Available online at www.sciencedirect.com
ScienceDirect
Pharmacology, Biochemistry and Behavior 86 (2007) 531 – 541
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Modafinil improves attention, inhibitory control, and reaction time in healthy, middle-aged rats

Russell E. Morgan *, Jaime M. Crowley, Roland H. Smith, Ronee B. LaRoche, Marsha M. Dopheide

Psychology Department, Western Illinois University, Macomb, IL61455 USA

Received 24 July 2006; received in revised form 7 January 2007; accepted 16 January 2007
Available online 23 January 2007

Abstract

This study examined the effect of the novel psychostimulant modafinil (Provigil) on a variety of cognitive and behavioral measures including associative learning, sustained attention, inhibitory control, and reaction time. Middle-aged female rats (18–20 months old) were administered oral doses of modafinil (0, 8, 32, and 64 mg/kg) and tested in a 3-choice visual discrimination and sustained attention task. Modafinil produced a dose-dependent pattern of improved response accuracy and impulse control (fewer premature responses) and shorter response latencies, without affecting omission errors, motivation or motor control. Although the biochemical mechanism of modafinil is unknown, these results suggest a profile differing from typical psychostimulants (e.g., amphetamine). The implications of these findings for treatment of narcolepsy, ADHD, and various arousal-related disorders are considered. Further research is needed to examine the relative safety, effectiveness, and addictive potential of modafinil, as well as, its effects in comparison with other performance-enhancing drugs (e.g., caffeine, nicotine, and amphetamines).

Keywords: Modafinil; Attention; Learning; Middle-age; Impulsivity; Reaction time

1. Introduction

Modafinil is a unique psychostimulant drug that has been approved for treatment of excessive sleepiness in persons with narcolepsy, sleep apnea/hypopnea syndrome and shift work sleep disorder. This drug has also shown potential as an alternative to amphetamines and methylphenidate for treatment of ADHD (Turner et al., 2004a; Taylor and Russo, 2000; Rugino and Copley, 2001; Biedermann et al., 2005), and for fatigue associated with a variety of neurological disorders including schizophrenia (Turner et al., 2004b), Parkinson's disease (Nieves and Lang, 2002; Högl et al., 2002), multiple sclerosis (Kraft et al., 2005; Zifko et al., 2002), and alcohol-induced organic brain syndrome (Saletu et al., 1993). Furthermore, modafinil has frequently been touted as a general wakefulness/arousal promoter similar to the broad-spectrum use psychostimulants caffeine and nicotine. Modafinil is often considered unique among psychostimulants because it appears to lack the unwanted side effects (e.g., tolerance, abuse potential, sleep rebound, and locomotor excitability) typically associated with most drugs in this class (Deroche-Gamonet et al., 2002). This improved side effect profile is thought to result from modafinil having a different biochemical mechanism than traditional psychostimulants. Specifically, the drug does not appear to directly affect dopamine (DA) release or DA receptors (Mignot et al., 1994; Simon et al., 1995; De Séréville et al., 1994; Engber et al., 1998; Lin et al. 1992), nor does it appear to have direct effects on other candidate neurotransmitter systems (e.g., norepinephrine, acetylcholine, GABA, serotonin, or orexin/hypocretin). The underlying biochemical mechanism is currently unknown, but activity of adrenergic α_1 and α_2 receptors, along with an intact DA transporter (DAT) system, appears necessary for modafinil effects to occur (Miller et al., 2007; Wisor et al., 2001; Wisor and Eriksson, 2005; Saper and Scammell, 2004). Others (Ishizuka et al., 2003; Scammell et al., 2000; Willie et al., 2005) suggest that the drug works by

* Corresponding author.
E-mail address: RE-Morgan@wiu.edu (R.E. Morgan).

0091-3057/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2007.01.015

increasing hypothalamic histamine activity/release, similar to the actions of orexins/hypocretins.

The wakefulness-promoting effects of modafinil are well-documented (Westenson et al., 2005), but the ability of the drug to improve cognition is more equivocal. Studies with sleep-deprived humans show clear facilitation of cognition by modafinil (Gill et al., 2006; Stivalet et al., 1998; Caldwell et al., 2000; Baranski et al., 2002; Westenson et al., 2005) as do other studies that have looked at modafinil effects on various cognitive impairments resulting from ADHD (Turner et al., 2004a), schizophrenia (Turner et al., 2004b), and alcohol-induced brain disorder (Saletu et al., 1993). However, the cognitive effects of modafinil in healthy, non-sleep-deprived adults are not as clear. Some studies (Baranski et al., 2004; Müller et al., 2004; Turner et al., 2003; Randall et al., 2005) have found evidence of enhanced working memory, impulse control, vigilance and sustained attention in healthy volunteers. However, the pattern of effects across studies has not been entirely consistent. For instance, while some (Turner et al., 2003; Randall et al., 2005) have found that modafinil lengthened reaction times (a speed–accuracy trade-off), others found that modafinil decreased reaction time (Baranski et al., 2004), and still others (Müller et al., 2004) have found no effects at all on reaction times. With regard to sustained attention, some have found evidence of modafinil-induced improvement (Baranski et al., 2004; Randall et al., 2005), but others (Turner et al. 2003 — RVIP task) did not. Still, other studies (e.g., Randall et al., 2003, 2004) have found little evidence of any modafinil-induced cognitive improvement in healthy, young or middle-aged adults. It remains unclear whether these discrepant findings are due to lack of drug efficacy in healthy adults or from differences in task difficulty (perhaps "ceiling effects") or lack of statistical power in these studies.

A number of animal studies have also investigated whether modafinil affects cognition in healthy adult rodents. A series of studies by Beracochea et al. (2001, 2002, 2003; Piérard et al., 2006) demonstrated that acute modafinil exposure in mice produced enhancement of serial-reversal learning (T-maze) and working memory (alternations tasks) that was dependent on task difficulty and baseline stress levels. Specifically, modafinil improved working memory with long, but not short, inter-trial intervals and the optimal dose was reduced under stress conditions (suggesting an inverted-U dose-response curve). Other researchers have also found evidence of improved working memory using a delayed non-matching to sample (DNMTS) task (Ward et al., 2004), and time- and dose-dependent effects of modafinil on object recognition memory (Grottick et al., 2004) and avoidance learning (Moreira et al., 2004) in rodents.

Besides these studies demonstrating a role for modafinil in facilitating learning and memory, two recent studies have begun to examine whether modafinil can enhance attentional processes in non-human animals. Milstein et al. (2003), using the 5-choice serial reaction time task (5-CSRT), a test of visual–spatial attention analogous to the continuous performance task used in humans, found that modafinil increased premature responses but decreased omission errors, effects qualitatively similar to those of D-amphetamine. Using the same task, Waters et al. (2005) found a similar increase in premature (inhibition) errors, but no improvement in sustained attention (no effect on omission errors or response accuracy). These equivocal findings are similar to the discrepancies observed in the human studies cited above. Thus, the effects of modafinil on attentional processes in both human and non-human animals remain to be determined. To address this issue, the present study examined the effects of modafinil on a variety of attentional processes, including impulsivity, choice accuracy, omission errors, reaction time, and motivation in middle-aged rats. The tests used in this study (described below) were similar to the 5-CSRT and have been validated in many previous studies (Bayer et al., 2000; Morgan et al., 2001, 2002).

2. Methods

2.1. Subjects

Forty female Long–Evans rats bred in the Western Illinois University animal colony were used in this study. The rats were approximately 18 months old at the beginning of the study (approximately 20 months of age by completion of the study). Animals were housed in same-treatment pairs in wire-mesh cages and maintained on a 12-hour reverse light/dark schedule with all behavioral testing and drug administration occurring during the dark portion of the daily cycle. Access to water was ad libitum, but feeding was restricted as described below. Beginning 1 week prior to the start of the study, the rats were handled 10 min/day and placed on a food deprivation schedule in which they were allowed 18 g of standard rat chow (LabDiet, Purina Mills, St. Louis, MO) each day and 4 h to consume this daily ration. Previous studies have shown that this feeding regimen is effective for maintaining performance on the operant tasks used in this study, while minimizing reductions in body weight (Morgan et al., 2001, 2002). All procedures were conducted in accordance with the ethical guidelines of the American Psychological Association and approval of the Western Illinois University IACUC.

