HUMAN PSYCHOPHARMACOLOGY
Hum Psychopharmacol Clin Exp 2003; **18**: 163–173.
Published online 11 December 2002 in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/hup.456

Modafinil affects mood, but not cognitive function, in healthy young volunteers

Delia C. Randall[1,2]*, John M. Shneerson[2], Komal K. Plaha[1] and Sandra E. File[1]

[1]*Psychopharmacology Research Unit, Centre for Neuroscience Research, King's College London, London, UK*
[2]*Respiratory Support and Sleep Centre, Papworth Hospital, Cambridge, UK*

Modafinil is a selective wakefulness-promoting agent with beneficial effects in narcolepsy and conditions of sleep deprivation. In a double-blind study we examined its effects in 30 healthy, non sleep-deprived students (19 men and 11 women, aged 19–23 years), who were randomly allocated to placebo, 100 or 200 mg modafinil and 3 h later completed 100 mm visual analogue scales relating to mood and bodily symptoms, before and after an extensive battery of cognitive tests (pen and paper and CANTAB). There were no significant differences between the three treatment groups on any of the cognitive tests used in this study. There was a significant post-treatment change in the factor measuring 'somatic anxiety' and in individual ratings of 'shaking', 'palpitations', 'dizziness', 'restlessness', 'muscular tension', 'physical tiredness' and 'irritability', which was mainly due to significantly higher ratings of somatic anxiety in the 100 mg group compared with the other two groups. Further changes in mood were revealed after the stress of cognitive testing, with the 100 mg group showing greater increases in the 'psychological anxiety' and the 'aggressive mood' factors (as measured from the Bond and Lader scales). Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS — anxiety; aggression; sleepiness; wakefulness; modafinil; cognition

INTRODUCTION

Modafinil (diphenylmethyl-sulfinyl-2 acetamide) is a relatively new wake promoting agent, which is licensed in the UK for the treatment of narcolepsy. Other clinical conditions in which modafinil has been shown to have beneficial effects include obstructive sleep apnoea (Pack *et al.*, 2001), attention deficit hyperactivity disorder (Taylor and Russo, 2000; Rugino and Copley, 2001), multiple sclerosis (Rammohan *et al.*, 2002) and Parkinson's disease (Happe *et al.*, 2001; Nieves and Lang, 2002). Peak plasma levels are reached 2–4 h after dosing and the half-life ranges from 10 to 15 h (Moachon *et al.*, 1996). Modafinil does not appear to have the cardiovascular side effects observed with central nervous system stimulants or addictive properties (Guilleminault and Pelayo, 2000). The most common side effect is headache.

In addition to its clinical indications, modafinil appears to have beneficial effects on cognitive performance and mood in conditions involving sleep deprivation (SD), with Pigeau *et al.* (1995) reporting modafinil to be as effective as amphetamine in maintaining these during the first night without sleep. An early study in healthy volunteers who underwent two 36 h SD periods reported clear antagonism by a single dose of modafinil (200 mg) of the impairments displayed in critical flicker fusion (CFF) frequency, choice reaction time and short-term memory tasks (Bensimon *et al.*, 1991). Subsequently, Lagarde and Batejat (1995) found that a repeated dose of modafinil (200 mg taken three times a day) during a longer period of SD (60 h) maintained performance on a battery of neuropsychological tests at a level similar to that observed during control trials without SD. Stivalet *et al.* (1998) also found that modafinil prevented a

* Correspondence to: Dr D. C. Randall, Respiratory Support and Sleep Centre, Papworth Hospital, Papworth Everard, Cambridge CB3 8RE, UK. Tel: +44 1480 364167. Fax: +44 1480 830620.
E-mail: Delia.Randall@papworth.nhs.uk

Received 1 July 2002
Accepted 28 October 2002

decrease in performance on tests of attention whilst Caldwell *et al*. (2000) reported that modafinil maintained simulated flight performance and self-reported vigour at or near baseline levels. Modafinil also attenuated subjective fatigue (Caldwell *et al.*, 2000). Lastly, modafinil 200 and 400 mg was shown to be comparable to 600 mg caffeine in maintaining performance and alertness in healthy young adults following sleep loss (Wesensten *et al.*, 2002).

Although modafinil is effective in controlling excessive daytime sleepiness (EDS), promoting alertness and maintaining cognitive performance in a range of disorders and in sleep-deprived volunteers, there has been minimal research on its effects in individuals who are not sleep-deprived. In addition, despite mood being an important aspect of evaluating the addictive properties of psychoactive drugs, formal assessment of the effects of modafinil on mood has so far been relatively ignored. This may have been due to over-attention to the effects of the drug on EDS. We therefore examined the effects of a single dose of modafinil on mood and cognitive performance in healthy student volunteers. Mood was assessed before the start of testing and at the end because previous studies have found these cognitive tests to be stressful, as indicated by increased ratings of somatic and psychological anxiety and aggression (File *et al.*, 2001a; 2002a,b; Fluck *et al.*, 2002). A parallel-groups design was adopted because this has previously been shown to be more sensitive to drug-induced memory impairments than a repeated-measures design (File, 1992a). This is mainly due to the very low variability in the students' scores, both within and between years (File *et al.*, 2001a,b; 2002a). The former type of study design was also found to be sensitive to the cognitive-enhancing effects of glycine (File *et al.*, 1999a). In addition, there are some major practice effects with many aspects of the CANTAB battery and a parallel-groups design avoids these.

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 effects of methamphetamine (Simon *et al.*, 2000), carbamazepine and phenytoin (Meador *et al.*, 1991), guanfacine and dextroamphetamine (Taylor and Russo, 2001), tibolone (Fluck *et al.*, 2002) and a high soya diet (File *et al.*, 2001b). The computerised 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 effects of methylphenidate (Elliott *et al.*, 1997), diazepam (Coull *et al.*, 1995a,b; Robbins *et al.*, 1997), clonidine (Coull *et al.*, 1995a, b), sulpiride (Mehta *et al.*, 1999), as well as scopolamine (Robbins *et al.*, 1997).

