



## Modafinil facilitates performance on a delayed nonmatching to position swim task in rats

Christopher P. Ward<sup>1</sup>, John R. Harsh, Kaki M. York, Krista L. Stewart, John G. McCoy\*

*Department of Psychology, Behavioral Neuroscience Laboratory, The University of Southern Mississippi, Box 5025, Hattiesburg, MS 39406, USA*

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### Abstract

Modafinil is a wake-promoting drug approved by the FDA for the treatment of narcolepsy. Recent evidence suggests that modafinil may improve learning and memory processes. To further evaluate possible cognitive properties associated with modafinil, male Sprague–Dawley rats were tested in a delayed nonmatching to position (DNMTP) task. A modified water maze allowed animals to make one of two choices for the location of the escape platform. Each trial consisted of two swims. On the information swim (IS), only one choice was open to the animal for escape. One minute later, a choice swim (CS) presented the animal with two choices with the escape platform in the opposite position. There were 10 trials per day for 10 days. Rats received 0, 30, 55, or 100 mg/kg ip of modafinil 30 min prior to testing. Locomotor activity was also assessed. Animals that received 55 and 100 mg/kg made significantly more correct choices, indicating that higher doses of modafinil learned the task faster than did controls. While animals that received 100 mg/kg did exhibit an enhancement of locomotor activity, this effect did not result in more efficient goal-directed behavior. The evidence is consistent with previous research showing that modafinil facilitates cognitive processes.

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### 1. Introduction

Modafinil (diphenyl-methyl-sulphinil-2-acetamide) has been found to be effective in the treatment of excessive daytime sleepiness associated with narcolepsy (Bastuji and Jouvet, 1988; Modafinil in Narcolepsy Multicenter Study Group, 2000), obstructive sleep apnea syndrome (Pack et al., 2001), and shift work sleep disorder (Roth and Roehrs, 1996). Therapeutic effects have also been reported in studies involving other disorders, including Parkinson's disease (Nieves and Lang, 2002; Hogg et al., 2002), depression (Kaufman et al., 2002), and attention deficit hyperactivity disorder (ADHD; Taylor and Russo, 2000; Rugino and Copley, 2001). It is unknown whether modafinil has clinical value beyond its ability to promote wakefulness in patients unable

to obtain adequate sleep. Modafinil's mechanism of action is not yet fully understood. Mapping studies using Fos immunohistochemistry or 2-deoxyglucose autoradiography suggest that modafinil activates neuronal circuits which are substantially different from those activated by classical stimulants, such as amphetamine or dexamphetamine (Lin et al., 1996; Engber et al., 1998). Dopamine transporters, however, appear to be necessary for the specific wake-promoting effects of both modafinil and methamphetamine, as the activational response to these drugs is not observed in dopamine transporter knockout mice (Wisor et al., 2001). The wake-promoting effects of modafinil also require a functioning alpha-1 adrenergic system as alerting effects are blocked by prazosin, an alpha-1 receptor antagonist (Lin et al., 1996). Modafinil's effects may be closely related to modification of glutamatergic, GABAergic, and serotonergic neurotransmission in regions of the brain involved in alertness and cognitive function (Ferraro et al., 1998, 1999, 2000).

A number of studies have documented beneficial effects of modafinil on cognitive performance in human subjects who have been experimentally sleep deprived (Lagarde and Batejat, 1995; Wesensten et al., 2002; Stivalet et al., 1998;

\* Corresponding author. Tel.: +1-601-266-4617; fax: +1-601-266-5580.

E-mail address: [John.McCoy@usm.edu](mailto:John.McCoy@usm.edu) (J.G. McCoy).

<sup>1</sup> Current address: Harvard Medical School and VA Medical Center, 940 Belmont Street, Brockton, MA 02301.