2.2. Apparatus

For each animal, testing was conducted in one of eight automated Plexiglas operant chambers. Each chamber was enclosed in a sound-resistant wooden box connected to an individual computer running a customized Visual Basic software program. Each rat was tested in the same chamber throughout the study. The test chamber consisted of a large square waiting area (26.5 × 25 × 30 cm) and a smaller testing alcove (11.5 × 7.5 × 7.5 cm), which was recessed into one wall and separated by a metal guillotine-like door that prohibited entry into the testing alcove between trials. The alcove contained three funnel-shaped ports, the left and right being at a 45° angle relative to the center port. The distance between the left and right ports was 8 cm. A set of infrared phototransistors and a light source monitored the entrance to the alcove and to each port. An LED above each of the three ports served as the discriminative visual cue in each of the tasks. Each LED emitted a 4-mA green light. A pellet dispenser (Med Associates)

delivered 45 mg Noyes pellets into the response alcove through a small trough underneath the center port.

2.3. Behavioral testing

2.3.1. Shaping

All animals were administered a sequence of automated shaping procedures intended to train them to make a 1-s nose-poke into any of the three ports, the behavioral response which constituted a choice in each of the succeeding tasks. This shaping procedure was conducted in four stages: in Stage 1, animals were rewarded with a single food pellet for each entry into the alcove. Following 50 such rewards, animals progressed to Stage 2, in which a nose-poke (of any duration) into any port was required to obtain a pellet. After 20 of these trials, the requirement for a reward was altered again, such that only nose-pokes of at least 0.5 s were rewarded (Stage 3 — 20 trials). In the final stage, only nose-pokes of ≥ 1.0 s were rewarded. This final stage lasted for 70 trials. Each daily session during shaping lasted a maximum of 120 min, with the animal automatically progressing from one stage to the next during the session. At the beginning of each session subsequent to the first, shaping began on the same stage at which the animal ended the previous session. All rats completed the shaping sequence within 2–4 daily sessions.

2.3.2. Simultaneous visual discrimination

Each animal progressed to the simultaneous visual discrimination task in the session immediately after completing the four-stage shaping program. Each trial began with the opening of the alcove door. Immediately after the animal broke the infrared beam at the alcove entrance, one of the three LED's was illuminated (one LED was located immediately above each port). The LED remained illuminated until the animal either made a 1-s nose-poke into one of the ports or 15 s elapsed, whichever came first. A correct response, defined as a 1-s nose-poke into the port under the illuminated LED, was rewarded (continuous reinforcement schedule) with a 45 mg Noyes pellet. A non-correction procedure was used. After the animal exited the alcove, the guillotine door was lowered, followed by a 10-s inter-trial interval. Trials on which the animal did not make a response were recorded as "nontrials" and did not contribute towards the maximum 200 trials per session. Discrimination training continued for each animal until it reached the performance criterion of one session (minimum 150 trials) in which performance averaged at least 80% correct (average number of sessions required to reach the criterion was 11). In this task and the subsequent task, each animal received one daily test session, 6 days per week. Each test session lasted until 200 trials were completed or 120 min elapsed, whichever came first.

2.3.3. Visual Attention Task (variable stimulus onset and duration)

Each animal progressed to the Visual Attention Task in the session immediately after it met criterion on the Simultaneous Visual Discrimination. The Visual Attention Task was a variation of the previous discrimination task with two modifications: 1) variable delays (0, 3, 6, or 9 s) were introduced between trial onset and cue presentation; and 2) the duration of cue illumination varied among trials within each session (400, 700, or 1000 ms). Thus, twelve possible combinations of stimulus duration and delay resulted from varying both of these parameters. The delay, duration, and cue location for each trial were selected pseudo-randomly, with the stipulation that these parameters were approximately balanced for the session.

Several distinct types of errors were distinguished in this task: 1) the trial was terminated and recorded as a premature response if the animal made a 1-s nose-poke prior to cue presentation. Premature responses were considered a measure of impulsivity and recorded as an incorrect choice. 2) An inaccurate choice occurred whenever a response was made within 15 s after illumination of the visual cue but to the wrong funnel. 3) An omission error was recorded when an animal entered the testing alcove but failed to respond within 15 s. Such errors were interpreted as lapses in attention. Omission errors were distinguished from nontrials, in which the animal did not enter the alcove within 15 s after the door was raised. Nontrials were not tallied as incorrect responses and did not count towards the maximum 200 trials per session, but rather served as a measure of motivation to perform the task. Alcove Latency (latency to enter the alcove after the guillotine door was raised allowing the rat access to the response alcove) was recorded as a measure of motivation/motor effects. Response Latency (latency to respond after the visual cue was presented) served as a measure of reaction time.

All animals were tested on this task for 20 sessions. If an animal did not complete at least 150 response trials in a session (but greater than 100), it was given a 100-trial session the following day, with the two partial sessions combined into a single session for data analysis. Testing sessions during which an animal completed less than 100 trials were repeated in their entirety. This procedure was designed to approximately equate the total number of trials on the task for each subject.

2.4. Drug administration

Exposure to either modafinil or vehicle began after completion of the shaping sessions, when rats began the visual discrimination task. Modafinil (Cephalon, Inc., West Chester, Pennsylvania, USA) was dissolved in sterile water and administered in doses of 0, 8, 32, or 64 mg/kg via oral gavage. All drug doses were prepared daily and administered at a volume of 2 ml/kg. Because modafinil is not highly water soluble, drug preparations were thoroughly shaken prior to each draw in order to ensure even distribution of the drug. Drug administration occurred 1 h prior to behavioral testing. Experimenters conducting the behavioral tests were unaware of the treatment designation for each subject.

2.5. Statistical procedures

All statistical analyses were conducted with the SAS 9.0 (SAS Institute, Cary, NC) software package using either the "GLM" procedure (for body weight data) or the "Mixed"

procedure, the latter of which allowed for hierarchical modeling of both between- (e.g., treatment) and within-group factors (e.g., Block, Stimulus Delay and Duration). Analyses of all dependent measures included both main effects and interaction effects. All pairwise comparisons were conducted using the Tukey/Kramer test. Throughout all data analysis procedures, differences were considered to be significant at ≤ 0.05. However, p-values >0.05 but <0.10 were considered to be trends and are discussed if they helped to clarify the nature and/or pattern of modafinil effects.

Two animals, both from the 32 mg modafinil group, died during data collection. One of these animals died prior to completing Task 1 (Simultaneous Visual Discrimination Task) so her data was not included in any data analyses. Another died after the seventh session of Task 2 (Visual Attention Task). Data from this latter rat was included in the Task 1 analyses, but not in any of the Task 2 analyses.

3. Results

3.1. Body weights

Body weights were analyzed following completion of each of the two behavioral tasks. Modafinil exposure did not produce differences in body weight at either test period [(Following Task 1: $F(3,35)=0.59$, $p>0.10$ with group means of 0 mg=267 g, 8 mg=264 g, 32 mg=267 g, 64 mg=274 g). Following Task 2: $F(3,35)=2.06$, $p>0.10$ with group means of 0 mg=258 g, 8 mg=253 g, 32 mg=259 g, 64=270 g)].

3.2. Simultaneous visual discrimination (Task 1)

For the initial task (Simultaneous Visual Discrimination), the between-group independent variable was drug treatment, consisting of four levels: 0, 8, 32, or 64 mg/kg modafinil. Dependent measures for this task included errors-to-criterion, trials-to criterion, percent nontrials, mean alcove latency (latency to enter the response alcove and initiate each trial), and mean response latency (latency to produce a 1-s nose-poke response following the onset of the visual cue). This task was analyzed using a series of between-group ANOVAs. For alcove and response latencies, the criterion (final) session was analyzed separately to more closely examine motivation, motor ability, and information processing speed (response latency) in the animals once they had learned the basic response rule.

