Naps and Modafinil as Countermeasures for the Effects of Sleep Deprivation on Cognitive Performance

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BATÉJAT DM, LAGARDE DP. *Naps and modafinil as counter-measures for the effects of sleep deprivation on cognitive performance.* **Aviat Space Environ Med 1999; 70:493–8.**

Disruptions in wake-sleep rhythms, particularly induced by sleep deprivation are limiting factors for military personnel in operations. The role of sleep and naps in the recovery of performance is generally accepted. Pharmacological aids, for example hypnotic or stimulant substances can also be effective countermeasures. Recently, a new stimulant compound, modafinil (MODIODAL®) has also proven effective. Considering the excellent results obtained with napping and modafinil, we have studied the combined effect of these two counter-measures on psychomotor performance under conditions simulating an operational situation. Beneficial effects of a few hours' nap on performance were confirmed. Consequently naps should be encouraged, even if limited and diurnal. Modafinil, which combines wakening and stimulating properties without any known side effects, was useful for longer periods of sleep deprivation and when there was no real possibility of sleep recovery. Modafinil did not prevent sleep if sleep opportunities were available. The combination of naps and modafinil demonstrated the best cognitive performance during sleep deprivation.

Keywords: wake-sleep rhythm, sleep deprivation, stimulant, modafinil, nap, psychomotor performance.

DISRUPTION IN WAKE-SLEEP rhythms, and particularly sleep deprivation of any length of time are limitating factors hindering the action of military personnel in operational settings (6,8,21). Various physiological counter-measures, such as napping are well known to be effective (9,14,19), while other solutions such as pharmacological aids are less well known. The effects of napping have been studied throughout the nycthemeron in order to define the optimal conditions for the best performance recovery after more or less prolonged sleep deprivation (19,23). The role of sleep in the restoration of performance is readily acknowledged but results vary as a function of the duration and timing of naps (19). Pharmacological aids mostly consist in the intake of hypnotic substances to induce restorative sleep (14,20) or in the intake of stimulants, like amphetamine, to keep the subjects awake (22,24). However, a new stimulant substance, modafinil (MODIODAL®) has been studied over the past few years, both in healthy subjects (17,18) and in subjects suffering from sleep disorders (2). Considering the excellent results obtained with napping and with modafinil individually, we believed it would be of interest to study the combined effect of these two countermeasures on wake-sleep rhythm disturbances.

METHODS

The effects of this combination of counter-measures on cognitive performance were studied under conditions simulating an operational situation. A long range attack mission of the bombing type (U.S. A6 Intruders), sea patrols (Atlantis French Navy) or watch patrols (AWACS) was simulated. The experimental timetable is as follows: Preparation of flight plan no. 1, 9 h; stand-by, 4 h; first flight mission accomplished, 14 h; sleep, 6 h; preparation of flight plan no. 2, 9 h; stand-by, 4 h; second flight mission accomplished, 14 h.

These experimental conditions are identical to those designed by the U.S. Naval Aerospace Medicine Research Laboratory in Pensacola, FL, to assess the effects of the administration of amphetamine (17). This current study was part of a U.S.-French cooperative project.

Subjects

Eight healthy male volunters aged 28–47 (mean age 37.25 ± 5.8 yr) from a French parachute detachment, participated in this study. All were submitted to a thorough medical examination before participation in the experiment and filled the questionnaire designed by Horme and Ostberg (11) to verify that they were neither "morning" or "evening" types.

After being informed of the purposes and protocol of the experiment, all subjects gave their written consent

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This manuscript was received for review in January 1998. It was revised in July 1998. It was accepted for publication in July 1998.

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according to the recommendations of the Helsinki convention.

Test Battery

Performance was measured using the seven tests of the AGARD STRES battery (Advisory Group for Aerospace Research and Development - Standardized Tests for Research with Environmental Stressors):

- *Reaction time task* for evaluation of five processing stages, stimulus processing or encoding, response choice, motor programming, motor activation and response execution, including five subtests with different stimulation: basic reaction time, inversion reaction time, uncertain reaction time, double response reaction time, coded reaction time;
- *Mathematical processing task* to assess processing resources associated with working memory;
- *Memory search task* including detection and recognition of target stimulus, memory search, comparison and response selection;
- *Spatial processing task* to assess spatial representation and visual short term memory;
- *Unstable tracking task* to measure resources used in the execution of continuous manual control responses;
- *Grammatical reasoning* task to measure the ability to manipulate grannnatical information in working memory;
- *Dual-task* combining unstable tracking and memory search to measure the ability to divide attention between two activities.

