Effects of Modafinil on Attentional Processes During 60 Hours of Sleep Deprivation

PHILIPPE STIVALET*, DOMINIQUE ESQUIVIÉ, PIERRE-ALAIN BARRAUD, DANIEL LEIFFLEN and CHRISTIAN RAPHEL

Unité de Psychologie, Centre de Recherches du Service de Santé des Armées, B.P. 87, 38702 La Tronche Cedex, France

The present study investigates the effects of modafinil (300 mg/24 h) versus a placebo on the performance of a visual search task during 60 h of sleep deprivation. Modafinil was administrated in doses of 100 mg three times per day during sleep deprivation. Six healthy volunteers participated in a double-blind experiment including two experimental sessions of 7 days each. The experiment used the visual search paradigm for an ‘O’ target among ‘Q’ distractors and the reverse. The speed and accuracy in detecting the target were measured by RTs slopes (i.e. search rates) and the number of errors (i.e. error rates), respectively. Many authors attribute rapid search rates obtained for ‘Q’ targets (low RTs slopes) to parallel/automatic processes and slow search rates obtained for ‘O’ targets (high RTs slope) to serial/attentional processes. The results revealed an asymmetrical search pattern for the detection of ‘Q’ versus ‘O’ targets across the sleep deprivation period (i.e. parallel versus serial search, respectively). Rapid search rates for ‘Q’ targets remained unchanged between placebo and modafinil conditions during sleep deprivation. However, slow search rates for ‘O’ targets increased linearly in placebo condition, but remained at the same level as the control-test in modafinil condition. Error rates and search rates also increased. For ‘O’ and ‘Q’ targets, the number of errors increased in the placebo condition, but remained stable in the modafinil condition. In summary, we can conclude that the administration of modafinil (300 mg/24 h) during sleep deprivation prevents the slowing of serial processes (attentional shifts) and the increasing of errors. © 1998 John Wiley & Sons, Ltd.

KEY WORDS — sleep deprivation; modafinil; early vision; spatial attention

INTRODUCTION
The debilitating effects of sleep deprivation on behavioural performance in many prolonged work situations are now well documented in the literature (for a review, see Krueger, 1989; Riback, 1983). Many studies have shown that the disruption of sleep–wake cycles impairs psychomotor and mental performance (Angus and Heslegrave, 1985; Heslegrave and Angus, 1985; Haslam, 1982; Opsad et al., 1978). Methods used to prevent the negative effects of sleep deprivation fall into two categories. The first includes non pharmacological procedures based on the training of subjects and on sleep management with strategically placed small naps used in sustained work situations (Naitoh and Angus, 1989; Angus et al., 1992). Such procedures rapidly proved to be insufficient to recuperate and overcome the effects of sleep loss (Naitoh, 1981).

The second category includes pharmacological methods based on the administration of alerting substances used as a complement to sleep management. Lagarde (1990) divided those substances into three categories: amphetaminic, xanthines derivatives and new synthetic substances. Although these substances keep you awake, amphetamines and xanthines are frequently inapplicable because they induce decrements in mental performance and adverse side effects such as euphoria, loss of appetite, increases in heart rate and blood pressure. In addition, greater Rapid Eye Movement (REM) sleep disturbances were observed with amphetamines than with modafinil (Buguet et al., 1995). Not to mention that d-amphetamines can be addictive. The third category is a new family of chemical molecules discovered by the Lafon Laboratory (adrafinil, modafinil, etc.). They have the same wakening properties but without side and rebound-effects (Buguet et al., 1995; Pigeau et al., 1995). Such substances belong to a new class of psychostimulants called eugregoric (eu = good, gregor = wakefulness) because of the good
wakefulness they induce. The quality of wakefulness is assessed by mental performance in cognitive tests (Lagarde and Batejat, 1995), whereas drowsiness is assessed by the theta/alpha spectral powers ratio (Pigeau et al., 1987; Bastuji and Jouvet, 1988). Modafinil, whose structural formula is diphenylmethyl-sulfinyl-2 acetamide, has been largely studied. Its euporigic effect is mediated by an agonist effect of central post-synaptic z1 adrenergic receptors (Duteil et al., 1990) and probably by dopaminergic mechanisms (Mignot et al., 1994). Modafinil administrated per os to healthy young volunteer adults is tolerated until 400 mg/24 h. Up to this dose, EEG effects (increases in EEG alpha rhythm and decreases in slow theta and delta activities) confirm the hypothesis of a higher level of wakefulness without toxic effects. Finally, psycho-behavioural studies on modafinil show that the most appropriate posology for us to obtain a good wakening effect varies between 200 and 400 mg every 24 h in adults (Lafon Laboratory, 1994).