Pigeau et al., 1995). These effects may be secondary to increased wakefulness. One study found no effects on cognitive performance in subjects who have not been experimentally sleep deprived (Randall et al., 2003). Turner et al. (2003), however, have recently reported modafinil-related improvement on neuropsychological tasks involving inhibition of prepotent responses. The latter may be related to modafinil's psychotherapeutic benefit in the treatment of ADHD (Taylor and Russo, 2000; Rugino and Copley, 2001).

In animals studied without experimental sleep deprivation, Beracochea et al. (2001) found that chronic dosing of mice with modafinil had a delay-dependent effect on spontaneous alternation rates in a T maze and concluded that modafinil improves working memory. Beracochea et al. (2002) found evidence that modafinil increased rate of learning in mice performing a serial spatial discrimination reversal (SSDR) task in a T maze. This task requires adoption of a win–stay response pattern (i.e., choosing the response alternative reinforced in the immediately preceding trial). More recently, this group found that even a single acute injection (64 mg/kg) of modafinil leads to a more rapid emergence of the win–stay strategy (Beracochea et al., 2003). In a separate experiment, it was shown that modafinil did not interfere with performance on a task with contingently reinforced alternation rates (i.e., a win–shift response pattern) over five successive days of testing (but neither did it facilitate learning on this task). The investigators suggested that modafinil has effects on areas of the brain involved in memory and cognitive flexibility. A published abstract by Miller et al. (2000) provides evidence of modafinil's effect on learning of an operant delayed alternation task by aged rats. The task required adoption of a win–shift response pattern (i.e., not choosing the response alternative reinforced in the immediately preceding trial). The authors reported the interesting finding that modafinil fully reversed an age-related decline in performance on this task. This and other findings led them to conclude that modafinil enhances information processing without necessarily improving short-term memory.

The purpose of the present study was to replicate and extend previous findings on the effects of modafinil on cognitive functioning in animals. Cognitive enhancement has been reported thus far in a study involving spontaneous alternation (Beracochea et al., 2001), in a study involving positive reinforcement of nonalternation (win–stay response pattern) in a sequential procedure (Beracochea et al., 2002), and in one of two studies involving positive reinforcement of alternation (win–shift response pattern) in a sequential procedure (Miller et al., 2000). The present experiment tests the effects of daily administration of modafinil on rats tested on a delayed nonmatching to position (DNMTP) protocol in a modified water maze. The protocol uses negative reinforcement (i.e., escape or avoidance of an aversive stimulus; cold water in this case) of a pattern of alternating responses (win–shift) in a sequential procedure. The behavioral response required is swimming as opposed to running. The

study is thus an effort to replicate the findings of Miller et al. (2000) using a similar sequential learning procedure with a different motivational system and a different response system. Locomotor activity was assessed using an open-field monitor to determine whether group differences in rate or accuracy in the DNMTP task might be secondary to activational effects of modafinil.

## 2. Materials and methods

### 2.1. Subjects

Forty young adult (60-day) male Sprague–Dawley rats (Harlan Sprague–Dawley, Indianapolis, IN) were housed under constant temperature ( $23 \pm 1$  °C) and a 12:12-h light–dark cycle (lights on at 2000 h). Food and water were available ad libitum. All testing was conducted during the dark phase of the light–dark cycle. All procedures were conducted in accordance with the *Principles of laboratory animal care* (NIH publication No. 85-23, revised 1985) and the Institutional Animal Care and Use Committee (IACUC) at the University of Southern Mississippi.

### 2.2. Drugs

Rats were randomly divided into four groups ( $n = 10$  per group). Animals were given intraperitoneal injections of vehicle, 30, 50, or 100 mg/kg of modafinil (Cephalon, West Chester, PA) in a 0.5% gum arabic suspension. The injection volume was 1 ml/1 kg of body weight. Injections were given on alternating sides of the abdomen to minimize the possibility of skin lacerations due to repeated needle (23 gauge) insertions. Treatments were administered once per day for 10 consecutive days. Injections were given 15 min prior to activity testing and 30 min prior to the DNMTP task.

