# Cognitive enhancing effects of modafinil in healthy volunteers

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ORIGINAL INVESTIGATION

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# Cognitive enhancing effects of modafinil in healthy volunteers

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**Abstract** *Rationale:* Modafinil, a novel wake-promoting agent, has been shown to have a similar clinical profile to that of conventional stimulants such as methylphenidate. We were therefore interested in assessing whether modafinil, with its unique pharmacological mode of action, might offer similar potential as a cognitive enhancer, without the side effects commonly experienced with amphetamine-like drugs. *Objectives:* The main aim of this study was to evaluate the cognitive enhancing potential of this novel agent using a comprehensive battery of neuropsychological tests. *Methods:* Sixty healthy young adult male volunteers received either a single oral dose of placebo, or 100 mg or 200 mg modafinil prior to performing a variety of tasks designed to test memory and attention. A randomised double-blind, between-subjects design was used. *Results:* Modafinil significantly enhanced performance on tests of digit span, visual pattern recognition memory, spatial planning and stop-signal reaction time. These performance improvements were complemented by a slowing in latency on three tests: delayed matching to sample, a decision-making task and the spatial planning task. Subjects reported feeling more alert, attentive and energetic on drug. The effects were not clearly dose dependent, except for those seen with the stop-signal paradigm. In contrast to previous findings with methylphenidate, there were no significant effects of drug on spatial memory span, spatial working memory, rapid visual information processing or attentional set-shifting. Additionally, no effects on paired associates learning were identified. *Conclusions:* These data indicate that modafinil selectively improves neuropsychological task performance. This improvement may be attributable to an enhanced ability to inhibit pre-potent responses. This effect appears to reduce impulsive responding, suggesting that modafinil may be of benefit in the treatment of attention deficit hyperactivity disorder.

**Keywords** Modafinil · Methylphenidate · Noradrenaline · Dopamine · Working memory · Attention

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## Introduction

The novel wake-promoting agent modafinil has been licensed in the UK since 1997 for the treatment of narcolepsy (Provigil 1997). It has largely superseded the use of conventional stimulants, such as methylphenidate, for the treatment of this disorder (Moldofsky et al. 2000). Traditional stimulants have been shown to be effective in maintaining and enhancing performance on tests of attention and working memory (Solanto 1998), although often with significant side effects and the risk of dependence (Kollins et al. 2001). In contrast, modafinil has been shown to be safe and effective in the management of narcolepsy, with significantly fewer side effects being observed in patients on modafinil relative to placebo (Billiard et al. 1994) and with little evidence of dependence (Jasinski 2000). Animal research suggests that, unlike amphetamine and methylphenidate, the psychomotor effects of modafinil are not mediated via a catecholamine mechanism (Ferraro et al. 1996), despite having a similar clinical profile to these drugs (Ferraro et al. 1997). Given the proven clinical efficacy of modafinil in ameliorating symptoms of narcolepsy and excessive daytime sleepiness (Broughton et al. 1997), the present study aims to evaluate the nootropic potential of this novel agent in healthy young volunteers.

The results of a recent study, comparing the relative efficacy of modafinil and dextroamphetamine in the treatment of adult attention deficit hyperactivity disorder (ADHD), revealed that modafinil significantly improves

scores on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV ADHD checklist (Taylor and Russo 2000), reinforcing its potential as a viable alternative to conventional treatments. Although only minimal cognitive testing was included in this study, trends towards improvement on modafinil were seen on tests of verbal fluency, task persistence and divided attention (Controlled Oral Word Association Test) suggesting this agent may be of psychotherapeutic value. Additionally, upon completion of the study, 52% of subjects elected to continue long-term treatment with modafinil (Taylor and Russo 2000). Similarly, a recent open-label pilot study in children with ADHD showed statistically significant improvements in clinical variables commonly used to index the severity of this disorder (Rugino and Copley 2001). This study demonstrated a very low incidence of side effects accompanied by a significant reduction in ADHD symptoms, particularly with regard to the hyperactive-impulsive features (Rugino and Copley 2001).

Despite indirect evidence that modafinil offers potential as a cognitive enhancer (Baranski and Pigeau 1997; Caldwell et al. 2000; Wesensten et al. 2002), there is a relative paucity of specific and sensitive empirical studies assessing the cognitive effects of modafinil in human subjects. A recent study using a highly demanding flight-simulator to explore the efficacy of modafinil in normal, sleep-deprived volunteers showed that a dose of 200 mg modafinil was effective at sustaining performance and alertness, despite the small sample size of this study ($n$=6) (Caldwell et al. 2000). In another sleep-deprivation study in healthy volunteers, 300 mg modafinil was shown to ameliorate the effects of sleep deprivation stress on cognitive performance on a perceptual judgement task and a complex mental addition task (Baranski and Pigeau 1997). Modafinil also improved performance on a four-choice serial reaction time task in humans for up to 6 h when administered after 47 h of sleep deprivation (Pigeau et al. 1995). Improvements in logical reasoning and digit-span performance were also reported. A recent study comparing the effects of modafinil and caffeine on measures of alertness and performance during 54.5 h sleep deprivation showed that objective cognitive performance improvements seen with 200 mg and 400 mg modafinil were comparable to those obtained with 600 mg caffeine (Wesensten et al. 2002). Although three doses of modafinil were used in this study (100 mg, 200 mg and 400 mg), no consistent, statistically significant differences between the doses were detected. Additionally, modafinil has been shown to be as effective as dextroamphetamine in ameliorating fatigue and declining mental performance in military personnel performing continuous cognitive work for 64 h, with far fewer physical side effects (Pigeau et al. 1995).