METHODS AND MATERIALS

Subjects

Thirty healthy student volunteers (19 men and 11 women) were recruited from King's College London. All subjects gave written informed consent. They were recruited by a fellow student (KP) and no pressure was exerted on them to take part. The study was approved by Guy's Hospital Research Ethics Committee. Exclusion criteria included any history of psychiatric, neurological, or cardiovascular illness, use of psychoactive medication, colour-blindness (as assessed by the Ishihara cards [Ishihara, 1998]), pregnancy (all women were required to take a pregnancy test before being given the tablets), any major sight, hearing or movement problems, and a marked foreign accent. In addition, subjects were excluded if they had an Epworth sleepiness scale (ESS) (Johns, 1991) score greater than 10, a hospital depression and anxiety scale (HADS) (Zigmond and Snaith, 1983) score $\geq$8, 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), and also if they consumed more than 8 cups of coffee (or $\geq$900 mg caffeine) per day or if they were regular recreational drug users. Only two subjects (one in each of the modafinil groups) smoked and they were not asked to abstain before testing. An estimate of premorbid verbal IQ was obtained by use of the national adult reading test (NART) (Nelson and Willison, 1991). Subjects were asked to abstain from alcohol and caffeine intake for 12 h and 3 h respectively before the test session.

Drug

On the day of the cognitive testing subjects received modafinil (100 or 200 mg) (Cephalon Inc, 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 campus between the time of administration and time of testing.

Visual analogue scales (VAS)

Prior to cognitive testing, subjects completed 100 mm analogue rating scales for mood (Bond and Lader, 1974), aggression (Bond and Lader, 1986) and bodily symptoms (Tyrer, 1976). 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 1¼ h later.

Sleepiness and fatigue rating scales

As part of the screening procedure, subjects completed the Epworth sleepiness scale (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 to 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.

Cognitive tests

All testing was carried out in the afternoon. A number of different tests was used in this study, with some being administered on a touch-sensitive portable computer screen and others by hand, using pre-designed 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, which was always first in the battery of cognitive tests and rapid visual information processing, which was always last.

Computerised tests

These were taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition, Cambridge, UK).

Motor screening (MOT)

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

Delayed matching to sample (DMTS) is a test of visual episodic memory based on the delayed matching to sample 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. The percent correct and latency to correct responses (in ms) were measured.

Intra/extra dimensional set shift (IED) is best known in the form of the Wisconsin card-sorting test 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 intra-dimensional shift) and lastly switch attention to the previously irrelevant dimension, the line (the extra-dimensional shift). Stages completed and number of errors were measured.

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 ms), as well as number of problems solved in minimum moves was scored.

Rapid visual information processing (RVP) 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: target sensitivity (A'), response bias (B''), total false alarms, total misses, and latency to correct detections (in ms).

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). This study used the Victoria version of the Stroop (Regard, 1981). Essentially, 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 s) and total errors for each card, and Stroop interference (calculated as ratio index of the amount of time required for the 'Colours' card versus the 'Dots' card).

Trail making test (A&B) (Partington and Leiter, 1949)—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 Part A and Part B were recorded (in s).

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'. For *'category fluency'*, the categories were 'house animals', 'jungle animals' and 'farm animals'. 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 s).

Statistical analysis

Two-way repeated measures multivariate analyses of variance (MANOVA) were used to analyse the factors of 'somatic anxiety' and 'aggressive mood', with the between-group factor being drug treatment and the repeated measure being time/stress. The use of MANOVA permits analysis of drug effects whilst controlling for inter-correlations among measures, thus reducing the risk of false-positives from a series of univariate analyses. Because both the MANOVAs showed significant drug effects, these were then followed by two-way repeated measures analyses of variance (ANOVA). The factors of 'psychological anxiety', 'well-being' and 'alertness' extracted from the Bond and Lader mood scale (1974) were analysed by two-way repeated measures ANOVA. The scores from the cognitive tests were analysed with one-way ANOVAs, except for Stroop total errors ('Words' and 'Colours'), Clock Drawing score, DMTS percent correct simultaneous, IED stages completed, total errors, and total errors adjusted, RVP B″ and total false alarms, and SOC initial thinking time for 2, 3 and 5 move problems, which were not normally distributed, as indicated by the Kolmogorov–Smirnov test. These data were therefore analysed by the non-parametric Kruskal–Wallis test.

All data were analysed using Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL, USA), version 10.0 for Windows.

RESULTS

Group characteristics

The three groups did not differ significantly in age, IQ, sleepiness, fatigue, anxiety or depression (Table 1). The 200 mg group had a slightly higher caffeine intake, but the group differences in this measure did not reach significance ($F_{(2,27)} = 1.5$, $p > 0.1$). The

Table 1. General characteristics of the three treatment groups. Values shown are mean ± SEM

	Placebo	100 mg	200 mg	$F_{(2,27)}$ / $\chi^2_{(2)}$	p
Age (years)	20.7 ± 0.4	20.3 ± 0.2	20.7 ± 0.3	0.9[K]	NS
HAD_A (anxiety)	3.5 ± 0.5	3.5 ± 0.7	3.6 ± 0.7	0.0	NS
HAD_D (depression)	1.6 ± 0.3	1.4 ± 0.5	1.4 ± 0.3	0.3[K]	NS
NART verbal IQ	116.6 ± 0.9	114.9 ± 1.4	113.7 ± 2.0	0.9	NS
Epworth sleepiness	5.5 ± 0.9	5.5 ± 0.9	5.5 ± 0.9	0.0	NS
11 item fatigue	12.1 ± 1.1	11.6 ± 1.1	10.5 ± 1.0	0.7	NS
Daily caffeine (units)	2.5 ± 0.5	1.7 ± 0.4	3.0 ± 0.6	1.5	NS
Weekly alcohol (units)	7.5 ± 2.4	12.6 ± 3.6	11.0 ± 2.6	0.8	NS

[K]Kruskal-Wallis. NS, not significant.