The data was stored on an IBM PC compatible microcomputer in our laboratory (1,16,17). Response time and percent of errors were measured in all the tests except for the tracking tests in which the parameters measured were an index of deviation of the cursor from the screen's center (calculated as root mean square deviation summed for each second) and the number of control losses recorded when the cursor reaches the edges of the display.

General Protocol

Testing began after double blind administration of modafinil and placebo for each subject. The four subjects who were administered modafinil in the first week of the experiment were administered placebo in the second week and vice versa. A dose of 200 mg of modafinil was administered each time. Various additional measurements were repetitively made throughout the two sleep deprivation episodes to complete the test battery used (12): MSLT (mean sleep latency test); clinical examination (arterial pressure, heart rate, body temperature); questionnaires on mood, vigilance, nutrition; blood samples (to study pharmacokinetics of the product) continuous night electrophysiological recordings (EEG, EMG, ECG, EOG); visual function contrast sensitivity test. Use of these measurements has been published (7) or will be discussed in a further report.

Experimental Procedure

Subjects were given 2 d of training to reach stable performance at the various tests prior to the beginning of the experiment. The experiment lasted 2 weeks. Considering the available equipment, training and experimental sessions were performed by groups of four subjects randomly selected. These two groups performed tasks at 1-h intervals; when one group was performing psychomotor tasks, the other group submitted to MSLT recordings, and vice versa. The experiment proceeded as described in **Table I**. The nap countermeasure from 9:00 a.m. to 3:00 p.m. on the second day of the experiment divided the two periods of wakefulness of 27 h each. Between psychomotor tasks and MSLT, subjects were submitted to all the other examinations included in the protocol. During rest periods, subjects were kept awake and participated in various activities (watching TV, playing batchi, reading, etc.).

Statistical Procedure

The first three sessions prior to sleep deprivation served as reference. Because of the small number of subjects, all results were processed by ANOVA, followed by a Newman-Keuls test when statistical conditions were met. The computer program used was PCSM 6.2 - DELTASOFT, France. For each measure, the two groups, placebo and modafinil, were compared for every experimental session during all the simulated operational situations and between the experimental sessions placed before and after the nap.

RESULTS

Complete results are presented for each one of the three countermeasures tested in this study: nap, modafinil, combination nap/modafinil.

Effects of Naps

In the placebo situation, the intermediate 6-h nap was sufficient to maintain performance at a level similar to that before sleep deprivation for reaction time tasks,

TABLE I. DETAILED PROTOCOL OF EACH EXPERIMENTAL WEEK AND TIMING OF TEST SESSIONS.

Normal control night Monday 11:00 p.m.—Tuesday 6:00 a.m.
* Tuesday 8:00 a.m. = session 1
* Tuesday 1:00 p.m. = session 2
Rest without sleep from 3:00 p.m. to 7:00 p.m.—(various diverting activities)
* Tuesday 9:00 p.m. = session 3
First treatment Tuesday 12:00 p.m.—(placebo or modafinil)
* Wednesday 4:00 a.m. = session 4 (post-treatment)
Nap from 9:00 a.m. until 3:00 p.m.
* Wednesday 5:00 p.m. = session 5
* Wednesday 10:00 p.m. = session 6
Rest without sleep from 12:00 p.m. to 4:00 a.m.—(various diverting activities)
* Thursday 6:00 a.m. = session 7
Second treatment Wednesday 9:00 a.m.—(placebo or modafinil)
* Thursday 12:00 a.m. = session 8 (post-treatment)
Recovery night Thursday 7:00 p.m.–Friday 6:00 a.m.
* Friday 8:00 a.m. = session 9