3.2.1. Errors-to-criterion and trials-to-criterion

As depicted in Fig. 1, modafinil did not influence learning of the basic visual discrimination as measured by errors-to-criterion [$F(3,35)=0.44$, $p=0.73$] or trials-to-criterion [$F(3,35)=0.49$, $p=0.69$].

3.2.2. Percent nontrials

The nontrials data were log transformed prior to analysis to normalize the distribution. There was no evidence of a treatment effect for percent nontrials [Group Means: 0 mg=11.24%, 8 mg=8.01%, 32 mg=10.07%, 64 mg=5.80%; $F(3,35)=1.02$, $p=0.40$]. Thus, modafinil did not influence the probability that the rat would enter the response alcove and respond to the visual cue. This finding provides evidence that basic motivation and motor processes were not modified by treatment with modafinil.

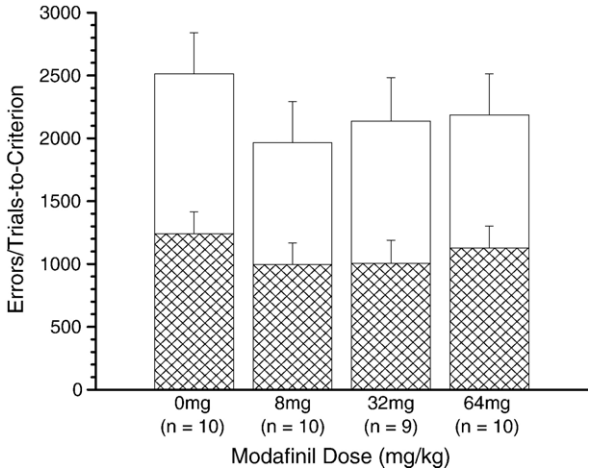

Fig. 1. Mean number of errors- and trials-to-criterion across treatments for the simultaneous visual discrimination task (Task 1). Hatched bars indicate errors-to-criterion. Clear bars indicate trials-to-criterion. Modafinil dose did not significantly affect either measure.

3.2.3. Alcove latency (AL)

The AL data were log transformed prior to analysis to normalize the distribution. The analysis of all sessions found no significant effects of modafinil on mean AL [$F(3,35)=1.14$, $p=0.35$], nor were there any effects on mean AL for the final session [$F(3,28)=1.92$, $p=0.15$]. These results suggest that modafinil treatment did not alter perceptual abilities, motor abilities, or motivation in these animals. These negative findings are important because they help eliminate potential non-cognitive explanations for treatment differences observed with other dependent measures (see Task 2).

3.2.4. Response latency (RL)

The RL data were log transformed prior to analysis to normalize the distribution. There was no effect of modafinil treatment on overall RL's [$F(3,35)=0.16$, $p=0.92$] or final session RL's [$F(3,28)=0.10$, $p=0.96$]. These RL data, particularly those from the final session in which the animals had learned the basic response rule, suggest that information processing speed and reaction time were not affected by modafinil.

3.3. Visual attention task (Task 2)

For the Visual Attention Task, three within-group independent variables were added to the data analyses and included testing block (Block 1 = sessions 1–4, Block 2 = sessions 5–8, Block 3 = sessions 9–12, Block 4 = sessions 13–16, Block 5 = sessions 17–20), Stimulus Delay (0, 3, 6, or 9 s.), and Stimulus Duration (400, 700, or 1000 ms). The addition of these variables resulted in 12 semi-random combinations of duration and delay, thus requiring a

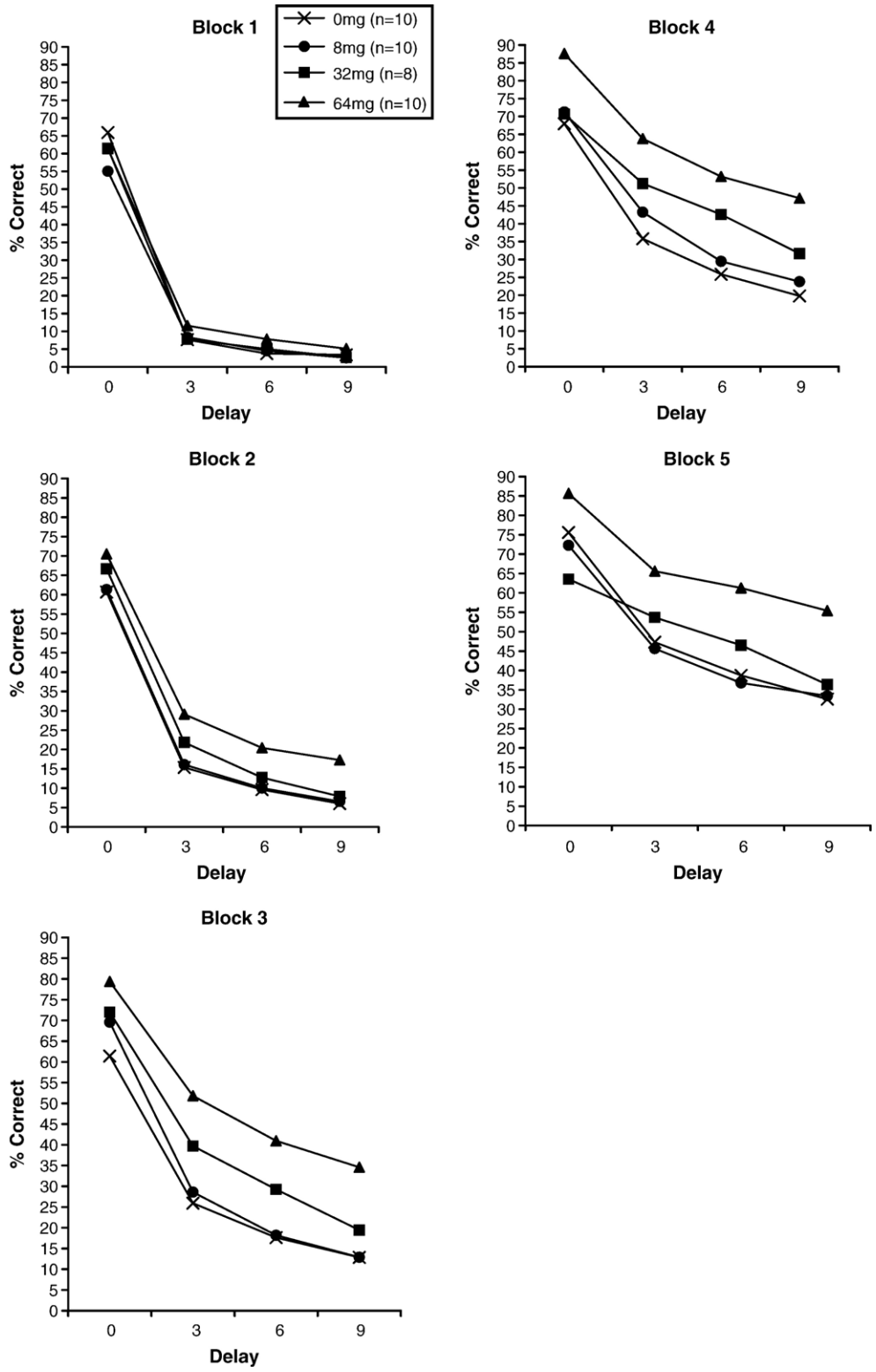

Fig. 2. Overall percent correct for the Visual Attention Task (Task 2). A significant 3-way interaction between Dose, Block, and Stimulus Delay is depicted. Each panel displays a separate block (1–5) of four testing sessions (20 total sessions). The 64 mg group performed significantly better than the 0 mg and 8 mg groups in blocks 3–5, but only when presentation of the visual cue was delayed (i.e., no effects at the 0-s Delay condition) (all p-values < 0.05).

