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SELF-MONITORING COGNITIVE PERFORMANCE DURING SLEEP DEPRIVATION: EFFECTS OF MODAFINIL, D-AMPHETAMINE AND PLACEBO

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Self-monitoring cognitive performance during sleep deprivation: effects of modafinil, d-amphetamine and placebo

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SUMMARY Self-monitoring refers to the ability to assess accurately one's own performance in a specific environment. The present study investigated the effects of the stimulating drugs modafinil (300 mg) and d-amphetamine (20 mg) on the ability to self-monitor cognitive performance during 64 h of sleep deprivation (SD) and sustained mental work. Two cognitive tasks were investigated: a visual (perceptual) judgment task and a complex mental addition task. Subjects in the placebo condition displayed marked circadian and SD effects on cognitive task performance but their self-monitoring was substantively undisturbed by SD. Subjects performing under the influence of d-amphetamine likewise displayed highly proficient self-monitoring throughout the SD period. In contrast, modafinil had a disruptive effect on self-monitoring, inducing a reliable 'overconfidence' effect (i.e. an overestimation of actual cognitive performance), which was particularly marked 2–4 h post-dose. Although modafinil has proven to be a safe and effective countermeasure to the effects of extensive SD on cognitive task performance, we encourage a more comprehensive understanding of the relation between its subjective and performance enhancing effects before the drug is recommended as a viable fatigue countermeasure.

KEYWORDS cognitive performance, confidence, d-amphetamine, modafinil, self-monitoring, sleep deprivation

INTRODUCTION

Media coverage of the recent 'Gulf War' provided world-wide audiences with striking footage of how advances in contemporary military technology permit 'round-the-clock' or sustained operations (SUSOPS). In sharp contrast, the human element embedded in this complex technological assembly has remained severely challenged by evolution: We must sleep. The inevitable consequence of this discrepancy between human need and technological capability has been a renewed and burgeoning interest in the human factors of SUSOPS. For example, recent initiatives such as the U.S. 'Aircrew Conditioning Program', employed in both Desert Storm and Desert Shield, have highlighted the importance of a generalized approach to the effective management of fatigue as a result of sleep loss. A component of this programme was the explicit recommendation to U.S. Air Force personnel to use d-amphetamine (5 mg) '30 min before critical stages of flight if they felt unduly fatigued' (Emonson and Vanderbeek 1995).

Although the effectiveness of amphetamine to combat the deleterious effects of sleep loss is now well documented (e.g. Newhouse *et al.* 1989, 1992), it is also well known that the amphetaminic class of compounds possess some undesirable properties (e.g. subjective euphoria, cardiovascular disturbances, insomnia, tolerance, and addiction). More recently, a new class of 'eugregoric' synthetic stimulants (see Lagarde and Batejat 1995) have attracted the attention of the sleep research community. Indeed one member of this class, modafinil (diphenylmethyl-sulfinyl-2 acetamide), has been promoted as an attractive alternative to amphetamine (Lyons and French 1991) and a recent study by Pigeau *et al.* (1995b) found the drug to be as effective as d-amphetamine in SUSOPS environments with far fewer physical side-effects.

Modafinil's mode of action is to date not fully understood (Mignot *et al.* 1994). However, the consensus of over 20 publications during the past 5 y is that the arousal inducing

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effect of modafinil derives from the stimulation of central alpha 1 adrenergic receptors. Accordingly, numerous studies have concluded that modafinil's behavioural (Bastuji and Jouvet 1988; Saletu *et al.* 1989; Buguet *et al.* 1995), subjective (Warot *et al.* 1993; Pigeau *et al.* 1995b), and pharmacological (e.g. Duteil *et al.* 1979, 1990; Lagarde 1990; Rambert *et al.* 1990; Herment *et al.* 1991; Lin *et al.* 1992; De Séréville *et al.* 1994; Simon *et al.* 1994; Shelton *et al.* 1995) properties are clearly distinct from that of amphetamine.

