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The cognitive-enhancing properties of modafinil are limited in non-sleep-deprived middle-aged volunteers

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Abstract

Modafinil is a selective wakefulness-promoting agent that has been shown to enhance cognitive performance under conditions of sleep deprivation but which has equivocal effects in normal young volunteers. In a double-blind parallel group design study, 45 non-sleep-deprived middle-aged volunteers (20 men and 25 women, aged 50–67 years) were randomly allocated to receive two capsules containing placebo, 100 or 200 mg modafinil, and 3 h later they completed 100 mm visual analogue scales of mood and bodily symptoms, before and after an extensive battery of cognitive tests [pen and paper and the Cambridge Neuropsychological Test Automated Battery (CANTAB)]. There were no significant treatment-associated changes in ratings of mood or bodily symptoms and no significant effects on most of the cognitive tests used in this study. The group treated with modafinil (200 mg) was significantly faster in a simple colour naming of dots and also significantly better in a test of constructional ability (Clock Drawing Test) compared with the placebo group. However, subjects in the 200-mg group also made significantly more total errors in the Intra/Extradimensional Set Shift (ID/ED) task than both the other groups. Thus, this study found limited evidence of cognitive-enhancing properties of modafinil in healthy middle-aged volunteers.
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Keywords: Cognition; Fatigue; Sleepiness; Wakefulness; Modafinil

1. Introduction

Modafinil 2-[(diphenylmethyl)sulfinyl]acetamide is a wakefulness-promoting agent, which is licensed in the UK for excessive daytime sleepiness in narcolepsy and obstructive sleep apnoea hypopnoea syndrome. In addition, modafinil reduces sleepiness and/or fatigue in Parkinson's disease (Nieves and Lang, 2002), multiple sclerosis (Rammohan et al., 2002; Zifko et al., 2002), depression (Menza et al., 2000) and myotonic dystrophy (MacDonald et al., 2002) and also produces clinical benefits in attention deficit hyperactivity disorder (Taylor and Russo, 2000; Rugino and Copley, 2001). Peak plasma levels are reached 2–4 h after oral dosing and the half-life ranges from 10 to 15 h (Moachon et al., 1996). The most common side effect of modafinil is headache, but it does not appear to have the cardiovascular side effects or addictive properties observed with central nervous system stimulants (Guilleminault and Pelayo, 2000).

In addition to its clinical indications, modafinil is effective in maintaining cognitive performance and subjective ratings of mood ('vigour,' 'fatigue' and 'sleepiness') at or near baseline levels in conditions involving sleep deprivation (Bensimon et al., 1991; Pigeau et al., 1995; Lagarde and Batejat, 1995; Stivalet et al., 1998; Caldwell et al., 2000; Wesensten et al., 2002), but findings relating to its potential as a cognition enhancer in young individuals who are not sleep-deprived have been equivocal. A recent study of the effects of modafinil (100 and 200 mg) in healthy young male volunteers found improved performance in 4 out of 11 cognitive tests, specifically Digit Span, Stop-Signal Reaction Time, Pattern Recognition Memory and the New Tower of London Test (Turner et al., 2003). Randall et al. (2003), on the other hand, failed to find any evidence of enhanced cognitive performance with the same doses of modafinil in their young healthy volunteers. The study of Turner et al. (2003) used a longer testing session (2 h vs. 1 1/4 h) and a fixed test order (as opposed to a counterbalanced order across subjects). This is likely to have

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resulted in fatigue by the end of the session, and indeed 2 out of 4 tests showing positive effects (i.e., Digit Span and Stop-Signal Reaction Time) were administered last (personal communication). Thus, it still remains a possibility that modafinil's effects are mainly seen when performance is degraded by fatigue or sleepiness.

Indeed, previous studies that found beneficial effects of modafinil in healthy volunteers had all included sleep deprivation as an experimental condition. It is possible that the effects of this drug are most evident when the performance of subjects is compromised by sleepiness or fatigue. No ratings of sleepiness or fatigue were taken in the study of Turner et al. (2003), and therefore (unfortunately) we are unable to determine whether their subjects differed from ours in these respects. Alternatively, it could be that modafinil can act as a cognitive enhancer to improve performance that is in general suboptimal or impaired in any way. This would lead to a rather nonspecific pattern of effects.

Moreover, equivocal findings are not restricted to human studies but have also been reported in three animal behavioural studies of modafinil, all of which tested modafinil during the light phase of the light–dark cycle. Beracochea et al. (2001, 2002) found that in mice, the drug enhanced working memory, as assessed by the spontaneous alternation task in a delay-dependent manner, and improved learning in a serial spatial discrimination reversal task, respectively. In contrast, Burnham et al. (2003) reported that modafinil was unable to enhance performance in the five-choice serial reaction time test in rats.