$4 \times 5 \times 4 \times 3$ mixed ANOVA for the analysis of this task. Dependent measures analyzed in this task included: 1) overall percent correct (number of correct trials divided by total number of trials), 2) percent accuracy (percent correct without including omission or premature errors), 3) percent omission errors (trials in which the rat entered the response chamber, but did not produce a response), 4) percent premature responses (trials in which the rat committed an error by responding prior to the cue onset), 5)

alcove latency (latency to initiate each trial by entering the response alcove), 6) response latency (latency to respond once the visual cue was presented), and 7) percent nontrials (trials in which the rat did not enter the response alcove).

3.3.1. Overall percent correct

Overall percent correct was calculated as the number of correct responses divided by the total number of response trials. This dependent variable is a global measure of performance because it included trials that resulted in both accurate and inaccurate responses, as well as trials that were recorded as omission or premature response errors.

A significant main effect of Treatment was found for overall percent correct [$F(3,34)=9.74$, $p<0.0001$]. Post-hoc (Tukey–Kramer) tests revealed that the 64 mg group had a higher percent correct than each of the other three treatment groups (all p-values <0.05). The 8 mg and 32 mg groups did not differ from the Controls (p's >0.05). There were also main effects of Block [$F(4,136)=163.15$, $p<0.0001$], Delay [$F(3,1868)=4272.00$, $p<0.0001$], and Duration [$F(2,1868)=141.69$, $p<0.0001$]. Post-hoc tests revealed that performance increased across all blocks of trials (Block 1, $M=19.60\%$; Block 2, $M=27.01\%$; Block 3, $M=38.39\%$; Block 4, $M=47.82\%$; Block 5, $M=53.14\%$; all p's <0.01), but decreased as the cue delay was lengthened (0 s, $M=68.99\%$; 3 s, $M=33.50\%$; 6 s, $M=25.71\%$; 9 s, $M=20.57\%$; p's <0.0001). Percent correct also increased as the cue duration was increased (400 ms, $M=33.3\%$; 700 ms, $M=38.39\%$; and 1000 ms, $M=39.88\%$, p's <0.001).

Results from the percent correct analysis also revealed a 3-way interaction between Treatment, Block, and Delay [$F(36,1868)=2.89$, $p<0.0001$]. These findings are depicted in Fig. 2. Tukey tests indicated that the 64 mg group performed significantly better than the 0 mg and 8 mg groups in blocks 3–5, but only when presentation of the visual cue was delayed (i.e., no effects at the 0-s Delay condition) (all p-values <0.05). The 4-way (Treatment × Block × Delay × Duration) interaction was not significant [$F(72,1868)=0.79$, $p=0.90$], nor were any of the other higher-order treatment-related effects [e.g., Treatment × Duration: $F(6,1868)=0.77$, $p=0.59$].

Overall, given the significant main effect of treatment and the pattern of interaction effects, it appears that the highest dose of modafinil (64 mg/kg group) conferred a clear advantage over all other groups in this global measure of performance. This effect of modafinil was dose-, experience-, and delay-dependent. Modafinil was significantly effective when given at the highest dose, when the animal had to wait for the cue, and as animals became more familiar with the task. Although these initial findings provided evidence that modafinil at 64 mg/kg improved performance on this visual attention task, the next three dependent measures, 1) percent accuracy, 2) percent omission errors, 3) percent premature responses, were analyzed with the intent of specifying the particular types of errors that were affected by modafinil administration. Keeping in mind that the overall percent correct measure was a global measure of performance comprised of all of these individual measures, the following analyses considered whether the modafinil-induced enhancement of performance was due to specific effects on any or all of these individual response measures.

3.3.2. Percent accuracy

Percent accuracy was determined by calculating percent correct after excluding trials that resulted in an omission or premature response error. This measure was included as a means of examining response accuracy when a response was made within the appropriate time frame (i.e., after the cue was presented and before the 15-s time limit). For this measure, results revealed main effects for all four independent variables: Treatment [$F(3,34)=7.31$, $p=0.0007$.], Block [$F(4,136)=101.37$, $p<0.0001$], Delay [$F(3,1860)=169.10$, $p<0.0001$], and Duration [$F(2,1859)=104.54$, $p<0.0001$]. Treatment and Block effects are illustrated in Fig. 3. Post-hoc comparisons showed that the 64 mg group ($M=72.81$) was significantly more accurate in their responses than the 0 mg ($M=60.53$, $p<0.01$) and 8 mg ($M59.4$, $p<0.001$) groups. However, mean accuracy for the 64 mg group was statistically different from the 32 mg group ($M=64.88$, $p=0.10$). The 8 mg and 32 mg groups did not differ from the Controls (p's >0.05). In addition, performance on percent accuracy improved significantly across all five blocks (all p's <0.001). Post-hoc comparisons for Delay showed that at the 0-s delay, S's were significantly more accurate than at the 3, 6, or 9-s delays, (p's <0.0001). The post-hoc testing on duration revealed that accuracy increased as cue duration increased, (p's <0.0001).

As shown in Fig. 3, a marginally significant Treatment × Block interaction [$F(12,136)=1.82$, $p=0.051$] suggested that the 64 mg group performed better than the 0 mg and 8 mg groups in Block 3 ($p=0.08/p=0.05$), Block 4 (p's <0.05) and Block 5 (p's <0.05). None of the other two-way or higher-order interaction effects reached statistical significance (p's >0.05). Similar to the overall percent correct data, the results from this accuracy measure revealed enhanced performance with the 64 mg/kg dose of modafinil.

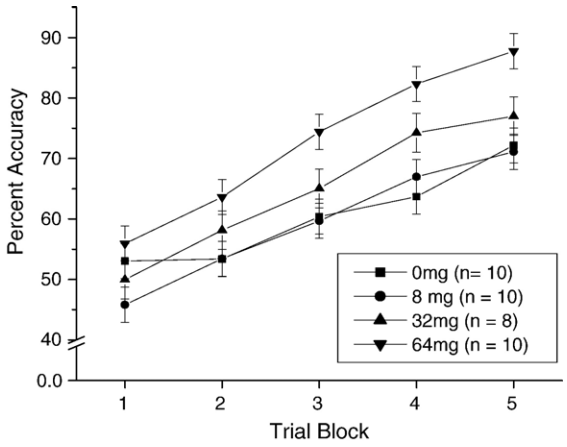

Fig. 3. Percent accuracy for the Visual Attention Task (Task 2). A marginally ($p=0.051$) significant Dose × Block interaction is depicted. Group comparisons indicated that the 64 mg/kg group responded more accurately than Control (0 mg/kg) and 8 mg/kg groups during blocks 3–5 of testing (each block contained 4 sessions of trials).

3.3.3. Percent omission errors

The data for percent omission errors were log transformed prior to analysis to normalize the distribution. Modafinil dose did not affect omission errors [$F(3,34)=0.11$, $p=0.96$]. However, there were significant main effects of Delay [$F(3,1964)=572.17$, $p<0.0001$] and Duration [$F(2,1964)=46.15$, $p<0.0001$]. As expected, *S*′s made more omission errors as the length of cue delay increased, (all p′s<0.01), and fewer omission errors as the cue duration increased from 400 ms ($M=17.17$) to 700 ms ($M=14.98$) to 1000 ms ($M=13.76$), (p′s<0.0001). A statistically significant Treatment×Delay interaction [$F(9,1964)=5.91$, $p<0.0001$] was found, however, pairwise comparisons with the Tukey test found no evidence of dose-related differences between groups. None of the other interaction effects were significant. Although modafinil did not influence omission errors, the significant main effects of Delay and Duration are notable here because they confirm the sensitivity of the task to variations in attentional demands.

