# Does Modafinil Enhance Cognitive Performance in Young Volunteers Who Are Not Sleep-Deprived?

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**Abstract:** In a double-blind, parallel groups study, 60 healthy student volunteers (29 men and 31 women, aged 19–22 years) were randomly allocated to receive placebo, 100 or 200 mg modafinil. Two hours later, in the early evening, they completed an extensive cognitive battery. The 3 groups did not differ in self-ratings of sleepiness or tiredness before the testing session, and there were no treatment-associated changes in these or in mood ratings during the tests. Modafinil was without effect in several tests of reaction time and attention, but the 200-mg group was faster at simple color naming of dots and performed better than placebo in the Rapid Visual Information Processing test of sustained attention. Modafinil was without effect on spatial working memory, but the 100-mg group performed better in the backward part of the digit span test. Modafinil was without effect on verbal short-term memory (story recall), but 100 mg improved digit span forward, and both doses improved pattern recognition, although this was accompanied by a slowing of response latency in the 200-mg group. There were no significant effects of modafinil compared with placebo in tests of long-term memory, executive function, visuospatial and constructional ability, or category fluency. These results suggest that the benefits of modafinil are not clearly dose-related, and those from 100 mg are limited to the span of immediate verbal recall and short-term visual recognition memory, which is insufficient for it to be considered as a cognitive enhancer in non–sleep-deprived individuals.

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Modafinil 2-[(diphenylmethyl)sulfinyl]acetamide is a selective wakefulness-promoting drug, which is licensed in the United Kingdom for the treatment of excessive sleepiness associated with chronic pathological conditions, including narcolepsy, obstructive sleep apnea/hypopnea syndrome and moderate to severe chronic shift-work sleep disorder.

Although modafinil has been reported to have a low abuse potential,[1,2] it was recently used by a small number of US athletes. Another area that has received attention recently is modafinil's potential as a cognitive enhancer in healthy individuals. Hall[3] noted that in the United States, healthy adults were increasingly requesting prescriptions for modafinil, as they believed it to improve cognitive performance and allow them to ''sleep less, stay up longer, work harder, and play more.'' However, there has been very little research investigating the potential cognitive-enhancing properties of modafinil in healthy volunteers who are not sleep-deprived,[4–6] and initial findings have been equivocal. The different results of Turner et al[4] and Randall et al[5,6] may have stemmed from different test orders, different lengths of testing, and/or the specific tasks used. It is also possible that, compared with Turner et al who used 20 subjects per group, Randall et al[5,6] used too small a sample size in both their studies (n = 10 subjects per group; n = 15 subjects per group, respectively) to detect the rather small effects of modafinil.

Therefore, the aim of this study was to address these issues. We increased the length of cognitive testing from 1.25 to 2.25 hours and used a mixture of fixed and counterbalanced test order, manipulations that we hoped would reveal any influence of ''test fatigue'' on the effects of modafinil. We also included some of the tests that showed positive effects of modafinil in the Turner et al study [eg, Digit Span and Pattern Recognition Memory (PRM)] and increased the sample size to 60 (ie, 20 subjects per group, as used by Turner et al). Finally, we arranged the testing session in the early evening, as we hoped that testing at the end of a normal working day (in this case, after a day of lectures and practical and library work) would further increase the ''fatigue condition.'' This, in turn, could offer more scope for detecting the effects of modafinil on cognitive performance.

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## MATERIALS AND METHODS

### Subjects

Sixty healthy student volunteers (29 men and 31 women, aged 19–22 years) were recruited from King's College London, and King's College London Research Ethics Committee approved the study. All subjects gave written informed consent, and they were paid £10 for participating in the study. The screening procedure, including exclusion criteria, was identical to that described by Randall et al.[6]

### Drug

Preparation of capsules was identical to that described in our previous studies.[5,6] Cognitive testing was started 2 hours after ingestion of the drug to coincide with peak plasma concentration of modafinil after oral ingestion.[7]

### Subjective Ratings

Most of the subjective ratings used in this study are described in detail elsewhere.[5,6] In addition, before and immediately after cognitive testing (approximately 2.25 hours later), subjects completed the Stanford Sleepiness Scale[8] and 100-mm Visual Analogue Scales of sleepiness and tiredness.

