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Enhancement of learning processes following an acute modafinil injection in mice

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Abstract

Modafinil is a wakeness-promoting drug, which is effective in the treatment of narcolepsy; its effects on learning processes are however little studied. Thus, the present study was aimed at determining the effects of an acute modafinil injection on a serial reversal discrimination task performed in a T-maze in mice. Independent groups of mice varying by the level of pretest training (either 1 or 4 days of training) were used. Mice were injected each day with a gum arabic solution before each session began. On the second or the fifth day of training, a single dose of modafinil was injected before testing. Modafinil at 64 mg/kg but not at 32 mg/kg dramatically improved performance as compared to controls in subjects being trained 4 days, but not in subjects being trained 1 day. This improvement of learning was due to the more rapid emergence of a win–stay strategy in modafinil-treated subjects as compare to controls. Thus, our data show that an acute modafinil injection enhances learning processes.

Keywords: Cognitive learning set; Modafinil; Memory; Win–stay strategy

1. Introduction

Modafinil (diphenyl-methyl)sulphinil-2-acetamide) is a wakeness-promoting drug that is effective in the treatment of narcolepsy and idiopathic hypersomnia (Bastuji and Jouvet, 1988). Several studies have shown that modafinil has an agonist action on α-1-adrenergic postsynaptic receptors (Lin et al., 1992) and an antagonist action on glutamatergic receptors (Lagarde et al., 1996). Modafinil also reduces the release of extracellular GABA, which decreases GABAergic transmission (Piérard et al., 1997). Modafinil therefore modifies both glutamatergic and GABAergic activities and their interaction (Piérard et al., 1995; Ferraro et al., 1997; Perez de la Mora et al., 1999).

The effects of modafinil on memory processes have not yet been extensively studied, either in humans or animals. To date, only three studies have reported an improvement of short-term memory functions in humans following modafinil intake, but in subjects suffering from severe sleep apnea syndrome (Arnulf et al., 1997) or chronic alcoholism (Saletu et al., 1993). In animals, one study showed that modafinil increases performance in operant conditioning tasks but this improvement was due to a facilitation of sensorimotor processes (Bizot, 1998). 2-DG autoradiography (Engberg et al., 1998), EEG power spectral analysis (Seban et al., 1999), and functional magnetic resonance imaging (Ellis et al., 1999) studies have shown that modafinil substantially modifies the activity of brain areas, such as the hippocampus and the prefrontal cortex. Given the involvement of these two brain areas in learning processes and memory functions (Thomas, 1984; Winocur, 1992), we studied in previous experiments the effects of acute modafinil administration on an "episodic working" memory task involving spatial information (Beracochea et al., 2000). We showed in this study that modafinil slowed

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down the forgetting rates as compared to control mice, without modifying exploratory activity or anxiogenic reactivity in a hole-board apparatus.

Our previous results have also shown that chronic modafinil administration enhances the rate of learning of a cognitive set rule in a serial spatial discrimination reversal (SSDR) task carried out in a T-maze (Beracochea et al., 2002). This task allows the study of the rate of acquisition of a cognitive learning set rule. Indeed, we previously showed that normal mice exhibited, in the SSDR task, a substantial and progressive improvement of performance insofar as the number of trials required to master the criterion decreased progressively over successive days of training. This phenomenon would be the result of an incremental learning process, based on the detection of invariance over successive discrimination sessions (Krazem et al., 1995; Borde and Béracochéa, 1999). We showed that daily injection of modafinil over five reversal sessions accelerated the rate of learning the SSDR task and that this anterograde and progressive cognitive enhancement was based on a more rapid development of a win–stay rule, as compared to controls (Beracochea et al., 2002).

The aims of the present study were to investigate the effects of an acute modafinil injection on learning processes. For that purpose, in a first experiment using independent groups, modafinil injections were given following two different learning stages of the SSDR task, either following a single day of training or following four consecutive days of training. Therefore, the aim of this first experiment was to determine if modafinil administered before testing at the fifth day of training would facilitate performance, as compared to controls. In so far as mice are obliged to repeat daily the same choice in the SSDR task, we have decided to evaluate the effects of modafinil on a series of contingently reinforced alternations run in the T-maze already used in the SSDR task. This second experiment allowed us to ensure that the ability to shift response functions normally in modafinil-treated animals and that eventual improvement of performance in modafinil-treated subjects in the SSDR task would not be due to indirect effects of modafinil on behavioral inhibition processes.