The purpose of the present study was to examine the effects of modafinil in a group of subjects whose performance was poorer, not because of fatigue or sleepiness, but because of age. Several studies report age-related cognitive impairments in healthy individuals (Huppert and Kopelman, 1989; Salthouse, 1996; Daum et al., 1996; Le Moal et al., 1997; File et al., 1999; Small et al., 1999; Fluck et al., 2001, MacPherson et al., 2002). If modafinil works as a cognitive enhancer to improve degraded performance, then positive effects may be detected in this group, which could be of great clinical benefit. However, if in healthy volunteers modafinil can only improve performance that is temporarily degraded by fatigue or sleepiness, then no benefits would be expected.

Therefore, in the present study, we examined the effects of a single dose of modafinil on mood and cognitive performance in healthy middle-aged volunteers using exactly the same study design as in our previous study of young volunteers. The battery of cognitive tests was selected to assess memory, attention, mental flexibility, planning, verbal fluency (letter and category) and constructional ability. The pen and paper tests have been widely used (Spreen and Strauss, 1998) and proved sensitive to the cognitive-enhancing effects of many drugs, including dexamfetamine and guanfacine (Taylor and Russo, 2001), citicoline (Spiers et al., 1996) and tibolone (Fluck et al., 2002). They have also proved sensitive to improvements resulting from 10 weeks of a high-soya diet (File et al., 2001). The Cambridge Neuropsychological Test Automated Battery (CANTAB) has been extensively validated (Sahakian et al., 1990; Owen et al., 1992; Robbins et al., 1994; Owen et al., 1995; Beats et al., 1996) and proved sensitive to the cognitive-enhancing effects of methylphenidate (Elliott et al., 1997).

2. Materials and methods

2.1. Subjects

Forty-five healthy volunteers (20 men and 25 women), aged 50–67 years, were recruited via circular e-mail at King's College London and newspaper advertisement in the Cambridge area. All subjects gave written informed consent. The study was approved by Guy's and Papworth Hospitals Research Ethics Committees. Exclusion criteria were any history of psychiatric, neurological or cardiovascular illness, use of psychoactive medication, colour blindness (as assessed by the Ishihara cards; Ishihara, 1989), any major sight, hearing or movement problems, a marked foreign accent, an Epworth Sleepiness Scale (ESS) (Johns, 1991) score greater than 10, a Hospital Depression and Anxiety Scale (HADS) (Zigmond and Snaith, 1983) score ≥ 11, a Restless Legs Syndrome Rating Scale (RLSRS) (Walters et al., 2001) score greater than 10, more than two positive replies on the CAGE alcoholism questionnaire (Ewing, 1984), consumption of more than eight cups of coffee (or ≥ 900 mg caffeine) per day, regular recreational drug use or familiarity with tests from the CANTAB battery relevant to this study. All women were required to be postmenopausal (defined as cessation of periods for 12 months or longer), and hence pregnancy testing was not carried out. In total, five volunteers were excluded: one had a history of arrhythmia, one had hypertension at screening (sitting systolic blood pressure ≥ 160 mm Hg), one was taking antidepressant medication and two had previously completed the Intra/Extradimensional Set Shift (ID/ED) and Delayed Matching to Sample (DMTS) tests from the CANTAB battery. Six subjects (three in the 100-mg modafinil group and three in the placebo group) smoked and they were not asked to abstain before testing because nicotine abstinence impairs cognitive performance in smokers (Hasenfratz and Battig, 1993; Snyder and Henningfield, 1989). An estimate of premorbid verbal IQ was obtained by use of the National Adult Reading Test-II (NART-II) (Nelson and Willison, 1991). Subjects were asked to abstain from alcohol and caffeine intake for 12 and 3 h, respectively, before the test session.

2.2. Drug

On the day of the cognitive testing, subjects received modafinil (100 or 200 mg) (Cephalon West Chester, PA, USA) or placebo in two unmarked capsules, each of which contained lactose or 100 mg modafinil (formulated by St

Thomas' Hospital Pharmacy). Because peak plasma concentration of modafinil is reached 2–4 h after ingestion (Moachon et al., 1996), cognitive testing was started 3 h after ingestion of the drug. The drug was administered in the morning so that the volunteers remained on Guy's campus or Papworth Hospital premises between the time of administration and time of testing.