No study to date, however, has examined the effect of modafinil on a wide range of cognitive functions using a comprehensive and well-validated neuropsychological test battery. The recommended single daily dose range for narcolepsy is 100–400 mg modafinil (Provigil 1997). These doses of modafinil have comparable wake-promoting efficacy to 20–40 mg doses of methylphenidate (Jasinski 2000), which have been used previously in cognitive studies by this research group (Elliott et al. 1997; Mehta et al. 2000). The present study therefore aimed to examine the effect of two doses of modafinil (100 mg and 200 mg) on the cognitive performance of healthy volunteers. Subjects completed an extensive battery of neuropsychological tests designed to assess the effect of the drug on short-term memory capacity, visuospatial learning and memory, and attention. The tasks used were taken mostly from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Sahakian and Owen 1992), which has been validated by a number of studies in different patient groups (Elliott et al. 1995; Owen et al. 1997; Rahman et al. 1999) as well as demonstrating a high degree of sensitivity to changes in cognitive functioning resulting from neurochemical manipulations (Coull et al. 1995, 1996; Mehta et al. 1999, 2001). Additionally, previous work conducted in this laboratory has established the cognitive profile of methylphenidate with these tasks (Elliott et al. 1997; Mehta et al. 2000). Using the same tasks permits direct comparison of the neuropsychological effects of these two agents. This in turn may permit inferences to be drawn about the neurochemical action of modafinil and its potential in disorders such as ADHD.

## Materials and methods

### Subjects and procedures

Sixty healthy young male adult volunteers (see Table 1 for demographics) were recruited by advertisement in the local community. Exclusion criteria included any significant psychiatric history, visual or motor impairment or the concurrent use of any psychotropic medications or any medication contra-indicated with modafinil. In addition, subjects with a history of hypertension, cardiac disorders, epilepsy or drug or alcohol abuse were also excluded. All volunteers were advised not to consume alcohol or

**Table 1** Mean age, National Adult Reading Test (NART) and education level for each group. Values shown are the mean and standard errors of the mean for each group. Age is given in years, NART is the predicted verbal IQ score and education level in years in formal education

| | Placebo $n$=20 | Low dose $n$=20 | High dose $n$=20 | $F$ value | $P$ value |
|---|---|---|---|---|---|
| Age (years) | 25.30±5.09 | 24.35±3.28 | 25.10±4.61 | 0.260 | 0.772 |
| NART | 115.05±3.43 | 114.90±3.61 | 114.92±3.61 | 0.024 | 0.977 |
| Education (years) | 15.70±3.37 | 16.40±2.44 | 15.75±2.75 | 0.368 | 0.694 |

caffeine-containing drinks for 12 h before the study. The study was approved by the Cambridge Local Research and Ethics Committee and written informed consent was given by all subjects prior to testing.

A double-blind, between-subjects design was used, with participants randomised to receive either a single oral dose of a lactose placebo, 100 mg modafinil or 200 mg modafinil. Groups were well matched for age, NART verbal IQ (as indexed by the National Adult Reading Test, Nelson 1982) and education level (Table 1).

Peak plasma concentrations of modafinil have been obtained 2–3 h after oral administration with an elimination half-life of 10–12 h (Wong et al. 1998). Subjects were, therefore, tested 2 h post-drug administration, for approximately 2 h.

## Physiological measures

Blood pressure and pulse measurements were taken using a Criticare Systems Inc. Comfort Cuff (model 507NJ) at four time points: before drug administration, immediately prior to testing (2 h post-drug), 1 h into testing (3 h post-drug) and on completion of the study (4 h post-drug).

## Psychological measures

Subjects were tested using well-validated tests mainly from the CANTAB battery (http://www.camcog.com) (Sahakian and Owen 1992). The test battery also included novel variants of some of the original CANTAB tasks, to allow for greater sensitivity in younger high-functioning adults. All subjects received the same tests in the same order. All computerised tasks were run on an Advantech personal computer (Model PPC-120T-RT), and responses registered either via the touch-sensitive screen or a response key, depending on the task. The majority of the tasks have been described elsewhere and readers are directed to the cited references, which were selected for their detailed descriptions.

### *Visual analogue scales*

Subjects were asked to complete visual analogue scales (Bond and Lader 1974) before administration of the drug and at intervals during the testing session: immediately prior to testing, 1 h into testing and on completion of testing. At each time point subjects were asked to rate their feeling in terms of 16 dimensions. The measures used in this study were alert–drowsy, calm–excited, strong–feeble, muzzy–clear headed, well coordinated–clumsy, lethargic–energetic, contented–discontented, troubled–tranquil, mentally slow–quick witted, tense–relaxed, attentive–dreamy, incompetent–proficient, happy–sad, antagonistic–amicable, interested–bored and withdrawn–gregarious. The dimensions were presented as 100-mm lines, the two extremes of the emotion (e.g. ‘alert’ and ‘drowsy’) written at each end, and subjects marked where they felt they ranked on each line.