### Cognitive Tests

The Trail-Making and Spatial Working Memory tests were always last in the battery. This was because of our interest in determining whether test fatigue might be responsible for obtaining positive effects with modafinil. Most of the tests used in this study, including those taken from the *Cambridge Neuropsychological Test Automated Battery* (Cambridge Cognition, Cambridge, UK), are described in detail by Randall et al[5,6] or Turner et al.[4] In addition, the present battery included several other attentional tasks of various degrees of difficulty (Symbol Copying,[9] Digit Symbol Substitution,[10] Digit Cancellation,[11] Paced Auditory Serial Addition Task,[12]).

### Statistical Analysis

The subjective ratings were analyzed by 2-way repeated-measures analysis of variance or multivariate analysis of variance, as appropriate, with the between-group factor being drug treatment and the repeated measure being time (before and after cognitive testing). The scores from the cognitive tests were analyzed with 1-way analysis of variance or the nonparametric Kruskal-Wallis and Mann-Whitney *U* tests, as appropriate. Measures analyzed with nonparametric tests are indicated in the tables and figure legends (superscript *K*; Kruskal-Wallis). Where effects reached significance, both F ratios and probability levels are presented. Where results did not reach significance, only the F ratios are given, and nonsignificance is indicated (NS). All data were

**TABLE 1.** Scores on Tests of Reaction Time, Attention (SC, Trail-Making Test A, DSS, DC, RVIP, and PASAT), and Memory (Digit Span, Spatial Working Memory, Logical Memory)

| | Placebo | 100 mg | 200 mg |
|---|---|---|---|
| RT | | | |
| Simple movement time (ms) | 372.7 ± 17.1 | 373.6 ± 20.0 | 346.4 ± 17.9 |
| Simple reaction time (ms)$^K$ | 347.6 ± 39.4 | 336.1 ± 13.4 | 309.6 ± 8.1 |
| 5-Choice movement time (ms) | 387.8 ± 13.3 | 359.3 ± 17.9 | 354.2 ± 13.9 |
| 5-Choice reaction time (ms) $^K$ | 319.2 ± 10.0 | 362.6 ± 27.6 | 326.7 ± 10.9 |
| SC | | | |
| No. correct | 157.2 ± 3.8 | 161.1 ± 5.1 | 152.5 ± 4.8 |
| Trail-making test A | | | |
| Time to complete (s) | 25.4 ± 2.4 | 21.3 ± 1.2 | 24.1 ± 1.4 |
| DSS | | | |
| No. correct | 71.4 ± 2.1 | 74.0 ± 2.8 | 69.0 ± 3.1 |
| DC | | | |
| No. correct | 59.7 ± 2.8 | 60.2 ± 2.4 | 60.4 ± 2.4 |
| No. misses | 23.3 ± 2.8 | 22.8 ± 2.4 | 22.6 ± 2.4 |
| RVIP | | | |
| B″$^K$ | 0.9 ± 0.01 | 0.95 ± 0.2 | 0.95 ± 0.01 |
| Total false alarms$^K$ | 1.6 ± 0.3 | 1.0 ± 0.02 | 1.1 ± 0.3 |
| Latency correct detections (ms)$^K$ | 452.0 ± 20.1 | 461.1 ± 23.0 | 410.4 ± 14.5 |
| PASAT | | | |
| Presentation speed (2.6 s) | 44.9 ± 3.0 | 49.2 ± 2.1 | 49.1 ± 1.8 |
| Presentation speed (1.9 s) | 38.2 ± 2.8 | 40.6 ± 2.1 | 42.6 ± 1.6 |
| Presentation speed (1.5 s) | 32.0 ± 2.4 | 32.7 ± 2.2 | 36.3 ± 1.6 |
| Presentation speed (1.2 s) | 28.0 ± 2.0 | 27.6 ± 2.5 | 29.4 ± 1.4 |
| Digit span | | | |
| Score (backward) | 8.2 ± 0.6 | 9.6 ± 0.5 | 8.5 ± 0.5 |
| SWM | | | |
| Total errors | 24.2 ± 4.3 | 27.0 ± 4.8 | 21.9 ± 4.9 |
| ''Within-search'' errors$^K$ | 1.6 ± 0.8 | 3.5 ± 1.3 | 2.8 ± 1.0 |
| ''Between-search'' errors | 23.0 ± 4.1 | 24.9 ± 4.6 | 20.5 ± 4.7 |
| Strategy | 30.8 ± 1.3 | 33.3 ± 1.3 | 31.5 ± 1.5 |
| Logical memory | | | |
| No. ''units'' recalled (immediate) | 14.6 ± 1.0 | 15.9 ± 1.0 | 16.0 ± 1.0 |
| No. ''units'' recalled (delayed) | 12.4 ± 1.2 | 14.2 ± 1.1 | 13.9 ± 1.1 |

Values shown are means ± SEM for each treatment group. RT indicates reaction time; SC, symbol copying; DSS, digit symbol substitution; DC, digit cancellation; PASAT, paced auditory serial addition task; SWM, spatial working memory.