2. Methods

2.1. Animals

The study was conducted using male mice of the C57 Bl/6 Jico strain obtained at 6 weeks of age from Iffa-Credo (Lyon, France). On arrival, mice were housed in groups in colony cages (40 cm long × 25 cm high × 20 cm wide; $n = 20$ per cage), matched for weight, and placed in an animal room (ambient temperature: 22 °C; automatic light cycle, the light periods being between 08:00 and 20:00 h) with free access to food and water. They remained in collective cages for at least 16 weeks. In all cases, at least 2 weeks before behavioral testing began, mice were housed in individual cages, with free access to food and water.

2.2. Apparatus

All tests were carried out in a T-maze constructed of gray Plexiglas. Stem and arms were 35 cm long, 10 cm wide and 25 cm high. The start box (10 × 12 cm) was separated from the stem by a horizontal sliding door. Horizontal sliding doors were also placed at the entrance of each arm. A low intensity diffuse illumination (10 lx) was provided above the apparatus.

2.3. Procedure

Both in the SSDR and in the alternation tasks, mice were handled for 10 min/day over three consecutive days before testing began. They were then submitted to a food deprivation schedule initiated over four consecutive days so that, at the time of training, the mice weighed 86–90% of their initial free-feeding weights. Food ration was adjusted individually to maintain the same level of deprivation throughout the ensuing experimental period.

2.4. Habituation

Habituation was carried out on the fourth day of deprivation. All animals were allowed 10-min free exploration of the apparatus to familiarize them with the experimental conditions. Food reward was available or given during this free-exploration session (BIOSERV pellets, 20 mg) to ensure that each animal learned to go to the end of the maze arms to obtain it.

2.5. SSDR task

The formal testing was composed of a learning phase including different phases: an acquisition phase (Day 1) followed by a series of four reversal sessions (Days 2–5). The acquisition session (Day 1) consisted of a succession of trials. On each trial, the mouse was placed in the start box and 20 s later, the door of the box was opened. When the animal entered one of the two arms, the door to that arm was closed. After a 20-s confinement in the chosen arm, the mouse was removed and placed again in the start box for the next trial. For each trial, the chosen arm and the time that elapsed between the opening of the door of the start box and the closing of the door of the chosen arm (running time) were recorded. For each mouse, the baited arm chosen on Day 1 was its "nonpreferred" arm during habituation (i.e., the arm opposite to the one that the animal had chosen first). The animal is required to enter repeatedly, during the acquisition phase, the same arm of the maze to be scored as making a correct response. To this aim, the acquisition session was continued until the subject reached the criterion of four correct responses out of four consecutive trials.

Following acquisition, daily reversal sessions took place over four consecutive days during which the baited arm was reversed from day to day. Each reversal session was pursued until the animal achieved the same criterion of four consecutive errorless trials. This behavioral paradigm enabled us to measure: (1) the number of trials needed to acquire the initial spatial discrimination (Day 1, (2) the performance on the first reversal session (Day 2), and (3) the performance savings over successive daily sessions (from Days 1 to 5).

2.6. Alternation task

All subjects were given daily sessions of six successive trials separated by a 5-s intertrial interval. To begin a trial, the subject was placed in the start box for 5 s before the door to the stem was opened. When the subject entered one of the arms, the door to that arm was closed. The chosen arm and the time that elapsed between opening the door and choosing the arm (choice latency) were registered. Following a 30-s confinement period in the chosen arm, the subject was removed and placed in the start box for a new trial. Visible traces of urine and feces were removed from the stem and arms between trials. In the alternation procedure used, the subjects were always rewarded (one food pellet) on the first trial of each session, but thereafter, they were rewarded only for alternation. When an error was made, food remained available in the opposite goal arm, so that the subjects correct themselves on the subsequent trial. The alternation task lasted five successive days.

The SSDR task and the contingently reinforced alternation task were run using independent groups.

2.7. Modafinil administration

In all experiments, modafinil was suspended in a 0.5% gum arabic solution and administered intraperitoneally (0.1 ml/10 g of mouse). Behavioral testing started 30 min after modafinil or vehicle injections. In all experiments, subjects were 24-week-old mice at the time of testing.