### *Digit span*

This task was taken from the Weschler Adult Intelligence Scale (Weschler 1981). Subjects were asked to repeat increasingly longer sequences of digits initially forwards and then backwards. Sequences started at two digits and went up to a maximum of nine. For each sequence length two different series of digits were presented, with a maximum of two points being awarded if both series were repeated correctly. Failure at the second attempt of any particular stage terminated the test. Scores for both the forwards and backwards tests were summed to yield an overall test score. Actual span, the highest number of digits correctly recalled, was also recorded.

### *Computerised tests taken from the CANTAB battery*

A brief description of the key measures for each of the CANTAB tasks is presented in Table 2. The computerised tests were preceded by a ‘sensorimotor’ task designed to familiarise the subjects with the touch-sensitive computer screen and the procedures. As this was a screening task the response measures are not reported here. Tests of visual memory administered were the pattern recognition memory (PRM) task, the paired associates learning (PAL) task and the delayed matching to sample (DMTS) task. Tasks taken from the CANTAB working memory and planning battery were the spatial working memory (SWM) task and the spatial span (SSP) task. To measure sustained attention the rapid visual information processing (RVIP) task was used. The test battery also included two novel variants of original CANTAB tasks to allow for greater sensitivity in younger subjects: a three-dimensional version of the attentional set-shifting task (IDED) and the ‘one-touch’ Tower of London spatial planning task (NTOL).

### *Decision making (gamble) task*

This task is described in detail elsewhere (Rahman et al. 2001). In brief, subjects were shown a display and told that the computer had hidden a yellow token randomly inside one of ten boxes at the top of the screen. The subject was trained to decide whether the computer had hidden the token in a red box or a blue box by touching either the response box marked ‘red’ or the one marked ‘blue’. They were then offered bets (in ascending and descending order – the order of presentation of which was randomised across groups) and instructed to try and increase their total points score by placing a bet on their choice being correct. Manipulation of the ratio of red and blue boxes from trial to trial made it possible to examine a subject’s decision-making behaviour over a variety of differentially weighted contingencies.

### *Stop-signal (stop) task*

This classic paradigm (Logan 1994), which measures pre-potent response inhibition, has previously been used to assess ADHD and the remedial effects of methylphenidate (Logan et al. 2000). Subjects were required to make a speeded response on ‘go’ trials (left response for left-pointing arrow, right response for right-pointing arrow), but to withhold their response on ‘stop’ trials (signalled by a 300-Hz tone). Stopping was made difficult by having a preponderance of ‘go’ trials (75%). The timing of the stop-signal was manipulated by means of a tracking algorithm (Osman et al. 1990) in such a way as to allow estimation of stop-signal reaction time (SSRT). Subjects performed five blocks of 64 trials each, and were given visual feedback after each block for their average correct ‘go’ reaction time and the number of discrimination errors made (incorrect response on ‘go’ trials). Subjects were not given feedback with regard to successful or failed inhibition, but were urged to do their best to stop, while continuing to respond as fast as possible on ‘go’ trials.

### *Statistical analysis*

To investigate the effect of experimental treatment on test performance, differences between group mean (or median) performance for single scores were analysed using a one-way analysis of variance (ANOVA; three levels) or the equivalent non-parametric Kruskal-Wallis ANOVA. To clarify the nature of any such differences, planned orthogonal contrasts comparing the effect of the two doses of drug, and the effect of placebo with the combined drug group, were performed where appropriate. In instances where several readings were taken for the same score, a repeated-measures ANOVA was used to test the effects of relevant independent within- and between-subjects variables.

Untransformed scores are displayed in tables and figures. However, in order to decrease skew and stabilise variances, data were transformed in preparation for parametric analysis. Logarith-

**Table 2** Summary of CANTAB tasks used

| Task | Description | Reference | Important measures |
|---|---|---|---|
| Visual memory battery | | | |
| PRM | A two-choice test of abstract visual pattern recognition memory | Mehta et al. 1999 | Percentage correct<br>Response latency (ms) |
| PAL | A test of the ability to form visuo-spatial associations, and the number of reminder presentations required to learn all the associations | Sahakian et al. 1988 | 1st trial memory score (sum of patterns correctly located on first presentation)<br>Total errors<br>Total trials |
| DMTS | A 4-choice test of simultaneous and delayed matching to sample of abstract patterns, which share colour or pattern with the distractors | Robbins et al. 1994 | Percentage correct<br>Latency (ms) |
| Working memory and planning | | | |
| SWM | A test of spatial working memory and strategy performance to find individually hidden 'blue tokens' without returning to a box where one has previously been found | Owen et al. 1990 | Strategy score<br>Total between errors (returning to a box where a token has been found)<br>Total within errors (returning to a box that has already been inspected) |
| SSP | A test of spatial memory span to recall the order in which a series of boxes were highlighted | Owen et al. 1990 | Span length<br>Total errors |
| NTOL | A spatial planning test, involving planning a sequence of moves to achieve a goal arrangement of coloured balls without moving the balls | Owen et al. 1995 | Mean attempts<br>Latency (ms) |
| Attentional battery | | | |
| RVIP | A test of sustained attention to detect infrequent 3-digit sequences from among serially presented digits | Park et al. 1994 | Mean latency (ms)<br>A' (measure of ability to detect sequences)<br>B'' (measure of the tendency to respond regardless of whether target is present) |
| IDED | Discrimination learning, testing the ability to selectively attend to and set-shift between shape, colour or number stimulus dimensions | Rogers et al. 1999 | Total errors<br>Total reversal errors<br>Total extra-dimensional shift (ED) errors |