Self-monitoring cognitive performance during sleep deprivation

It is well known that subjective reports of fatigue or sleepiness are correlated with cognitive performance decrements during sleep deprivation (SD) (e.g. Dinges *et al.* 1984; Angus and Heslegrave 1985; Babkoff *et al.* 1991; Gillberg *et al.* 1994). Thus, the subjective estimate of how one feels can provide an overt, preliminary indication that mental performance is (or may soon be) sub-optimal. Importantly, however, the often extreme situational demands of certain occupations (e.g. military personnel, police and fire fighters, medical professionals, truckers, etc.) can engender passive inattention to, or active disregard of, the momentary subjective assessment of fatigue or sleepiness. If this occurs, then the decision to actively pursue fatigue countermeasures (e.g. sleep, use stimulants, or disengage from the relevant activity) will be based on either intrinsic or extrinsic evidence concerning actual performance. Specifically, in certain situations (e.g. night driving), distinct environmental cues can provide the sleep deprived individual with explicit and fairly immediate feedback about their declining performance (e.g. momentary loss of vehicular control). Conversely, in many critical situations, explicit feedback from the environment may not be immediately available or may be absent altogether (e.g. surveillance operations, work requiring extensive vigilance, see Pigeau *et al.* 1995a). In such circumstances, an accurate assessment of one's own performance provides the only means by which to identify a potentially life-threatening state.

Throughout this paper, we use the term 'self-monitoring' to denote the 'meta-cognitive' ability to assess accurately one's own performance in a given environment. To date, the self-monitoring of performance has been studied at two levels. The first concerns the validity of subjective (confidence) assessments made on a trial-by-trial basis during a specific task (for reviews see Lichtenstein *et al.* 1982; Keren 1991; Baranski and Petrusic 1994; Harvey 1994; McClelland and Bolger 1994). In terms of the effect of SD stress on the validity of confidence judgments, Baranski *et al.* (1994) found that trial-by-trial self-monitoring was unaffected by 64 h of SD despite pronounced circadian and SD effects on primary task performance (i.e. mental addition). This finding provided preliminary evidence of a reliable 'internal-feedback' mechanism during SD stress.

In contrast to self-monitoring at the level of the individual trial, the second level of self-monitoring involves an assessment of the validity of more global subjective (frequency) estimates of performance made immediately before and/or immediately after a specific cognitive task (for reviews see Gigerenzer *et al.* 1991; Griffin and Tversky 1992; Harvey 1994; Stone 1994; Treadwell and Nelson 1996). Hence, in the context of the study to be reported, the relation between the pre-task evaluation and actual performance provides an index of how well individuals can anticipate a sleep-deprivation induced change in cognitive performance (i.e. prospective self-monitoring). Conversely, the relation between the post-task evaluation and actual performance provides an index of how well individuals can detect a sleep-deprivation induced change in cognitive performance once it has occurred (i.e. retrospective self-monitoring).

The present research was motivated by two principle questions. First, in the absence of explicit feedback from the environment, to what extent can individuals accurately quantify and articulate cognitive performance deficits during SD? Second, to what extent do modafinil and d-amphetamine – two stimulants that are known to affect subjective mood, fatigue, and performance (Warot *et al.* 1993; Pigeau *et al.* 1995b) – affect the ability to assess accurately one's own cognitive performance? Based on the findings of Baranski *et al.* (1994), we expected subjects in the placebo condition to demonstrate profound circadian and SD effects on cognitive task performance but, concomitantly, display relatively accurate self-assessments of their performance. In contrast, although d-amphetamine may effectively ameliorate cognitive performance deficits becaues of SD, its rather potent subjective effects may induce exaggerated (i.e. overconfident) self-assessments of performance, e.g. '... oral administration of 2.5–15 mg dextroamphetamine produces feelings of alertness, energetic vitality, *confident assertiveness* and a decrease in appetite and fatigue' (Mitler *et al.* 1994, p. 362, italics added). On the other hand, several early studies have shown that amphetamine does not have an antagonistic effect on the subjective judgment of one's own performance in non-sleep deprived individuals (e.g. Hauty and Payne 1957; Smith and Beecher 1960; see the review by Weiss and Laties 1962; but cf. Smith and Beecher 1964). In addition, modafinil has shown no evidence of euphoric subjective effects in non-sleep deprived individuals (Warot *et al.* 1993). However, to date the effects of modafinil and d-amphetamine on the ability to self-monitor cognitive performance during SD have not been studied. This will constitute the focus of the present research.