During the sessions preceding the modafinil injection (pretest phase), mice received each day a single intraperitoneal injection of a gum arabic solution 30 min before testing. For all tasks, there were three groups of mice: a vehicle group that received a daily gum arabic solution ($n = 10$) and two modafinil groups (32 mg/kg; $n = 10$, i.e., M32 and 64 mg/kg: $n = 10$, i.e., M64). The choice of these doses was based according to previous studies showing that the M64 but not the M32 doses of modafinil induced anterograde memory and learning improvements (Beracochea et al., 2000, 2002). Using independent groups, the effects of the M64 dose on performance were studied in the present study by giving the subjects a single modafinil injection 30 min before testing began, either the second day of testing (M32A, $n = 10$; M64A, $n = 10$) or on the fifth day of testing (M32B, $n = 10$, or M64B, $n = 10$) in the SSDR task. In so far as the aim of the experiment was to evaluate the effects of modafinil as a function of the stage of learning, the M32A and the M64A groups were no longer used in the study; indeed, these two groups were specifically devoted to specifically assess the effects of modafinil following the initial acquisition session (Day 1 of testing).

In the alternation task, each mouse received a daily injection of a gum arabic solution on four consecutive days (pretest phase). On the fifth day of testing, they were injected either with the M32 ($n = 10$) or the M64 ($n = 10$) dose or with the gum arabic solution (control group, $n = 10$). This drug administration procedure (pretest injections phase followed by the modafinil injection day) was similar to the one used in the SSDR task for "B" groups.

2.8. Data analysis

In the SSDR task, the results are expressed either as the number of trials necessary to reach criterion (learning) or as the percent correct responses (retention). In the alternation task, results are expressed as percentage of correct choices. To use normal distribution statistics, the number of trials necessary to reach criterion was coneverted into square root and the data expressed in percentage in arc sin values. Homogeneity of the variance of the transformed data was verified with Bartlett's and Lenvene's statistical tests. Two-way analysis of variance (ANOVA) with one repeated measure (either days of testing or retention intervals) were performed to assess the effects of several treatments on the animal's performance. Difference between groups (controls, M32A, M32B, M64A, and M64B) was analyzed by factorial or repeated measures ANOVA.

2.9. Ethical statement

All pharmacological and experimental procedures were in accordance with official French Regulations for the Care and Use of Laboratory Animals.

3. Results

3.1. Experiment 1: Effects of modafinil on the SSDR task

3.1.1. Acquisition (Day 1)

On Day 1 of testing (first discrimination), all five groups (controls, M32A, M32B, M64A, and M64B) received a gum arabic injection before testing. The number of trials required to reach the criterion was not significantly different among the five groups [groups: $F(4,44) = 1.2$, $P = .31$]. In addition, choices of the left or right arm at the first trial were evenly distributed among all groups.

3.1.2. Performance savings over days of testing (from Days 1 to 4)

This analysis was performed using mice of the control, M32B, and M64B groups. During the first four days of

testing, mice of each of these groups received a daily injection of the gum arabic solution. Results are shown in Fig. 1A. A global analysis showed that the number of trials necessary to reach the criterion decreased significantly over days of testing [days: $F(3,81) = 223.4$, $P < .0001$]. The rate of learning over days was not significantly different between groups [Groups × Days: $F(6,81) = 0.18$] and no between-groups difference was also observed [groups: $F(2,27) = 0.82$]. These analyses reveal a significant enhancement of learning processes induced by repetitive testing from Days 1 to 4, which was very similar in all groups.

3.1.3. First reversal (Day 2)

Results are shown in Fig. 1B. On the first reversal trial (Day 2), three groups received a gum arabic solution (controls, M32B, and M64B) and two groups (M32A and M64A) received the modafinil injections. A factorial analysis showed a nonsignificant between-groups difference on Day 2 of testing (first reversal) [groups: $F(4,44) = 0.9$] and no significant interaction was found between groups and days (Days 1 and 2) of testing [Groups × Days: $F(4,44) = 1.9$, $P = .11$].

3.1.4. Effects of modafinil on learning processes

Results are shown in Fig. 1C. On Day 5 of testing, the M64 ($n = 10$) and the M32 ($n = 10$) doses of modafinil were administered, whereas controls ($n = 10$) still received the gum arabic solution. Results showed a between-groups difference [groups: $F(2,27) = 30.6$, $P < .001$]. This difference was due to the M64 group, which required less trials (8.4 ± 1.2) as compared to controls (11.0 ± 0.90) or M32 mice (12.0 ± 0.94). Repeated ANOVA performed on Days 4 and 5 revealed a significant interaction between groups and days of testing [Groups × Days: $F(2,27) = 15.1$, $P < .0001$]. This was due to the faster intrasession learning rates observed in the M64 group; indeed, analyses performed on Days 4 and 5 of testing showed a significant between-groups difference [groups: $F(1,18) = 9.9$, $P = .05$] and a significant interaction between groups and days of testing [$F(1,18) = 18.9$, $P = .0004$ as compared to controls], which was not observed in the M32 group [groups: $F(1,18) = 2.7$ and $F(1,18) = 2.9$, respectively; $P > .05$ as compared to controls in all analyses].