mic transformations ($x=\log_{10}y$) were performed for latency and arcsine transformations $\left(x = 2\arcsin\sqrt{y}\right)$ for proportional data.

As the motivation for this study was to determine the overall cognitive profile of modafinil, our interest lies equally in ascertaining the lack of an effect on particular variables, as in identifying the presence of a significant group difference on other variables. The former conclusion of a 'lack of effect' is subject to type-II errors and the latter – the presence of an effect – to type-I errors (Howell 1997). Taking this into consideration, we have taken $P>0.1$ in reporting 'no effect' and $P<0.05$ in reporting 'an effect'.

## Results

### Physiological effects – blood pressure and pulse

Physiological readings were taken at four time points during the experiment. Groups were matched on all physiological measures at baseline. Repeated-measures ANOVA revealed a significant main effect of drug on systolic blood pressure. This effect was attributable to subjects in both the drug groups showing higher mean systolic blood pressure than those in the placebo group ($F_{2,57}=5.60$, $P=0.006$). Subjects receiving modafinil also showed a tendency towards increased systolic blood pressure over time. Repeated-measures ANOVA, however, showed that this effect failed to reach significance ($F_{6,171}=1.90$, $P=0.083$). There were no significant differences between the treatment groups or any drug × time interactions with regard to diastolic blood pressure or pulse ($P>0.1$).

**Table 3** Summary of test results. Values shown for each variable are the mean and standard errors of the mean for each group. The reported *P* values were derived from one-way or repeated-measures ANOVAs, as appropriate, performed for all three groups (unless the overall distribution of the score within the cohort differed from normality in which case the equivalent non-parametric Kruskal-Wallis procedure was applied (see table notes). For statistically significant effects of group, contrasts were performed to establish the exact nature of the differences. These results are reported in the 'contrasts' column where P v D is placebo versus the combined drug group ($F_{1,58}$, $\chi^2(2)$) and L v H is the low dose versus the high dose group ($F_{1,38}$, $\chi^2(2)$)

| | Means±SD | | | ANOVA *P* value | Contrasts | |
|---|---|---|---|---|---|---|
| | Placebo | Low dose | High dose | | P v D | L v H |
| Digit span | | | | | | |
| Forwards actual span[a] | 6.5±1.28 | 7.7±1.08 | 7.6±1.10 | 0.004 | * | ns |
| Backwards actual span[a] | 5.1±1.19 | 5.9±1.07 | 6.1±1.50 | 0.047 | * | ns |
| Forwards score[a] | 9.60±2.62 | 11.6±1.35 | 11.5±1.67 | 0.026 | ** | ns |
| Backwards score[a] | 8.65±2.41 | 10.7±1.87 | 9.9±2.34 | 0.046 | * | ns |
| PRM | | | | | | |
| Percentage correct | 91.7±10.64 | 98.1±2.86 | 96.7±3.96 | 0.010 | ** | ns |
| Response latency (ms) | 1926±618 | 1921±556 | 1781±391 | 0.623 | | |
| PAL | | | | | | |
| 1st trial memory score | 16.9±3.51 | 17.5±2.91 | 17.2±2.76 | 0.801 | | |
| Total errors[a] | 9.4±15.32 | 4.9±6.21 | 4.5±3.68 | 0.482 | | |
| Total trials[a] | 7.9±3.17 | 6.8±1.45 | 6.7±1.17 | 0.590 | | |
| DMTS | | | | | | |
| Percentage correct[a] | 90.3±13.24 | 93.7±5.91 | 95.3±5.34 | 0.549 | | |
| Latency (ms) | 3552±1443 | 4788±1651 | 4217±1185 | 0.031 | * | ns |
| SWM | | | | | | |
| Strategy score | 25.6±6.63 | 26.4±5.56 | 26.6±5.59 | 0.858 | | |
| Between errors[a] | 8.4±12.48 | 3.3±2.95 | 7.4±10.34 | 0.521 | | |
| Within errors[a] | 0.9±2.20 | 0.05±0.22 | 0.4±0.75 | 0.212 | | |
| SSP | | | | | | |
| Span length[a] | 7.7±1.30 | 7.7±1.35 | 7.2±1.14 | 0.239 | | |
| Total errors | 28.3±24.6 | 25.7±26.4 | 38.8±22.9 | 0.217 | | |
| NTOL | | | | | | |
| Mean attempts (all moves) | 7.7±1.79 | 6.61±0.50 | 6.55±0.40 | 0.002 | ** | ns |
| Latency (all moves) (ms) | 17931±6070 | 19954±8768 | 23808±8016 | 0.086 | | |
| RVIP | | | | | | |
| Mean latency (ms) | 425.6±43.0 | 421.8±69.8 | 429.9±67.4 | 0.915 | | |
| A' | 0.936±0.05 | 0.955±0.04 | 0.947±0.04 | 0.409 | | |
| B''[a] | 0.945±0.07 | 0.84±0.48 | 0.959±0.06 | 0.454 | | |
| IDED | | | | | | |
| Total errors | 18.3±9.29 | 16.7±7.67 | 18.0±11.02 | 0.847 | | |
| Total reversal errors[a] | 10.5±9.88 | 6.9±4.71 | 7.5±6.17 | 0.376 | | |
| Total EDS errors[a] | 5.4±3.95 | 7.2±7.15 | 6.2±6.12 | 0.853 | | |
| Gamble | | | | | | |
| Probability of choosing most likely outcome | 0.987±0.002 | 0.988±0.002 | 0.981±0.004 | 0.704 | | |
| % bet | 61.16±9.31 | 60.77±4.59 | 64.60±9.10 | 0.259 | | |
| Deliberation time (ms) | 1688±169 | 2203±808 | 1880±699 | 0.038 | * | ns |
| Stop | | | | | | |
| Go reaction time (ms) | 426.0±54.68 | 406.9±50.22 | 427.7±55.05 | 0.396 | | |
| Stop-signal reaction time (ms) | 161.0±32.73 | 154.6±32.67 | 125.1±26.53 | 0.001 | - | ** |
| Errors[a] | 4.5±4.88 | 2.9±1.84 | 1.6±1.67 | 0.027 | - | * |

