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Cognitive effects of modafinil in student volunteers may depend on IQ

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Abstract

The results of two previous studies on the effects of modafinil, a selective wakefulness-promoting agent, in healthy university students were combined in a retrospective analysis. This allowed determination of whether the effects of modafinil were dependent on IQ and whether the larger sample size ($n=89$) would reveal more cognitive benefits. A battery of cognitive tests was completed 2–3 h after dosing. In the whole sample, modafinil (200 mg) significantly reduced the number of missed targets in a test of sustained attention (RVIP). However, interestingly, several interactions between modafinil and IQ emerged. Modafinil (100 and 200 mg) significantly improved target sensitivity in the RVIP test, but only in the group of 'lower' IQ (mean ± sem = 106 ± 0.6), not in the 'higher' IQ group (mean ± sem = 115.5 ± 0.5). Furthermore, there were significant modafinil × IQ interactions in two further tests. Modafinil significantly reduced speed of responding in a colour naming of dots, and in clock drawing, but only in the 'lower' IQ group. Thus, the cognitive benefits of modafinil seem particularly marked in tests of vigilance and speed, in which sleepiness would be an important factor. Furthermore, the results indicate that high IQ may limit detection of modafinil's positive effects.

Keywords: Modafinil; Cognition; IQ; Sleepiness; Wakefulness

1. Introduction

Modafinil 2-[(diphenylmethyl)sulfinyl]acetamide was originally licensed for the treatment of excessive daytime sleepiness (EDS) in narcolepsy, but the licence now also includes EDS in obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and chronic shift-work sleep disorder. It has also been reported to have some cognitive benefits in certain clinical conditions. In patients with narcolepsy, accuracy was improved in tests of speed (Boivin et al., 1993; but see Broughton et al., 1997) and sustained attention (Hirshkowitz and Harsh, 2004). In OSAHS patients, modafinil reduced the frequency of lapses of attention and improved reaction times in the Psychomotor Vigilance Task (Dinges and Weaver, 2003; but see Kingshott et al., 2001). A rather different pattern of cognitive improvement was reported in adults with attention deficit/hyperactivity disorder (ADHD), where modafinil was reported to improve Digit Span, pattern recognition memory, spatial planning and stop-signal motor inhibition (Turner et al., 2004a). Modafinil was also found to improve Digit Span and attentional set-shifting in schizophrenic patients (Turner et al., 2004b). It is thus possible that the pattern of cognitive benefits resulting from modafinil depend on the disorder, with improvements in vigilance and speed of responding being most marked in disorders of sleepiness, and improvements in memory and executive function being most marked in disorders of dopaminergic function.

In sleep-deprived healthy adults, modafinil counteracted the cognitive impairments resulting from sleep loss (Bensimon et al., 1991; Lagarde and Batejat, 1995; Pigeau et al., 1995; Stivalet et al., 1998; Caldwell et al., 2000; Wesensten et al., 2002; Wesnes and Macher, 2004). Many of the tasks that showed positive effects of modafinil included attentional and reaction time components.

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More recently, modafinil has received publicity in the general press for its use as a potential cognitive-enhancer and thus its effects in volunteers who are not sleep-deprived are of particular importance. In a group of high IQ (mean 115) university students, Randall et al. (2003) failed to detect any positive effects on cognitive performance of modafinil (100 and 200 mg) and Liepert et al. (2004) found no effects of modafinil (200 mg) on the performance of a small battery of tests (reaction time, nine-hole-peg and letter cancellation tasks) in healthy male subjects (mean age 27 years, IQ not specified). In a group of high IQ (mean 118) middle-aged volunteers, modafinil (200 mg) improved performance in a simple speed test (colour naming of dots) and in a clock-drawing test (Randall et al., 2004). Using a somewhat different range of tests, and combining the data for the 100 and 200 mg doses, Turner et al. (2003) found that modafinil improved performance of a high IQ (mean 115) group of young men (mean age 25 years) in the Digit Span, Pattern Recognition Memory (PRM), Stop-Signal Reaction Time and spatial planning (New Tower of London) tests. Finally, Randall et al. (2005) found that modafinil improved performance in a group of students (mean IQ 109) in Digit Span (100 mg), PRM (100 and 200 mg), colour naming of dots (200 mg) and in a test of sustained attention (Rapid Visual Information Processing, RVIP; 200 mg). Müller et al. (2004) found that the positive effects of modafinil (200 mg) in students (IQ not specified) were limited to two relatively difficult and monotonous computerised working memory tests.