### 2.3. Apparatus

The water maze as utilized in our laboratory has been described previously (Ward et al., 2002; Williams et al., 2001). Briefly, animals were trained in a round pool, 1.83 m in width and 0.6 m in depth, containing opaque (nontoxic paint) water held constant at  $21 \pm 1$  °C. The water was changed weekly, and a tablespoon of bleach was added daily as an antibacterial agent. The pool was in the center of a square room ( $5 \times 5$  m) containing several distal cues, including furniture and posters with distinctive patterns. Illumination was held constant. A T-shaped aluminum partition was inserted into the water tank to create a start section and two choice sections.

### 2.4. Delayed nonmatching to position

The DNMTP task was modified from Markowska et al. (1996) and Comer and Means (1989). This protocol began

with an initial shaping phase for 3 days. A T-shaped aluminum partition with a sliding gate was inserted into the water tank to create a start section and two choice sections. Day 1 of shaping consisted of animals being placed in a closed choice section and allowed to find a visible platform (10 × 10 cm) raised above the water surface (10 trials). The choice quadrant was alternated between trials, and the animal started from what would be the entrance to the quadrant. If the rat did not find the platform within 60 s, the experimenter guided the animal to the platform. The rat remained on the platform for approximately 5 s and was then returned to a holding cage for approximately 10 min before the next trial. Day 2 of shaping consisted of the same procedures except the gate to the choice quadrant was open (10 trials). Rats started from the entrance to the quadrant. Once again, the rat was allowed 60 s to find the visible platform. The rat remained on the platform for approximately 5 s and then was returned to a holding cage for approximately 10 min before the next trial. Day 3 of shaping consisted of the rat placed in the start position of the pool (10 trials). Both choice quadrants were now open. The rat was trained to find the visible platform in alternating choice quadrants. There was a cutoff of 60 s for the rat to find the visible platform before being led to the platform. The rat remained on the platform for approximately 5 s and then was returned to a holding cage for approximately 10 min before the next trial.

After the 3-day shaping procedure was completed, the DNMTTP protocol commenced and lasted 10 consecutive days. An injection of either drug or vehicle was given 30 min prior to each DNMTTP session on each of 10 consecutive days. For the DNMTTP protocol (see Fig. 1), each trial consisted of two parts: an information swim (IS) and a choice swim (CS). For IS trials, only one section was open. Platform locations followed a predetermined semirandom sequence based on a series of two-choice tasks developed by Fellows (1967). The hidden platform (submerged 1 cm below the water surface) was located in the open section. The rat was released in the start section and allowed 60 s to locate the platform before the experimenter guided the animal to the platform. After 5 s on the platform, the rat was placed in a holding cage for 60 s. For the CS trial, both choice sections were open, but the platform was located in the section that was closed previously to the rat. Choice accuracy and time to find the platform (i.e., latency) were

the dependent variables. For choice accuracy, correct and incorrect responses were recorded. Animals making an incorrect first choice were allowed to continue swimming until they found the platform or until 60 s had elapsed. A correct or incorrect choice on a given CS had no bearing on the location of the platform in the succeeding trial. For latency measures, sessions were recorded to video and scored manually by an independent observer. The observer was blind to the conditions. One day consisted of 10 IS–CS trials (intertrial interval was approximately 10 min). Testing continued for 10 consecutive days.

### 2.5. Locomotor activity

Locomotor activity of rats was assessed in an open-field activity monitor (San Diego Instruments) over a 5-min interval. Testing was performed in two transparent Plexiglas cages (60 × 60 cm) surrounded by a frame containing four infrared beams on each side. The frames were connected to a computer system (San Diego Instruments) that records the number of infrared beam breaks. Activity counts (i.e., beam breaks) were summed across all beams at the end of the 5-min interval.