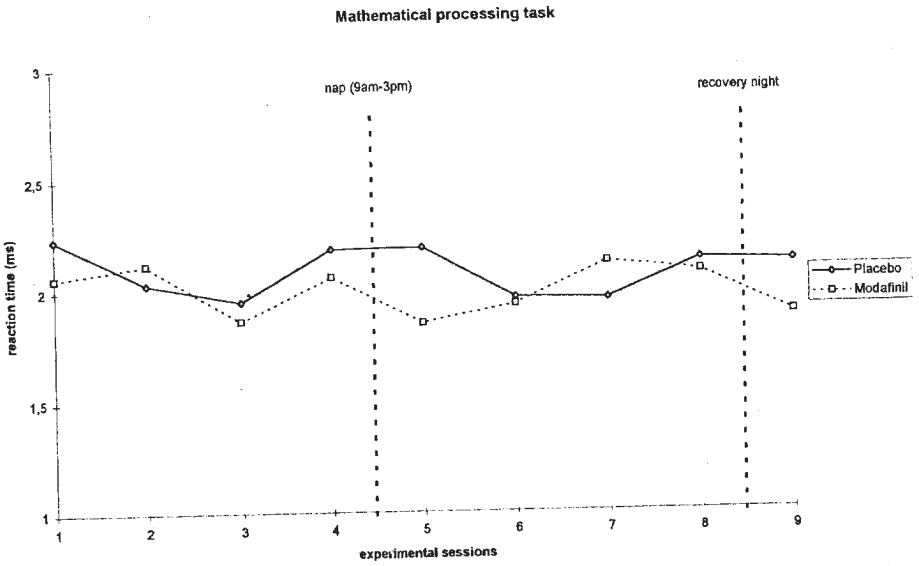

Fig. 1. Mathematical Processing Task: Reaction time evolution during the two periods of 27-h sleep deprivation with placebo and modafinil.

mathematical processing task (**Fig. 1**) and spatial processing task.

Performance was deteriorated on memory search task at the end of the two work periods. This was shown by a significantly longer response time ($p < 0.05$) for the two-letter memory set at Wednesday 04:00 a.m. (session 4) and Thursday 12:00 a.m. (session 8) and for the four-letter memory set at Wednesday 4:00 a.m. (session 4), and by a significant increase ($p < 0.05$) in the number of errors for the four-letter memory set at Thursday 12:00 a.m. (session 8) for the placebo group. This effect was stronger for the four-letter than for the two-letter memory search task where it was attenuated, particularly after sleeping. Performance was therefore deteriorated by 27 h of sleep deprivation, the Wednesday 4:00 a.m. and Thursday 12:00 a.m. sessions being the last two sessions of the two sleep deprivation periods. However, in spite of the time lag, performance was restored for a few hours to its reference level after the 6-h nap (**Fig. 2**).

There was a significant difference in response times at the grammatical reasoning task obtained under placebo between Wednesday 4:00 a.m. (session 4) and Wednesday 5:00 p.m. (session 5) sessions, showing the beneficial effect of the nap on performance recovery.

Performance at the tracking task showed no significant difference between sessions. However, cursor deviation from the target increased after the placebo treatment at the Wednesday 4:00 a.m. (session 4) and Thursday 12:00 a.m. (session 8) sessions (**Fig. 3**).

Very few control losses were recorded; their mean number increased (up to 3.5 and 3.75) for the placebo group at the same sessions (**Fig. 4**).

During the dual-task, cursor deviation from the target significantly increased at the Wednesday 4:00 a.m. (session 4) and Thursday 6:00 a.m. (session 7) sessions, both for the two and four-letter memory sets. In the placebo situation, response times at the memory search task associated with tracking were statistically different ($p < 0.05$) for the two and four-letter memory sets, as a function of the time at which the test was performed. Significant differences were identified by the Newman-Keuls test. The highest increase ($p < 0.05$) in response times was observed for the four-letter memory sets at the Wednesday 04:00 a.m. (session 4), Thursday 6:00 a.m. (session 7) and Thursday 12:00 a.m. (session 8) sessions. The largest number of errors ($p < 0.05$) was measured at the Wednesday 04:00 a.m. (session 4) and Thursday 12:00 a.m. (session 8) sessions. Performance was restored to its initial level after the recovery night.