Thus, there is some consistency in the tests in which improvements have been found in young adults who are not sleep deprived and, although they include simple speed tests and sustained attention, they are not restricted to these and include tests of short-term and working memory. It is, however, possible that the high IQ of the groups studied has limited detection of positive effects of modafinil. In the Müller et al. (2004) study, the difficult manipulation condition of a numeric working memory task showed positive effects of modafinil, but only in the poorer performing students. Similarly, Mehta et al. (2000) noted that the positive effects of methylphenidate (40 mg) on spatial working memory performance were greatest in those volunteers with lower baseline working memory capacity. In a study of the effects of ginkgo biloba in healthy young adults, Stough et al. (2001) found improved performance in the Trail-Making Test A only in the half with the lower verbal IQ. If modafinil is a cognitive enhancer, then it might well be expected that its effects would be more readily detected at levels of lower performance, where there is likely to be more scope for improvement. The purpose of the present study was to investigate this possibility by combining the data from our two previous student volunteer studies, thus providing a sample size ($n=89$) large enough to divide the group according to IQ.

A second advantage of this meta-analysis is that it allows us to determine whether additional effects of modafinil will be detected with a larger sample size. The two studies that found no effects both used small samples: $n=30$ in a parallel-groups design (Randall et al., 2003) and $n=10$ in a crossover design (Liepert et al., 2004). The studies that did detect positive effects used sample sizes from 45–60 in parallel-groups designs (Randall et al., 2004, 2005; Turner et al., 2003) and 16 in a crossover design (Müller et al., 2004). If inadequate sample sizes have been limiting the detection of some effects, then this analysis should reveal additional actions of modafinil that might help to clarify the pattern of its cognitive benefits.

2. Methods

2.1. Subjects and drug

This is a retrospective analysis of 89 healthy, non-sleep-deprived student volunteers (47 men and 42 women, aged 19–23 years), who had been recruited from King's College London to our double-blind, parallel-groups studies of the effects of modafinil on cognitive performance (Randall et al., 2003, 2005). The studies were approved by King's College London Research Ethics Committee. All subjects gave written informed consent and they were paid £10 for participating. The screening procedure, including exclusion criteria, is described in detail by Randall et al. (2003, 2004). On the day of cognitive testing, subjects received 100 or 200 mg modafinil (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). Volunteers were asked to abstain from alcohol the day before testing and from caffeine 3 h before the test session. Because nicotine abstinence has been shown to impair cognitive performance in smokers (Snyder and Henningfield, 1989; Hasenfratz and Battig, 1993), subjects were not asked to abstain before the testing session. Eleven subjects smoked (4 in the placebo group, 4 in the 100 mg and 3 in the 200 mg). Cognitive testing was carried out 2–3 h after dosing in order to coincide with peak plasma concentration of modafinil of 2–4 h after oral ingestion (Robertson and Hellriegel, 2003).

The National Adult Reading Test-II (NART-II; Nelson and Willison, 1991) was used to obtain an estimate of verbal IQ. Subjects were allocated to one of two groups: 'lower' IQ (≤ 110; $n=42$; mean IQ=106.1, SEM=0.6; 19 male, 23 female) and 'higher' IQ (≥ 111; $n=47$; mean IQ=115.5, SEM=0.5; 28 male, 19 female).