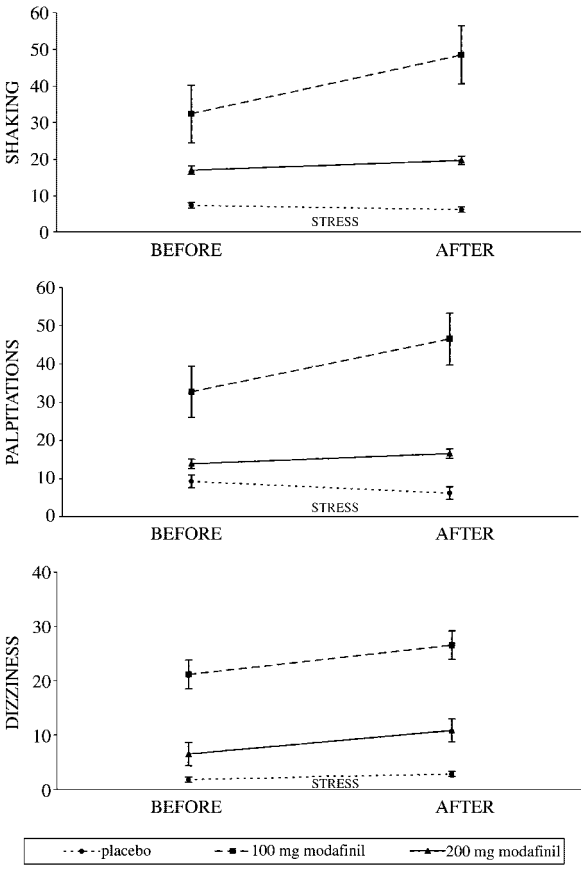

Figure 1. Mean ± SEM scores on self-ratings of 'shaking', 'palpitations', and 'dizziness', before and after the stress of cognitive testing

100 mg group had a slightly higher alcohol intake, but again the group differences did not reach significance ($F_{(2,27)} = 0.8$, $p > 0.1$).

Mood ratings

All of the items from the bodily symptoms scale were entered into a factor of 'somatic anxiety'. There was a significant change associated with drug treatment in this (MANOVA, $F_{(18,38)} = 2.2$, $p < 0.02$), which was due to higher ratings of anxiety in the 100 mg group (Figure 1). Several individual ratings of bodily symptoms also showed significant changes associated with drug treatment (Table 2). These were: 'shaking' ($F_{(2,27)} = 12.1$, $p < 0.0005$), 'palpitations' ($F_{(2,27)} = 9.8$, $p < 0.005$), 'dizziness' ($F_{(2,27)} = 7.8$, $p < 0.005$), 'restlessness' ($F_{(2,27)} = 6.7$, $p < 0.005$), 'muscular tension' ($F_{(2,27)} = 5.7$, $p < 0.01$), 'physical tiredness' ($F_{(2,27)} = 4.8$, $p < 0.05$) and 'irritability' ($F_{(2,27)} = 4.1$, $p < 0.05$). In all cases, *post hoc* tests (Bonferroni) showed the 100 mg group to differ significantly from placebo ($p < 0.05$). In addition, *post hoc* tests showed the 100 mg group to also differ significantly from the 200 mg group on individual ratings of 'shaking', 'palpitations' and 'dizziness' ($p < 0.05$). The rating of the individual item 'anxiety' showed a significant change after the stress of cognitive testing (stress x treatment interaction, $F_{(2,27)} = 6.8$, $p < 0.005$). This was due to subjects in the 100 mg group rating themselves as more anxious than did subjects in the placebo group at the end of the testing session, although this just missed significance on a *post hoc* test ($p = 0.07$).

Further mood differences between the groups were revealed after the stress of cognitive testing. All of the items from the aggressive mood scale were entered in

Table 2. Scores on ratings of bodily symptoms that showed significant effects of drug treatment and scores on the factors of 'alertness' and 'well-being' extracted from the Bond and Lader mood rating scales, before and after the stress of cognitive testing. Values shown are mean ± SEM for each treatment group

	Placebo		100 mg		200 mg	
	Before	After	Before	After	Before	After
Restlessness	15.1 ± 6.3	10.1 ± 5.5	35.2 ± 7.3[a]	48.3 ± 9.8[a]	26.1 ± 5.8	21.9 ± 5.8
Muscular tension	4.4 ± 2.2	7.9 ± 5.2	28.6 ± 8.3[b]	36.9 ± 8.4[b]	25.5 ± 7.7	21.5 ± 6.9
Physical tiredness	23.1 ± 5.9	11.9 ± 5.8	45.4 ± 7.2[b]	49.5 ± 9.3[b]	27.6 ± 7.6	33.1 ± 8.1
Irritability	10.6 ± 5.6	9.0 ± 5.0	20.8 ± 5.8[b]	43.6 ± 10.7[b]	14.7 ± 5.7	19.9 ± 6.4
Factor 1[c] (alertness)	41.5 ± 3.2	40.5 ± 4.4	38.1 ± 4.2	35.4 ± 6.0	44.8 ± 2.8	38.4 ± 4.2
Factor 2[c] (well-being)	48.5 ± 3.2	50.0 ± 3.9	46.2 ± 3.1	40.1 ± 5.1	48.8 ± 4.0	42.5 ± 3.8

[a] $p < 0.005$ compared with the placebo group.
[b] $p < 0.05$ compared with the placebo group.
[c] NS, not significant.

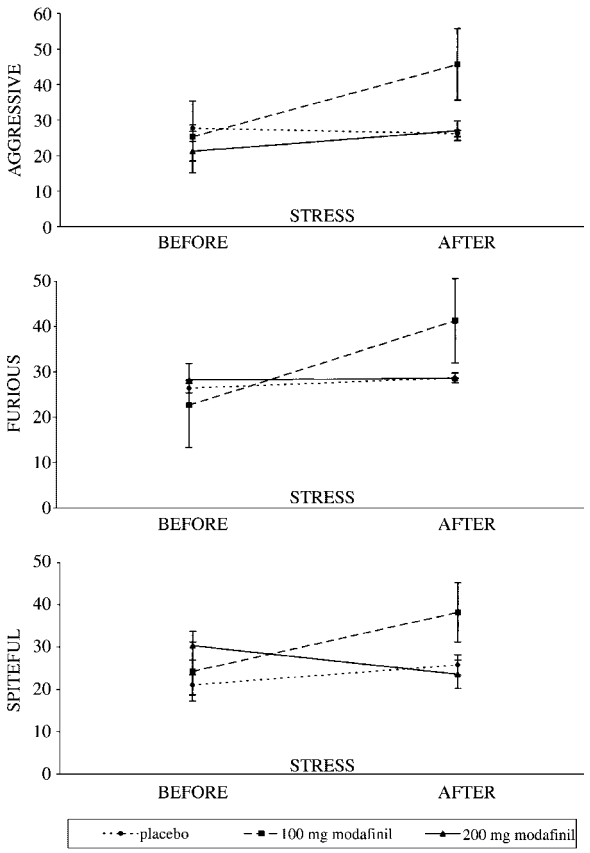

Figure 2. Mean ± SEM scores on self-ratings of 'aggressive', 'furious', and 'spiteful', before and after the stress of cognitive testing