2.3. Sleepiness and fatigue rating scales

As part of the screening procedure, which took place prior to administering the capsules, subjects completed the ESS (Johns, 1991), a self-administered questionnaire that measures sleep propensity or the probability of falling asleep under certain circumstances. The subjects were asked to rate on a scale of 0–3 how likely they were to doze off or fall asleep in each of eight different daily situations. All subjects also completed the 11-Item Fatigue Questionnaire developed by Chalder et al. (1993), which is a self-rating scale used to measure the severity of fatigue. It consists of 11 items and the subjects were asked to rate how they had felt over the last month and compare themselves to how they had felt before this time period. This was then scored according to whether there had been an increase or decrease in symptoms.

2.4. Rating scales for bodily symptoms, aggressive mood, alertness, well-being and anxiety

Prior to cognitive testing, subjects completed 100-mm analogue rating scales for bodily symptoms (Tyrer, 1976), aggressive mood (Bond and Lader, 1986), alertness, well-being and anxiety (Bond and Lader, 1974). Subjects were instructed to mark with a vertical line the point on each individual scale that corresponded best with how they were feeling at that time. Administration of all rating scales was repeated at the end of the test session, approximately 1 1/4 h later.

2.5. Cognitive tests

All testing was carried out in the afternoon. A number of different tests were used in this study, with some being administered on a touch-sensitive portable computer screen and others by hand, using predesigned test sheets. To ensure minimisation of order effects, such as practice and fatigue, tasks were administered in a counterbalanced order across subjects, except for Motor Screening (MOT), which was always first in the battery of cognitive tests, and Rapid Visual Information Processing (RVIP), which was always last.

2.6. Computerised tests

These were taken from the CANTAB (Cambridge Cognition, Cambridge, UK).

2.6.1. Motor Screening

This initial test was used to relax the subjects and to practice them in the use of the touch-sensitive screen. The scores on this test were not analysed.

2.6.2. Delayed Matching to Sample

DMTS is a test of visual episodic memory based on the DMTS paradigm used extensively in primate research (Sahakian and Owen, 1992). The subjects were required to identify the pattern that they had seen previously from four patterns presented on the computer screen. The patterns were presented at delays of 0, 4 and 12 s (a total of 30 trials). A simultaneous condition was also included (10 trials). Percent correct and latency to correct responses (in milliseconds) were measured.

2.6.3. Intra/Extradimensional Set Shift

ID/ED is best known in the form of the Wisconsin Card-Sorting Test (Grant and Berg, 1984) and measures mental flexibility by the ability to reverse rules and learn new rules. This task is described in detail elsewhere (Owen et al., 1991). Initially, subjects were required to learn simple discrimination (i.e., which of two shapes was correct), then simple reversal (i.e., the previously incorrect shape became correct), then attend to new exemplars within the same dimension, the shape (the intradimensional shift, which is Stage 6 of the test) and lastly switch attention to the previously irrelevant dimension, the line (the extradimensional shift, which is Stage 8 of the test). Stages completed and number of errors (i.e., total number of errors, total number of errors adjusted for the number of stages successfully completed, number of errors made at the extradimensional shift stage and number of errors made prior to the EDS stage) were measured.

2.6.4. Stockings of Cambridge

SOC is a spatial planning task based on the 'Tower of London' Test (Shallice, 1982) and is described in detail by Owen et al. (1990). Subjects had to move coloured balls on the bottom half of the computer screen to match an arrangement displayed on the top half of the screen. Initial and subsequent thinking time (in milliseconds) as well as number of problems solved in minimum moves (out of 12 possible 'perfect solutions') were scored.

2.6.5. Rapid Visual Information Processing

RVIP is a test of vigilance (sustained attention) with a small working memory component. The test was adapted by Sahakian et al. (1989) from that of Wesnes and Warburton (1984). Subjects had to detect consecutive sequences of digits that appeared on the computer screen and register responses by pressing a pad when the last digit of a target sequence was displayed. The primary outcome measures were as follows: target sensitivity (A'), response bias (B''), total false alarms, total misses and latency to correct detections (in milliseconds).

Table 1
General characteristics of the three treatment groups. Values shown are means ± S.E.M.