2.2. Cognitive tasks

The computerised tests were taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition, Cambridge, UK), and are described in detail by Sahakian et al. (1989) and Owen et al. (1990, 1991). The pen-and-paper tests are described in detail by

Table 1
Cognitive tasks

Test and cognitive ability	Outcome measure
Trail-Making Test (A and B; Reitan and Wolfson, 1985)	
-visual search, speed of attention, motor function (A and B); sequencing and mental flexibility (B)	-time to complete each part (s)
Rapid Visual Information Processing (RVIP; CANTAB)	-target sensitivity (A′)
-vigilance (sustained attention); small working memory component	-response bias (B″)
	-total missed targets
	-total false alarms
	-latency to correct detections (ms)
Logical Memory (Wechsler Memory Scale—Revised; Wechsler, 1987)	-total number of story 'units' (out of 25) recalled at immediate and delayed recall
-short and long-term verbal memory	
Controlled Oral Word Association Test (COWAT; Spreen and Strauss, 1998)	-total words generated for the letters 'F', 'A' and 'S'
-letter and category fluency	-total words generated for the categories 'house animals', 'jungle animals' and 'farm animals'
Stockings of Cambridge (SOC; CANTAB)	-initial and subsequent thinking time at each level of difficulty (ms)
-spatial planning	-total number of problems solved in the minimum moves (out of 12 possible 'perfect' solutions)
Stroop Test (Stroop, 1935)	-time to complete each part (s)
-selective attention and mental flexibility	-total errors for each part
	-Stroop interference index (calculated as ratio index of the amount of time required for the difficult 'colours' part versus the easy 'dots' part)
Intra/Extra Dimensional Set Shifting (ID/ED; CANTAB)	-total errors
-mental flexibility	-total errors adjusted for the number of stages completed
	-EDS errors (errors made at the extra dimensional shift stage)
	-pre-ED errors (errors made prior to the extra dimensional shift stage)
Clock Drawing (Spreen and Strauss, 1998)	-drawing score (1–10)
-visuospatial and constructional ability	-time to complete (s)

Spreen and Strauss (1998). This meta-analysis was conducted on the tasks that were common to the two studies, see Table 1. Randall et al. (2005) also used the following tasks: Reaction Time, Pattern Recognition Memory and Spatial Working Memory (all sub-tests of CANTAB), Symbol Copying (Kornetsky et al., 1959), Digit Symbol Substitution Test and Digit Span (sub-tests of the Wechsler Adult Intelligence Scale-Revised; Wechsler, 1981), Digit Cancellation (Curran et al., 1991) and Paced Auditory Serial Addition Test (Gronwall, 1977). The Delayed Matching to Sample test from the CANTAB was used by Randall et al. (2003), but not by Randall et al. (2005).

2.3. Statistical analysis

Where possible the data were analysed by 3-factor analyses of variance with study (at 2 levels), modafinil (at 3 levels) and IQ (at 2 levels) as the independent factors. In no case was there a significant ($p<0.05$) study x modafinil interaction and thus this analysis of the combined studies was considered legitimate. Where the scores did not meet the requirements for parametric analysis (denoted # in the tables and figure legends) nonparametric tests were carried out. In these cases, Kruskal–Wallis tests were used to determine overall main effects of treatment (regardless of

Table 2
General characteristics

Characteristic	Placebo		100 mg		200 mg	
	'Lower' IQ	'Higher' IQ	'Lower' IQ	'Higher' IQ	'Lower' IQ	'Higher' IQ
Age (years)	20.5±0.2	20.8±0.3	20.1±0.2	20.4±0.2	20.9±0.3	20.7±0.2
NART verbal IQ	105.9±0.9	116.6±0.7	106.6±0.9	114.6±0.8	105.9±1.2	115.2±0.9
HAD_A (anxiety)	4.3±0.8	4.0±0.5	5.1±0.7	3.9±0.7	5.1±0.8	3.9±0.5
HAD_D (depression)	2.9±0.9	1.4±0.3	2.4±0.6	1.9±0.5	3.1±0.7	1.5±0.3
Epworth sleepiness	6.9±0.6	5.3±0.6	6.4±0.6	4.9±0.7	6.8±0.9	4.7±0.8
11-Item fatigue	12.2±0.8	11.8±0.8	12.2±0.5	11.6±0.7	12.1±0.7	10.8±0.7
Daily caffeine (cups)	2.2±0.5	2.1±0.4	2.4±0.4	1.5±0.4	1.7±0.2	2.9±0.5
Weekly alcohol (units)	3.9±1.1	8.1±2.4	7.0±2.0	9.2±2.8	6.2±1.5	10.8±2.4

Values shown are means±SEM for each treatment and IQ group.