one factor, and this overall factor of 'aggressive mood' showed a significant stress x treatment interaction (MANOVA, $F_{(16,40)} = 2.0$, $p < 0.05$). For three of the individual items ('cool-headed–aggressive', 'calm–furious', and 'benevolent–spiteful') there were significant stress x treatment interactions ($F_{(2,27)} = 6.4$, $p < 0.01$; $F_{(2,27)} = 4.1$, $p < 0.05$; $F_{(2,27)} = 3.8$, $p < 0.05$ respectively). It can be seen in Figure 2 that the 100 mg group rated themselves as feeling more aggressive, furious and spiteful than did the other two groups after completing the battery of cognitive tests, whereas the 200 mg group felt more spiteful at the start of testing. However, on *post hoc* tests there were no significant differences between individual groups ($p > 0.2$).

Following factor analysis, Bond and Lader (1974) isolated three independent factors from their mood rating scale. On the 'psychological anxiety' factor there was a significant stress x treatment interaction

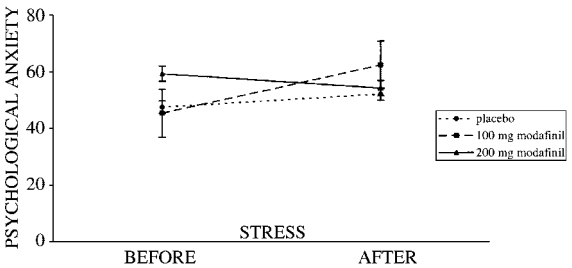

Figure 3. Mean ± SEM scores on the factor of 'psychological anxiety' extracted from the Bond and Lader mood rating scales, before and after the stress of cognitive testing

($F_{(2,27)} = 5.7$, $p < 0.01$), with subjects in the 100 mg group rating themselves as more anxious after the stress of cognitive testing than did subjects in the placebo and 200 mg groups. The subjects in the 200 mg group, on the other hand, differed from the other two groups in their pre-test ratings of 'psychological anxiety' (Figure 3). However, on *post hoc* tests there were no significant differences between individual groups ($p > 0.5$). There were no treatment-associated changes in the factors measuring 'alertness' ($F_{(2,27)} = 0.8$, $p > 0.4$) or 'well-being' ($F_{(2,27)} = 1.8$, $p > 0.1$) (Table 2).

Cognitive tests

There were no significant effects of modafinil on the performance of any of the cognitive tests (Tables 3 and 4).

DISCUSSION

We did not find any evidence for improved cognitive performance after administration of modafinil (100 or 200 mg) in healthy students who were not sleep-deprived. This is in agreement with previous studies in which no improvements were found under normal conditions, without sleep deprivation (Lagarde and Batejat, 1995; Stivalet *et al.*, 1998), whereas modafinil was able to reduce the deficits that resulted from SD (Lagarde and Batejat, 1995; Pigeau *et al.*, 1995; Stivalet *et al.*, 1998; Brun *et al.*, 1998; Baranski *et al.*, 1998; Wesensten *et al.*, 2002). We think it unlikely that our negative findings are due to a selection of inappropriate tests. We used a wide range of standardised tests that have proved sensitive to the effects of other psychoactive drugs, such as methylphenidate (Elliott *et al.*, 1997), diazepam (Coull *et al.*, 1995a,b; Robbins *et al.*, 1997), clonidine (Coull *et al.*, 1995a,b), metamphetamine (Simon *et al.*, 2000), sulpiride (Mehta *et al.*, 1999), as well as scopolamine (Robbins

Table 3. Scores on the CANTAB tests for each treatment group. Values shown are mean ± SEM

	Placebo	100 mg	200 mg	$F_{(2,27)}$ / $\chi^2_{(2)}$	*p*
DMTS					
% Correct—all delays	85.8 ± 3.1	87.5 ± 1.8	87.0 ± 2.8	0.1	NS
% Correct—simultaneous	100.0	98.8 ± 1.3	99.1 ± 0.9	1.3[K]	NS
Mean correct latency—all (ms)	3163.8 ± 279.4	3038.1 ± 351.1	2950.8 ± 223.6	0.2	NS
Mean correct latency—simultaneous	2478.2 ± 143.0	2646.4 ± 314.4	2466.2 ± 189.2	0.2	NS
IED					
Stages completed	8.8 ± 0.2	8.8 ± 0.3	8.8 ± 0.2	0.1[K]	NS
Total errors	12.8 ± 2.7	12.5 ± 2.4	16.3 ± 3.4	0.2[K]	NS
Total errors—adjusted	15.1 ± 4.9	15.6 ± 5.5	18.5 ± 5.04	0.2[K]	NS
EDS errors	4.8 ± 2.4	5.1 ± 2.8	9.4 ± 3.03	0.9	NS
Pre-ED errors	6.8 ± 0.8	5.9 ± 0.4	5.9 ± 0.7	0.6	NS
SOC					
Initial thinking time (ms)					
—2 moves	2177.9 ± 184.8	1547.6 ± 298.7	1889.1 ± 213.8	2.2[K]	NS
—3 moves	4694.4 ± 719.5	2690.4 ± 510.5	4015.6 ± 633.3	4.8[K]	NS
—4 moves	8920.0 ± 1079.4	11217.1 ± 2220.1	10332.8 ± 2040.0	0.4	NS
—5 moves	11962.1 ± 1773.5	12698.8 ± 2937.7	23517.1 ± 7457.0	3.3[K]	NS
Subsequent thinking time (ms)					
—2 moves	107.8 ± 69.2	174.9 ± 96.6	46.6 ± 20.6	0.9	NS
—3 moves	454.7 ± 198.5	115.8 ± 97.6	88.1 ± 31.2	2.4	NS
—4 moves	1405.5 ± 558.5	657.0 ± 178.6	704.4 ± 229.0	1.2	NS
—5 moves	735.2 ± 151.2	567.1 ± 146.2	374.7 ± 155.4	1.5	NS
Problems solved in minimum moves	9.0 ± 0.7	9.6 ± 0.7	10.3 ± 0.6	1.1	NS
RVP					
A'	0.9 ± 0.0	0.9 ± 0.0	0.9 ± 0.0	0.7	NS
B''	1 ± 0.0	1 ± 0.0	0.8 ± 0.2	0.1[K]	NS
Total false alarms	0.9 ± 0.5	0.4 ± 0.2	0.4 ± 0.2	0.4[K]	NS
Total misses	6.3 ± 1.0	6.5 ± 1.1	5 ± 1.1	0.6	NS
Latency correct detections (ms)	393.7 ± 39.5	394.3 ± 9.8	420.6 ± 28.6	0.3	NS