3.3.4. Percent premature responses

A significant main effect of Treatment [$F(3,34)=5.21$, $p=0.005$] indicated that rats in the 64 mg group ($M=32.51$) made *fewer* premature responses than did those in the 0 mg ($M=49.93$) and 8 mg ($M=48.57$) groups (p′s<0.01). Main effects of Block [$F(4,136)=222.23$, $p<0.0001$] and Delay [$F(2,340)=658.90$, $p<0.0001$] once again indicated improvement across all Blocks (fewer premature responses; p′s<0.0001), but more premature responses at each successively longer delay (3 s, 6 s, and 9 s; p′s<0.0001). (Note: the 0-s delay is not included in this analysis because when the cue is presented immediately there is no opportunity for a premature response to occur.)

The Treatment×Delay interaction was also significant [$F(6,340)=2.49$, $p=0.02$] and is depicted in Fig. 4. Pairwise comparisons indicated that the 64 mg group made fewer premature responses than both the 0 mg and 8 mg groups at the 6-s and 9-s delays, (p′s<0.05), and a trend towards fewer premature responses than the 0 mg group at the 3-s delay ($p<0.06$). Thus, as Fig. 4 suggests, modafinil appeared to reduce premature responses more effectively as the Stimulus Delay was lengthened and the demand for inhibitory control was increased. These findings suggest that the high dose of modafinil decreased impulsivity and/or aided these animals with the ability to sustain attention and wait for the cue.

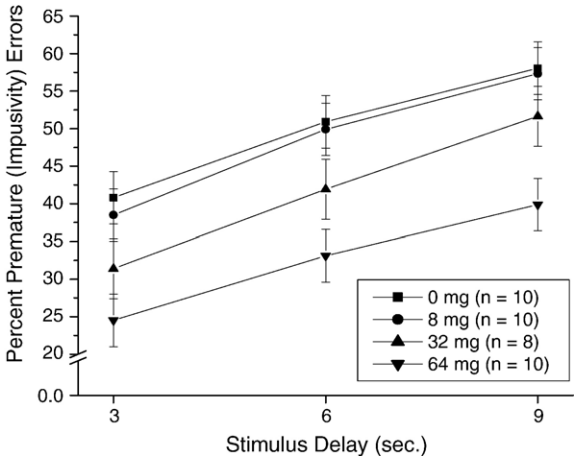

Fig. 4. Percent premature responses for the Visual Attention Task (Task 2). A significant Dose×Delay interaction is depicted. Tukey comparisons indicated that the 64 mg group made fewer premature responses than both the 0 mg and 8 mg groups at the 6-s and 9-s delays, (p′s<0.05), and a trend towards fewer premature responses than the 0 mg group at the 3-s delay ($p<0.06$).

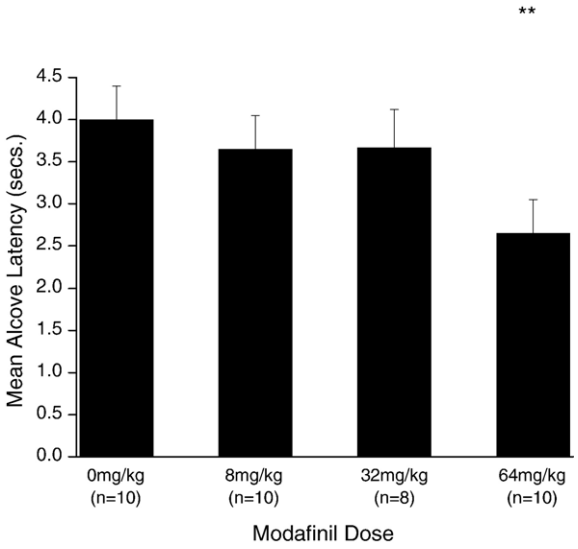

Fig. 5. Mean alcove latency (AL) for the Visual Attention Task (Task 2). Although the omnibus ANOVA was only marginally significant ($p=0.057$), a significant Tukey test suggested that the 64 mg group initiated trials more rapidly (i.e., shorter alcove latencies) than Controls (0 mg group).

3.3.5. Alcove latency (AL)

Analyses of alcove latency, the latency to initiate the trial after the alcove door is opened, were of interest as a measure of "motivation" to perform the task. As suggested in Fig. 5, there was a marginally significant main effect of Treatment [$F(3,34)=2.76$, $p=0.057$] on AL's. The Tukey post-hoc test suggested that the 64 mg group ($M=0.91$) had shorter AL's than the Controls ($M=1.3$, $p=0.05$). The 8 mg and 32 mg groups did not differ from Controls (p′s$=0.96/.81$) the 64 mg group (p′s$=0.14/.36$) or each other ($p=0.97$). There was no Treatment×Block interaction [$F(12,136)=0.90$, $p=0.55$]. Although only marginally significant, these AL results suggested that the high (64 mg/kg) dose of modafinil may have increased motivation or general locomotor activity in these animals.

3.3.6. Response latency (RL)

Response latencies, the length of time between presentation of the visual cue and a 1-s nose-poke response, were log transformed prior to analysis in order to normalize the skewed distribution. Although the main effect of Treatment only approached statistical significance, [$F(3,34)=2.36$, $p=0.089$], a significant Treatment×Delay interaction was found [$F(9,1868)=7.19$, $p<0.0001$]. As displayed in Fig. 6, the general pattern of results indicated that the 64 mg dose of modafinil improved response latency (i.e., reaction time) compared to the 0 mg and 8 mg groups; however, the Tukey-adjusted p-values

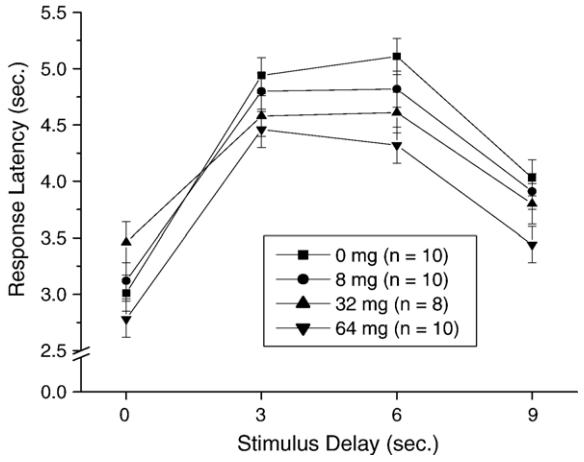

Fig. 6. Mean response latency (RL) for the Visual Attention Task (Task 2). A statistically significant Dose × Delay interaction is depicted. The 64 mg group responded significantly faster than Controls in the 6-s Stimulus Delay condition.

indicated that the only statistically significant difference was found between the 64 mg and 0 mg groups at the 6-s delay.

3.3.7. Percent nontrials

Drug treatment did not have a statistically significant effect on the percentage of nontrials that occurred [$F(3,34)=1.97$, $p=0.14$]. This finding supports the conclusion that modafinil did not have a negative impact on motivation. Moreover, although not statistically significant, group means for percent nontrials were in the direction of *fewer* nontrials for the modafinil-treated groups (64 mg=8.6%, 32 mg=11.4%, 8 mg=11.0%, and 0 mg=16.2%).

4. General discussion

In the current study healthy, middle-aged rats were administered one of three doses of modafinil (8, 32, or 64 mg/kg) or placebo, and tested in two versions of a visual discrimination/attention task. These particular tasks provided an examination of the drug's effects on basic rule learning, visual discrimination, sustained attention, impulsivity, and reaction time. Furthermore, these tasks were able to dissociate these aspects of cognition from non-cognitive factors (e.g., motivation, locomotor activation) that could influence behavior. In summary, the findings indicated that healthy, non-sleep-deprived middle-aged rats given modafinil dose-dependently made fewer premature (impulsive) responses and displayed improved response accuracy and reaction time compared to controls. Details of the findings and their implications are discussed in the following paragraphs.