	Placebo	100 mg	200 mg
Age (years)	55.7 ± 1.2	58.8 ± 1.4	58.2 ± 1.1
NART verbal IQ	117.3 ± 1.7	116.3 ± 2.1	119.5 ± 1.4
Daily caffeine (cups)	4.1 ± 0.7	3.2 ± 0.6	4.3 ± 0.7
Weekly alcohol (units)	7.1 ± 1.7	8.6 ± 2.1	10.4 ± 2.7
Epworth sleepiness	4.1 ± 0.7	4.5 ± 0.9	4.9 ± 0.9
11-item fatigue	11.7 ± 0.8	12.2 ± 0.6	12.0 ± 0.5
HAD_A (anxiety)	5.3 ± 0.7	3.8 ± 0.5	4.1 ± 0.7
HAD_D (depression)	1.7 ± 0.2	2.7 ± 0.4	1.9 ± 0.5

2.7. Pen and paper tests

Logical Memory (subtest of the Wechsler Memory Scale-Revised; Wechsler, 1987) is a widely used test of verbal memory. Subjects were asked to recall a short story immediately after they had heard it and approximately 20 min later. The total number of 'units' recalled at immediate and then again at delayed recall was recorded.

The Stroop Test (Stroop, 1935) measures the ability to shift perceptual set "to conform to changing demands and suppress a habitual response in favour of an unusual one" (Spreen and Strauss, 1998). For the 'dots' part, the subjects had to name as quickly as possible the colour of 24 dots printed in blue, green, red or yellow. The 'words' part was similar to the 'dots' part, except that the dots were replaced by common words ('when,' 'hard' and 'over'). In the 'colours' or incongruent part, subjects were required to name the colour that a word was printed in rather than reading the colour word itself. Primary outcome measures were time to complete (in seconds) and total errors for each part and Stroop interference index (calculated as ratio index of the amount of time required for the 'colours' part vs. the 'dots' part).

Trail-Making Test (A and B) (Reitan and Wolfson, 1985)—these are tests of speed of attention, sequencing, mental flexibility and of visual search and motor function (Spreen and Strauss, 1998). The subjects had to connect, by making pencil lines, 25 encircled numbers randomly arranged on a page in proper order (Part A) and 25 encircled numbers and letters in alternating order (Part B). The times to complete Parts A and B were recorded (in seconds).

Controlled Oral Word Association Test (COWAT) evaluates the spontaneous production of words within a limited period of time (Spreen and Strauss, 1998). For 'letter fluency,' the letters used were 'F,' 'A' and 'S' and the time allowed for each letter was 60 s. For 'category fluency,' the categories were 'house animals,' 'jungle animals' and 'farm animals' and subjects had a total of 60 s to generate as many words as possible. The sums of all admissible words for the three letters and the three animal categories were recorded.

Clock Drawing is a test of visuospatial and constructional ability (Spreen and Strauss, 1998). The subjects were asked to draw the face of a clock with all the numbers on it and after this were instructed to draw the hands pointing at 20 to 4. Primary outcome measures were drawing score (1–10) and time taken to complete the task (in seconds).

2.8. Statistical analysis

The factors of 'alertness,' 'well-being' and 'anxiety' extracted from the Bond and Lader (1974) Mood Scale and the individual ratings of bodily symptoms and 'aggressive mood' were analysed by two-way repeated measures analyses of variance (ANOVA), 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 analysed with one-way ANOVA, except for Stroop total errors ('dots' and 'colours'), Clock Drawing score and time to complete, DMTS percent correct simultaneous, ID/ED stages completed and all error scores, RVIP B″ and total false alarms and SOC subsequent thinking time for two and three moves and number of problems solved in minimum moves, which were not normally distributed, as indicated by the Kolmogorov–Smirnov test. These data were therefore analysed by the nonparametric Kruskal–Wallis or

Table 2
Scores on individual ratings of bodily symptoms ('muscular tension,' 'anxiety'), aggressive mood ('resentful,' 'furious,' 'quarrelsome,' 'aggressive') and on the three factors extracted from the Bond and Lader Mood Rating Scale, before and after cognitive testing