[K]Kruskal-Wallis. NS, not significant.

et al., 1997), tibolone (Fluck *et al.*, 2002) and a high soya diet (File *et al.*, 2001b).

We also think it unlikely that our use of a parallel-groups design was a major factor in our finding no effects on cognition. This is because there was a small variability in scores resulting from a uniform student population. Similar designs, using similar group sizes, have previously shown significant effects of lorazepam (File *et al.*, 1992; File, 1992a,b; Fluck *et al.*, 1998), temazepam (Joyce and File, 1995) and glycine (File *et al.*, 1999a). One of our reasons for not using a crossover design is the fairly marked practice effects in some of these tests. In particular, the extra-dimensional shift of the IED test cannot be used on more than one occasion. We think it unlikely that modafinil effects would have been detected if we had practised all subjects to asymptote, as the higher the level of performance the harder it is to observe drug-induced improvements. We tested all our subjects in the afternoon and it is possible that a post-prandial dip slightly impaired their performance. However, this was insufficient to see any true effects and perhaps modafinil's effects are more evident under conditions of greater cognitive impairment (File *et al.*, 1999a; Fluck *et al.*, 2001).

However, although cognitive performance did not change, it is clear that treatment with modafinil was associated with significant changes during these tests in the mood of our volunteers. In particular, subjects in the 100 mg group scored significantly higher on ratings of 'somatic anxiety' and, after stress, showed increases on ratings of 'psychological anxiety' and 'aggressive mood'. The clinical significance of our findings is uncertain but similar results have been obtained in two other studies. Broughton *et al.* (1997) have also reported that modafinil (400 mg) increased profile of mood states (POMS) ratings of 'tension–anxiety' in narcoleptic patients compared with the placebo level, although they found no change in 'anger–hostility'. This may be because they did not test under conditions of stress, which seemed to be necessary to reveal the changes in aggressive mood. Caldwell *et al.* (2000) have reported subjective adverse events such as increased nausea, vertigo, nervousness, dizziness, heartburn and headache following three doses of 200 mg modafinil in their sleep

Table 4. Scores on the pen and paper tests for each treatment group. Values shown are mean ± SEM

	Placebo	100 mg	200 mg	$F_{(2,27)}$ / $\chi^2_{(2)}$	*p*
Logical memory					
Total no. 'units'—immediate recall	15.4 ± 0.8	16.6 ± 1.7	16.5 ± 0.9	0.4	NS
Total no. 'units'—delayed recall	16.5 ± 2.6	15.8 ± 1.5	16.2 ± 1.0	0.4	NS
Stroop					
Time to complete (s)					
—Dots	10.5 ± 0.4	11.8 ± 0.8	11.1 ± 0.8	0.7	NS
—Words	12.8 ± 0.7	14.5 ± 1.6	13.6 ± 1.0	0.6	NS
—Colours	19.1 ± 1.2	21.0 ± 2.1	21.7 ± 1.9	0.7	NS
Total errors					
—Dots	0.0	0.0	0.0	—	
—Words	0.0	0.1 ± 0.1	0.0	2.8^K	NS
—Colours	0.2 ± 0.2	0.6 ± 0.3	0.3 ± 0.2	2.2^K	NS
Interference (Colours/Dots)	1.8 ± 0.1	1.8 ± 0.1	2.0 ± 0.1	0.6	NS
Trail making test					
Time to complete part A (s)	26.3 ± 2.2	23.3 ± 2.3	28.1 ± 4.4	0.5	NS
Time to complete part B (s)	51.2 ± 4.0	49.9 ± 4.7	63.6 ± 7.6	1.7	NS
COWAT					
Total no. words—letter fluency	47.6 ± 3.0	50.0 ± 3.9	44.7 ± 3.8	0.5	NS
Total no. words—category fluency	22.9 ± 1.3	22.4 ± 0.8	22.8 ± 0.7	0.1	NS
Clock drawing					
Drawing score	8.8 ± 0.5	9.4 ± 0.4	8.9 ± 0.6	0.8^K	NS
Time to complete (s)	29.1 ± 2.5	25.4 ± 3.4	26.3 ± 1.9	0.6	NS

^{K}Kruskal-Wallis. NS, not significant.

deprivation study and Broughton *et al.* (1997) found a greater incidence of nausea and nervousness in narcoleptic patients after chronic treatment with 400 mg modafinil. Thus, our subjective effects are generally in agreement with those previously reported, although we found them after a lower dose.