Besides the effects of modafinil to maintain a high-level of vigilance, the investigations of the mental abilities in healthy subjects (Lagarde and Batejat, 1995; Pigeau et al., 1995) reveal that performance remains at control level for up to 44 h after an administration of 600 mg of modafinil every 24 h. On the whole, performance scores on most behavioural tasks are not affected by sleep deprivation when modafinil is administrated. Since those results are obtained from global performance scores on various mental tasks, they do not indicate the nature of the processes involved in maintaining a high level of wakefulness with modafinil. Since spatial attention is an important component of vigilance, we studied the mechanisms through which modafinil becomes effective in visual attentional processes. Many theories of vision agree with the existence of two visual processing stages involving preattentional processes and attentional processes (Julesz, 1981; Marr, 1982; Neisser, 1967; Treisman and Gelade, 1980; Zeki, 1993). Using an experimental paradigm involving the detection of an ‘O’ target among a set of ‘Q’ distractors and the reverse (‘Q’ target among ‘O’ distractors), Treisman (1985) observed an asymmetrical processing in the detection of ‘O’ versus ‘Q’ targets: a serial/attentional processing versus a parallel/preattentional processing. Most models of human visual processing stipulate that covert shifts of attention play an important role in visual search. The preattentional processing is characterized by the absence of attentional shifts. The search is described as ‘parallel’ because the search time is not affected by the number of stimuli in the array. Conversely, the attentional processing is characterized by the presence of attentional shifts. The search is described as ‘serial’ because the search time increases as a function of the number of stimuli in the array (Julesz and Bergen, 1983; Treisman and Souther, 1985; Prinzmetal et al., 1986; Wolfe, 1994).

The purpose of this experiment was to study the effects of sleep loss on parallel and serial processes in early vision (i.e. preattentional vision) and to investigate more precisely the compensatory effects of modafinil in visual operating processes. This study was carried out as part of a more general project whose goal was to investigate whether the administration of modafinil in doses of 100 mg three times per day could maintain the subject’s cognitive abilities at a high level during sleep deprivation of 60 h.

MATERIALS AND METHODS

Subjects
Six adult male volunteers (age 20–30) participated in the experiment. Their eyesight was normal or corrected to normal. Medical and psychological examinations were normal, without psychiatric antecedent nor sleep disturbance. Results of the Horne and Ostberg (1976) questionnaire revealed that subjects were not markedly categorized as being of the morning or evening type, and that they experienced normal anxiety according to the Cattell anxiety scale (Rickels and Cattell, 1965). The number of subjects was limited to six for technical reasons: (i) the constant supervision of subjects to maintain their wakefulness or to ensure their security was time consuming, (ii) some experimental settings for other tests and psychophysiological recordings in the experiment do not allow more than six subjects in each testing period. After the protocol was approved by the Ethical Committee for the protection of persons involved in biomedical research, subjects were medically screened and were provided with detailed information on the experiment. Each subject signed an informed consent and received payment for their participation.

General experimental design
The experiment took place in the psychology laboratory during the winter in Grenoble to avoid
seasonal effects. Each subject underwent two sessions of 7 days, with a control test before each period of sleep deprivation, and nights followed by continuous activities — i.e. free time between the experimental tests was occupied by interactive video games and parlor games; moreover an experimenter had the specific task to speak to the subjects and to control that nobody was trying to sleep — and medical supervision during 3 nights and 4 days, ending with one recovery night and day with a second control test. Electroencephalographic (EEG) recordings were taken by physiologists during the first night before the experiment to make sure that they had no sleep disturbance (i.e. REM sleep and non-REM sleep alterations), also during the recovery night after sleep deprivation. The other parameters were taken on separate channels: electrooculogram, electromyogram, electrocardiogram and body surface temperature. Polygraphic traces were scored blind as to subjects and drug condition in 20 s epochs following classical criteria for the scoring of wakefulness, Stages 1, 2, 3, and 4 of non REM sleep, Stages 3 and 4 constituting slow-wave sleep (SWS), and REM sleep (Rechtschaefen and Kales, 1968; Buguet et al., 1995).

Subjects were kept under constant supervision in the lab with a physician and a supervisor to monitor their wakefulness. They had their meals in the lab. Alcohol, caffeine or theine were not permitted. A typical day (24 h) included two periods of 4 h (24:00–4:00 and 13:00–19:00) to carry out conjointly the visual search task and the physiological measures (ECG, pulse, blood pressure, rectal temperature, etc.). We did not postulate any correlation between the physiological measures and the performance scores on the visual processing task. This paper therefore only presents the investigations on visual search in early vision.