An analysis carried out on the first five reacquisition trials of the fifth day of testing (from the second trial to the sixth trial) showed that M64-treated mice developed more rapidly than controls a tendency to choose more often the arm baited during the ongoing session (win–stay strategy), which was evidenced by a decrease of alternated trials [groups: $F(2,27) = 13.0$, $P = .0001$]. Such a win–stay strategy was significantly observed in M64 mice as compared to controls [2.2 ± 0.35 and 4.2 ± 0.7, respectively; $F(1,18) =$

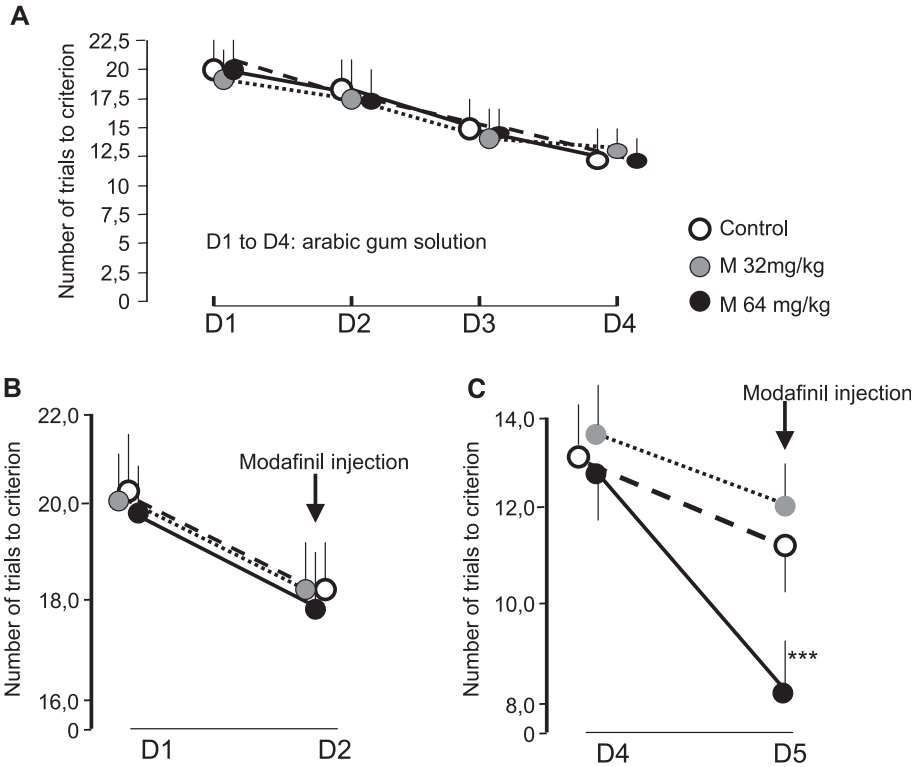

Fig. 1. (A) Mean number of trials required to master the criterion (four successive errorless trials) over the 4 days of the learning phase. Each mouse receives only the gum arabic solution. (B) Effects of acute modafinil administration (32 or 64 mg/kg) on Day 2 of testing. Modafinil did not significantly modify performance as compared to controls. (C) Effects of acute modafinil administration (32 or 64 mg/kg) on Day 5 of testing. The M64 dose significantly reduced the number of trials required to reach the criterion as compared to the other two groups (*** $P < .001$).