**TABLE 2.** Scores on Tests of Executive Function (Trail-Making Test B, SOC, the Stroop Test, Letter Fluency, IDED), Constructional Ability (Clock Drawing), and Category Fluency

| | Placebo | 100 mg | 200 mg |
|---|---|---|---|
| Trail-making test B | | | |
| Time to complete (s) | 56.0 ± 3.7 | 47.4 ± 3.2 | 51.0 ± 3.1 |
| SOC | | | |
| Initial thinking time (ms) | | | |
| 2 Moves$^K$ | 1541.3 ± 334.5 | 1624.3 ± 200.3 | 1317.0 ± 139.4 |
| 3 Moves$^K$ | 4340.5 ± 750.8 | 4197.3 ± 756.4 | 3279.9 ± 404.2 |
| 4 Moves$^K$ | 7271.2 ± 1460.7 | 10735.3 ± 2588.4 | 9063.4 ± 1752.4 |
| 5 Moves$^K$ | 10130.1 ± 2832.7 | 10288.6 ± 1779.6 | 11865.6 ± 2639.8 |
| Subsequent thinking time (ms) | | | |
| 2 Moves$^K$ | 153.1 ± 51.4 | 182.1 ± 73.3 | 68.6 ± 40.4 |
| 3 Moves$^K$ | 369.3 ± 155.3 | 87.1 ± 31.9 | 168.7 ± 79.2 |
| 4 Moves | 693.8 ± 139.9 | 812.0 ± 103.9 | 773.0 ± 170.1 |
| 5 Moves$^K$ | 650.3 ± 168.8 | 714.2 ± 261.6 | 518.7 ± 113.8 |
| Problems solved in minimum moves | 8.8 ± 0.4 | 9.4 ± 0.5 | 8.9 ± 0.6 |
| Stroop | | | |
| Time to complete (s) | | | |
| Words | 13.8 ± 0.5 | 13.2 ± 0.5 | 13.0 ± 0.7 |
| Colors | 22.0 ± 0.9 | 19.8 ± 0.9 | 20.3 ± 1.0 |
| Total errors | | | |
| Dots$^K$ | 0.05 ± 0.05 | 0 | 0 |
| Words$^K$ | 0.1 ± 0.07 | 0.05 ± 0.05 | 0.05 ± 0.05 |
| Colors$^K$ | 0.4 ± 0.2 | 0.3 ± 0.2 | 0.4 ± 0.2 |
| Interference index (colors/dots) | 1.7 ± 0.07 | 1.7 ± 0.07 | 1.9 ± 0.1 |
| COWAT | | | |
| Total no. words (letter fluency) | 47.0 ± 2.7 | 46.4 ± 2.3 | 55.3 ± 3.0 |
| IDED | | | |
| Stages completed$^K$ | 9.0 ± 0.0 | 8.3± 0.5 | 9.0 ± 0.0 |
| Total errors$^K$ | 14.2 ± 1.4 | 14.6 ± 1.8 | 12.3 ± 1.1 |
| Total errors adjusted | 14.2 ± 1.4 | 29.8 ± 11.4 | 12.3 ± 1.1 |
| EDS errors$^K$ | 4.3 ± 0.7 | 4.9 ± 0.8 | 4.0 ± 0.9 |
| Pre-ED errors$^K$ | 7.1 ± 0.8 | 7.8 ± 1.6 | 6.5 ± 0.5 |
| Clock drawing | | | |
| Score$^K$ | 9.1 ± 0.2 | 8.9 ± 0.3 | 9.0 ± 0.3 |
| Time to complete (s) | 23.8 ± 2.0 | 24.3 ± 1.7 | 21.5 ± 1.8 |
| COWAT | | | |
| Total no. words (category fluency) | 23.5 ± 0.8 | 25.9 ± 1.2 | 25.1 ± 1.1 |

Values shown are means ± SEM for each treatment group. SOC indicates Stockings of Cambridge; COWAT, Controlled Oral Word Association Test; IDED, Intra/Extra Dimensional Set Shift; EDS, extra-dimensional shift; ED, extra-dimensional.

analyzed using Statistical Package for the Social Sciences (Chicago, Ill, USA) version 10.0 for Windows.