Table 3
Mean±SEM scores on CANTAB tests for which no significant effects of modafinil were found

Test and measure	Placebo		100 mg		200 mg	
	'Lower' IQ	'Higher' IQ	'Lower' IQ	'Higher' IQ	'Lower' IQ	'Higher' IQ
RVIP						
Total false alarms[#]	1.9±0.4	0.9±0.4	0.9±0.2	0.7±0.2	1.2±0.4	0.5±0.2
Response bias (B″)[#]	0.92±0.02	0.96±0.02	0.95±0.02	0.96±0.02	0.94±0.02	0.86±0.1
Latency correct (ms)[#]	467.5±25.6	425.9±18.3	458.1±29.9	398.4±27.3	409.4±19.8	417.8±19.0
SOC						
Initial thinking time (ms)						
2 moves	1615.7±432.6	1913.9±205.2	1561.6±234.4	1643.2±237.1	1368.9±175.6	1644.5±177.2
3 moves	4866.1±954.5	4123.9±579.9	3708.6±921.0	3824.8±705.3	3378.3±553.1	3674.9±444.3
4 moves	8567.7±1870.0	7270.3±974.2	7965.4±2225.6	13780.4±3042.9	9610.9±2069.8	9402.2±1774.8
5 moves	11786.9±3734.2	9939.9±1514.3	9002.6±1994.7	12951.8±2207.2	14289.8±3603.7	17408.4±5177.0
Subsequent thinking time (ms)						
2 moves[#]	140.1±45.9	133.3±66.5	125.9±44.0	234.2±108.1	96.1±56.4	31.7±14.7
3 moves[#]	364.1±207.5	432.6±140.8	83.4±35.2	107.1±61.8	115.2±58.6	160.6±83.5
4 moves[#]	649.3±137.5	1222.0±401.3	816.8±116.7	718.6±138.2	1039.4±251.3	509.2±107.7
5 moves[#]	642.0±176.6	715.9±165.8	408.0±105.7	936.4±358.1	629.4±161.1	334.3±92.5
Problems solved in minimum moves[#]	8.9±0.5	8.9±0.5	9.1±0.5	9.8±0.5	8.4±0.7	10.2±0.5
ID/ED						
Total errors[#]	15.7±1.8	11.9±1.9	16.6±2.4	11.6±1.5	14.0±1.6	13.4±2.2
Total errors adjusted[#]	15.7±1.8	13.5±3.4	38.1±15.9	13.4±3.2	14.0±1.6	14.9±3.4
EDS errors[#]	5.1±0.8	3.9±1.7	4.8±1.0	5.1±1.6	5.4±1.4	6.4±2.1
Pre-ED errors[#]	7.8±1.0	6.4±0.6	9.0±2.2	5.4±0.5	6.7±0.7	5.9±0.5

[RVIP, Rapid Visual Information Processing; SOC, Stockings of Cambridge; ID/ED, Intra/Extra Dimensional Set Shift].