Modafinil's performance-enhancing effects were most clearly revealed as task difficulty was increased. This task-dependency was supported by the fact that there was a complete lack of treatment effects during the initial discrimination task, thus no evidence of a modafinil-induced benefit to basic learning processes. The modafinil-induced improvements in performance were not observed until the attentional demands of the task were increased by making stimulus onset and duration unpredictable. Of course, due to the fact that the visual discrimination task had to take place prior to the visual attention task (in order for rats to learn the basic response rule), the increase in task difficulty is also confounded with length of drug administration. Thus, it remains possible that the observed effects of modafinil in the visual attention task were due to sensitization associated with the increased length of drug exposure, compared to the more acute exposure during the initial (visual discrimination) task. This alternative explanation seems unlikely because modafinil is known to be fully metabolized in rats within 4 h (Waters et al., 2005), thus the dosing regimen in the present study (1×/day, 5×/week) does not likely qualify as "chronic" exposure. It is not known conclusively whether sensitization occurs with prolonged exposure to modafinil (similar to effects seen with the traditional psychostimulants amphetamine and nicotine), thus this alternative explanation cannot yet be discarded.

Previous studies (Beracochea et al., 2002, 2003) have reported improvement in basic learning processes after both acute and chronic administration of modafinil to mice at doses similar to those used in the present study. The discrepancy in results between these earlier studies and the present findings could be due to species' differences, the use of middle-aged vs. young animals, or differences in the specific cognitive aspects of the tasks. The studies by Beracochea and colleagues all used young-adult mice in a T-maze task that was more spatially-oriented and was learned much more rapidly (5 sessions) than the visual discrimination task used in the current study (average of 11 sessions, or 2200 trials, to complete). Still, others have found evidence of enhanced performance in young (Ward et al., 2004) and aged (Miller et al., 2000) rats given modafinil. However, in these studies it is not clear whether the improved performance was due to modafinil effects on 1) learning of the response rule, or 2) working memory. Perhaps the discrepancy is due at least in part to the lack of a "working memory" component in the current visual discrimination task.

Whether modafinil improves sustained attention, as measured by improved accuracy and a reduction in omission errors, has been a matter of debate in both clinical and pre-clinical studies (Baranski et al., 2004; Turner et al., 2003; Randall et al., 2005; Waters et al., 2005; Milstein et al., 2003). In the present study response accuracy improved with modafinil, but omission errors were unaffected. It is possible that the occurrence of omission errors in the present study were so rare (only 15% of trials were omissions) to occlude any opportunity for the drug to enhance performance on this measure. Previous studies have found that modafinil reduced omission errors in humans (Baranski et al., 2004) and rats (Milstein et al., 2003). However, other studies (Waters et al., 2005; Turner et al., 2003) have reported that modafinil did not affect sustained attention. Modafinil-induced improvements of sustained attention have been consistently observed; however, when testing was conducted with participants whose baseline cognitive performance was measurably impaired (Turner et al., 2004a; Randall et al., 2005; Westenson et al., 2005). Thus, the modafinil-induced improvements in attention in middle-aged rats in the current study are consistent with previous findings indicating

that the drug can improve attentional performance. Further studies are needed to examine whether these effects can be reliably found in young adults without any form of attentional impairment.

The decrease in premature responses indicated that modafinil administration reduced impulsivity. These effects were particularly pronounced at the longer cue delay conditions, where the requirements for inhibitory control were most demanding. Indeed, modafinil facilitated the ability to inhibit premature responding and wait for the cue in these middle-aged animals. Although reduced impulsivity under the influence of a psychostimulant drug may at first seem counter-intuitive, modafinil, which has a distinctive pharmacological/behavioral profile, has also been shown to reduce impulsivity in clinical studies (Turner et al., 2003, 2004a), an effect opposite from that of traditional dopamine-agonist psychostimulants such as amphetamine, but typical of alpha-1 agonists (Puumala et al., 1997). However, the two previous animal studies examining attention-related effects of modafinil found a treatment-related *increase* in premature responses (Milstein et al., 2003; Waters et al., 2005). These two studies using the 5-CSRTT differed from our 3-choice task in that "attentional load" was not manipulated within test sessions. For instance, Waters et al. (2005) manipulated stimulus duration and intensity, but only between sessions. In the present study, stimulus duration and delay ("ITI" in the 5-CSRTT studies) were varied within sessions, potentially making the attentional load even greater due to the within-session unpredictability of the visual cues. Notably, these previous studies also differed from the current study because healthy, young-adult rats were tested. Although a direct comparison of middle-aged and young rats' performance was beyond the scope of the current study, previous studies have shown that cognitive decline is evident by middle-age (Jucker et al., 1988; Kadar et al., 1990; Li, 2002). Perhaps then, once again, the effects of modafinil may differ depending on whether the cognitive abilities of the test subjects are "impaired" in some manner. Particularly, the drug effects may resemble an inverted-U function in which the drug can actually reduce some aspects of performance when an organism is already performing optimally (or at optimal arousal levels).

Although the pattern of results seen in this study suggests that modafinil-induced enhancement of cognition is highly task-dependent, a look at other studies that have attempted to measure attentional effects of modafinil in rats suggests that the effects might be better considered as "baseline ability-dependent". For instance, Waters et al. (2005) did not find any evidence that modafinil enhanced performance (indeed, it tended to increase premature errors) even though their manipulations of stimulus intensity and duration successfully influenced performance. In other words, even though the task was made demonstratively more difficult, modafinil did not enhance cognition in their young-adult rats. However, in the current study, the performance of older middle-aged rats was markedly enhanced by modafinil when testing occurred under the more difficult (variable stimulus onset and duration) conditions. Combined, these studies appear to indicate that modafinil effects on attention-related processes are most easily observed when some type of cognitive impairment (aging, in this case) is present and task difficulty (i.e., attentional demands) are high. As mentioned earlier, it remains to be seen whether the duration of drug exposure (acute or chronic) also plays an important role.

Previous clinical studies have suggested a speed–accuracy trade-off effect of modafinil in which response latencies are slowed presumably due to increased impulse control (Turner et al., 2003, 2004b). However, in the present study response latencies were not indicative of a speed–accuracy trade-off, instead, modafinil-treated animals displayed a slight improvement in reaction time as seen by decreased response latencies. Together with the overall evidence of improved performance, this response latency effect suggests that modafinil facilitated accuracy and speed of information processing. Thus, in contrast to the Turner et al. (2003, 2004b) findings, slower processing was not necessary to accomplish the increased accuracy and decreased impulsivity displayed by modafinil-treated animals in this visual attention task. One potential explanation for this discrepancy is that this task does not involve the same type of complex thought processes required for the tasks with human subjects which showed the speed–accuracy trade-off effect (spatial planning, DMTS, and decision-making). In the Turner et al. (2003 and 2004b) studies, this effect was especially seen in the more difficult tasks. Consistent with this idea, sleep-deprived volunteers given modafinil showed faster reaction time in a 4-choice serial reaction time task (Pigeau et al., 1995), a task which does not require complex thought processes. While the cue delay and duration effects observed in the present study confirm that the attention task used in this study was cognitively taxing, visual discrimination and attention tasks likely recruit different cognitive processes than do tasks involving decision-making and spatial planning (the tasks in which response speed was decreased in the Turner studies). Additionally, the inconsistent results could involve differences between the subjects (e.g., species differences or age of the subjects). The one study that has tested modafinil in aged rats (23 months old), using an operant delayed alternation task, found evidence of improved reaction times (Miller et al., 2000). In this study, Miller and colleagues showed that aged rats typically respond more slowly and less accurately than young rats, but both deficits significantly improved with modafinil. However, this does not explain the Turner et al. (2003 and 2004a,b) findings of decreased response speed with modafinil, unless the inverted-U explanation (based on baseline reaction time) is once again invoked. In other words, perhaps reaction times in the young-adult participants tested by Turner et al. may have been increased when given the drug because no baseline impairment existed prior to treatment.