**Drug administration and medical surveillance**

Double-blind random assignment was used to determine the order of modafinil and placebo in a session and consisted of either a placebo pill or 100 mg of modafinil every 8 h (300 mg/24 h). During a session, subjects always received seven pills: one every 8 h (i.e. 8 p.m. on Tuesday, followed by 4 a.m., 12 a.m., 8 p.m. on both Wednesday and Thursday). The $T_{\text{max}}$ of modafinil is about 4 h and the $T_{\frac{1}{2}}$ is 13-6 h when administered at intervals throughout the day. Sessions were separated by a wash-out period of 15 days to ensure a complete elimination of the drug.

An observation chart was filled in every 8 h to assess side effects. Blood pressure, pulse, body temperature and ambient temperature were measured.

**Specific experimental design**

**The visual search task.** The visual search task consisted of detecting a target letter 'Q' among a varying number of distractor letters 'O' and the reverse (see Figure 1). This visual search task used by Treisman (1985) reveals that the detection of a ‘Q’ target involves parallel processing (i.e. response times are identical whatever the number of distractors), while the detection of an ‘O’ target involves serial processing (i.e. increasing of response times as a function of the number of distractors). This asymmetrical search pattern (‘parallel versus serial’) is used to identify the two processes involved in early vision.

![Figure 1. Examples of the letter arrays. (A) 10 items with 'O' target present among 'Q' distractors; (B) 10 items with 'Q' target present among 'O' distractors](image)

The ‘Q’ target pops out among ‘O’ distractors because it is the only item with a vertical line segment (target-distractor dissimilarity). Conversely, the ‘O’ target requires a longer visual searching time among ‘Q’ distractors because the ‘O’ target shares all its characteristics with the ‘Q’ distractor (target-distractor similarity).

**Apparatus and stimuli.** The stimuli arrays were generated by a computer and displayed in a dark room on an oscilloscope screen (P31-1311A Hewlett Packard Display). Displays consisted of 4, 10, 16 letters arrays (‘O’ and/or ‘Q’). There were 16 displays of each set size with the target present and 16 without target. The position of the targets

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and distractors on the screen was different on each display. The positions of the targets were preset so that four would appear in each quadrant of the display at $4.5^\circ \pm 0.4$ eccentricity. The angular distance between two neighbouring letters was more than the size of a letter, and distractor letters were randomly distributed over the whole visual field.

Procedure. Each display was preceded by a central fixation dot (displayed for 800 ms) and followed by a random line mask (displayed for 1.5 s). Arrays remained on the screen until a response was provided by the subject. Subjects were required to respond as quickly and accurately as possible and asked to specify whether or not the target was present with a trigger control in each hand.

Two counterbalanced blocks (i.e. one with a ‘O’ target among ‘Q’ distractors and one with a, ‘Q’ among ‘Os’) consisted respectively of 24 practice trials followed by 96 experimental trials whose half were with target present. The trials blocks were presented in random order with the constraint that subjects could not give the same answer more than three times in a row. Response times diverging from the mean by more than $+2$ s were considered as erroneous responses and were discarded.

Statistical analysis. The dependent variables were the slope of the best fitted linear regression of the RTs as a function of the number of elements (search rates) and the mean response errors rate (error rates). The former measured the search rates in milliseconds per letter, the latter measured the error rates in percentage. The response data computed concerned only the arrays with target present because the fatigue of sleep loss often involved strategies of verification to find the target in absent-target arrays (re-examination). The time of verification did not correspond exactly to the visual search time.

Results were subjected to non parametric tests for dependent samples. The Wilcoxon matched-pairs signed-ranks test was used to verify the absence of any learning effect in the two sessions or a rebound effect comparing the control tests before and after sleep deprivation, and to compare the substance effect (‘modafinil versus placebo’). The Friedman test was used to evaluate the effect of sleep deprivation. The null hypothesis was rejected at the level of $p < 0.05$.

RESULTS

Control data

Because of the few subjects number, before and after each experimental session, control measurements were done to assess the stability of mental performance. The control data (search rates and error rates) obtained before sleep deprivation and after one recovery night, respectively, were not significantly different between the two sessions. Therefore, in the following analyses and in the data plotted in Figure 2, we used as control data the mean values of the responses obtained before sleep deprivation in the two sessions. We confirmed the usual observation of the asymmetrical search pattern for ‘O’ versus ‘Q’ targets both on search rates and error rates. The slopes were 12.7 ms/letter for ‘O’ targets and 0.8 ms/letter for ‘Q’ targets (Wilcoxon Test, $z = 2.82; p < 0.004$). The percentage of errors was 4% for ‘O’ targets and 1.5% for ‘Q’ targets (Wilcoxon Test, $z = 2.53; p < 0.01$).