Rats were tested in the open-field activity monitor 1 day prior to DNMTTP training to assess baseline activity levels. During the 3 days of shaping trials, activity was measured to examine the effects of the maze on activity without drug. Once administration of modafinil began, locomotor activity was tested once per day (15 min postinjection) for the duration of the experiment.

### 2.6. Statistical analysis

A mixed within-subject factorial design was employed. Dose of modafinil (0, 30, 55, and 100 mg/kg) was the between-subjects variable while sessions (10) was the within-subjects variable. Therefore, a mixed-model analysis of variance (ANOVA) [Drug × (Session × Subject)] was conducted. Main effects and interaction effects were further evaluated using appropriate post hoc analyses. A separate mixed-model ANOVA was used to evaluate the effect of modafinil on locomotor activity. Additionally, a trend analysis was conducted to assess whether changes in locomotor activity were dose related.

## 3. Results

### 3.1. Choice accuracy

The groups' mean percentage of correct choices for each day averaged across subjects is shown in Fig. 2. A mixed-model ANOVA was utilized to evaluate the accuracy of choice in the CS across the four testing groups (Day × Group). There was a Group × Day interaction [ $F(27,324) = 2.32, P < .001$ ]. Utilizing a 95% confidence interval, animals

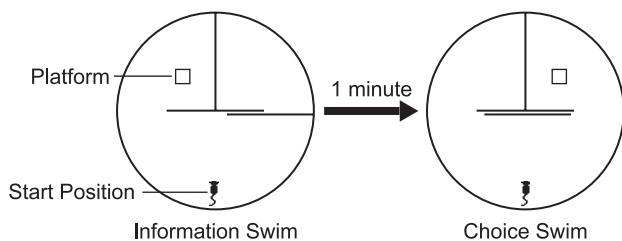


Fig. 1. A schematic drawing of the DNMTTP task. Each rat underwent the IS and CS pair 10 times a day for 10 consecutive days.

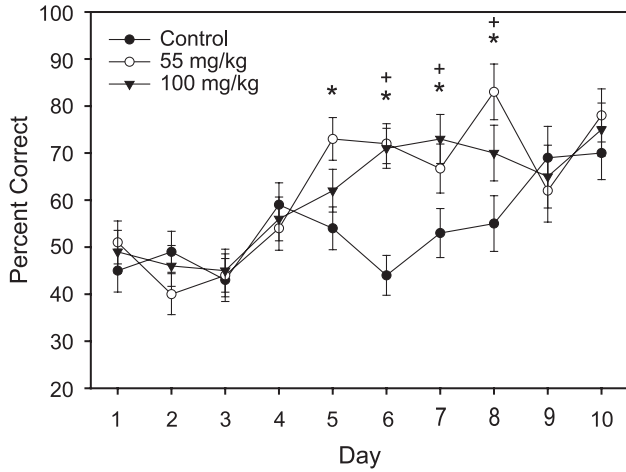


Fig. 2. Mean ( $\pm$  S.E.M.) percent correct responses made by animals given 0, 55, or 100 g/kg of modafinil ( $n = 10$  per group) over 10 consecutive days of DNMTTP testing. Choice accuracy of animals receiving 30 mg/kg of modafinil did not differ significantly from controls. Confidence intervals (95%) determined using control data were used to assess whether choice accuracy differed significantly on each of the 10 days of testing. \* Significant difference in choice accuracy (55 mg/kg vs. control) on Days 5–8. + Significant difference in choice accuracy (100 mg/kg vs. control) on Days 6–8.

that received 55 mg/kg were significantly different from controls on Days 5 through 8 of testing while animals that received 100 mg/kg made significantly more correct choices on Days 6 through 8 of testing. The ANOVA revealed a main effect for groups [ $F(3,36) = 3.613, P = .022$ ]. A Dunnett's  $t$  test revealed that rats receiving 55 and 100 mg/kg made significantly more correct choices than control [ $P = .018$  and  $P = .047$ , respectively] while rats receiving 30 mg/kg were not significantly different from controls. The number of animals in each group to reach a criterion of 80% correct responses on CSs for each day of testing was also determined (see Fig. 3).

