Psychopharmacology (2004) 177: 161–169
DOI 10.1007/s00213-004-1926-3

ORIGINAL INVESTIGATION

Ulrich Müller · Nikolai Steffenhagen · Ralf Regenthal · Peter Bublak

Effects of modafinil on working memory processes in humans

Received: 6 January 2004 / Accepted: 10 March 2004 / Published online: 24 June 2004

Abstract *Rationale:* Modafinil is a well-tolerated psychostimulant drug with low addictive potential that is used to treat patients with narcolepsy or attention deficit disorders and to enhance vigilance in sleep-deprived military personal. So far, understanding of the cognitive enhancing effects of modafinil and the relevant neurobiological mechanisms are incomplete. *Objectives:* The aim of this study was to investigate the effects of modafinil on working memory processes in humans and how they are related to noradrenergic stimulation of the prefrontal cortex. *Methods:* Sixteen healthy volunteers (aged 20–29 years) received either modafinil 200 mg or placebo using a double blind crossover design. Two computerized working memory tasks were administered, a numeric manipulation task that requires short-term maintenance of digit-sequences and different degrees of manipulation as well as delayed matching task that assesses maintenance of visuo-spatial information over varying delay lengths. The battery was supplemented by standardized paper pencil tasks of attentional functions. *Results:* Modafinil significantly reduced error rates in the long delay condition of the visuo-spatial task and in the manipulation conditions, but not in the maintenance condition of the numeric task. Analyses of reaction times showed no speed-accuracy trade-off. Attentional control tasks (letter cancellation, trail-making, catch trials) were not affected by modafinil. *Conclusions:* In healthy volunteers without sleep deprivation modafinil has subtle stimulating effects on maintenance and manipulation processes in relatively difficult and monotonous working memory tasks, especially in lower performing subjects. Overlapping attentional and working memory processes have to be considered when studying the noradrenergic modulation of the prefrontal cortex.

Keywords Human · Modafinil · Noradrenaline · Prefrontal · Working memory

U. Müller
Department of Psychiatry, University of Leipzig,
Leipzig, Germany

U. Müller (✉)
Departments of Experimental Psychology & Psychiatry,
University of Cambridge,
Downing Site,
Cambridge, CB2 3EB, UK
e-mail: um207@cam.ac.uk
Tel.: +44-1223-333535
Fax: +44-1223-333564

N. Steffenhagen
Max-Planck-Institute of Cognitive Neuroscience,
Leipzig, Germany

R. Regenthal
Department of Clinical Pharmacology, University of Leipzig,
Leipzig, Germany

P. Bublak
Department of Psychology, Ludwig-Maximilians-Universität,
München, Germany

Introduction

Working memory processes, i.e. the short-term maintenance and manipulation of modality-specific information, are mediated by neuronal networks involving prefrontal and parietal cortices as shown by numerous lesion and neuroimaging studies in monkeys and humans (Fuster 1995; Goldman-Rakic 1996). The efficacy of neuronal processing related to working memory is modulated by neurotransmitters including dopamine and noradrenaline (Arnsten and Robbins 2002). The catecholamine modulation of the prefrontal cortex serves the fine-tuning of cognitive functioning in emotionally relevant situations (Aston-Jones et al. 1999; Robbins 2000). Pharmacological studies in monkeys and humans have shown that both short-term memory and executive processes can be improved by noradrenaline agonists, dopamine agonists, and psychostimulant drugs (Arnsten 1998; Robbins 2000; Ellis and Nathan 2001; Müller 2002). In healthy volunteers visual and visuo-spatial working memory performance were dose-dependently modulated by clonidine, a mixed α_1/α_2 noradrenaline receptor agonist (Coull

et al. 1995), and guanfacine, an α2 agonist (Jäkälä et al. 1999). Dose-response relationships are critical and seem to follow an inverted-U curve with both too low and too high levels of catecholamines having detrimental effects on cognition (Arnsten and Robbins 2002).

Modafinil (2-[(diphenylmethyl)sulfinyl]acetamide) is a non-amphetamine psychostimulant drug that is licensed in many countries for the treatment of excessive daytime sleepiness in narcolepsy in doses ranging between 100 and 400 mg per day (McClellan and Spencer 1998; US Modafinil in Narcolepsy Multicenter Study Group 2000; Thorpy et al. 2003; Becker et al. 2004). There seems to be a therapeutic potential in attention deficit hyperactivity disorder (ADHD), both in children (Rugino and Copley 2001) and adults (Taylor and Russo 2000; Turner et al. 2004), as well as in several neuropsychiatric diseases with excessive daytime sleepiness (Högl et al. 2002; Rammohan et al. 2002; DeBattista et al. 2003; Talbot et al. 2003). The mechanism of action of modafinil is still unclear. Its relatively low abuse potential argues against a dopaminergic mechanism (Jasinski 2000). In animal experiments, behavioural effects of modafinil could be antagonized by noradrenergic drugs, but not by a dopamine antagonist (Duteil et al. 1990; Lin et al. 1992). More recent data indicate activation of the hypothalamic arousal (hypocretin) system (Scammell et al. 2000). A pharmacological functional magnetic resonance imaging (fMRI) study with modafinil showed enhanced brain activity during visual processing both in patients with narcolepsy and controls (Ellis et al. 1999).

