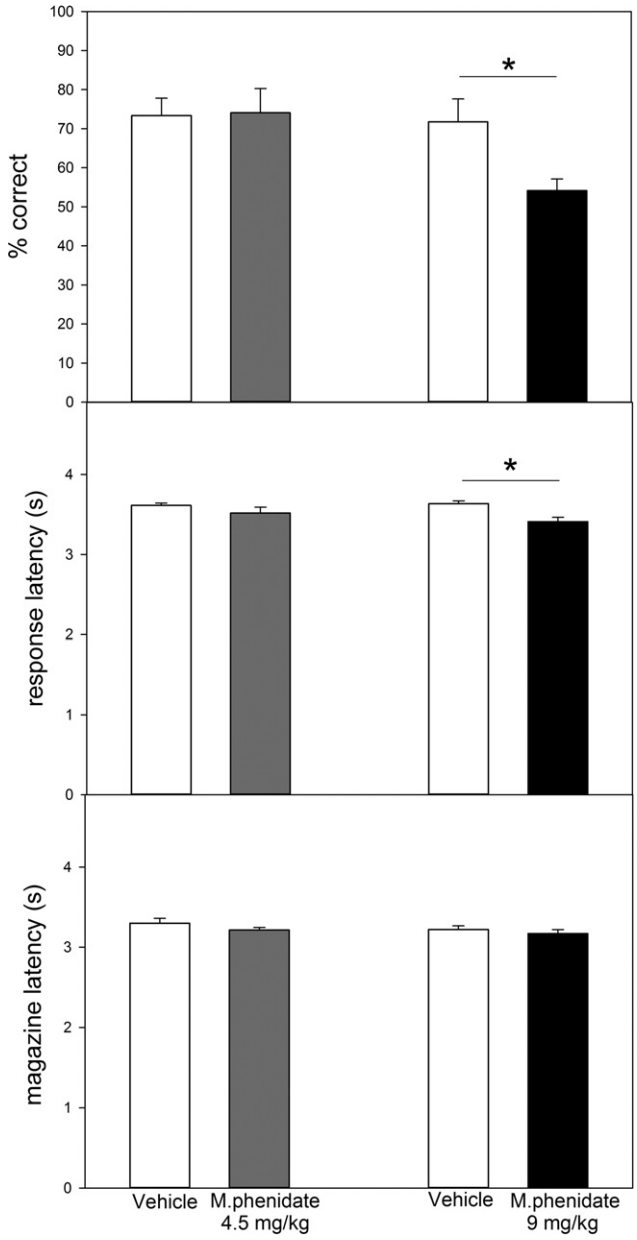

Figure 2. Effects of methylphenidate (4.5, 9.0 mg/kg) on PAL performance. Percent correct responses, response latencies and magazine latencies are given as means ± SEM. The higher drug dose significantly decreased % correct responses and response latencies ((*) $P < 0.05$, paired *t*-test). No other significant effects were detected.

memory (de Quervain et al. 2007; Schutsky et al. 2011). Thus, an amphetamine-induced increase of hippocampal noradrenaline efflux could provide one mechanism to account for reduced choice accuracy in PAL seen here. Of course, amphetamine effects in PAL could involve actions in other brain areas as well, however, causal evidence for a role of, for instance, the prefrontal cortex to support PAL is missing.

Results further demonstrate that the higher (9 mg/kg) but not lower dose (4.5 mg/kg) of methylphenidate markedly reduced correct choices and response latencies. Likewise, in a touchscreen-based visual discrimination task, methylphenidate at higher doses (≥10 mg/kg) reduced performance and response speed (Galizio et al. 2009). As we observed no changes in magazine latencies and no correlation between choice accuracy and response latencies in methylphenidate-treated animals, it is unlikely that impaired choice accuracy may directly result from methylphenidate-induced behavioral activation or impulsivity (Milstein et al. 2010; Sommer et al. 2014). Furthermore, as this drug decreased rather than increased response latency, an impaired visual discrimination seems unlikely. Hence, reduced PAL performance under methylphenidate (9 mg/kg) may not reflect impaired visual discrimination or sustained attention.

Of note, there is evidence that methylphenidate facilitates memory for aversive events (Bethancourt et al. 2009) and can improve spatial learning and memory retrieval in a radial maze task (Zhu et al. 2007, but see Rostron et al. 2013). Interestingly, methylphenidate was also able to compromise object recognition memory (Heyser et al. 2004). Remarkably, electrophysiological studies in vitro revealed that methylphenidate amplifies hippocampal long-term potentiation as well as long-term depression, findings that could explain why methylphenidate was able both to improve and impair learning and memory (Dommett et al. 2008). Here, we found no evidence in favor of enhanced memory retrieval under methylphenidate. Rather, methylphenidate at the higher dose impaired PAL performance. Yet, respective comparisons across studies are limited by the fact that spatial tasks such as PAL and radial maze tasks may involve hippocampal processing but could differ in terms of task complexity or spatial strategies to solve the task.