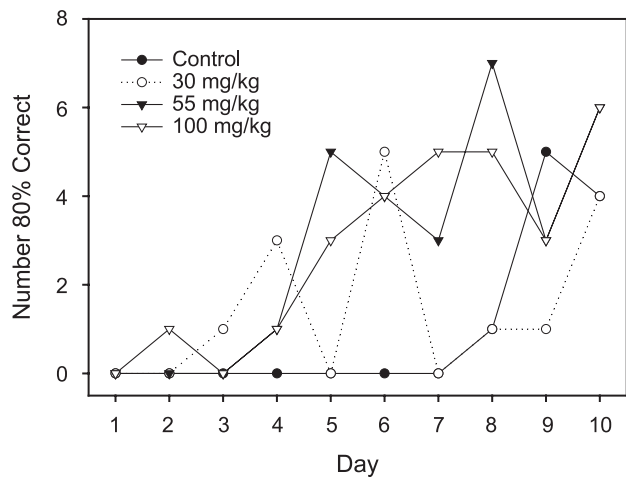


Fig. 3. Number of animals reaching 80% correct responses on CSs over 10 consecutive days of DNMTTP testing. Animals were given 0, 30, 55, or 100 mg/kg of modafinil ( $n = 10$  per group).

### 3.2. Escape latency

A mixed-model ANOVA was utilized to examine group differences in time to find the hidden platform across the 10