	Placebo		100 mg		200 mg	
	Before	After	Before	After	Before	After
Muscular tension	11.6 ± 2.8	13.5 ± 3.6	11.6 ± 3.5	19.4 ± 5.0	8.9 ± 1.4	16.4 ± 3.6
Anxiety	11.9 ± 3.2	17.5 ± 6.4	14.5 ± 4.1	23.3 ± 7.2	11.1 ± 2.3	17.7 ± 5.5
Resentful	12.1 ± 1.6	16.3 ± 3.1	13.6 ± 3.3	17.5 ± 4.6	9.5 ± 1.9	17.4 ± 4.6
Furious	12.0 ± 1.9	15.0 ± 3.4	15.4 ± 3.4	19.5 ± 4.2	10.2 ± 2.4	16.6 ± 3.9
Quarrelsome	8.6 ± 1.4	13.1 ± 4.0	10.4 ± 2.5	16.8 ± 4.4	12.2 ± 3.9	16.6 ± 4.9
Aggressive	11.9 ± 2.1	17.6 ± 4.1	15.8 ± 4.2	19.1 ± 3.6	14.3 ± 3.9	18.6 ± 4.0
Factor 1 (Alertness)	52.8 ± 3.3	51.5 ± 3.9	54.0 ± 2.6	50.4 ± 3.2	55.1 ± 2.0	51.9 ± 3.4
Factor 2 (Well-being)	60.6 ± 2.0	57.5 ± 3.3	58.5 ± 2.1	55.2 ± 2.6	60.7 ± 1.4	57.7 ± 2.5
Factor 3 (Anxiety)	37.8 ± 2.2	46.5 ± 4.3	44.2 ± 4.4	52.6 ± 5.2	44.7 ± 4.8	45.8 ± 4.0

Values shown are means ± S.E.M. for each treatment group.

Table 3
Scores on tests of executive function (SOC, ID/ED, Trail-Making Test B, the Stroop Test and letter fluency) for each treatment group

	Placebo	100 mg	200 mg
SOC			
Initial thinking time (ms)			
2 moves	3104.4 ± 325.3	2481.8 ± 368.9	2463.3 ± 271.4
3 moves	6972.4 ± 1006.1	7767.0 ± 1423.6	5905.5 ± 786.7
4 moves	8602.9 ± 986.3	9814.6 ± 1035.2	9382.7 ± 1510.6
5 moves	13969.9 ± 2137.3	12698.8 ± 2882.3	12584.3 ± 1819.4
Subsequent thinking time (ms)			
2 moves	269.8 ± 92.6	752.3 ± 377.7	336.3 ± 214.8
3 moves	453.7 ± 196.8	849.8 ± 335.1	176.1 ± 82.8
4 moves	2374.3 ± 465.5	2097.5 ± 350.1	2238.9 ± 592.0
5 moves	1823.3 ± 408.4	1291.5 ± 220.6	1276.5 ± 232.6
Problems solved in minimum moves	7.9 ± 0.3	7.6 ± 0.5	7.9 ± 0.6
ID/ED			
Stages completed	8.7 ± 0.2	8.9 ± 0.1	8.7 ± 0.2
Total errors—adjusted	20.1 ± 4.6	16.0 ± 3.4	31.6 ± 5.0
EDS errors	7.7 ± 2.5	5.2 ± 1.6	13.3 ± 2.8
Pre-ED errors	8.0 ± 1.6	7.8 ± 1.2	11.1 ± 2.2
Trail-Making Test			
Time to complete part B (s)	71.7 ± 7.0	67.8 ± 5.1	68.9 ± 4.9
Stroop			
Time to complete (s)			
Words	17.7 ± 1.2	15.7 ± 0.8	16.0 ± 0.9
Colours	27.0 ± 1.9	25.8 ± 2.0	24.3 ± 1.1
Total errors			
Dots	0.1 ± 0.1	0	0
Words	0	0	0
Colours	1.0 ± 0.4	0.2 ± 0.1	0.9 ± 0.4
Interference index (colours/dots)	1.9 ± 0.1	1.8 ± 0.1	2.2 ± 0.1
COWAT			
Total number of words—letter fluency	46.3 ± 3.1	51.9 ± 3.2	52.4 ± 2.4

Values shown are means ± S.E.M.

Mann–Whitney tests. Due to technical problems, there were missing data on DMTS for one subject and on SOC for another subject. Where effects reached significance, both F ratios and probability levels are given. Where results did not reach significance, only the F ratios are presented and nonsignificance is indicated (NS). All data were analysed using Statistical Package for the Social Sciences (SPSS Chicago, IL, USA) version 10.0 for Windows.

3. Results

3.1. Group characteristics

The three groups did not differ significantly in IQ, caffeine or alcohol intake, fatigue, sleepiness, anxiety or depression [for all these measures, $F(2,42) \leq 2.0$, NS], see Table 1. The placebo group was slightly younger, but the group differences in age did not reach significance [$F(2,42) = 1.8$, NS].