[a] For these measures, the overall distribution of the score within the cohort differed from normality and, therefore, the equivalent non-parametric Kruskal-Wallis procedure was applied
* $P<0.05$
** $P\leq0.01$

## Psychological effects

As shown in Table 3, performance on several of the subtests of the CANTAB battery (namely the PAL, SWM, SSP, RVIP and IDED tests) did not differ between drug and placebo groups. By contrast, digit span, PRM, DMTS, NTOL, gamble and stop performance did differ significantly between groups. The nature of these statistically significant group differences is considered in detail below.

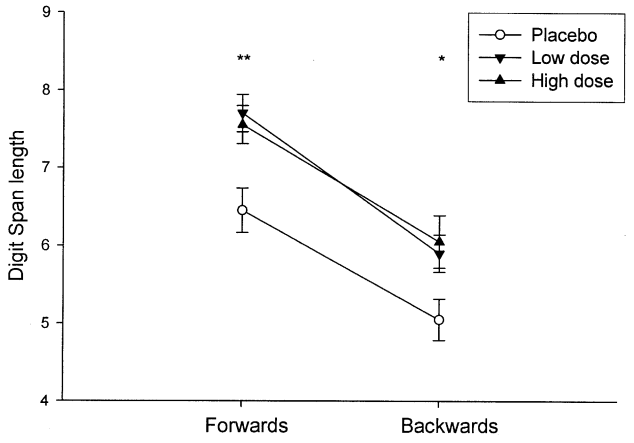


**Fig. 1** Digit span performance. The mean performance for each group, with standard error bars, for both the forwards and backwards conditions is shown. The graphs clearly illustrate the improvement seen in span length in the drug groups. *$P<0.05$, **$P\leq0.01$

*Visual analogue scales*

Over time, subjects in both drug groups reported feeling more alert ($F_{6,171}=3.90$, $P=0.001$) and attentive ($F_{6,171}=2.60$, $P=0.020$) than those subjects in the placebo group. Subjects on both doses of modafinil also reported feeling more energetic than the group on placebo [between subjects main effect of drug on lethargy ($F_{2,57}=3.25$, $P=0.046$]. There were no other significant effects of drug or drug × time interactions on any of the other self-reported measures ($P>0.05$).

*Digit span*

The figure illustrating digit span performance (Fig. 1) shows a clear pattern: the drug groups exhibited equivalently improved performance relative to placebo in both the forwards and backwards conditions of the test [main effect of group on both digit span and span score in both the forwards and backwards conditions ($\chi^2(2)\geq6.12$, $P<0.05$]. The two doses of modafinil did not differ in magnitude of effect on any digit span variable ($\chi^2\leq1.64$, $P>0.2$).

*PRM*

Subjects receiving modafinil made significantly fewer errors in pattern recognition than subjects in the placebo group ($F_{2,57}=5.02$, $P=0.010$). Again, no significant differences were detected between the two doses ($F_{1,38}=1.78$, $P=0.190$). Additionally, no significant differences in latency were identified between groups ($F_{2,57}=0.48$, $P=0.623$).