Effects of Modafinil

The effect of modafinil was only noticeable in tasks affected by limited sleep deprivation. Performance at the memory search task was improved after each administration of modafinil (Wednesday 4:00 a.m. and Thursday 12:00 a.m. sessions). The analysis of results for the modafinil group shows a significant difference ($p < 0.05$) in response times between the Thursday 6:00 a.m. session and the others sessions both for the two and four-letter memory sets. For the same session, the number of errors was much higher ($p < 0.05$) for memory search with four-letter memory set only. The Thursday 6:00 a.m. session was performed immediately prior to the administration of modafinil which induced an increase in performance in subsequent sessions. No improvement of performance was observed after the placebo treatment.

The overall performance at the tracking task was better for the modafinil group than for the placebo group. The administration of modafinil prevented the deterioration of performance observed after the administration of placebo at the Wednesday 4:00 a.m. and Thursday 12:00 a.m. sessions.

For the dual-task, the same trend was observed as for each one of the individual tasks (tracking and memory search tasks). The intake of modafinil induced an improvement of performance at the Wednesday 4:00 a.m.

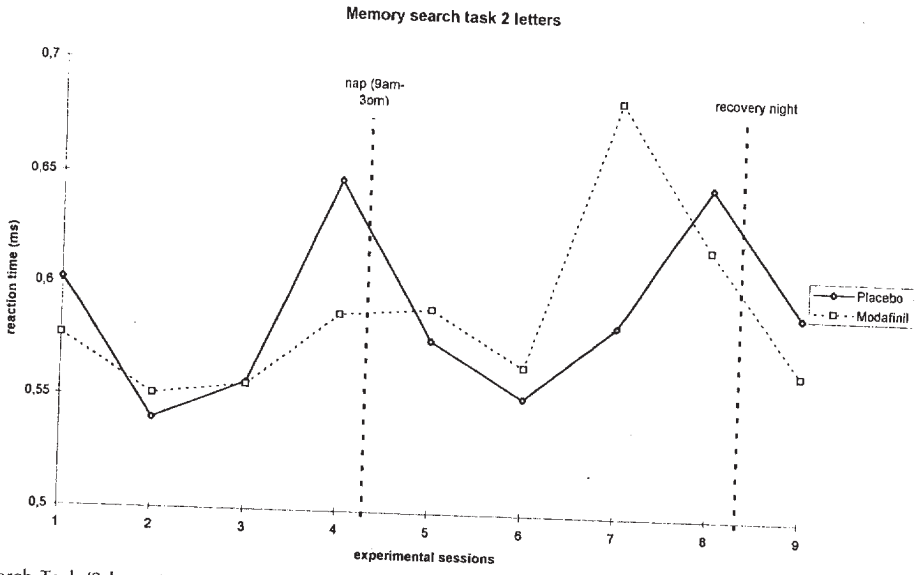

Fig. 2. Memory Search Task (2 letters): Reaction time evolution during the two periods of 27-h sleep deprivation with placebo and modafinil.

and Thursday 12:00 a.m. sessions. No improvement of performance was observed after the placebo treatment.

Response times at the memory search task were statistically different ($p < 0.05$) for the two and four-letter memory sets, as a function of the time at which the task was performed. The Newman-Keuls tests showed that the greatest drop in performance occurred at the Thursday 6:00 a.m. session, particularly for memory search with the two-letter memory set. No significant difference was observed for error scores.

Effects of Combination Naps/Modafinil

The combination naps/modafinil more markedly increased performance at the Wednesday 5:00 p.m. session (session 5). A similar improvement was also noticed for tasks whose performance was not deteriorated by the first period of lack of sleep.

The analysis of variance showed significant differences ($p < 0.05$) between the placebo and modafinil groups for response times at the mathematical processing task. The combination nap/modafinil markedly decrease the response time at the Wednesday 5:00 p.m. session. This response time was 300 ms lower in the modafinil group than in the placebo group at the same session. However, in the placebo group, the 6-h nap was sufficient to maintain the same level of performance in the second part of the experiment as in the first part.

Performance at the tracking task was not deteriorated at the Wednesday 4:00 a.m. and Thursday 12:00 a.m. sessions in the modafinal group. Modafinil also enhanced performance recovery after the Thursday 6:00 a.m. session, which was not the case for the placebo group.