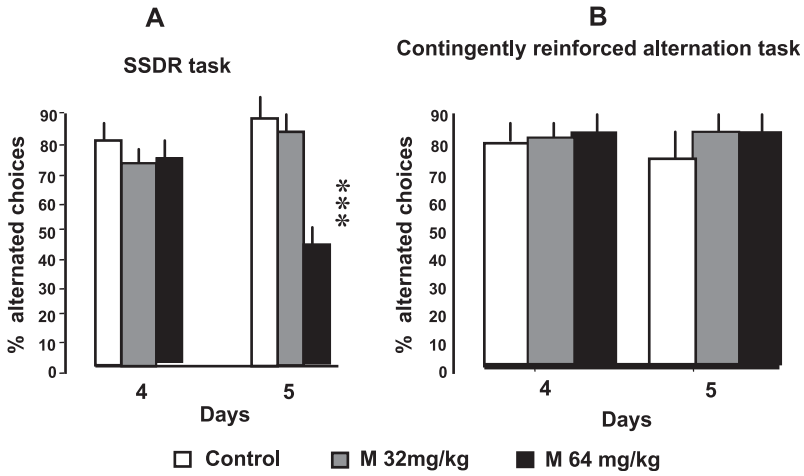

Fig. 2. (A) Percentage of intrasession alternated choices in modafinil and control subjects on Day 5 of testing in the SSDR task. As can be seen, M64-treated mice developed a significant decrease of alternated choices due to the emergence of a win–stay strategy as compared to the two other groups (* * * $P < .001$). (B) Percentage of intrasession alternated choices in modafinil and control subjects on Day 5 of testing in the contingently reinforced alternation task. Modafinil did not significantly modify alternation rates as compared to controls.

34.06, $P < .0001$] but not in the M32 group [3.9 ± 0.87; $F(1,18) = 0.29$, $P > .05$ as compared to controls] (see Fig. 2A).

In addition, we analysed the first choice emitted on Day 5 of testing. We found that the M64, M32, and control groups entered, at similar rates, the arm that was rewarded the day before [groups: $F(2,27) = 0.26$; 80.0 ± 13.3, 90.0 ± 10.0, and 90.0 ± 10.0 for controls, M64, and M32 mice, respectively]. The second choice of the Day 5 session was, however, characterized mainly by an alternation response (70 ± 15.2, 70 ± 15.2, and 80 ± 13.3 for control, M64, and M32 mice, respectively; groups: $F(2,27) = 0.15$].

3.2. Experiment 2: Effects of modafinil on contingently reinforced alternation

Results are shown in Fig. 2B. During the pretest phase, there was no significant increase of alternation rates over days of testing [days: $F(3,81) = 1.3$, $P = .25$]. The mean alternation rates over the 4 days of testing was similar in all groups ($76.8 \pm 3.2\%$, $81.5 \pm 3.6\%$, and $79.5 \pm 2.8\%$ for controls, M32, and M64, respectively) [groups: $F(2,27) = 1.66$, $P = .20$] and the evolution of performance across days of testing was also similar in all groups [Groups × Days: $F(6,81) = 0.26$]. On the fifth day of testing, the M32 and M64 dose were administered. Results showed no overall significant between-groups difference [groups: $F(2,27) = 2.77$, $P = .08$], although both the M32 ($82 \pm 4.6\%$) and the M64 ($82.0 \pm 3.7\%$) groups almost reached the statistical level of significance as compared to controls [$68.0 \pm 5.3\%$; groups: $F(1,18) = 3.9$ and $F(1,18) = 3.6$, respectively, $P > .05$ in all analyses].

Modafinil-treated animals exhibited the shortest running latencies as compared to controls (10.4, 12.3, and 14.7 s for M64, M32, and controls, respectively), but these difference were not statistically significant [groups: $F(2,27) = 1.6$, $P = .21$].

4. Discussion

As compared to controls, modafinil administration at 64 mg/kg but not at 32 mg/kg induced behavioral changes in the SSDR task. More specifically, modafinil-treated subjects required fewer trials than controls to master the criterion on the fifth day days of testing whereas the same dose did not modify performance when administered on the second day of testing. The M64 mice also exhibited normal alternation behavior in a contingently reinforced procedure.

As shown during the first four days of testing, all groups (which received only the gum arabic solution) exhibited a significant and similar improvement of learning rates. More precisely, the number of trials required to reach the criterion (four successive correct responses) decreased significantly over days of testing. This phenomenon shows that the animals were able to develop a learning set rule from session to session. These results are in agreement with previous data from our group, which showed that increasing the number of sessions dramatically reduced the number of trials required to master the criterion per session in normal mice (Meunier et al., 1991; Beracochea et al., 2002). This improvement was due to the progressive emergence of a win–stay strategy over the sessions, but it required additional days of training to appear, as compared to the procedure used in the present experiment. Given our previous findings, we consider that, in the present experiment, animals had significantly but only partially acquired the SSDR rule at the fourth day of testing. Indeed, we already shown that a longest training period (8–10 days of testing) substantially decreases the

number of trials required to master the criterion as compared to Day 5 (Meunier et al., 1991; Krazem et al., 1995; Borde and Béracochéa, 1999).