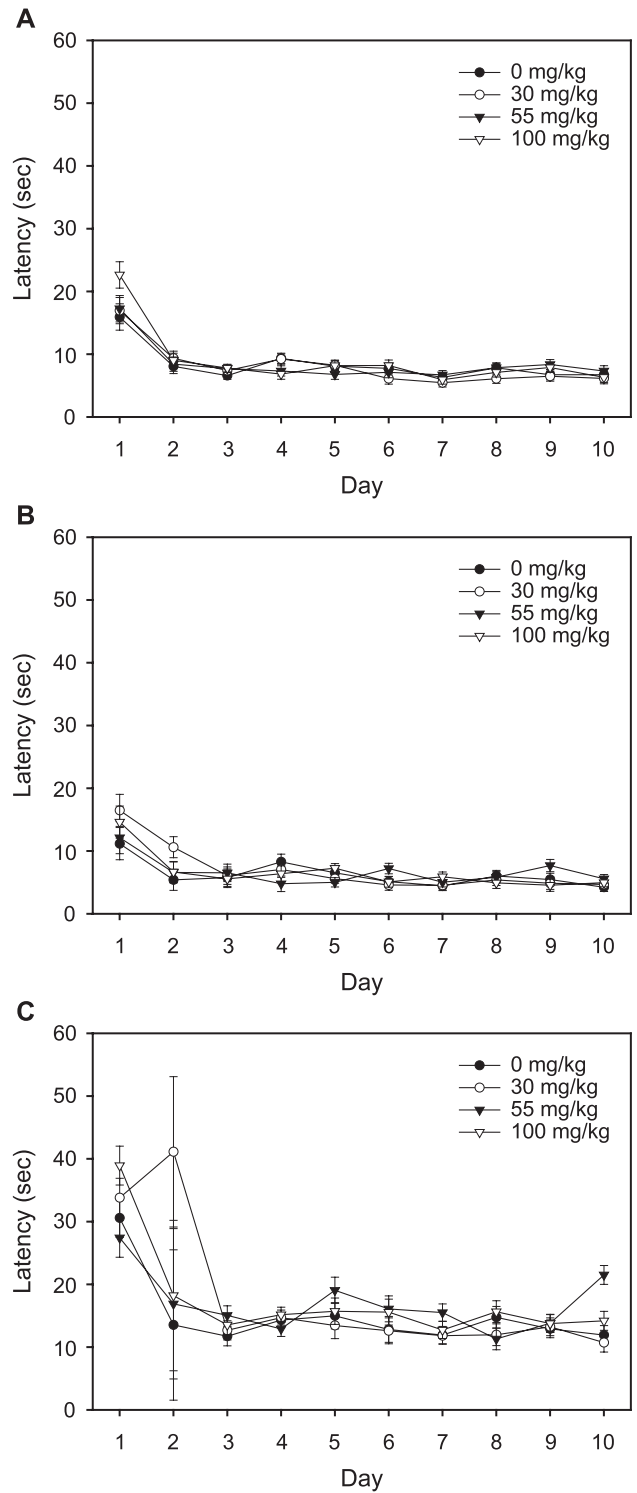


Fig. 4. Mean ( $\pm$  S.E.M.) latency for animals given 0, 30, 55, or 100 mg/kg of modafinil ( $n = 10$  per group) to reach the hidden platform during the IS (A), during the CS when animals made a correct choice (B), or during the CS when animals made an incorrect choice (C).



days of testing. No significant differences in time to find the hidden platform were noted between groups (see Fig. 4A). There was a significant main effect for day [ $F(9,324)=63.157$ ,  $P<.001$ ] where the latency to find the platform decreased over the days of the trial. During the IS, there was a significant Groups  $\times$  Days interaction [ $F(27,324)=1.940$ ,  $P=.004$ ]. However, the variance in latency within individual groups was quite low (i.e., the standard errors ranged from 0.62 to 2.09 s). Therefore, any differences between groups on any given day were not considered to be meaningful (see Fig. 4A).

The latency to find the platform during the CS when a correct choice was made decreased across days. The ANOVA yielded a significant main effect for days [ $F(9,324)=16.379$ ,  $P<.001$ ]. Neither the main effect for drug dose nor the Groups  $\times$  Days interaction was significant (Fig. 4B). A significant main effect for days was also found when examining latency to find the platform on CSs when rats made an incorrect choice [ $F(9,324)=9.223$ ,  $P<.001$ ]. Again, there was no significant main effect for drug dose nor was there a Group  $\times$  Days interaction (Fig. 4C).

### 3.3. Activity monitor

A mixed-model ANOVA was used to analyze the data from the locomotor activity monitor (see Fig. 5). There was a significant difference between groups in total number of beam breaks [ $F(3,36)=4.064$ ,  $P=.014$ ]. Only rats receiving 100 mg/kg of modafinil had significantly more beam breaks than controls as assessed by Dunnett's  $t$  test ( $P=.008$ ). However, trend analysis revealed a dose-related linear increase in activity ( $P=.001$ ). There was also a significant main effect for days [ $F(9,324)=16.853$ ,  $P<.001$ ] with activity counts increasing during the experiment. A signif-

icant linear trend across days ( $P=.001$ ) indicated the same. There was also an interaction effect [ $F(27,324)=1.835$ ,  $P=.008$ ]. Confidence intervals (95%) were used to determine significant differences in locomotor activity between drug- and vehicle-treated animals on each of the 10 days. As compared to controls, the 30-mg/kg group had significantly more beam breaks on Days 7 and 9. The 55-mg/kg group showed greater activity than controls on Days 6 through 10, while the 100-mg/kg groups showed significantly more activity on Days 5 through 10. There was also a significant linear trend interaction between days of trials and dose of modafinil ( $P=.001$ ). Higher doses had a greater effect on activity over time than did lower doses.