METHODS

Subjects

Forty-one Canadian Forces personnel (39 males, 2 females; mean age = 24 y) participated for 6 consecutive days in exchange for their basic wages plus $260.00 (Cdn.) stress allowance. Two subjects did not complete all of their sessions as a result of illness; their data were not analysed. This study was approved by Health Canada and adhered to the guidelines of the DCIEM Ethics Board for research involving human subjects.

Materials

Subjects worked alone in 3 × 4 m experimental rooms which were equipped with a DEC VT100 terminal and keyboard, IBM PC and keyboard, table, chair, desk lamp and a bed. Cognitive tasks were controlled by a DEC VAX 6410 computer and were displayed on the subjects' computers. Closed-circuit televisions were used to monitor the subjects and slave monitors displayed the subjects responses to the experimenters.

Procedure

Subjects were randomly assigned to one of three drug conditions using a double-blind manipulation: modafinil (300 mg), d-amphetamine (20 mg) and placebo. The modafinil dose was established after consultation with Laboratiore L. Lafon so as to be comparable with the d-amphetamine dose. Subjects in each drug condition ingested the same drug three times during the course of the study: (1) at 23.30 hours of the first night of sleep deprivation; this was to determine if the stimulants could prevent the anticipated 'first-night' decline in cognitive performance, (2) at 05.30 hours of the second night of SD; this was to determine if the stimulants could recuperate cognitive performance relative to the placebo condition, and (3) at 15.30 hours of the third day of SD; this was to examine further the recuperative effects of the drugs and to investigate their effects on recovery sleep (see Buguet *et al.* 1995).

Subjects participated in groups of six (because of a last minute withdrawal, there was one group of five) but worked independently and at their own pace. Upon arrival (Sunday 09.00 hours), subjects were briefed on the experimental protocol and were given training sessions on the full battery of cognitive tasks to be used in the experiment. A more formal, 6-h 'baseline' session was conducted between 12.00 and 18.00 hours on Monday. The subjects were allowed 8 h of sleep on Monday night and were awakened at 06.00 hours on Tuesday whereupon they immediately began the SUSOPS portion of the experiment, which continued until 18.00 hours on Thursday. The subjects retired at 22.00 hours on Thursday and were permitted a maximum of 13 h of recovery sleep. The subjects then participated in a 6-h recovery session between 12.00 and 18.00 hours on Friday. Following a second night of recovery sleep (8 h), the subjects were debriefed and were released from the laboratory at ≈10.00 hours on Saturday.

Throughout the SD period the subjects performed continuous cognitive work in 2-h sessions; 1-h and 45 min of work followed by a 15 min break. During the breaks, subjects consumed food, used the restroom facilities, watched movies and conversed with the other subjects. EEG, ECG, blood pressure and core and surface body temperatures were recorded throughout the study (these data are not reported here). Subjects performed a variety of cognitive tasks (see Pigeau *et al.* 1995b; for a review of the findings) but we focus here on the two tasks that were used to assess the effects of modafinil, d-amphetamine and placebo on the ability to self-monitor cognitive performance: a visual (perceptual) judgment task and a mental addition task involving a high memory workload These tasks were chosen because they address very differen cognitive abilities and because their task parameters are we understood (Baranski and Petrusic 1992; Baranski *et al.* 1994

Perceptual comparison task

The perceptual comparison task required relative judgment of line lengths. Each trial began with the presentation of ar instruction (LONGER or SHORTER) which was centred near the top of the PC monitor. The visual stimulus was presented 1 s later and consisted of two horizontal line segments which extended different lengths to the left and right of a short vertica mid-line. The subject's task was to determine which of the two lines was longer or shorter, depending on the instruction Subjects responded by depressing either the left or right buttor on the PC mouse. In order to avoid floor and ceiling effect on performance (i.e. percentage of correct responses) we selected sets of line length pairs that would provide ar intermediate level of judgment difficulty (see Baranski and Petrusic 1994, 1995).