Table 4
Mean±SEM scores on pen-and-paper tests where no significant effects of modafinil were found

Test and measure	Placebo		100 mg		200 mg	
	'Lower' IQ	'Higher' IQ	'Lower' IQ	'Higher' IQ	'Lower' IQ	'Higher' IQ
Logical memory						
No. 'Units' Recalled						
Immediate	14.0±1.3	15.7±0.6	16.1±1.3	16.0±1.2	16.5±1.4	15.9±0.8
Delayed	11.7±1.5	14.6±0.8	14.4±1.2	14.9±1.3	13.6±1.4	15.6±0.9
The Stroop test						
Time to complete (s)						
Words	14.1±0.6	12.9±0.5	13.0±0.6	14.1±1.0	13.9±1.0	12.7±0.6
Colours	22.8±1.1	19.3±0.8	18.9±0.9	21.3±1.4	22.4±1.5	19.5±1.1
No. errors						
Colours[#]	0.4±0.2	0.3±0.1	0.5±0.3	0.3±0.2	0.4±0.2	0.3±0.1
Interference index (colours/dots)	1.8±0.1	1.8±0.1	1.7±0.1	1.7±0.1	2.0±0.1	1.9±0.1
Trail-making test						
Time to complete (s)						
Part A	27.2±3.0	24.4±1.8	20.7±1.5	23.0±1.5	25.2±1.9	25.8±2.9
Part B	54.9±4.3	53.6±3.7	44.4±3.7	51.7±3.5	54.4±5.0	56.4±5.0
COWAT						
Total no. words						
Letter fluency	45.9±3.1	48.3±2.6	45.1±2.9	49.7±2.6	50.1±3.7	52.7±3.5
Category fluency	24.1±1.0	22.6±1.0	26.3±1.6	23.5±0.9	24.6±1.3	24.0±0.9
Clock drawing						
Score[#]	9.1±0.3	8.9±0.3	8.9±0.4	9.2±0.3	8.9±0.3	9.0±0.4

[COWAT, Controlled Oral Word Association Test].

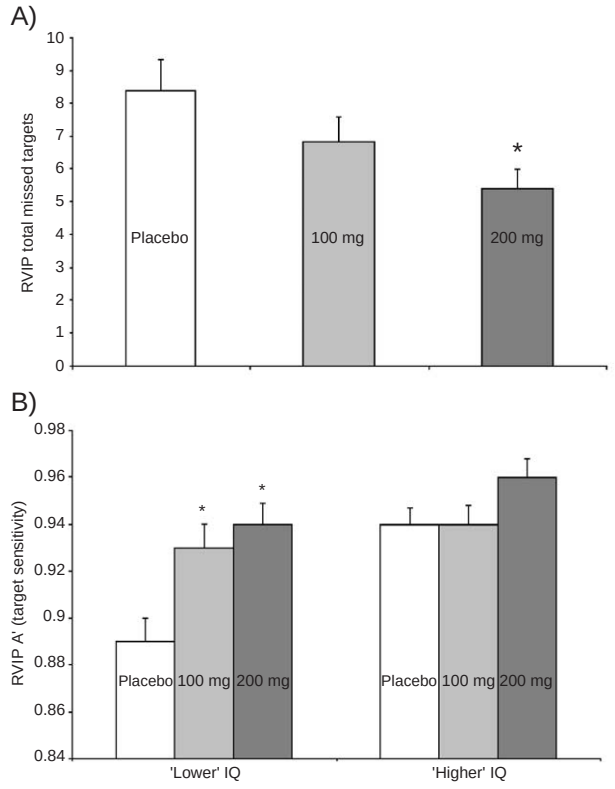

Fig. 1. (A) Mean (±SEM) total missed targets in the RVIP test; *$p<0.05$, compared with placebo; (B) Mean (±SEM) A′ (target sensitivity[#]) in the RVIP test; *$p<0.05$, compared with placebo.

IQ level). These were followed by Mann–Whitney U tests to compare treatment effects in each of the IQ groups. All data were analysed using the Statistical Package for the Social Sciences (SPSS; Chicago, IL, USA), version 12.0 for Windows.