Modafinil's action in promoting wakefulness appears to be due to its ability to reduce the GABAergic inhibitory output of the ventrolateral preoptic nucleus. In this way the arousal mechanisms, including orexin-releasing neurons and the histaminergic projections to the cerebral cortex from the tuberomammillary nucleus, are activated (Scammell *et al.*, 2000). This mechanism may also underlie the increase in anxiety that we have observed, but other actions, either alone, or together, could be responsible. Ferraro *et al.* (1996; 1999) found that modafinil decreased GABA concentrations and increased glutamate concentrations in the medial preoptic area and the posterior hypothalamus. If modafinil produces similar changes in GABA and glutamate in the dorsomedial hypothalamus, this could well explain the modafinil-induced increases in anxiety that we observed after stress. This nucleus has been shown to be important for mediating the response to benzodiazepines in an animal model of anxiety (File *et al.*, 1999b). Furthermore, injection of $GABA_A$ receptor agonists into this region in rats decreased anxiety, heart rate and blood pressure, whereas injection of $GABA_A$ receptor antagonists or excitatory amino acids produced the opposite changes (Shekhar and Katner, 1995; Soltis and DiMicco, 1991a,b).

EEG power spectral analysis (Sebban *et al.*, 1999) and functional MRI (Ellis *et al.*, 1999) have shown that modafinil modifies activity in the hippocampus and frontal cortex, areas that play important roles in anxiety, cognition and alertness. It is thought that reciprocal neural circuits linking the medial prefrontal cortex, amygdala and hypothalamus play a major role in anxiety and stress responding (LeDoux, 1992). Modafinil has been shown to increase 5-HT release from frontal cortex and amygdala (Ferraro *et al.*, 2000; 2002) and increased 5-HT release in terminal areas is associated with increases in anxiety (File *et al.*, 2000; Gonzalez *et al.*, 1996; Cheeta *et al.*, 2000).

The increases in anxiety were not seen with the higher dose of modafinil, which suggests that there must be another pharmacological action that is counteracting those underlying the anxiogenic effects. One possibility is the increased 5-HT release in the dorsal raphé nucleus (Ferraro *et al.*, 2002). Increased 5-HT release in the dorsal raphé nucleus would act on the 5-HT_{1A} autoreceptors, which would in turn decrease the firing rate and result in a decreased 5-HT release in the terminal areas. Direct stimulation of the 5-HT_{1A} autoreceptors in the dorsal raphé nucleus has anxiolytic effects (Higgins *et al.*, 1992; Hogg *et al.*, 1994; File

and Gonzalez, 1996) as does indirect activation by nicotine via increased 5-HT release in this area (Cheeta *et al.*, 2001). Ferraro *et al.* (2002) have found that there are regional differences in the sensitivity of the 5-HT system to modafinil and thus it is possible that at higher doses, release in some brain regions is acting to counteract the anxiogenic effects of increased 5-HT release in other areas.

In summary, this study found that a single dose of modafinil had no effect on cognitive performance in healthy young volunteers who were not sleep-deprived but 100 mg was associated with significantly higher subjective 'somatic anxiety'. Thus, in this population, modafinil's effects on mood, particularly those relating to somatic anxiety, are greater than its effects on cognition.

REFERENCES

Baranski JV, Cian C, Esquivie D, Pigeau RA, Raphel C. 1998. Modafinil during 64 hr of sleep deprivation: dose-related effects on fatigue, alertness, and cognitive performance. *Milit Psychol* **10**: 173–193.

Beats BC, Sahakian BJ, Levy R. 1996. Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychol Med* **26**: 591–603.

Bensimon G, Benoit D, Lacomblez L, *et al.* 1991. Antagonism by modafinil of the psychomotor and cognitive impairment induced by sleep-deprivation in 12 healthy volunteers. *Eur Psychiatry* **6**: 93–97.

Bond A, Lader M. 1974. The use of analogue scales in rating subjective feelings. *Br J Med Psychol* **47**: 211–218.

Bond A, Lader M. 1986. A method to elicit aggressive feelings and behaviour via provocation. *Biol Psychol* **22**: 69–79.

Broughton RJ, Fleming JAE, George CFP, *et al.* 1997. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. *Neurology* **49**: 444–451.

Brun J, Chamba G, Khalfallah Y, *et al.* 1998. Effect of modafinil on plasma melatonin, cortisol and growth hormone rhythms, rectal temperature and performance in healthy subjects during 36 h sleep deprivation. *J Sleep Res* **7**: 105–114.

Caldwell JA, Caldwell JL, Smythe NK, Hall KK. 2000. A double-blind, placebo-controlled investigation of the efficacy of modafinil for sustaining the alertness and performance of aviators: a helicopter simulator study. *Psychopharmacology* **150**: 272–282.

Chalder T, Berelowitz G, Pawlikowska T, *et al.* 1993. Development of a fatigue scale. *J Psychosom Res* **37**: 147–153.

Cheeta S, Irvine EE, Kenny PJ, File SE. 2001. The dorsal raphé nucleus is a crucial structure mediating nicotine's anxiolytic effects and the development of tolerance and withdrawal responses. *Psychopharmacology* **155**: 78–85.

Cheeta S, Kenny PJ, File SE. 2000. Hippocampal and septal injections of nicotine and 8-OH-DPAT distinguish among different animal tests of anxiety. *Prog Neuro-Psychopharmacol Biol Psychiatry* **24**: 1053–1067.

Coull J, Middleton HC, Robbins TW, Sahakian BJ. 1995a. Contrasting effects of clonidine and diazepam on tests of working memory and planning. *Psychopharmacology* **120**: 311–321.

Coull JT, Middleton HC, Robbins TW, Sahakian BJ. 1995b. Clonidine and diazepam have differential effects on tests of attention and learning. *Psychopharmacology* **120**: 323–332.

Elliott R, Sahakian BJ, Matthews K, Bannerjea A, Rimmer J, Robbins TW. 1997. Effects of methylphenidate on spatial working memory and planning in healthy young adults. *Psychopharmacology* **131**: 196–206.

Ellis CM, Monk C, Simmons A, *et al.* 1999. Functional magnetic resonance imaging neuroactivation studies in normal subjects and subjects with the narcoleptic syndrome. Actions of modafinil. *J Sleep Res* **8**: 85–93.

Ewing JA. 1984. Detecting alcoholism: the CAGE questionnaire. *JAMA* **252**: 1905–1907.

Ferraro L, Antonelli T, Tanganelli S, *et al.* 1999. The vigilance promoting drug modafinil increases extracellular glutamate levels in the medial preoptic area and the posterior hypothalamus of the conscious rat: prevention by local $GABA_A$ receptor blockade. *Neuropsychopharmacology* **20**: 346–356.