## 4. Discussion

Results from this study are consistent with prior evidence (Miller et al., 2000; Beracochea et al., 2001, 2002, 2003), suggesting that the drug modafinil acts either directly or indirectly to enhance cognitive processing. That is, subjects that received the highest two doses of modafinil (55 and 100 mg/kg) exhibited significantly higher choice accuracy in learning a task typically employed to assess working memory. Although close inspection of Fig. 2 reveals a downward trend in performance among control animals on Day 5, this is unlikely to account for the significant differences in choice accuracy. As shown in Fig. 3, the number of control animals to reach the 80% correct criterion remained at or close to zero until Day 9, when suddenly 5 out of 10 control animals reached criterion. This sudden improvement seems to indicate that the animal has learned the rule (i.e., go to opposite platform).

In contrast, the modafinil-treated animals appear to learn the rule much earlier. For example, half of the animals treated with 55 mg reached the 80% criterion by Day 5 and 7 out of 10 reached criterion on Day 8 (Fig. 3). A more consistent and gradual increase in numbers of animals reaching criterion can be seen in animals receiving the highest dose of modafinil. Animals in all conditions appeared to reach a similar plateau in performance. Thus, modafinil did not improve the final level of performance per se. Rather, it facilitated faster learning of the rule necessary to complete the task successfully. Of course, it is not known for certain whether peak performance was reached without additional training.

A linear dose-dependent increase in activity level was also observed. Specifically, higher doses had a differentially greater effect on activity across trials. Edgar and Seidel (1997) also have found that modafinil increased activity in rats at doses of 100 or 300 mg/kg, but not 30 mg/kg. The effects on activity levels and on DNMT performance appeared at approximately the same time (Days 5–6). Although this may indicate that a drug buildup in the system is necessary for some behavioral effects, Beracochea et al. (2003) have demonstrated that even a single dose (64 mg/kg) of modafinil can improve learned performance.

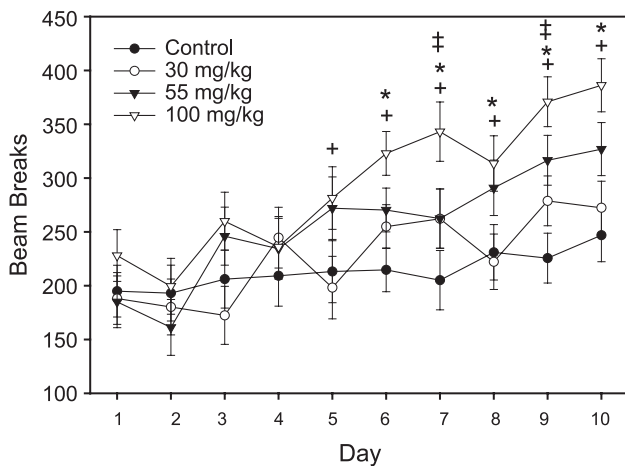


Fig. 5. Mean ( $\pm$  S.E.M.) beam breaks in the locomotor activity monitor for animals given 0, 30, 55, or 100 mg/kg of modafinil ( $n=10$  per group) on each of the 10 days. †Significant difference in activity (30 mg/kg vs. control) on Days 7 and 9. \*Significant difference in activity (55 mg/kg vs. control) on Days 6–10. ‡Significant difference in activity (100 mg/kg vs. control) on Days 5–10.

Nonetheless, the observation that both behavioral effects became apparent at the same time may suggest that increases in choice accuracy could be secondary to an increase in activity.

While the significant linear trend suggests that differential effects on activity may account for some of the variance in DNMTP performance, it is unlikely to be the sole explanation for differences in choice accuracy on this task. It is important to note that there were still increases in activity levels (55 or 100 mg/kg versus control) on Days 9 and 10. By this time, there were no differences between groups in choice accuracy. The 30-mg/kg dose had no effect on choice accuracy although it did increase activity levels on Days 7 and 9. Moreover, the increase in activity level did not seem to result in more efficient goal-directed behavior. There were no differences between groups in escape latency during either the ISs or the CSs. On the other hand, the lack of differences in escape latency may have been due to a 'floor effect.' For both the information and CSs, escape latencies declined substantially from the first to the second day of testing, but remained relatively stable after the second day of testing (Fig. 4). If the choice accuracy differences were due to locomotor facilitation, then the existence of a floor effect should have eliminated any differences in choice accuracy in the DNMTP task.