Prior to beginning each session, the subjects were prompted on the screen for a pre-task estimate of their performance Their task was to type on the PC keyboard the percentage of trials that they thought 'they would answer' correctly Immediately following the completion of each session, subjects were prompted for a post-task estimate of performance. Here their task was to type in the percentage of trials they thought 'they had answered' correctly. It was emphasized during the baseline training sessions and in the instructions that accompanied each prompt that an estimate of 100% was to denote that all trials were (or would be) answered correctly and, because there were only two choices on each trial for this task, that 50% correct could be achieved by chance responding.

Subjects performed two 4.5-min sessions of the comparison task in every 2-h block; in all analyses to be reported we combined the data over these two sessions in order to obtain more reliable estimates of task performance. Throughout the study, feedback about the accuracy of the perceptual judgments or the appropriateness of the subjective estimates of performance was not provided.

Mental addition task

The addition task required subjects to add a random sequence of 8 numbers (between 1 and 16) which were presented on the computer monitor at a rate of one number every 1.25 s. The sequence was terminated by the presentation of a visual prompt (=>) at which time subjects typed in their response and then pressed the 'Enter' key. Subjects performed one 12-min session of the serial addition task in each of the 12 6-h blocks in the study (block 1, performed on Monday, was considered a baseline).

As with the comparison task, subjects were prompted fo pre- and post-task estimates of performance immediately befor and immediately after each session of the mental addition tas

espectively. Here, we emphasized during the baseline sessions and in the prompt that accompanied each estimate that a response of 100% was to denote that all trials were (or would be) answered correctly and that a response of 0% was to denote that all trials were (or will be) answered incorrectly. In other words, it was made clear to the subjects that a 'half-range' scale (i.e. 50–100%) should be used for the perceptual comparison task and a 'full-range' scale (i.e. 0–100%) should be used for the addition task. As with the comparison task, feedback on the accuracy of the judgments or the validity of the subjective estimates was not provided at any point during the study.

Statistical analyses

Laboratiore L. Lafon (1994) has reported that the half-life for modafinil (300 mg) is between 2 and 4 h. In addition, Warot *et al.* (1993) have confirmed this result and demonstrated a parallel finding for d-amphetamine (15mg). Accordingly, the primary analyses involved a comparison of self-monitoring performance for sessions immediately preceding and immediately following each drug administration. Throughout, repeated measures mixed ANOVAs and contrasts involving Bonferroni *t*-tests were used to evaluate the results.

RESULTS

The results for the comparison task will be presented first, followed by the results for the addition task. The data of two subjects were excluded from the analyses of the perceptual task; perhaps because of a visual impairment, performance for these subjects remained at chance responding throughout the study. Hence the results for the comparison task are based on the data of 37 subjects (13 placebo, 12 d-amphetamine, 12 modafinil) whereas the results for the addition task are based on the data of 39 subjects (13 placebo, 12 d-amphetamine, 14 modafinil).

Perceptual comparison task

Figure 1 provides a plot of performance in the perceptual comparison task as a function of experimental session, separately for each drug condition. Mean judgment accuracy (% correct responses) is denoted by filled circles, mean pre-task estimates by up-triangles and mean post-task estimates by down-triangles. Perfect self-monitoring is indicated when the estimates match response accuracy, underconfidence is denoted by estimates that fall below response accuracy, and overconfidence is denoted by estimates that exceed the percentage of correct responses.

Judgment accuracy

In terms of cognitive task performance (filled circles), the first dose of modafinil and d-amphetamine was highly effective in preventing the 'first-night dip' in performance, which is clearly evident in the placebo condition. Similarly, the second dose of modafinil and d-amphetamine was clearly restorative; performance increased whereas performance in the placebo condition declined once again. However, unlike with d-amphetamine, the third dose of modafinil was ineffective.