Ferraro L, Fuxe K, Tanganelli S, Fernandez M, Rambert FA, Antonelli T. 2000. Amplification of cortical serotonin release: a further neurochemical action of the vigilance-promoting drug modafinil. *Neuropharmacology* **39**: 1974–1983.

Ferraro L, Fuxe K, Tanganelli S, Tomasini MC, Rambert FA, Antonelli T. 2002. Differential enhancement of dialysate serotonin levels in distinct brain regions of the awake rat by modafinil: possible relevance for wakefulness and depression. *J Neurosci Res* **68**: 107–112.

Ferraro L, Tanganelli S, O'Connor WT, Antonelli T, Rambert F, Fuxe K. 1996. The vigilance promoting drug modafinil decreases GABA release in the medial preoptic area and in the posterior hypothalamus of the awake rat: possible involvement of the serotonergic $5\text{-}HT_3$ receptor. *Neurosci Lett* **220**: 5–8.

File SE. 1992a. Effects of lorazepam on psychomotor performance: a comparison of independent-groups and repeated-measures designs. *Pharmacol Biochem Behav* **42**: 761–764.

File SE. 1992b. A comparison of the effects of a secondary task and lorazepam on cognitive performance. *J Psychopharmacol* **6**: 258–264.

File SE, Dinnis AK, Heard JE, Irvine EE. 2002a. Mood differences between male and female light smokers and nonsmokers. *Pharmacol Biochem Behav* **72**: 681–689.

File SE, Fluck E, Fernandes C. 1999a. Beneficial effects of glycine (Bioglycin) on memory and attention in young and middle-aged adults. *J Clin Psychopharmacol* **19**: 506–512.

File SE, Fluck E, Leahy A. 2001a. Nicotine has calming effects on stress-induced mood changes in females, but enhances aggressive mood in males. *Int J Neuropsychopharmacol* **4**: 371–376.

File SE, Gonzalez LE. 1996. Anxiolytic effects in the plus-maze of $5\text{-}HT_{1A}$-receptor ligands in dorsal raphé and ventral hippocampus. *Pharmacol Biochem Behav* **54**: 123–128.

File SE, Gonzalez LE, Gallant R. 1999b. Role of dorsomedial hypothalamus in mediating the response to benzodiazepines on trial 2 in the elevated plus-maze test of anxiety. *Neuropsychopharmacology* **21**: 312–320.

File SE, Heard JE, Rymer J. 2002b. Trough oestradiol levels associated with cognitive impairment in post-menopausal women after 10 years of oestradiol implants. *Psychopharmacology* **161**: 107–112.

File SE, Jarrett N, Fluck E, Duffy R, Casey K, Wiseman H. 2001b. Eating soya improves human memory. *Psychopharmacology* **157**: 430–436.

File SE, Kenny PJ, Cheeta S. 2000. The role of the dorsal hippocampal serotonergic and cholinergic systems in the modulation of anxiety. *Pharmacol Biochem Behav* **66**: 65–72.

File SE, Sharma R, Shaffer J. 1992. Is lorazepam-induced amnesia specific to the type of memory or to the task used to assess it? *J Psychopharmacol* **6**: 76–80.

Fluck E, Fernandes C, File SE. 2001. Are lorazepam-induced deficits in attention similar to those resulting from aging? *J Clin Psychopharmacol* **21**: 126–130.

Fluck E, File SE, Rymer J. 2002. Cognitive effects of 10 years of hormone-replacement therapy with tibolone. *J Clin Psychopharmacol* **22**: 62–67.

Fluck E, File SE, Springett J, Kopelman MD, Rees J, Orgill J. 1998. Does the sedation resulting from sleep deprivation and lorazepam cause similar cognitive deficits? *Pharmacol Biochem Behav* **59**: 909–915.

Gonzalez LE, Andrews N, File SE. 1996. 5-HT_{1A} and benzodiazepine receptors in the basolateral amygdala modulate anxiety in the social interaction test, but not in the elevated plus-maze. *Brain Res* **732**: 145–153.

Guilleminault C, Pelayo R. 2000. Idiopathic central nervous system hypersomnia. In *Principles and Practice of Sleep Medicine*, 3rd edn, Kryger MH, Roth T, Dement WC (eds). WB Saunders Company: Philadelphia; 687–692.

Happe S, Pirker W, Sauter C, Klosch G, Zeitlhofer J. 2001. Successful treatment of excessive daytime sleepiness with modafinil. *J Neurol* **248**: 632–634.

Higgins GA, Jones BJ, Oakley NR. 1992. Effect of 5-HT_{1A} receptor agonist in two models of anxiety after dorsal raphé injection. *Psychopharmacology* **106**: 261–267.

Hogg S, Andrews N, File SE. 1994. Contrasting behavioural effects of 8-OH DPAT in the dorsal raphé nucleus and ventral hippocampus. *Neuropharmacology* **33**: 343–348.

Ishihara S. 1998. *The Series of Plates Designed as a Test for Colour-Deficiency.* Kanehara & Co. Ltd: Tokyo.

Johns MW. 1991. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* **14**: 540–545.

Joyce EM, File SE. 1995. Temazepam impairs effortful but not automatic processing of stimulus elements. *Hum Psychopharmacol Clin Exp* **10**: 449–453.

Lagarde D, Batejat D. 1995. Disrupted sleep-wake rhythm and performance: advantages of modafinil. *Milit Psychol* **7**: 165–191.

LeDoux JE. 1992. Brain mechanisms of emotion and emotional learning. *Curr Opin Neurobiol* **2**: 191–197.

Meador KJ, Loring DW, Allen ME, *et al.* 1991. Comparative cognitive effects of carbamazepine and phenytoin in healthy adults. *Neurology* **41**: 1537–1540.

Mehta MA, Sahakian BJ, McKenna PJ, Robbins TW. 1999. Systemic sulpiride in young adult volunteers simulates the profile of cognitive deficits in Parkinson's disease. *Psychopharmacology* **146**: 162–174.

Moachon G, Kanmacher M, Clenet M, Matinier D. 1996. Pharmacokinetic profile of modafinil. *Drugs Today* **32**: 23–33.