*DMTS*

Modafinil produced a significant increase in the time taken to select the correct response ($F_{2,57}=3.69$, $P=0.031$). This difference was found to be statistically significant for the simultaneous presentation, short 0-s and medium 4-s delays ($F_{2,57}\geq3.18$, $P<0.05$), but not the longest 12-s delay ($F_{2,57}=1.26$, $P=0.291$). No significant differences were found between the low- and high-dose drug groups at any latency ($F_{2,57}\leq2.78$, $P>0.1$). There were no statistically significant differences between the groups with regard to accuracy ($\chi^2(2)\leq0.82$, $P\geq0.22$), although it is possible that this was due to ceiling effects, with almost asymptotic performance in all groups.

*NTOL*

Subjects on drug required significantly fewer attempts to obtain a correct solution than those in the placebo group ($F_{2,57}=7.22$, $P=0.002$; Fig. 2a). This difference was most marked at the more difficult levels of the task (4- to 6-move problems). There was also a significant drug × move interaction ($F_{10,285}=3.52$, $P=0.003$) with respect to accuracy. Subjects in the drug groups also tended to take longer to make their first attempt relative to the placebo group (Fig. 2b; again particularly at the more difficult problems). This difference approached significance ($F_{2,57}=2.60$, $P=0.086$), with a significant drug × move interaction with respect to latency ($F_{10,285}=2.28$, $P=0.036$). There were no significant differences between the two drug doses either for latency or accuracy ($F_{1,39}<5.21$, $P>0.2$).

*Gamble*

In this decision-making task there was no effect of drug on either the probability of choosing the most likely outcome ($F_{2,54}=0.35$, $P=0.704$) or on the percentage bet placed on the decision ($F_{2,54}=1.39$, $P=0.259$). There was, however, a main effect of drug on deliberation time ($F_{2,54}=3.47$, $P=0.038$), with subjects on drug taking longer to make their decision as to the coloured box the token was hidden in. As expected, response time, choice of contingency and size of bet, all differed as a function of the ratio of red to blue boxes – there was a main effect of ratio on the deliberation time, the probability of choosing the most likely outcome and the percentage bet ($F_{3,57}>6.61$, $P<0.001$). With regard to the percentage bet, all groups selected significantly higher bets in the descend condition than the ascend condition ($F_{1,57}=50.60$, $P<0.001$), although there were no significant differences between groups for either condition. Thus, subjects receiving modafinil performed similarly to those in the placebo group, with a significant slowing in deliberation time.

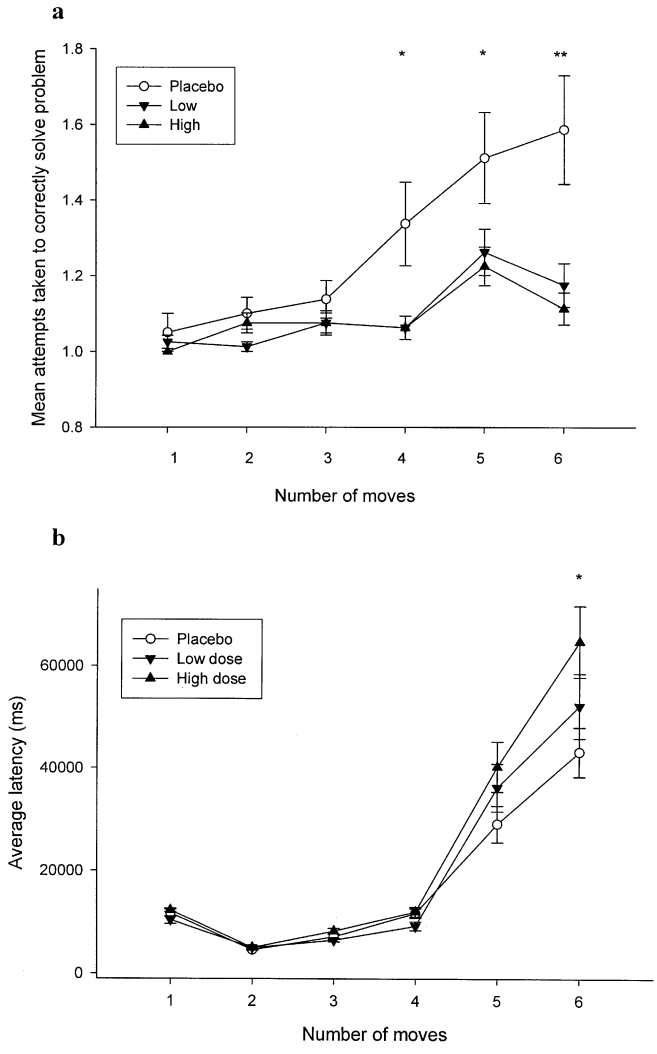


**Fig. 2a, b** 'One-touch' Tower of London spatial planning task (NTOL) mean attempts and response times. Subjects on drug required significantly fewer attempts ($P$=0.002) to achieve the correct answer than those on placebo, particularly at the harder moves (**a**). In addition, there was a significant drug × move interaction with respect to latency ($P$=0.036), with subjects on both doses of drug taking longer to select their answer (**b**), again, particularly at the harder moves. There were no significant differences between the two doses of modafinil. *$P$<0.05, **$P$≤0.01