As methylphenidate, like amphetamine, amplified catecholamine release in numerous brain areas including the hippocampus (Kuczenski and Segal 1997; Borgkvist et al. 2012), we speculate that, as discussed above for amphetamine, an enhanced hippocampal noradrenaline efflux could provide one neurochemical mechanism through which methylphenidate impaired PAL performance. In contrast, the lower dose of methylphenidate did not modify PAL performance. In line with this latter finding, studies on elderly volunteers revealed that low to intermediate clinical doses of methylphenidate (20, 40 mg) failed to alter PAL performance (Turner et al. 2003b).

Modafinil did not affect correct choices in PAL as well as response and magazine latencies. As the drug doses used here (32, 64 mg/kg) were behaviorally active in various cognitive tasks for rats (Minzenberg and Carter 2008), inappropriate dosing might not account for negative results. Morgan et al. (2007) examined the effects of modafinil (8–64 mg/kg) in intact rats on visual discrimination and visual sustained attention and were able to show that this drug enhanced sustained attention, i.e., increased accuracy to respond to light emitting diodes in a dose- and delay-dependent manner. Thus, the failure to detect PAL effects suggests that an enhanced sustained attention under modafinil as such may be not sufficient to facilitate PAL performance. However, in intact rats that performed the five-choice serial reaction time task, modafinil (32–128 mg/kg) did not improve attention measures (Waters et al. 2005). Likewise, in rats tested in a signal-stop task, modafinil (3–100 mg/kg) did not alter attention (Eagle et al. 2007). Thus, the extent to which modafinil can influence attentional processes and the relevance of such effects in the context of PAL performance remains questionable. Previous studies using an object recognition task showed that modafinil recovered recognition memory in memory-impaired rats, but did not improve memory consolidation and retrieval in naïve rats (Garcia et al. 2013), a finding that is consistent with our negative results in naïve rats. Likewise, in healthy humans, modafinil did not alter performance in PAL (Turner et al. 2003a; Muller et al. 2013).

The NMDA receptor antagonist MK-801 at 0.12 mg/kg but not 0.08 mg/kg significantly reduced choice accuracy without concomitant effects on response and magazine latencies suggesting that impaired PAL performance might not be related to drug-induced behavioral activation (Murschall and Hauber

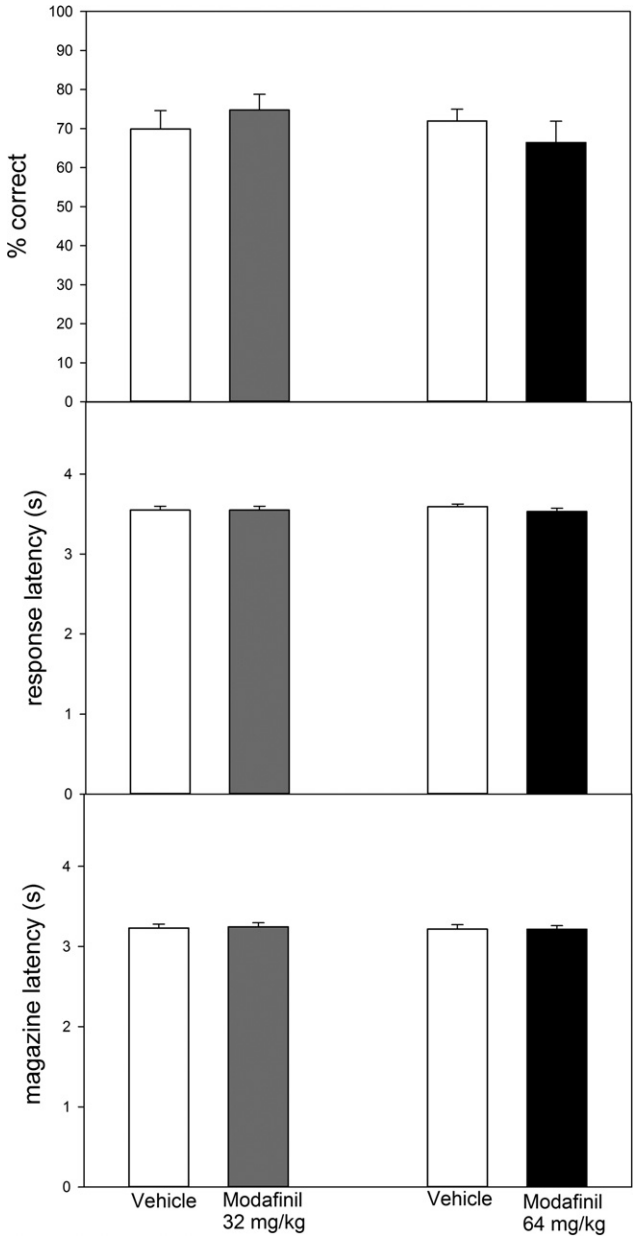

Figure 3. Effects of modafinil (32, 64 mg/kg) on PAL performance. Percent correct responses, response latencies and magazine latencies are given as means ± SEM. Modafinil had no significant effects on either measure.