The lack of significant modafinil effects on body weight, alcove latencies and nontrials throughout both tasks indicated that treatment with modafinil did not have a negative impact on motivation or motor abilities. In fact, non-significant trends in both measures were in the opposite direction, suggesting, if anything, that motivation may have been increased in the drug-treated animals. Despite some early indications that modafinil may have anorexic effects through direct or indirect actions on hypothalamic orexin or histamine receptors (Nicolaidis and De Saint Hilaire, 1993; Shelton et al., 1995; Makris et al., 2004), the

current findings indicate that the drug did not reduce body weight or suppress appetite resulting in decreased food-reward motivation. These non-effects are consistent with previous research (Beracochea et al., 2002, 2001; Edgar and Seidel, 1997) and highlight another way in which the effects' profile for modafinil differs from most psychostimulants (e.g., amphetamines, methylphenidate, and nicotine) which typically reduce appetite and increase locomotor activity (Makris et al., 2004).

In conclusion, although the pattern of results seen in this and previous studies suggest that modafinil-induced enhancement of cognition is highly task-dependent, a look at other studies that have attempted to measure attentional effects of modafinil in rats suggests that the effects might be equally dependent on the baseline cognitive abilities of those tested with the drug (Randall et al., 2005; Waters et al., 2005). For instance, Waters et al. (2005) did not find any evidence that modafinil enhanced performance (indeed, it tended to increase premature errors) even though their manipulations of stimulus intensity and duration successfully influenced performance. In other words, even though the task was made demonstratively more difficult, modafinil did not enhance cognition in their young-adult rats. However, in the current study, the performance of older middle-aged rats was markedly enhanced by modafinil when testing occurred under the more difficult (variable stimulus onset and duration) conditions. Combined, these studies appear to indicate that modafinil effects on attention-related processes are most easily observed when some type of cognitive impairment (aging, in this case) is present and task difficulty (i.e., attentional demands) are high. As mentioned previously, it remains to be seen whether the duration of drug exposure (acute or chronic) also plays an important role.

Over the past few years, modafinil has been increasingly investigated for potential use in treating the cognitive impairments associated with disorders such as ADHD, schizophrenia, Parkinson's disease, depression, sleep-deprivation, and age-related dementias. The cognitive profile emerging from both applied and basic research investigations with modafinil seems to hold promise for many of these applications. The evidence that modafinil may actually decrease impulsivity while improving attention, combined with a side effect's profile that includes reduced abuse potential and little development of tolerance compared to amphetamine, suggests that modafinil may offer a valuable alternative to classic psychostimulants (Jasinski, 2000). However, further studies need to address the issue of whether modafinil produces a noticeable enhancement of cognitive functions in healthy, young adults, or whether the facilitative effects of the drug are limited to instances where cognitive decrements are present. While some research exists comparing modafinil with caffeine and amphetamines in sleep-deprived humans (Westenson et al., 2002 and 2005), further investigation of the similarities and differences with regard to safety and effectiveness in healthy, non-sleep-deprived, and elderly subjects is needed. Furthermore, because findings from the current study and others (Beracochea et al., 2001; Piérard et al., 2006; Ward et al., 2004) indicate dose-dependent and task-dependent effects with modafinil, future research should continue to examine various doses under a variety of experimental conditions in order to determine the most appropriate circumstances for the use of the drug.

References

Baranski JV, Gil V, McLellan TM, Moroz D, Buguet A, Radomski M. Effects of modafinil on cognitive performance during 40 hr of sleep deprivation in a warm environment. Mil Psychol 2002;14(1):23–47.

Baranski JV, Pigeau R, Dinich P, Jacobs I. Effects of modafinil on cognitive and meta-cognitive performance. Hum Psychopharmacol 2004;19:323–32.

Bayer LE, Brown A, Mactutus CF, Booze RM, Strupp BJ. Prenatal cocaine exposure increases sensitivity to the attentional effects of the dopamine D1 agonist SKF81297. J Neurosci 2000;20:8902–8.

Beracochea D, Cagnard B, Celerier A, le Merrer J, Peres M, Pierard C. First evidence of a delay-dependent working memory-enhancing effect of modafinil in mice. Neuroreport 2001;12(2):375–8.

Beracochea D, Celerier A, Borde N, Valleau M, Peres M, Pierard C. Improvement in learning processes following chronic systemic administration of modafinil in mice. Pharmacol Biochem Behav 2002;73:723–8.

Beracochea D, Celerier A, Peres M, Pierard C. Enhancement of learning processes following an acute modafinil injection in mice. Pharmacol Biochem Behav 2003;76:473–9.

Biedermann J, Swanson JM, Wigal SB, Kratochvil CJ, Boellner SW, Earl CQ, et al. Efficacy and safety of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder: results of a randomized, double-blind, placebo-controlled, flexible-dose study. Pediatrics 2005;116(6):e777–84.

Caldwell JA, Caldwell JL, Smythe NK, Hall KK. A double-blind, placebo-controlled investigation of the efficacy of modafinil for sustaining the alertness and performance of aviators: a helicopter simulator study. Psychopharmacology 2000;150:272–82.

Deroche-Gamonet V, Darnaudéry M, Bruins-Slot L, Piat F, Le Moal M, Piazza PV. Study of the addictive potential of modafinil in naïve and cocaine-experienced rats. Psychopharmacology 2002;161:387–95.

De Séréville JE, Boer C, Rambert FA, Duteil J. Lack of pre-synaptic dopaminergic involvement in modafinil activity in anaesthetized mice: *in vivo* voltammetry studies. Neuropharm 1994;33(6):755–61.

Edgar DM, Seidel WF. Modafinil induces wakefulness without intensifying motor activity or subsequent rebound hypersomnolence in the rat. J Pharmacol Exp Ther 1997;283(2):757–69.

Engber TM, Dennis SA, Jones BE, Miller MS, Contreras PC. Brain regional substrates for the actions of the novel wake-promoting agent modafinil in the rat: comparison with amphetamine. Neuroscience 1998;87(4):905–11.

Gill M, Haerich P, Westcott K, Godenick KL, Tucker JA. Cognitive performance following modafinil versus placebo in sleep-deprived emergency physicians: a double-blind randomized crossover study. Acad Emerg Med 2006;13(2):158–65.

Grottick AJ, Bontempi B, Tran P, Menzaghi F. Cognitive enhancing properties of modafinil in the mouse. Program no. 777.15. 2004 Abstract viewer/itinerary planner. Washington, DC: Society for Neuroscience; 2004. Online.

Högl B, Saletu M, Brandauer E, Glatzl S, Frauscher B, Ulmer H, et al. Modafinil for the treatment of daytime sleepiness in Parkinson's disease: a double blind, randomized, crossover, placebo controlled polygraphic study. Sleep 2002;25:905–9.

Ishizuka T, Sakamoto Y, Sakurai T, Yamatodani A. Modafinil increases histamine release in the anterior hypothalamus of rats. Neurosci Lett 2003;339(2):143–6.

Jasinski DR. An evaluation of the abuse potential of modafinil using methylphenidate as a reference. J Psychopharmacology 2000;14(1):53–60.

Jucker M, Oettinger R, Battig K. Age-related changes in working memory performance and locomotor activity in the Wistar rat. Behav Neural Biol 1988;50(1):24–36.

Kadar T, Silbermann M, Brandeis R, Levy A. Age-related structural changes in the rat hippocampus: correlation with working memory deficiency. Brain Res 1990;512(1):113–20.

Kraft GH, Bowen J, Stankoff B, Waubant E, Lubetzki C, Clanet M, et al. Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study. Neurology 2005;65:1995–7.

Li SC. Connecting the many levels and facets of cognitive aging. Curr Dir Psychol Sci 2002;11:38–43.

Lin JS, Roussel B, Akaoka H, Fort P, Debilly G, Jouvet M. Role of catecholamines in the modafinil and amphetamine induced wakefulness, a comparative pharmacological study in the cat. Brain Res 1992;591:319–26.