3.2. Rating scales for bodily symptoms, aggressive mood, alertness, well-being and anxiety

There were no significant drug effects on ratings of bodily symptoms [in all cases, $F(2,42) < 2.5$, NS], see Table

Table 4
Scores on tests of episodic memory (DMTS, Logical Memory), attention (RVIP, Trail-Making Test A), constructional ability (Clock Drawing) and category fluency for each treatment group

	Placebo	100 mg	200 mg
DMTS			
% Correct—all delays	83.6 ± 2.6	82.3 ± 1.8	86.2 ± 1.8
% Correct simultaneous	95.3 ± 1.3	97.3 ± 1.5	97.1 ± 1.3
Mean correct latency—all (ms)	3327.8 ± 235.1	3876.9 ± 337.1	3861.1 ± 204.5
Mean correct latency—simultaneous (ms)	2886.3 ± 169.9	2875.0 ± 179.3	2909.3 ± 128.5
Logical Memory			
Total number of 'units'—immediate recall	13.3 ± 1.0	13.7 ± 1.0	14.5 ± 1.0
Total number of 'units'—delayed recall	12.3 ± 1.2	12.1 ± 0.9	13.7 ± 0.9
RVIP			
A′	0.9 ± 0.0	0.9 ± 0.0	0.9 ± 0.0
B″	1.0 ± 0.0	1.0 ± 0.0	0.8 ± 0.1
Total false alarms	1.1 ± 0.4	0.8 ± 0.2	1.1 ± 0.2
Total misses	8.2 ± 1.2	7.8 ± 1.5	8.1 ± 1.4
Latency correct detections (ms)	479.9 ± 27.3	470.0 ± 25.4	483.9 ± 14.1
Trail-Making Test			
Time to complete part A (s)	32.2 ± 2.2	28.7 ± 2.0	30.6 ± 2.4
Clock Drawing			
Time to complete (s)	22.5 ± 1.4	27.4 ± 4.7	25.4 ± 3.5
COWAT			
Total number of words—category fluency	23.5 ± 1.0	25.1 ± 1.0	24.3 ± 1.1

Values shown are means ± S.E.M.

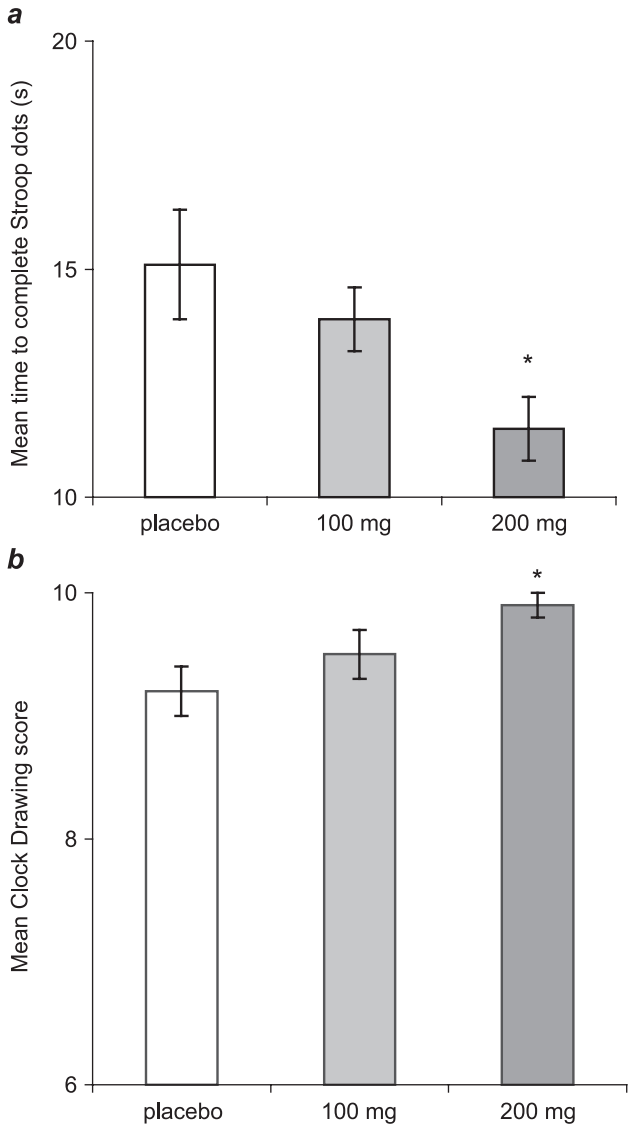

Fig. 1. (a) Mean (± S.E.M.) time taken by each treatment group to complete the colour naming part of the Stroop Test. * $P<.05$ compared with placebo. (b) Mean (± S.E.M.) score obtained on the Clock Drawing task by each treatment group. * $P<.05$ compared with placebo.

2, but all three groups scored significantly higher on two items after cognitive testing. These were 'muscular tension' [$F(1,42)=9.7$, $P<.005$] and 'anxiety' [$F(1,42)=4.0$, $P=.05$], see Table 2.