A repeated measures mixed ANOVA was conducted on the (arcsine transformed) percentage correct measure with DRUG (3) as a between-subjects factor and ADMINISTRATION (3), SESSION (2), and BEFORE vs. AFTER DRUG (2) as within-subject factors. The ANOVA confirmed a main effect of ADMINISTRATION ($F(2,68)=16.61$, $P<0.0001$), which was qualified by a three-way interaction involving DRUG, ADMINISTRATION, and BEFORE vs. AFTER DRUG ($F(4,68)=3.99$, $P<0.006$); as discussed above, performance in the modafinil and d-amphetamine conditions differed from the placebo condition following administrations 1 and 2, whereas performance in only the modafinil condition declined following administration 3.

Self-monitoring performance

In terms of the ability to self-monitor cognitive performance, note first that all groups display clear underconfidence during the early sessions. Subsequently, the d-amphetamine group displays exceptional self-monitoring for the duration of the study. A very similar pattern is evident in the placebo condition until the 54th h of SD, after which there is some evidence of a loss of self-monitoring. However, in the modafinil condition we see a different picture. Specifically, each drug administration is shown to induce a substantial increase in the self-estimates of performance which is not commensurate with actual performance, resulting in a clear overconfidence effect between 2 and 4 h post-dose.

The ANOVA reported above was employed using the difference between the actual and estimated proportion of correct responses as dependent measures. There was a main effect of ADMINISTRATION for the pre-task estimates ($F(2,68)=11.93$, $P<0.0001$) and the post-task estimates ($F(2,68)=8.35$, $P<0.001$). Most importantly, the critical interaction between DRUG and BEFORE vs. AFTER DRUG was significant for the pre-task estimates ($F(2,34)=5.91$, $P<0.006$) and the post-task estimates ($F(2,34)=4.59$, $P<0.017$), confirming a significant difference among the drug groups following administration. Planned comparisons confirmed that the drug-induced overconfidence effect was restricted entirely to the modafinil condition (pre-task estimates: mean overconfidence following drug administration = 9.57%, $P<0.0001$; post-task estimates: mean overconfidence following drug administration = 9.49%, $P<0.0001$). In addition, as is evident in the middle panel of Fig.1, the initial disturbance to self-monitoring incurred by the first administration of modafinil had a rather long-lasting effect. Indeed, virtually all of the Wednesday afternoon and evening session's show a degree of overconfidence which is reliable with a conventional student's *t*-test ($P<0.05$). Finally, note that just prior to the second administration of Modafinil (some 24 h following the first administration), there is evidence that self-monitoring returns,