What then does account for the improvements in choice accuracy following modafinil administration? Beracochea et al. (2001) have attributed the action of modafinil to an enhancement of working memory, while leaving long-term memory unaffected (Beracochea et al., 2002). In the present experiment, choice accuracy was assessed on the DNMTP task over a 10-day period. Acquisition of the task requirement involves at least two factors: (1) learning of the rule and (2) working memory. Rats must recruit cognitive processes necessary for learning the rule (i.e., choose the other location on the CS). However, rats must also employ working memory (i.e., memory of the original location during the preceding IS) for the duration of each trial. From the present results, it is impossible to delineate which of these two processes are affected by modafinil.

Because the DNMTP task requires animals to learn a win–shift rule, it is not clear why Beracochea et al. (2002) were only able to observe improvements when animals learned a win–stay but not a win–shift rule (i.e., contingently reinforced alternation rates). Besides species difference, it is possible that the short intertrial interval (5 s) used by Beracochea et al. (2002) might not be optimal for that particular task. Another possibility concerns the large difference in training. We used a total of 100 trials, compared to 30 total trials (6 trials  $\times$  5 days) used by Beracochea et al. (2002). Indeed, we did not observe any differences between modafinil- and vehicle-treated animals until Day 5 (Trials 41–50). Finally, it may be that modafinil's effect on the learning of a win–shift rule depends on whether a positive reinforcement task (Beracochea et al., 2002) or a negative reinforcement (DNMTP) task is employed; tasks that appear

to be mediated by separable neuronal substrates (Reynolds and Berridge, 2003).

Given the differences between studies in task requirements, species tested, and age, substantial differences in results were to be expected. Nonetheless, improvements following modafinil administration have now been confirmed in animal studies using three different experimental protocols. Cognitive effects have now been documented in mice (Beracochea et al., 2001, 2002, 2003) and in both young and aged rats (Miller et al., 2000). Taken together, these studies suggest that the effects of modafinil on cognitive processing are robust and have external validity.

Because the mechanism of action for modafinil has not been elucidated, the biochemical role played by modafinil in learning and memory is also unknown. Some evidence suggests that modafinil may have neuroprotective properties. For example, modafinil has been shown to counteract ischemic lesions produced by endothelin-1 microinjections into the neostriatum in rats (Ueki et al., 1993). Modafinil has also been shown to protect against pharmacological damage to the nigrostriatal pathway both in vitro (Aguirre et al., 1999) and in vivo (Jenner et al., 2000) as assessed by restoration of motor function. These neuroprotective properties could feasibly account for an attenuation of cognitive decline associated with normal aging or with age-related dementias. However, it is more difficult to envision how these neuroprotective properties could account for the improvement in working memory observed in young adult animals or humans. As noted previously, modafinil has been shown to reduce daytime sleepiness in humans with narcolepsy without inducing the withdrawal symptoms associated with amphetamine-like stimulants, such as rebound hypersomnia and sleepiness (Jasinski and Kovacevic-Ristanovic, 2000). The emerging recognition that modafinil has significant cognitive properties is particularly interesting, in light of the fact that sleep and sleep rhythms are known to have important consequences for learning and memory consolidation (Maquet, 2001; Stickgold et al., 2001). Evaluation of this possible interrelationship awaits further laboratory investigations.

In conclusion, the present research has demonstrated that modafinil given to young adult rats can improve the rate of learning on a nonmatching to position swim task. Some differences in locomotor activity were noted. However, it is unlikely that the effects of modafinil on choice accuracy in the working memory task could have been due solely to locomotor activity facilitation. The mechanism(s) of action for the cognitive effects of modafinil remain unknown.

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