There were no significant drug effects on ratings of 'aggressive mood' [in all cases, $F(2,42)<3.0$, NS], see Table 2, but four items showed a significant effect of time. Thus, all three groups rated themselves as feeling more 'resentful' [$F(1,42)=9.4$, $P<.005$], 'furious' [$F(1,42)=7.7$, $P<.01$], 'quarrelsome' [$F(1,42)=7.3$, $P=.01$] and 'aggressive' [$F(1,42)=4.5$, $P<.05$] after completing the battery of cognitive tests, see Table 2.

Following factor analysis, Bond and Lader (1974) isolated three independent factors from their mood rating scale. There were no significant drug effects on the factors of 'alertness,' 'well-being' or 'anxiety' [in all cases, $F(2,42)<1.0$, NS], see Table 2. On the 'anxiety' factor, there was a significant effect of time [$F(1,42)=8.0$, $P<.01$], with volunteers rating themselves as more anxious after cognitive testing than at the start of the testing session. There was no effect of time in the factors measuring 'alertness' [$F(1,42)=2.4$, NS] and the decrease with time in ratings reflecting 'well-being' just missed significance [$F(1,42)=3.3$, $P=.08$].

3.3. Cognitive tests

There were no significant differences between the placebo and modafinil groups in the performance of three tests of executive function [SOC, Trail-Making Test B, letter fluency; in all cases $F(2,42)<1.5$, NS], see Table 3. Similarly, there were no significant differences between the placebo and modafinil groups in the performance of two tests of episodic memory (DMTS, Logical Memory), attention (RVIP, Trail-Making Test A) or category fluency; in all cases $F(2,42)<1.5$, NS, see Table 4.

Modafinil significantly improved the time taken to complete the colour naming part of the Stroop Test [i.e., where subjects were simply required to name the colours of printed dots; $F(2,42)=4.0$, $P<.05$], and post hoc tests (Bonferroni) showed that this was due to subjects in the 200-mg group being significantly quicker than those on placebo ($P<.02$), see Fig. 1a. In the incongruent part of the Stroop Test (i.e., where subjects were required to name the colour that a word was printed in rather than reading the colour word itself), there was no significant difference between treatment groups [$F(2,42)=0.6$, NS], see Table 3.

Modafinil also significantly improved constructional ability [$\chi_{(2)}^2=9.4$, $P<.01$] and the Mann–Whitney test showed that this was due to subjects in the 200-mg group obtaining a

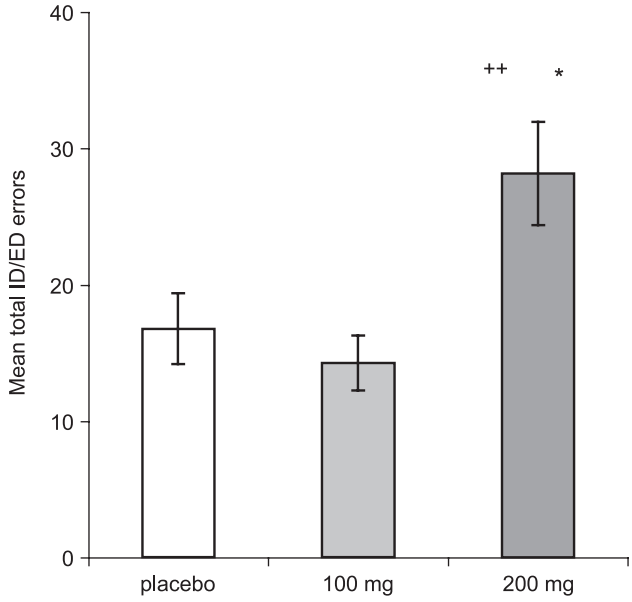

Fig. 2. Mean (± S.E.M.) total errors made by each treatment group in the ID/ED test. ++ $P<.005$ compared with 100 mg. * $P<.05$ compared with placebo.

better score in the Clock Drawing task compared with those in the placebo group ($U=51.5$, $P<.05$), see Fig. 1b.

In the attentional set-shifting task (ID/ED), there was evidence that modafinil produced a decrement in performance, as reflected in an increased number of errors [total number of errors $\chi_{(2)}^2=8.9$, $P<.05$; total number of errors adjusted for the number of stages successfully completed $\chi_{(2)}^2=7.4$, $P<.05$; and number of errors made at the extradimensional shift stage $\chi_{(2)}^2=5.8$, $P=.05$]. Mann–Whitney tests revealed that subjects in the 200-mg group made significantly more total errors on this task than did subjects in the 100-mg and placebo groups ($U=44$, $P<.005$; $U=59$, $P<.05$, respectively), see Fig. 2. The same group also made more total errors adjusted for the number of stages successfully completed ($U=48$, $P<.05$) and more errors at the EDS stage ($U=60$, $P<.05$) than did subjects the 100-mg group, see Table 3.