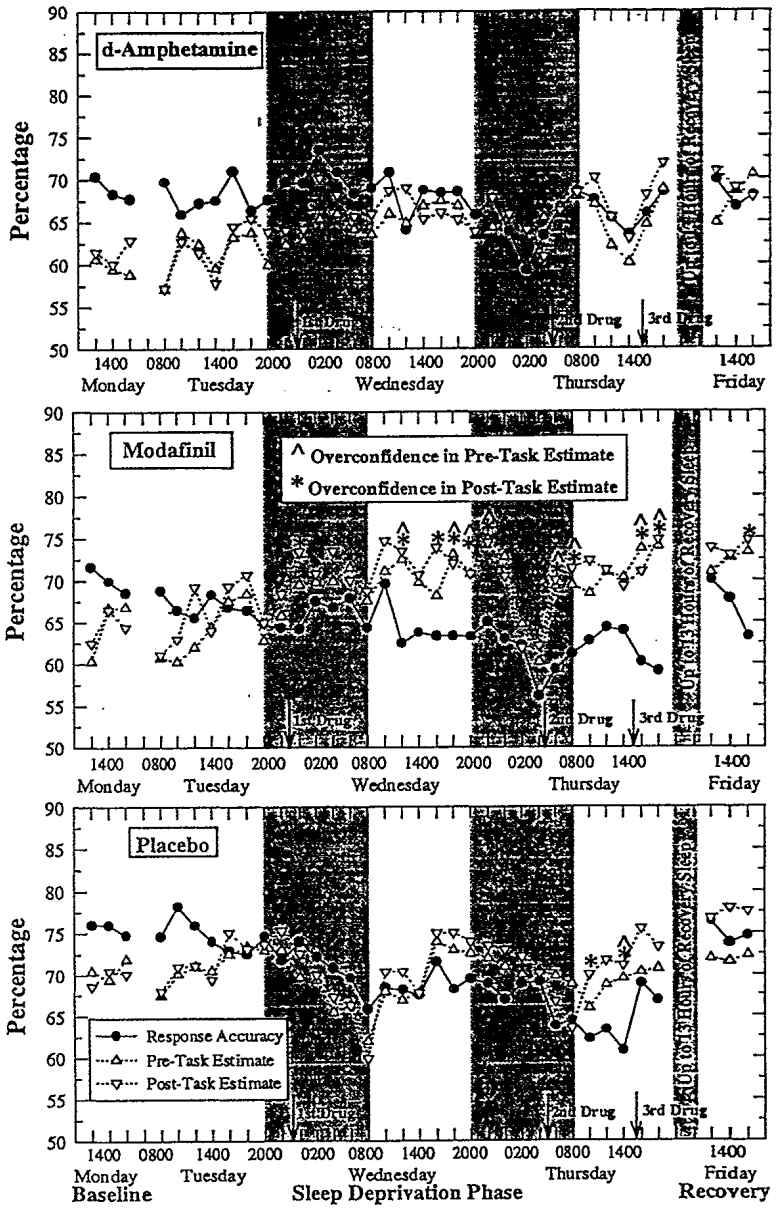

Figure 1. Percent correct (filled circles), pre-task estimates (up-triangles), and post-task estimates (down-triangles) as a function of experimental session for the three drug conditions in the perceptual comparison task. Evening periods are denoted by large shaded bars. Arrows indicate the times at which drugs were administered. Symbols indicate significant overconfidence in the estimate ($P<0.05$).

only to be disrupted again by the second administration. Taken together, these results provide clear evidence that modafinil (300 mg) has a disruptive effect on the ability to self-monitor cognitive performance in a visual judgment task.

Mental addition task

Judgment accuracy

Figure 2 provides a summary of performance in the mental addition task. In terms of cognitive task performance (filled circles), the first administration of modafinil and d-amphetamine once again prevented the first-night dip in performance, which is evident in the placebo condition. In addition, the second administrations were clearly recuperative, relative to the placebo condition who's performance declined (note that no sessions were scheduled following the third drug administration). Thus, as in the perceptual comparison task, modafinil and d-amphetamine display equivalent preventative and recuperative effects on cognitive task performance during SD.

A repeated measures mixed ANOVA was conducted on the (arcsine transformed) percentage correct measure with DRUG (3) as a between-subjects factor and ADMINISTRATION (2 and BEFORE vs. AFTER DRUG (2) as within-subject factor. The ANOVA confirmed an interaction between DRUG and BEFORE vs. AFTER DRUG ($F(2,36)=12.46$, $P<0.0001$