Nelson HE, Willison JR. 1991. *Restandardisation of the NART Against the WAIS-R.* NEFR-Nelson: Windsor.

Nieves AV, Lang AE. 2002. Treatment of excessive daytime sleepiness in patients with Parkinson's disease with modafinil. *Clin Neuropharmacol* **25**: 111–114.

Owen AM, Downes JJ, Sahakian BJ, Polkey CE, Robbins TW. 1990. Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia* **28**: 1021–1034.

Owen AM, James M, Leigh PN, *et al.* 1992. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain* **115**: 1727–1751.

Owen AM, Roberts AC, Polkey CE, Sahakian BJ, Robbins TW. 1991. Extra-dimensional versus intra-dimensional shift set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia* **29**: 993–1006.

Owen AM, Sahakian BJ, Semple J, Polkey CE, Robbins TW. 1995. Visuo-spatial short-term recognition memory and learning after temporal lobe excision, frontal lobe excision or amygdalo-hippocampectomy in man. *Neuropsychologia* **33**: 1–24.

Pack AI, Black JE, Schwartz JR, Matheson JK. 2001. Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea. *Am J Resp Crit Care Med* **164**: 1675–1681.

Partington JE, Leiter RG. 1949. Partington's Pathway Test. *Psycholog Serv Bull* **1**: 9–20.

Pigeau R, Naitoh P, Buguet A, *et al.* 1995. Modafinil, D-amphetamine and placebo during 64 hours of sustained mental work. I. Effects on mood, fatigue, cognitive performance and body temperature. *J Sleep Res* **4**: 212–228.

Rammohan KW, Rosenberg JH, Lynn DJ, Blumenfeld AM, Pollack CP, Nagaraja HN. 2002. Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. *J Neurol Neurosurg Psychiatry* **72**: 179–183.

Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt PM. 1994. The Cambridge Neuropsychological Test Automated Battery CANTAB: a factor analytical study in a large number of normal elderly volunteers. *Dementia* **5**: 266–281.

Robbins TW, Semple J, Kumar R, *et al.* 1997. Effects of scopolamine on delayed-matching-to-sample and paired associates tests of visual memory and learning in human subjects: comparison with diazepam and implications for dementia. *Psychopharmacology* **134**: 95–106.

Rugino TA, Copley TC. 2001. Effects of modafinil in children with attention-deficit/hyperactivity disorder: an open-label study. *J Am Acad Child Adolesc Psychiatry* **40**: 230–235.

Sahakian BJ, Downes JJ, Eagger S, *et al.* 1990. Sparing of attentional relative to mnemonic function in a subgroup of patients with dementia of the Alzheimer type. *Neuropsychologia* **28**: 1197–1213.

Sahakian BJ, Morris RG, Evenden JL, *et al.* 1989. A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. *Brain* **111**: 695–718.

Sahakian BJ, Owen AM. 1992. Computerised assessment in neuropsychiatry using CANTAB: discussion paper. *J Roy Soc Med* **85**: 399–402.

Scammell TE, Estabrooke IV, McCarthy MT, *et al.* 2000. Hypothalamic arousal regions are activated during modafinil-induced wakefulness. *J Neurosci* **20**: 8620–8628.

Sebban C, Tesolin-Decros B, Millan MJ, Spedding M. 1999. Contrasting EEG profiles elicited by antipsychotic agents in the prefrontal cortex of the conscious rat: antagonism of the effects of clozapine by modafinil. *Br J Pharmacol* **128**: 1055–1063.

Shallice T. 1982. Specific impairments in planning. *Phil Trans R Soc B* **298**: 199–209.

Shekhar A, Katner JS. 1995. Dorsomedial hypothalamic GABA regulates anxiety in the social interaction test. *Pharmacol Biochem Behav* **50**: 253–258.

Simon SL, Domier C, Carnell J, Brethen P, Rawson R, Ling W. 2000. Cognitive impairment in individuals currently using metamphetamine. *Am J Addictions* **9**: 222–231.

Soltis RP, DiMicco JA. 1991a. GABAA and excitatory amino acid receptors in dorsomedial hypothalamus and heart rate in rats. *Am J Physiol* **260**: R13–R20.

Soltis RP, DiMicco JA. 1991b. Interaction of hypothalamic GABAA and excitatory amino acid receptors controlling heart rate in rats. *Am J Physiol* **261**: R427–R433.

Spreen O, Strauss E. 1998. *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary.* Oxford University Press: Oxford; New York.

Stivalet P, Esquivie D, Barraud P-A, Leifflen D, Raphel, C. 1998. Effects of modafinil on attentional processes during 60 hours of sleep deprivation. *Hum Psychopharmacol Clin Exp* **13**: 501–507.

Stroop JR. 1935. Studies of interference in serial verbal reaction. *J Exp Psychol* **18**: 643–662.

Taylor FB, Russo J. 2000. Efficacy of modafinil compared to dextroamphetamine for the treatment of attention deficit hyperactivity disorder in adults. *J Child Adolesc Psychopharmacol* **10**: 311–320.

Taylor FB, Russo J. 2001. Comparing guanfacine and dextroamphetamine for the treatment of adult attention-deficit/hyperactivity disorder. *J Clin Psychopharmacol* **21**: 223–228.

Tyrer P. 1976. *The Role of Bodily Feelings in Anxiety.* Oxford University Press: London.

Walters AS, Hening WA, Rosen R, LeClerq C, Hirsch LC, Dhar A. 2001. A test of the reliability and validity of a brief, patient-completed severity questionnaire for restless legs syndrome: the international RLS study group rating scale. *Sleep* **24**: A356.

Wechsler D. 1987. *Wechsler Memory Scale—Revised*. The Psychological Corporation: San Antonio.

Wesensten NJ, Belenky G, Kautz MA, Thorne DR, Reichardt RM, Balkin TJ. 2002. Maintaining alertness and performance during sleep deprivation: modafinil versus caffeine. *Psychopharmacology* **159**: 238–247.

Wesnes K, Warburton DM. 1984. Effects of scopolamine and nicotine on human rapid visual information processing performance. *Psychopharmacology* **82**: 147–150.

Zigmond AS, Snaith RP. 1983. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* **67**: 361–370.