Analyses of the results showed that the improvement of the rate of learning the discrimination on Day 5 with the M64 dose is due to a more rapid emergence of a "win–stay" strategy as compared to controls. Indeed, the enhancement of learning by modafinil depends on the level of training. Modafinil did not improve performance following one day of training (Day 2) but increased performance following 5 days of training. The analyses performed on the six first trials of the reversal sessions showed that modafinil-treated animals emitted less frequently than controls the response learned the day before; in contrast, they developed a tendency to enter more frequently the arm baited during the *ongoing* session; this strategy requires only to make a simple association between a *specific* body-turn and the reward location in the maze, regardless of the association learned the day before.

The SSDR procedure does not allow us to determine which kind of cue (egocentric versus allocentric) supports the win–stay behavior. Indeed, if one looks at the first trial of the Day 5 session, animals entered the arm baited the day before; they choose however to alternate at the second trial of the Day 5 session. Such opposite behavioral patterns can be supported by either allocentric or egocentric cues. This analysis, however, demonstrates that mice are able to shift behavioral patterns, to reset the previously learned response and to adopt rapidly the strategy allowing to make a correct response, whatever the cues used to support their behavior. This requires a cognitive flexibility from session to session that is enhanced by the M64 treatment. Additionally, this analysis and the results drawn from the contingently reinforced alternation task show that the development of the win–stay strategy is not due to any side effect of modafinil on win–shift abilities. Sensorimotor effects would seem to be ruled out by the absence of drug effects on initial acquisition.

One could think that the lack of significant enhancing effects of modafinil on performance in the alternation task is surprising, insofar as the sequential procedure used in the SSDR task also involves behavioral flexibility. In the present study, trials in the alternation procedure were separated only by a short (5-s) intertrial interval. The 5-s intertrial interval induced high levels of alternation rates in controls reducing therefore the possibility to observe any significant improvement of performance following modafinil administration (ceiling effect). However, we already showed that the M64 dose enhanced alternation rates at long (60 and 180 s) but not at a short (5-s) intertrial interval (Beracochea et al., 2000).

It has been shown that the SSDR task is sustained by the activity of the cingulate cortex. Indeed, damage of the anterior but not of the posterior cingulate cortex impaired the learning of the SSDR task (Meunier et al., 1991). The anterior cingulate cortex receives anatomical inputs from the mediodorsal thalamus (Meunier, 1988) whose lesion also produced similar impairments in the SSDR task (Krazem et al., 1995). These findings are congruent with both clinical studies showing that in humans, frontal lobe pathology dramatically impaired reversal learning (Oscar-Bermann and Zola-Morgan, 1987; Schacter, 1987) and with experimental studies in animals showing impairments in reversal discrimination tasks following mediodorsal thalamic (Slotnick and Kaneto, 1981; Kolb et al., 1982; Staubli et al., 1987) or frontal cortical lesions (Kolb, 1984; Winocur, 1992). The improvement in the SSDR task induced by the modafinil administration may be due to its effects on brain structures involved in arousal or in the sleep–wakefulness cycle (Lagarde et al., 1995; Lin et al., 1996, 2000; Engberg et al., 1998) but also, more specifically, on brain structures involved in memory processes and cognitive flexibility. Thus, it has been shown that modafinil injection increases the number of Fos-immunoreactive neurons in the cingulate cortex (Scammell et al., 2000), a brain area that, as mentioned above, is critically involved in the SSDR task and reversal learning. Nevertheless, other cortical areas could be responsible for the learning enhancing effects of modafinil insofar as a recent study has also reported an enhancement of extracellular monoamines in the prefrontal cortex after modafinil administration in the rats (de Saint-Hilaire et al., 2001) and it has been already shown that the anterior cingulate cortex, the posterior cingulate cortex and the prelimbic cortex intervene, although differently, in the ability to learn stimulus–reward associations, or to reverse stimulus–reward associations (Bussey et al., 1997; Ragozzino et al., 1999; Brown and Bowman, 2002).

In conclusion, the data of the present study show that acute modafinil administration facilitates the emergence of a cognitive learning set rule as a function of the amount of training and that this improvement of the Day 5 intrasession learning processes in modafinil-treated animals is not due to an impairment of the ability to shift responses from trial to trial. Thus, besides its well-known effects on sleep/wakefulness processes, our study also reveals the cognitive enhancing effects of an acute injection of modafinil.

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