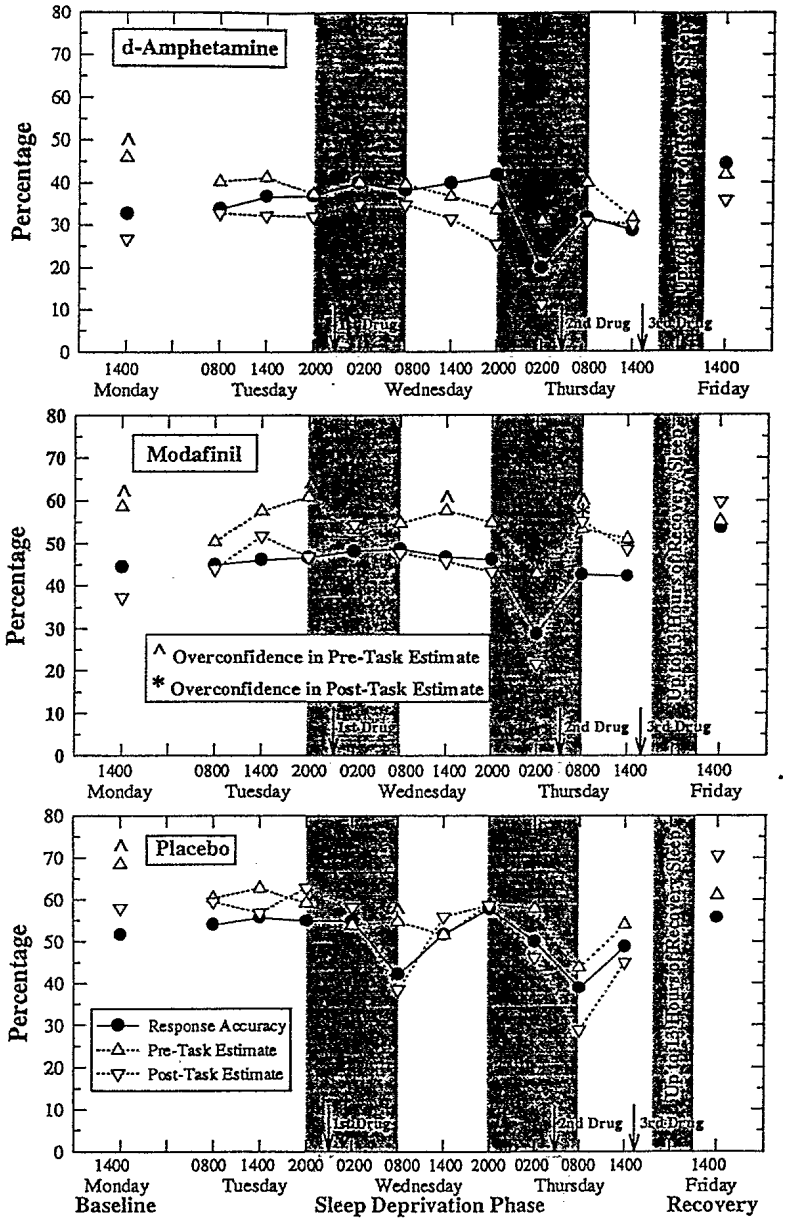

Figure 2. Percent correct (filled circles), pre-task estimates (up-triangles), and post-task estimates (down-triangles) as a function of experimental session for the three drug conditions in the addition task. Evening periods are denoted by large shaded bars. Arrows indicate the times at which drugs were administered. Symbols indicate significant overconfidence in the estimate ($P<0.05$).

which was qualified by a three-way interaction between DRUG, ADMINISTRATION, and BEFORE vs. AFTER DRUG ($F(2,36)=6.95$, $P<0.003$); as discussed above, performance in the modafinil and d-amphetamine conditions either improved or was maintained following drug administration whereas performance in the placebo condition declined.

Self-monitoring performance

In terms of self-monitoring task performance, note that all groups display a clear overconfidence in the pre-task estimate that precedes session 1 (i.e. before ever doing the task). After that, the d-amphetamine group once again displays good self-monitoring for the duration of the study. A very similar pattern is evident in the placebo condition, except for session 6 (08.00 hours Wednesday); the 'first-night' dip in performance was not anticipated (pre-task estimate) but was subsequently fully appreciated (i.e. the post-task estimate was accurate). In addition, subsequent circadian effects on performance in the placebo condition were fully anticipated and confirmed. In contrast, the modafinil condition once again shows evidence of overconfidence, particularly for the post-task estimates that immediately follow each drug administration: Following the first drug administration, performance remained constant but

the post-task estimate rose by over 6%; following the second drug administration, performance rose by 12% but the post-task estimate increased by over 34%.