Makris AP, Rush CR, Frederich RC, Kelly TH. Wake-promoting agents with different mechanisms of action: comparison of effects of modafinil and amphetamine on food intake and cardiovascular activity. Appetite 2004;42: 185–95.

Mignot E, Nishino S, Guilleminault C, Dement WC. Modafinil binds to the dopamine uptake carrier site with low affinity. Sleep 1994;17(5):436–7.

Miller MS, Contreras PC, Roux S, Porsolt R. Modafinil improves cognitive function in aged rats measured by a delayed alternation task. Sleep 2000;23 (Suppl 2):A209.

Miller DK, Dopheide MM, Rodvelt KR, Schachtman TR, Morgan RE. The behavioral effects of modafinil are mediated by the dopamine transporter. Presentation at Annual Meeting of American Society for Pharmacology and Experimental Therapeutics (ASPET); 2007. April/May Washington D.C.

Milstein JA, Dalley JW, Theobold DEH, Robbins TW. Effects of modafinil on performance of the 5-choice serial reaction time task in rats. Program no. 516.10 2003 Abstract viewer/itinerary planner. Society for Neuroscience; 2003. Online.

Moreira KM, Hipolide RV, Fornari RV, Oliveira MGM. Improvement of rats performance on inhibitory avoidance task after modafinil administration. Program No. 1006.8. 2004 Abstract Viewer/Itinerary PlannerSociety for Neuroscience; 2004. Online.

Morgan RE, Garavan H, Smith EG, Driscoll LL, Levitsky DA, Strupp BJ. Early lead exposure produces lasting changes in sustained attention, response initiation, and reactivity to errors. Neurotoxicol Teratol 2001;23:519–31.

Morgan RE, Garavan HP, Mactutus CF, Levitsky DA, Booze RM, Strupp BJ. Enduring effects of prenatal cocaine exposure on sustained attention and reaction to non-reward in rats. Behav Neurosci 2002;116:624–33.

Müller U, Steffenhagen N, Regenthal R, Bublak P. Effects of modafinil on working memory processes in humans. Psychopharmacology 2004;177:161–9.

Nicolaidis S, De Saint Hilaire Z. Nonamphetamine awakening agent modafinil induces feeding changes in the rat. Brain Res Bull 1993;32:87–90.

Nieves AV, Lang AE. Treatment of excessive daytime sleepiness in patients with Parkinson's disease with modafinil. Clin Neuropharmacol 2002;25 (2):111–4.

Piérard C, Liscia P, Valleau M, Drouet I, Chaveau F, Huart B, et al. Modafinil-induced modulation of working memory and plasma corticosterone in chronically-stressed mice. Pharmacol Biochem Behav 2006;83:1–8.

Pigeau R, Naitoh P, Buguet A, McCann C, Baranski J, Taylor M, et al. Modafinil, D-amphetamine and placebo during 64 hours of sustained mental work. I. Effects on mood, fatigue, cognitive performance and body temperature. J Sleep Res 1995;4:212–28.

Puumala T, Riekkinen P, Sirvio J. Modulation of vigilance and behavioral activation by alpha-1 adrenoceptors in the rat. Pharmacol Biochem Behav 1997;56(4):705–12.

Randall DC, Shneerson JM, Plaha KK, File SE. Modafinil affects mood, but not cognitive function, in healthy young volunteers. Hum Psychopharmacol 2003;18:163–73.

Randall DC, Fleck NL, Shneerson JM, File SE. The cognitive-enhancing properties of modafinil are limited in non-sleep-deprived middle-aged volunteers. Pharmacol Biochem Behav 2004;77:547–545 Pharmacol Biochem Behav; 82: 133–139.

Randall DC, Shneerson JM, File SE. Cognitive effects of modafinil in student volunteers may depend on IQ. Pharmacol Biochem Behav 2005;82:133–9.

Rugino TA, Copley TC. Effects of modafinil in children with attention-deficit/hyperactivity disorder: an open-label study. J Am Acad Child and Adolecs Psych 2001;40(2):230–5.

Saletu B, Saletu M, Grunberger J, Frey R, Anderer P, Mader R. Treatment of the alcoholic organic brain syndrome: double-blind, placebo-controlled clinical, psychometric and electroencephalographic mapping studies with modafinil. Neuropsychobiology 1993;27:26–39.

Saper CB, Scammell TE. Modafinil: a drug in search of a mechanism. Sleep 2004;27:11–2.

Scammell TE, Estabrooke IV, McCarthy MT, Chemelli RM, Yanagisawa M, et al. Hypothalamic arousal regions are activated during modafinil-induced wakefulness. J Neurosci 2000;20(22):8620–8.

Shelton J, Nishino S, Vaught J, Dement WC, Mignot E. Comparative effects of modafinil and amphetamine on daytime sleepiness and cataplexy of narcoleptic dogs. Sleep 1995;18:817–26.

Simon P, Hemet C, Ramassamy C, Costentin J. Non-amphetaminic mechanism of stimulant locomotor effect of modafinil in mice. Eur Neuropsychopharmacol 1995;5:509–14.

Stivalet P, Esquivie D, Barraud P, Liefflen D, Raphel C. Effects of modafinil on attentional processes during 60 hours of sleep deprivation. Hum Psychopharmacol 1998;13:501–7.

Taylor FB, Russo J. Efficacy of modafinil compared to dextroamphetamine for the treatment of attention deficit hyperactivity disorder in adults. J Child Adolesc Psychopharmacol 2000;10(4):311–20.

Turner DC, Robbins TW, Clark L, Aron AR, Dowson J, Sahakian BJ. Cognitive enhancing effects of modafinil in healthy volunteers. Psychopharmacology 2003;165:260–9.

Turner DC, Clark L, Dowson J, Robbins TW, Sahakian BJ. Modafinil improves cognition and response inhibition in adult attention-deficit/hyperactivity disorder. Biol Psychiatry 2004a;55(10):1031–40.

Turner DC, Clark L, Pomarol-Clotet E, McKenna P, Robbins TW, Sahakian BJ. Modafinil improves cognition and attentional set shifting in patients with chronic schizophrenia. Neuropsychopharmacology 2004b;29:1363–73.

Ward CP, Harsh JR, York KM, Stewart KL, McCoy JG. Modafinil facilitates performance on a delayed nonmatching to position swim task in rats. Pharmacol Biochem Behav 2004;78:735–41.

Waters KA, Burnham KE, O'Conner D, Dawson GR, Dias R. Assessment of modafinil on attentional processes in a five-choice serial reaction time test in the rat. J Psychopharmacol 2005;19(2):149–58.

Westenson NJ, Belenky G, Kautz MA, Thorne DR, Reichardt RM, Balkin TJ. Maintaining alertness and performance during sleep deprivation: modafinil versus caffeine. Psychopharmacology 2002;159:238–47.

Westenson NJ, Killgore WD, Balkin TJ. Performance and alertness effects of caffeine, dextroamphetamine, and modafinil during sleep deprivation. J Sleep Res 2005;14:255–66.

Willie JT, Renthal W, Chemelli RM, Miller MS, Scammell TE, Yanagisawa M, et al. Modafinil more effectively induces wakefulness in orexin-null mice than in wild-type littermates. Neuroscience 2005;130:983–95.

Wisor JP, Nishino S, Sora I, Uhl GH, Mignot E, Edgar DM. Dopaminergic role in stimulant-induced wakefulness. J Neurosci 2001;21(5):1787–94.

Wisor JP, Eriksson KS. Dopaminergic–adrenergic interactions in the wake promoting mechanism of modafinil. Neuroscience 2005;132:1027–34.

Zifko UA, Rupp M, Schwarz S, Zipko HT, Maida EM. Modafinil in treatment of fatigue in multiplesclerosis: results of an open-label study. J Neurol 2002;249:983–7.