## RESULTS

### Group Characteristics

Before treatment administration (ie, at the screening stage), the 3 groups did not differ significantly in any of the following characteristics: age, verbal IQ, or habitual sleepiness, fatigue, depression, anxiety, alcohol, or caffeine consumption [in all cases, $F_{(2,56)} \leq 1.7$, NS], data not shown.

### Subjective Ratings

There were no significant drug effects on measures of current sleepiness or fatigue (ie, the Stanford Sleepiness Scale and Visual Analogue Scales of sleepiness and tiredness) or on ratings of mood and bodily symptoms [$F_{(2,56)} < 3.0$, multivariate analysis of variance $F_{(26,90)} < 1.0$,

multivariate analysis of variance $F_{(30,86)} \leq 0.5$, respectively, NS in all cases], data not shown.

## Cognitive Tests

There were no significant differences between the placebo and modafinil groups in the performance of most cognitive tests used [in all cases $F_{(2,56)} < 2.0$; $\chi_{(2)}^2 < 5.0$, NS], see Tables 1 and 2.

However, in the control condition of the Stroop test (ie, where subjects were simply required to name the colors of printed dots), modafinil significantly improved the time taken to complete the task [$F_{(2,56)} = 4.7$, $P < 0.05$]. Post hoc (Bonferroni) tests showed that this was because of subjects in the 200-mg group being significantly quicker than those in the placebo group ($P < 0.05$), see Figure 1A. Significant improvement with modafinil was also found in the Rapid Visual Information Processing (RVIP) test of sustained attention [$F_{(2,56)} = 4.3$, $P < 0.05$], and this was because of the 200-mg group showing significantly greater target sensitivity, as measured by $A'$ ($P < 0.05$) and missing significantly fewer targets ($P < 0.05$) than did the placebo group, see Figures 1B and C. There were no other significant differences between groups on this task [$\chi_{(2)}^2 < 5.0$, NS], see Table 1.

Furthermore, significant improvement with modafinil was observed in the Digit Span test, which measures the span of immediate verbal recall, both in the forward and backward [in all cases, $F_{(2,56)} = 4.7$, $P < 0.05$; $\chi_{(2)}^2 > 6.0$, $P < 0.05$] parts. The effects observed in the forward part

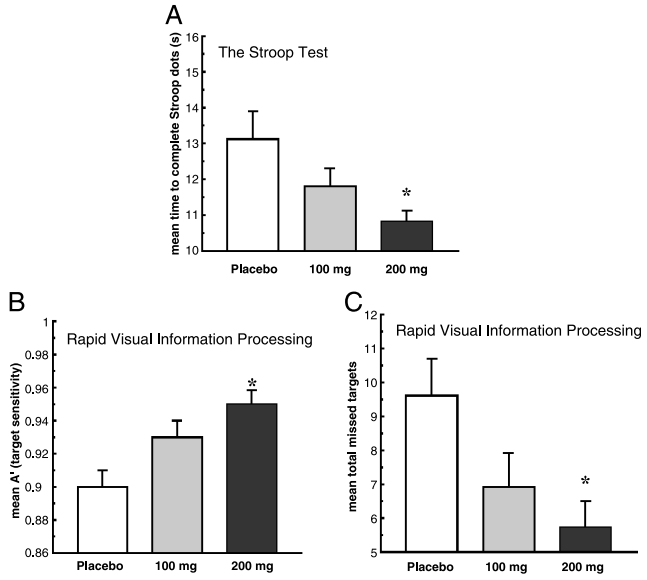


**FIGURE 1.** Mean (±SEM) time taken by each treatment group to complete the control condition of the Stroop test (A); mean (±SEM) $A'$ (target sensitivity) (B) and total missed targets (C) for each treatment group in the RVIP task. *$P < 0.05$ compared with placebo.