The ANOVA reported above was employed using the difference between the actual and estimated percentage of correct responses as dependent measures. The only reliable effect involved the critical interaction between DRUG and BEFORE vs. AFTER DRUG, which was highly significant for deviations between response accuracy and the post-task estimates ($F(2,36)=5.74$, $P<0.007$). Once again, a planned comparison revealed that this effect was entirely as a result of the modafinil condition (post-task estimate: mean overconfidence = 12.58%, $P<0.05$). Hence, although the disruption to self-monitoring was significant only for the post-task estimates, the present data provide additional support for a modafinil-induced overconfidence effect. In addition, it is worth reiterating that no experimental sessions were scheduled for the addition task following the third drug administration where the modafinil induced overconfidence was most pronounced in the perceptual comparison task.

DISCUSSION

Extending the findings of Baranski *et al.* (1994), subjects in the placebo condition of the present study demonstrated that the ability to self-monitor cognitive performance remains intact and viable long after the effects of SD are evident in cognitive task performance. Thus, in the absence of explicit feedback from the environment, subjects apparently have access to fairly reliable 'internal-feedback' about their declining cognitive performance during SD*. Importantly, however, our studies to date have been based on paradigms which involve continuous work schedules (SUSOPS). Thus it is possible that participants can effectively self-monitor their performance only under conditions that demand continuous self-assessment. Accordingly, it is important to determine if effective self-monitoring generalizes to SD studies involving intermittent work periods and/or more variable assessment schedules.

The present findings, taken together with those reported by Pigeau *et al.* (1995b), suggest that modafinil and d-amphetamine work equally well in terms of their ability to ameliorate the effects of SD stress on cognitive performance. However, d-amphetamine did not disrupt the ability to self-monitor performance whereas modafinil induced overconfident assessments, particularly during the first few hours following drug administration. These latter results are surprising given that d-amphetamine has well-known euphoric properties, whereas modafinil yields no such effects. For example, Warot *et al.* (1993) compared the temporal subjective profile of modafinil (300 mg) with that of d-amphetamine (15 mg), caffeine (300 mg), and placebo. Their aim was to determine if modafinil possessed the euphoric properties of d-amphetamine, which may serve as a precursor to subsequent physiological addiction. Whereas d-amphetamine produced the anticipated profiles for euphoria and subjective well-being, the subjective profile of modafinil paralleled that of caffeine. Thus it is unlikely that the modafinil induced overconfidence in the present study was based on feelings of subjective euphoria or well-being. Evidently, a comprehensive theory of modafinil's mode of action is clearly needed and such a theory should provide an avenue for elucidating the basis for the present findings.

In conclusion, numerous studies have highlighted the potential utility of stimulating drugs in sustained operational settings (for a review see Babkoff and Krueger 1992). Indeed, there is no doubt that cognitive performance can be maintained at a higher level, and for a longer duration, with stimulating drugs than without. In addition, modafinil is an attractive alternative as it appears to ameliorate the effects of SD on cognitive performance (Lagarde and Batejat 1995; Pigeau *et al.* 1995b) without physiological side-effects or subsequent sleep disturbances (Buguet *et al.* 1995). However, as with any stimulant, modafinil induces subjective effects. When such effects are consistent with overt performance, then there is much to benefit in terms of increased performance and productivity. On the other hand, if subjective effects are not consistent with overt performance, then the potential for human error necessarily increases. Accordingly, we encourage a more comprehensive understanding of the relation between modafinil's subjective and performance enhancing effects before it is recommended as a safe and reliable fatigue countermeasure.

*Of course, as with subjective estimates of fatigue or sleepiness, individuals can always choose to disregard 'meta-cognitive' information. The critical point here is that we seem to be equipped with several lines of defense to SD stress (i.e. momentary subjective estimates of fatigue or sleepiness, attention to explicit feedback from the environment, and internal feedback about our own cognitive abilities). That we sometimes fail to heed these warning signs is an unfortunate reality (Coren 1996; Leger 1994).

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