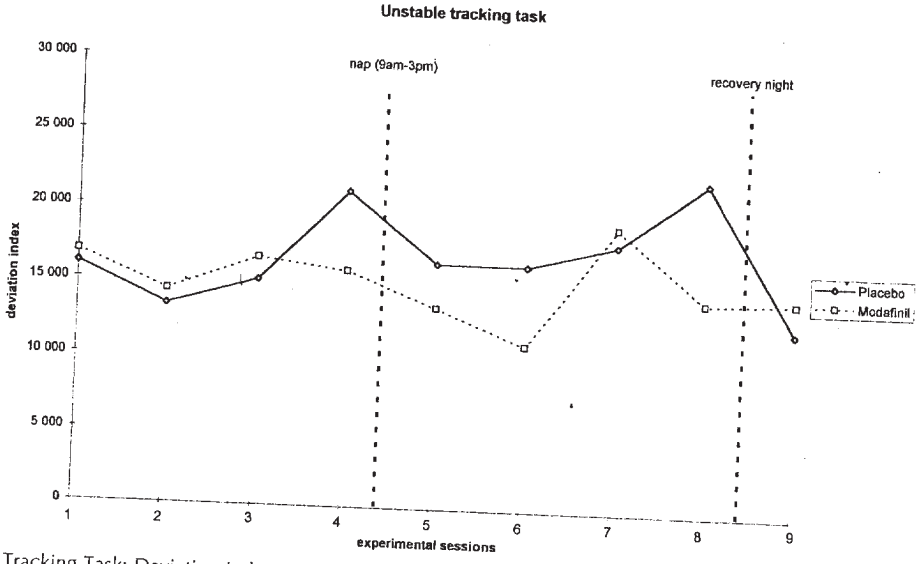

Fig. 3. Unstable Tracking Task: Deviation index evolution during the two periods of 27-h sleep deprivation with placebo and modafinil.

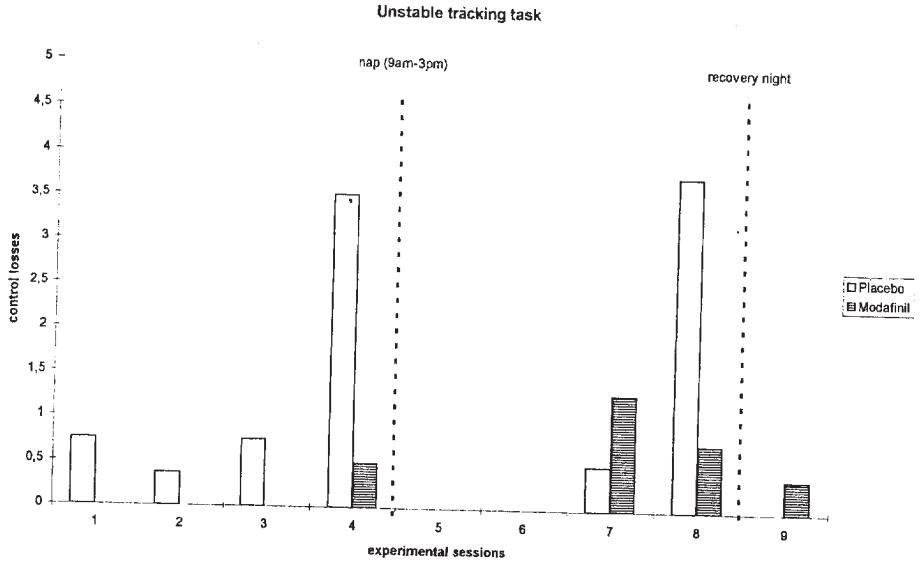

Fig. 4. Unstable Tracking Task: Control losses evolution during the two periods of 27-h sleep deprivation with placebo and modafinil.