Sleep deprivation data

Overall data observed under sleep deprivation shows that mean slopes were respectively 16.12 ms/letter for ‘O’ targets and 4.13 ms/letter for ‘Q’ targets (Wilcoxon Test: $z = 4.88$; $p < 0.05$).
confirming the asymmetrical search pattern between 'O' targets (serial processing) and 'Q' targets (parallel processing).

For 'O' target trials, mean slopes were respectively 12.36 ms/letter with modafinil and 19.87 ms/letter with the placebo (Wilcoxon Test: \( z = 2.17; p < 0.02 \)). For 'Q' target trials, mean slopes were respectively 3.97 ms/letter with modafinil and 4.29 ms/letter with the placebo (\( z = 0.74; \text{n.s.} \)). Thus, the substance effect (i.e. modafinil versus placebo) was significant for the serial processing ('O' target search), but it was not for the parallel processing ('Q' target search).

Moreover, the effect of sleep deprivation — from \( t_0 = \text{control test} \) to \( t_{56h} = \text{the 56th hour of sleep deprivation} \) — was significant with the placebo for the two types of targets (Figure 3), respectively for 'O' targets (Friedman Test: Chi-Square (4) = 11.96; \( z < 0.01 \)) and for 'Q' targets (Friedman Test: Chi-Square (4) = 11.23; \( z < 0.02 \)), but was not significant with modafinil for any targets ('O' target: Chi-Square (4) = 6.83; n.s.; 'Q' targets: Chi-Square (4) = 6.23; n.s.). Thus, with the modafinil, error rates did not increase significantly during sleep deprivation for any targets, while with the placebo they significantly increased for both 'O' and 'Q' targets.

**DISCUSSION AND CONCLUSION**

Figure 2 shows that search rates are higher for 'O' target detection than for 'Q' target detection throughout the period of sleep deprivation. This suggests that search time for 'O' targets steeply increased as a function of the number of distractors and very smoothly for the 'Q' targets.

Visual search results for detecting a 'Q' target among 'O' distractors of variable number and the reverse 'O' target among 'Q' distractors, are characterized by an asymmetrical search pattern observed throughout the sleep deprivation period. This search asymmetry was attributed by Treisman (1985) and Wolfe (1994) to the existence of two visual stages. The preattentional stage is characterized by the absence of attentional shifts. Such search processing is described as 'parallel' because it is not affected by the number of stimuli in the configuration. The preattentional stage is supported by parallel processes which operate
According to Schwartz (1977) and to the erroneous perceptual decision making. Attributed to a dysfunction of identification processes due to control error rates. Errors of detection are attributed to deprivation and are not significantly different from control error rates. Errors of detection are attributed to an overlearning of the task. Though performance improvement observed at the 56th hour is not significant and can probably be attributed to an overlearning of the task. Though this kind of search task is not affected by learning, a small learning effect can be observed after blocks of several hundreds of trials.

The error rates increased as a function of sleep deprivation in the same way as the mean search rates, except for the ‘Q’ target where error rates increased significantly in the placebo condition. There is no evidence for a shift in the speed-accuracy trade-off. Subjects who are more efficient in their visual search do not make more errors. Errors rates increase as a function of sleep deprivation time for ‘O’ and ‘Q’ targets in the placebo condition. But, the most striking result was observed in the modafinil condition where error rates do not increase significantly during sleep deprivation and are not significantly different from control error rates. Errors of detection are attributed to a dysfunction of identification processes due to an erroneous perceptual decision making. According to Schwartz et al. (1977) and to the models of McCann and Johnston (1992), this processing stage matches the stimulus features with the template of the target loaded in visual short term memory (VSTM). The successful analysis of similarities between the letters and the target template involves an accurate identification (Duncan and Humphreys, 1989, 1992). As a consequence, sleep deprivation seems to disturb these processes, while the administration of modafinil protects the visual system against such degradation. Total mean errors decrease by 50% with modafinil as compared to placebo. The analysis of error rates as a function of sleep deprivation time shows the positive effect of modafinil beyond the 42nd hour of sleep deprivation (Figure 3).

In summary, this study shows the positive effects of modafinil on attentional processes when administered in doses of 100 mg three times per day during a sleep deprivation of 60 h. Its administration does not increase performance scores, but maintains the speed of attentional scanning and the performance of identification processes at a mean level which enables the subject to perform cognitive tasks without major disturbance.

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