3. Results

3.1. Group characteristics

Characteristics of all the sub-groups are presented in Table 2. There were no significant effects of modafinil or interactions between modafinil and IQ on any of the following measures: NART verbal IQ, habitual sleepiness (the score on the Epworth Sleepiness Scale; Johns, 1991), fatigue (the score on the '11-Item Fatigue Questionnaire'; Chalder et al., 1993), anxiety and depression scores (Hospital Anxiety and Depression Scale; Zigmond and Snaith, 1983), caffeine and alcohol intake (in all cases, $F_{(2,78)}<2.0$, NS). Age also showed no significant effect of modafinil or interactions between modafinil and IQ ($F_{(2,78)}=3.0$, NS). Unsurprisingly, there was a significant main effect of IQ level on the NART verbal IQ measure, with subjects in the 'higher' IQ group having higher IQ scores than subjects in the 'lower' IQ group ($F_{(2,78)}=60.2$, $p<0.0001$).

3.2. Cognitive tasks

Several measures showed no significant effects of modafinil or interactions between modafinil and IQ (in all cases, $F_{(2,78)}\leq 2.5$; $\chi(2)^2\leq 5.7$, NS), see Tables 3 and 4.

3.2.1. Main effects of modafinil

In the RVIP task of sustained attention, modafinil 200 mg significantly ($p<0.05$) reduced the number of missed targets, see Fig. 1A. There was no modafinil × IQ interaction on this measure ($F_{(2,78)}<1.0$, NS).

3.2.2. Modafinil × IQ interactions

In the RVIP test there was also a main effect of modafinil on target sensitivity (measured by A′; $\chi(2)^2=6.4$, $p<0.05$). However, this was due to a significant effect in the 'lower' ($\chi(2)^2=6.9$, $p<0.05$), but not the 'higher' ($\chi(2)^2=3.1$, NS) IQ group. Mann–Whitney U tests subsequently showed that both doses improved target sensitivity in the 'lower' IQ group (100 mg Z=2.0, 200 mg Z=2.5; $p<0.05$ in both cases), see Fig. 1B.

There was a significant modafinil × IQ interaction in the time taken to name coloured dots in the control condition of the Stroop Test ($F_{(2,78)}=3.9$, $p<0.03$). This is because modafinil mainly improved performance in the 'lower' IQ group, see Fig. 2A. There was also a significant modafinil x

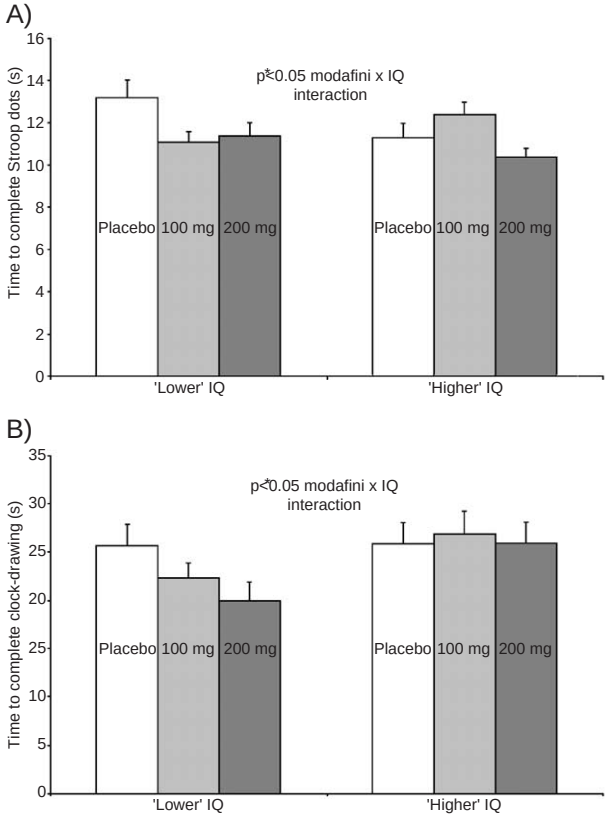

Fig. 2. Mean (±SEM) time taken to complete (A) the colour naming of dots from the Stroop Test and (B) the Clock Drawing test. In both cases, modafinil × IQ interaction, *$p<0.05$, see text for details.

IQ interaction for the time taken to draw a clock ($F_{(2,78)}=4.0$, $p<0.02$), and this was because both doses improved performance in this task, but only in the 'lower' IQ group, see Fig. 2B.