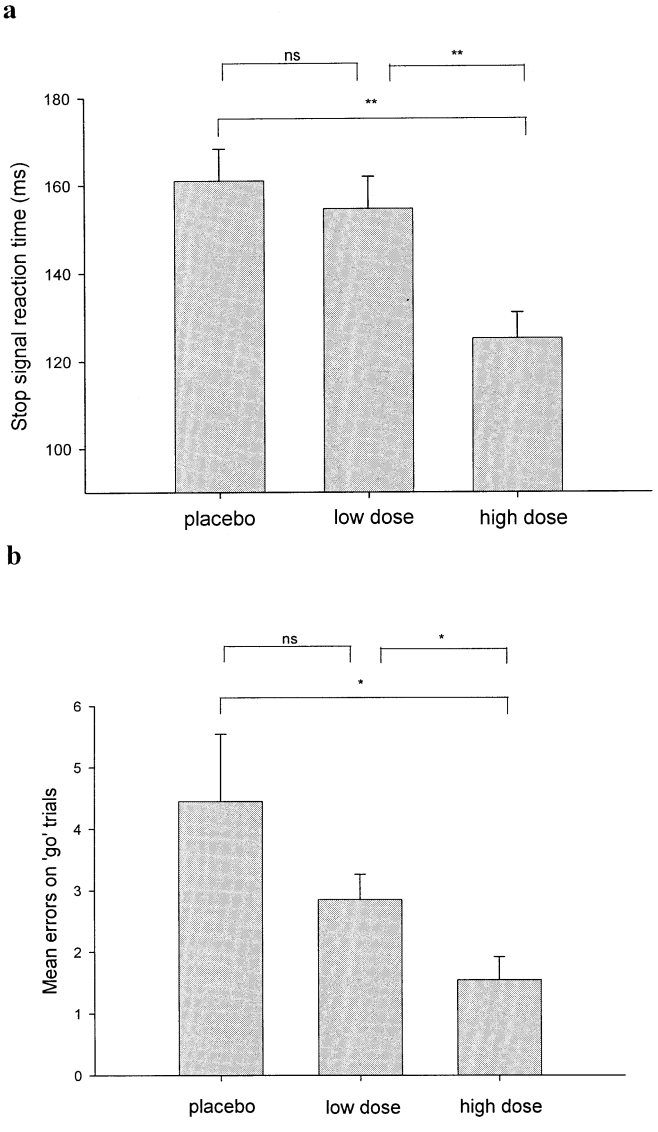


**Fig. 3a, b** Stop errors and stop-signal reaction time (SSRT). There was a highly significant decrease in the SSRT on drug (**a**), with subjects on drug also making significantly fewer errors on 'go' trials than those on placebo (**b**), particularly at the highest dose. *$P$<0.05, **$P$≤0.01

*Stop*

The shortest SSRT and, thus, the greatest capacity to inhibit responding was observed in the high dose group ($F_{2,57}$=7.75, $P$=0.001; Fig. 3a). Subjects receiving drug also performed more accurately, with significantly fewer discrimination errors being made on the 'go' trials ($\chi^2(2)$=7.22, $P$=0.027; Fig. 3b). Dose-dependent effects were identified on this task, with the high-dose group performing optimally [with the shortest SSRT ($F_{1,38}$=9.86, $P$=0.003) and least number of errors ($\chi^2(1)$=5.46, $P$=0.019)]. Importantly, mean speed of responding was the same regardless of group, with no group differences on the median 'go' reaction time being detected ($F_{2,57}$=0.94, $P$=0.396). Thus, the improved response inhibition on modafinil cannot be attributed to slower responding on the 'go' trials.

## Discussion

The results of this study demonstrate that modafinil is associated with a specific pattern of cognitive enhancement. Modafinil improved performance on tests of digit span, visual PRM, spatial planning (NTOL) and SSRT, accompanied by a slowing in latency on the DMTS, NTOL and gamble tasks. The effect on latency was not a simple psychomotor effect of drug. Standard reaction

time, as measured by the median 'go' reaction time on the stop-signal task, remained unaffected by modafinil. Subjects reported feeling significantly more alert, attentive and energetic on drug than placebo and showed increased systolic blood pressure, although there were no effects of drug on diastolic blood pressure or pulse.

The effects were independent of drug dose, except for those seen with the stop-signal paradigm, where there was a dose-related improvement in SSRT, accompanied by a similar dose-dependent reduction in the number of errors made on drug. Unlike methylphenidate (Elliott et al. 1997; Rogers et al. 1999), no significant effects of drug on SWM, SSP, sustained attention (RVIP) or set-shifting (IDED) were seen. There was also no effect of modafinil on the PAL task. Additionally, in contrast to methylphenidate (Elliott et al. 1997), no impairments were shown with modafinil using this battery of tests.

Modafinil appears to enhance adaptive response inhibition, an effect most clearly demonstrated with the stop-signal paradigm. Deficits in inhibitory and attentional mechanisms mediated by the frontal lobes have been implicated in the impulsive symptoms of ADHD (Solanto 1998). Consequently, the improvement in SSRT observed with subjects on modafinil is of particular interest, as it is well established that this measure is correlated with clinical measures of impulsivity in normal children and those children suffering from ADHD (Logan et al. 1997). Schachar and Logan (1990) found that hyperactive children were more impaired on stop-signal trials – they were slower to inhibit than normal controls and also less likely to inhibit altogether, despite normal detection of the stop signal. This effect of modafinil at improving stop task performance is similar to that found with methylphenidate (Tannock et al. 1989), and might account for the therapeutic efficacy (as indexed by clinical measures) of modafinil seen in ADHD (Taylor and Russo 2000; Rugino and Copley 2001).