DISCUSSION

Results from the various psychomotor tasks confirm the already well documented effects of limited sleep deprivation on performance (4,10,21,25). They are also consistent with findings yielded by the same tests in a previous laboratory study on the effects of prolonged sleep deprivation (3,4,15). During prolonged sleep deprivation (60 h) the overall performance deteriorates over time, this deterioration being more or less gradual, and different for different tasks. In the present study, the overall performance was also decreased during the first period of sleep deprivation of 27 h however, disruptions remained limited, and the 6-h nap restored performance to a level similar to that during the first hours of sleep deprivation period. Nevertheless, these results have to be modulated according to the circadian rhythmicity of the psychomotor performance as observed by Batejat and Lagarde (3).

Beneficial effects on performance of a few hours' nap, even diurnal, are thus confirmed. The effects of napping have been extensively studied. They depend on three factors: duration, situation in the nycthemeron and duration of sleep deprivation before the nap. Webb (23) compared the effects of a 4-h nap from 8:00 p.m. to 12:00 a.m., and of 2-h nap from 10:00 p.m. to 12:00 a.m. after a night without sleep, and showed that the longest nap was the most efficient with respect to performance. Naitoh (19) showed that after 53 h of sleep deprivation, a 2-h nap from 12:00 p.m. to 2:00 p.m. had better effect on performance than a nap of the same duration from 4:00 a.m. to 6:00 a.m. after 45 h of sleep deprivation. The studies by Haslam (9) on trained soldiers during sustained operations with 90 h of sleep deprivation showed a 50% drop in performance compared with the control group. This deterioration of performance reduced to 37% if subjects were allowed a 1.5 h nap every 24 h during the first 3 d of the study. Haslam (8) also showed that an experienced group could remain "efficient" on the field 3 d without any sleep, 6 d with a 1.5 nap per 24 h and 9 d with a 3-h nap per 24 h. On the other hand, Bonnet et al. (5) showed that performance is directly proportional to prophylactic nap length. All these studies clearly show the need for a minimum amount of sleep per 24 h to maintain performance at a satisfactory level.

In the present study, the administration of modafinil maintained an adequate level of performance at tasks which were the most deteriorated by the conditions of sleep deprivation imposed on the subjects.

The wakening and stimulating properties of modafinil, free of any side effects, have already been demonstrated in a former study with 60 h of sleep deprivation (17). The effects of modafinil on cognitive performance during sleep deprivation suggest that his mechanism could act at two different levels. First and foremost modafinil maintains an efficient level of CNS general activation close to awakening, but it seems also to have a more specific action on neuro-physiological mechanisms underlying short-term memory.

The mechanism of action of this molecule is not fully understood. Modafinil may act by activating central α-1 and β post-synaptic adrenergic receptor, and by inhibiting GABAergic transmission. In addition, the mechanism of action of modafinil could also imply excitatory aminoacids (17).

Compared with other well-known stimulating substances such as caffeine and amphetamine (24), modafinil has the advantage of combining wakening and stimulating properties which are remarkable in terms of duration and magnitude, with an appreciable absence of unwanted side effects.

The similar experiment conducted by Shappel et al. (22) with dextro-metamphetamine showed good results quite equivalent with those obtained with modafinil. But the authors stated that future research efforts involving d-amphetamine should focus on the side effects as subjects pertain to aircrew, and on effects of multiple doses of the drug on aircrew performance and mental status.

In conclusion, when choosing countermeasures to

alleviate the effects of wake-sleep rhythm disruptions during prolonged operations, it appears that sleep should be the first choice countermeasure, even if it can be limited and diurnal (14). The use of modafinil becomes necessary for longer sleep deprivations or when periods without sleep become so repetitive that they do not allow any real possibility of recovery. We know that in this case modafinil does not prevent the natural drive of subjects to fall asleep (13) if the opportunity to sleep arises, and it has also been shown that the combination nap/modafinil induces better recovery of performance at tasks which are the most sensitive to sleep deprivation. The use of a wakening substance, such as modafinil in this case or caffeine in the Bonnet experiment (5), in conjonction with naps might offer the best combination of benefits.

ACKOWLEDGEMENT

This research was supported by DRET contract no. 94/14 (Délegation Générale de l'Armement). LAFON Laboratory supplied modafinil (MODIODAL®).

Charles DEJOHN and David NERI gave us very excellent advices, and we are grateful. Special thanks are extended to Doctor MOURAREAU team for his precious help and to D. FREUND and J. FRENCH (from U.S. Air Force) for their help in translation.

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