4. Discussion

This retrospective analysis, using a large sample size ($n=89$), revealed significant effects of modafinil that have been reported in previous studies. Improved performance in the RVIP test of sustained attention had been previously found by Randall et al. (2005) in a sample of 60 students with a mean IQ of 109. No effects had been found in a smaller sample of 30 students with a mean IQ of 115 (Randall et al., 2003), which may have resulted from a combination of a small sample and a higher IQ group. A faster speed in naming coloured dots had previously been found by Randall et al. (2004, 2005), using sample sizes of 45 and 60, respectively. Improved performance in clock drawing had previously been found in the group of middle-aged volunteers (Randall et al., 2004), but not in the student studies, where the level of performance in this task was higher (Randall et al., 2003, 2005). However, this meta-analysis did not reveal any more effects of modafinil on cognitive performance than those previously reported with smaller sample sizes and even with our larger sample size we were unable to find any improvement in spatial planning, as had been reported by Turner et al. (2003). This suggests that this may not be an ability that is generally improved by modafinil and that the improvement is very task specific, i.e. seen in New Tower of London, but not in Stockings of Cambridge, which may be because the former is a more difficult task.

The results of the present study strongly suggest that our failure to detect widespread effects of modafinil on performance in our previous studies was not due to insufficient statistical power. As the Digit Span and PRM tasks were used only in our second student study (Randall et al., 2005), these tasks could not be included in the meta-analysis, but improvements by modafinil have been reported in more than one study (Turner et al., 2003, 2004a,b; Randall et al., 2005). The results of the present analysis confirm our previous conclusion (Randall et al., 2005) that modafinil appears to improve performance only in specific tasks. Tests of sustained attention and speed of responding have been affected, but not all speed measures showed positive effects, making the overall pattern of cognitive improvement difficult to classify. Unfortunately, because of the nature of the particular measures of performance in the various tasks (e.g. not all provided speed measures or % accuracy), it was not possible to conduct a meta-analysis of all the tasks. However, this would provide a useful approach for future studies.

The finding of greatest importance in the present study is that the high IQ in many of the samples studied may have limited detection of some of modafinil's effects. Three of the measures showed significant effects of modafinil only in the 'lower' IQ group. This group was still above average IQ and so it would be most interesting to investigate the effects of modafinil in less high-performing groups. Although our middle-aged group showed age-related poorer performance in the speed with which tasks were performed, it was a very high IQ group and this may well have limited detection of positive effects. Our results would also give further support to the findings of Müller et al. (2004), who found that the difficult manipulation condition of a numeric working memory task showed positive effects of modafinil (200 mg) only in the group of poorer performing students. We felt it was important to study students since they are likely to be tempted by the possibility of 'boosting' their 'brainpower' with modafinil and might be particularly likely to use it during examination periods. Our findings, and those of Müller et al. (2004), who observed only subtle performance-enhancing effects of 200 mg in two computerised working memory tasks, should provide evidence that modafinil is unlikely to offer great cognitive benefits to high-performing individuals. The failure to detect substantial positive effects of modafinil in such a population is, according to Müller et al. (2004), not unusual.

The available evidence so far suggests that modafinil is not a 'global cognitive enhancer', but instead can benefit specific cognitive abilities, especially if sleep deprivation or certain pathology is involved. Attentional tasks that are monotonous/boring, and/or lengthy, are sensitive to sleep deprivation (Dinges and Kribbs, 1991) and in these tasks Wesnes and Macher (2004) found positive effects of modafinil. In a review of the literature on stimulant drugs and vigilance performance, Koelega (1993) identified the RVIP task as particularly good for detecting the effects of stimulants. Our students were not sleepy, as assessed on the Epworth Sleepiness Scale, but we were unable to take any objective measures of sleepiness. It is possible that in a sleepy population the effects of modafinil in this task might be even more marked. Although our findings in a high IQ middle-aged group suggested that modafinil might have relatively little effect on age-related cognitive decline, this may well not be the case in a lower IQ group and would also be worthy of further investigation.

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