Modafinil also appears to enhance performance accuracy, accompanied by a slowing of response latency relative to placebo. This is particularly evident in the NTOL task (Fig. 2) where subjects on drug took longer to select their responses but were significantly more accurate, particularly at the more difficult problems. Modafinil may therefore serve to improve accuracy by causing an increased tendency to evaluate a problem before initiating a response, in addition to its effects on motor impulsivity as seen with the stop-signal task. This evaluative effect accords with current theories of reflection, a conceptually different form of impulsivity, in which preparation is impaired due to a deficit in utilising all available information before making a decision (Evenden 1999). Theoretical models of prefrontal function also highlight the construct of cognitive impulsiveness as accounting for some of the behavioural impairments associated with prefrontal cortex dysfunction in neurosurgical and neuropsychiatric disorders (Rahman et al. 1999; Bechara et al. 2002).

This neuropsychological profile suggests that modafinil is functionally distinct from conventional psychostimulants, with a different profile of cognitive improvement. Methylphenidate enhances learning of the extra-dimensional shift relative to the intra-dimensional shift in the IDED task (Rogers et al. 1999), an effect that was not seen with modafinil. Elliott et al. (1997), in a cross-over design study, observed enhanced performance on the RVIP sustained-attention task in terms of the speeding of responses in normal, young, male volunteers after they had received 40 mg methylphenidate. Additionally, in contrast to modafinil, methylphenidate was found to improve SSP, SWM and NTOL performance (although it is noteworthy that these effects were all limited to the first test session when the tasks and testing situation were novel to the subjects). The improvement in NTOL appears similar to that seen with modafinil, although it would be interesting to examine whether this effect was similarly limited to a novel presentation of the task with modafinil.

We failed to find dose-dependent effects of 100 mg versus 200 mg modafinil on cognitive performance, with the exception of the effect seen in the stop-signal task. At present there are no studies investigating the cognitive effects of modafinil at doses below 100 mg, where dose dependency may be apparent in healthy volunteers (Wesensten et al. 2002). It remains quite plausible, however, that in individuals with impaired cognitive function, such as ADHD, there is a greater capacity for dose-dependent effects at the standard treatment doses.

Despite numerous preclinical studies, a well-defined biochemical action for modafinil has not yet been identified (Rush et al. 2002). The most striking difference between modafinil and conventional stimulants (Solanto 1998) is that modafinil appears to produce arousal through a mechanism that does not involve dopaminergic activity (Lin et al. 1992, 1996; Ferraro et al. 1997; Taylor and Russo 2000; although cf. Wisor et al. 2001). Modafinil, unlike amphetamine, does not appear to stimulate the release of dopamine from preloaded synaptosomes (Simon et al. 1994), has no anxiogenic effects (Simon et al. 1994) and does not induce stereotypy in rats (Duteil et al. 1990). Additionally, doses of up to 600 mg modafinil revealed practically no psychoactive effects in cocaine addicts (Rush et al. 2002).

Modafinil also does not bind to adrenergic receptors or to the uptake site for noradrenaline (Mignot et al. 1994) or alter the firing of noradrenergic neurones in vivo (Akaoka et al. 1991). Nevertheless, while modafinil is neither a direct nor indirect adrenergic agonist, its mechanism of wake-promotion in vivo appears to require an intact alpha-1 adrenergic system (Lin et al. 1992). One mechanism for linking all these findings is that a catecholaminergic 'tone', particularly in the cortical noradrenergic neurones, must exist for modafinil to exert its 5-HT mediated inhibition of $\gamma$-aminobutyric acid (GABA) release in the cerebral cortex (Tanganelli et al. 1994, 1995). That is, modafinil, by acting on the noradrenergic system, indirectly activates inhibitory 5-HT neuronal systems leading to a reduction in cortical GABA outflow. These results suggest that possibly the arousal effect of

modafinil does not depend on the availability of endogenous catecholamines but results rather from an indirect enhancement of alpha-1 and beta-receptor activity, in which the adrenergic system may play a 'permissive' role in the actions of modafinil. In humans modafinil has been shown to increase heart rate and blood pressure in a recent experiment in cocaine addicts (Rush et al. 2002). This supports our physiological data, in which an increase in systolic blood pressure was found, and complements a possible indirect involvement of the noradrenergic system. Nevertheless, while these cardiovascular effects of modafinil are statistically significant, it has been previously indicated that these effects are not clinically significant (Rush et al. 2002) and that modafinil continues to be regarded as a very well tolerated drug.

Therefore, in conclusion, the results of this investigation suggest that modafinil offers significant potential as a cognitive enhancer, particularly with respect to its effects on planning, accuracy and inhibition. These results also indicate that modafinil may be of value as an alternative therapy for ADHD due to its cognitive enhancing abilities in addition to facilitating the inhibition of pre-potent responses.

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