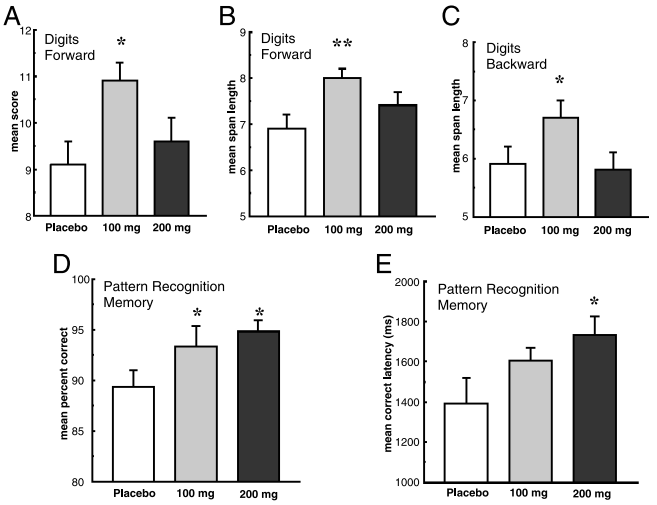


**FIGURE 2.** Mean (±SEM) score obtained by each treatment group in the forward part of the Digit Span test (A); mean (±SEM) span length for each treatment group in the forward$^K$ (B) and backward$^K$ (C) parts of the Digit Span test; mean (±SEM) percent correct$^K$ (D) and correct latency (E) for each treatment group in the PRM task. (A, D, E) *$P < 0.05$ compared with placebo; (C) *$P < 0.05$ compared with placebo and 200 mg; (B) **$P < 0.01$ compared with placebo.

were because of subjects in the 100-mg group obtaining a significantly better score ($P < 0.05$) and showing a longer span length ($U = 94.5$, $P < 0.01$) than did subjects in the placebo group, see Figures 2A and B. In the backward part, the effect was because of the 100-mg group showing a significantly longer span length than did both the placebo and 200-mg groups ($U = 119.5$ and $U = 121.5$, respectively, $P < 0.05$ in both cases), see Figure 2C. Lastly, significant improvement with modafinil was also evident in the PRM task [$\chi_{(2)}^2 = 7.3$, $P < 0.05$], which is a test of visual short-term recognition memory. This was because of both modafinil groups recognizing significantly more patterns than did the placebo group (100 mg, $U = 114.5$; 200 mg, $U = 104.5$, $P < 0.05$ in both cases), see Figure 2D. However, the improved accuracy was accompanied by a slowing of response latency in the 200-mg group compared with the placebo group ($P < 0.05$), see Figure 2E.

## DISCUSSION

The results of the present study, which had greater statistical power than our previous 2 studies, because of the considerably larger sample size, suggest that modafinil has some cognitive-enhancing properties, albeit limited, in young volunteers who are not sleep-deprived. Test order did not influence any of the effects obtained with modafinil, and we cannot attribute the improved performance with modafinil to test fatigue, because none of the tasks that showed positive effects were administered at the end of the long testing session.

Most importantly, in the present investigation, we replicated earlier findings of better performance in healthy individuals after modafinil in the simple control condition of the Stroop test, which measures general speed of response, and the Digit Span and PRM tests. Also important is the fact that we failed to replicate our earlier finding of impaired attentional set-shifting performance with 200 mg modafinil,[6] which suggests that this may have been a type 1 error (ie, a ''false positive'') in our previous study. The present results suggest that ''task specificity'' (ie, the specific tests used) plays a major role in obtaining positive effects with modafinil and could have been responsible for the different earlier results. Neither study by Randall et al[5,6] included Digit Span or PRM in the battery of cognitive tests. This indicates that, at least in healthy individuals who are not sleep-deprived, it is the specific tasks used that are the most important factor in detecting the effects of modafinil. Moreover, the specificity of positive effects in short-term memory tasks may be of theoretical interest and also prove relevant for clinical conditions that are characterized by memory problems.

It is also possible that ''day fatigue'' (ie, testing in the early evening, at the end of a normal working day) may have been responsible for the positive effects obtained in the color naming of dots from the Stroop task and in the Rapid Visual Information Processing test, as the young subjects on placebo in the present study were slower than the young volunteers on placebo in our first study[5] in the control condition of the Stroop test (mean 13.1 vs. 10.5 seconds) and also slower in the RVIP task (mean 452.0 vs. 393.7 milliseconds). However, it is interesting that subjective ratings of current sleepiness and tiredness remained relatively low in the present study (ie, all volunteers rated themselves as feeling fairly alert) before the start of cognitive testing, which indicates that the manipulation was only partially successful. Hence, we cannot rule out the possibility that, had our subjects been more sleepy or fatigued before testing began, we might have detected more positive effects of modafinil.

The benefits of modafinil in this study were not clearly dose-related. The effects obtained by Turner et al[4] were independent of drug dose, except for those observed in the Stop-Signal task, where there was a dose-related improvement in the stop-signal reaction time and reduction in the number of errors.

In summary, the present results suggest that modafinil enhances performance only in very specific, relatively simple tasks. These limited cognitive effects are insufficient for it to be considered as a cognitive enhancer in non–sleep-deprived, nonsleepy individuals, although its positive effects on some aspects of memory may prove of therapeutic benefit in some clinical conditions.

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