4. Discussion

This study found limited evidence of cognition-enhancing properties of modafinil in middle-aged volunteers who were not sleep-deprived. Nonetheless, several subjects in the high dose did report feeling unusually alert during the evening following cognitive testing, although at the time of testing no differences was reported. The experimenter, who was involved with testing the subjects, also correctly guessed all three treatments. Subjects treated with the 200-mg dose showed better performance in the simple, colour naming part of the Stroop Test and in a task of constructional and visuospatial ability (Clock Drawing test) compared with subjects treated with placebo. However, the higher dose of modafinil may be associated with greater carelessness, as evidenced by increased total errors in the attentional set-shifting task. We thus found improvements in 2 and impairment in 1 out of 9 tests with this age group, as opposed to no cognitive effects in the younger group in our previous study. It is therefore possible that modafinil has greater benefits when there is some degree of impaired performance. However, it is also possible that the improvements have occurred by chance.

Considering the three studies of modafinil that did not involve sleep deprivation (Turner et al., 2003; Randall et al., 2003; present study), there was better performance after modafinil in 6 out of a total of 29 cognitive tests used. These were Digit Span, Pattern Recognition Memory, New Tower of London, Stop-Signal Reaction Time (study of Turner et al., 2003), the simple colour naming of dots from the Stroop Test and Clock Drawing (present study). If we look at the individual test outcome measures, only 10% of the measures (10 out of 106 outcome measures) showed significant improvement with modafinil, and thus this may have occurred by chance. No meaningful pattern of improvement is apparent after modafinil. Positive effects were found in tasks that assess a wide range of cognitive abilities (e.g., speed of response, constructional ability, working memory, spatial planning) and are of various degrees of difficulty (e.g., easy in the case of naming of coloured dots in the Stroop Test and hard in the case of the New Tower of London test, especially at four, five and six moves). The lack of a meaningful pattern of positive effects also applies to the sleep deprivation studies of modafinil, which reported benefits in tasks that had been degraded by sleep deprivation. These tests also cover a variety of cognitive abilities and include the Critical Flicker Fusion test and a paired word associate task (Bensimon et al., 1991), a visual search test (Stivalet et al., 1998), the Psychomotor Vigilance Task as well as 4- and 10-choice reaction time tests (Wesensten et al., 2002), mathematical and spatial processing, grammatical reasoning, memory search and tracking tests (Lagarde and Batejat, 1995) and even helicopter-simulated flights (Caldwell et al., 2000).

Another possibility for our finding only minimal positive effects is that we used too small a sample size to detect the rather small effects of modafinil. We used 15 subjects per treatment group, as opposed to 20 subjects per group in the study of Turner et al. (2003). Furthermore, the positive effects in the study of Turner et al. (2003) were only demonstrated by combining both doses into one drug group, thereby further increasing the sample size. If large group sizes are needed to demonstrate positive effects of modafinil, this may mean that it is of limited individual benefit to subjects who are not sleep-deprived. It may be that some individuals would show greater benefit from modafinil, but this cannot be seen in a parallel group design, as used both by ourselves and Turner et al. (2003). We chose a parallel group design because of the marked practice effects seen with some of these cognitive tests (Hartley et al., 2003). Wesensten et al. (2002) also used a parallel group design, with 10 subjects per treatment group in their sleep deprivation study, which compared modafinil (100, 200 and 400 mg) with placebo and 600 mg caffeine, and found that modafinil maintained performance at or near predeprivation levels compared with placebo. It is therefore unlikely that the study design and/or small sample size are solely responsible for our results.

Considering all the results published so far, it would still seem that cognitive benefits from modafinil are most likely to be seen when performance is degraded by sleepiness or fatigue. Some researchers have also suggested that traditional psychostimulants, such as amfetamines and caffeine, also have few beneficial effects on cognitive performance in the absence of fatigue or sleep deprivation (Spiegel, 1978; Dews, 1984). The results of our present study would not indicate major benefits in a nonsleepy middle-aged group. It is possible that in subgroups, for example, a postmenopausal group suffering from poor sleep, modafinil may have greater benefits. It is also possible that greater benefits would be detected in

volunteers tested at the end of a normal working day, with a longer battery of tests than the one used in the present study.

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