2005). A recent study demonstrated that MK801 at 0.075 mg/kg markedly reduced choice accuracy and increased response and magazine latencies in PAL (Talpos et al. 2015). The reasons for these discrepancies are elusive. Furthermore, the NMDA receptor antagonist PCP reduced accuracy of rats in PAL (Talpos et al. 2014). In contrast, the NMDA receptor antagonist ketamine, for unknown reasons, did not affect PAL performance in rats (Talpos et al. 2014) but in subhuman primates (Taffe et al. 2002), while in humans the effects of NMDA receptor antagonists have not yet been tested. Previous studies using a related touchscreen-based simple visual discrimination task demonstrate that MK801 at 0.1 mg/kg but at not lower doses reduced choice accuracy and increased response and magazine latencies (Talpos et al. 2012). These findings point to the possibility that MK801 effects on choice accuracy in this simple visual discrimination task could be secondary to nonspecific drug effects. However, in the complex version of the touchscreen-based visual discrimination task that involves morphed stimulus pairs, MK801, like amphetamine, dose-dependently impaired choice accuracy. However, there was no dose × perceptual complexity interaction suggesting that MK801 did not affect visual discrimination (Talpos et al. 2012). Of note, in well-trained rats, intrahippocampal microinfusion of MK-801 markedly reduced the number of correct responses in the PAL task used here but not in a simpler PAL task version with lower cognitive but similar perceptual demands (Talpos et al. 2009). Hence, a deficient hippocampal NMDA-receptor-dependent retrieval of paired associates could account, at least in part, for MK801-induced impaired PAL performance seen here.

Taken together, our results demonstrate that the stimulant drugs methylphenidate and modafinil, shown to have some pro-cognitive effects in rats (Morgan et al. 2007; Carmack et al. 2014), did not enhance performance in PAL, a task that is sensitive to hippocampal dysfunction and may serve as a translational model of PAL in humans. Rather, methylphenidate at a higher dose, like higher doses of amphetamine and MK801, impaired PAL performance most likely by interfering with cognitive functions, e.g., retrieval of learned paired associates, rather than with motor or perceptual functions. The observation that methylphenidate and modafinil failed to improve PAL performance in rats is consistent with reports that these drugs at low to intermediate clinical doses did not facilitate PAL performance in healthy individuals (Muller et al. 2013) and patients with dementia (Dolder et al. 2010).

Together, these findings imply that stimulant drugs such as methylphenidate and modafinil might not facilitate performance in hippocampus-related cognitive tasks. Moreover, it is important to consider procedural differences in rodent und human PAL. For instance, in rat PAL, correct responses in a subset of trials (termed here "unique-configuration trials," i.e., trials 1 and 6; Supplemental Fig. S1, left panel) may rely on correct object-location associations (i.e., "flower is always correct on the left position"/trial 1; "airplane is always correct on the right position"/trial 6). However, correct responses in another subset of trials (termed here "common configuration trials," i.e., trials 2–5; Supplemental Fig. S1, left panel) could also involve an alternative strategy, i.e., conditional rules based on the configuration of both presented objects. Examples for such rules are "if flower is left to spider, respond to flower" (trial 2), or, "if flower is right to spider, respond to spider" (trial 4). Given that animals used differential strategies across these trial categories and unique configuration trials are more complex, then, performance should be inferior in unique relative to common configuration trials. In vehicle-treated animals, a post hoc analysis of correct choices as a function of configuration category provided partial evidence in favor of this notion. Yet, none of the drugs tested here impaired correct choices in unique configuration trials (see Supplemental Material). However, these findings are preliminary because (1) we performed post hoc hypothesis testing, (2) the power of our assessment is limited due to the low number of subjects included, (3) the effect assessment is biased as sample sizes of unique ($n = 24$) versus common ($n = 48$) configuration trials per session ($n = 72$ trials) differed markedly. Future studies should investigate in detail an influence of stimulus configuration on correct responding to clarify whether the rat PAL task assesses object-location learning as tested in the human version. One possibility could be subsequent testing using a variant of the PAL task ("sPAL") that may not be solved with a configural strategy (Horner et al. 2013) but is, however, less sensitive to hippocampal dysfunction (Talpos et al. 2009) and requires relearning.

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