Several studies have investigated the effects of different doses of modafinil on cognitive performance of young military personnel after sleep deprivation of 35 h and more: most studies used attentional tasks like critical flicker fusion, simple or choice reaction time or mental arithmetic and showed that doses above 100 mg modafinil improve attentional functions and sleepiness (Bensimon et al. 1991; Lagarde and Batejat 1995; Pigeau et al. 1995; Baranski and Pigeau 1997; Baranski et al. 1998; Wesensten et al. 2002). In sleep deprivation studies with more comprehensive cognitive tasks 3×100 mg per day reduced error rates in a visual search task (Stivalet et al. 1998) and 600 mg normalized error rates in a complex flight simulator task as well as EEG parameters and sleepiness (Caldwell et al. 2000). For military missions up to 24 h modafinil is considered to be preferable to naps, for longer missions a combination of naps and modafinil is recommended (Buguet et al. 2003).

Two recent modafinil studies in non-sleep deprived healthy volunteers used computerized tasks focusing on memory, executive and attentional functions, mainly from the Cambridge neuropsychological test automated battery (CANTAB) (Robbins et al. 1998). Turner et al. (2003) found improved performance after modafinil in the digit spans, delayed matching to sample, pattern recognition memory and stockings of Cambridge planning task. However, only the effects of modafinil on planning time for the most difficult problems and on stop signal reaction time were dose-dependent. Randall et al. (2003) found some effects on mood ratings but no cognitive effects of either 100 or 200 mg modafinil. Negative findings in the latter study can be explained by insufficient power due to the small number of subjects (ten per group in a between subjects design) and possible ceiling effects in high performing students. Taken together, these studies in healthy young volunteers show that (a) it is difficult to improve cognition in well rested subjects (b) mainly doses of 200 mg or higher have cognitive enhancing effects and (c) it is not clear which attentional or working memory processes are influenced by modafinil.

The aim of our study was to investigate the effects of modafinil on subprocesses of working memory. A placebo-controlled crossover study was performed in healthy volunteers using a single dose of modafinil 200 mg and computerized cognitive tasks in order to disentangle subtle drug effects on maintenance and manipulation processes. Two working memory tasks were selected that have been extensively used in monkey and human research on working memory: The visuo-spatial delayed matching task is similar to the delayed response task that has been established by the monkey research groups at Yale University (Goldman-Rakic 1996; Arnsten 1998). The manipulation task requires short-term maintenance and manipulation of a numeric sequence. Variants of this task with digit, letter or word sequences and different reordering instructions have been used in clinical (Bublak et al. 2000, 2002; Lewis et al. 2003a), pharmacological (Müller et al. 2004; Honey et al. 2003) and neuroimaging studies (D'Esposito et al. 1999; Gruber et al. 1999; Postle et al. 1999; Barde and Thompson-Schill 2002; Lewis et al. 2003b).

The present study addressed two questions: First, can a single medium dose of modafinil enhance working memory performance in healthy volunteers without sleep deprivation? Second, are the effects of modafinil on human working memory modality or process specific? Facilitating drug effects were predicted for the most difficult conditions of the two working memory tasks, i.e. manipulation of all positions and longest delays.

Materials and methods

Subjects Sixteen healthy students (ten male, six female; mean age 24.1±1.9, range 20–29 years) were recruited by advertisement in the local community and included after medical examination. They had no history of psychiatric, neurological or cardiovascular illness and no major vision or motor impairments. All subjects were advised to sleep sufficiently during the preceding night. Subjects were asked to abstain from alcohol for 12 h as well as for caffeine and nicotine for 3 h before the test sessions. There was a financial compensation of €75 for each participant (plus €25 for blood sampling). The study protocol was approved by the Ethics Committee of the University of Leipzig and all subjects participated with written informed consent.

Design A double-blind, randomised and balanced cross-over design was used. An oral dose of modafinil 200 mg (Vigil, Merckle GmbH, Blaubeuren, Germany) or a placebo (lactose) tablet, both hidden in identical opaque gelatin capsules, was administered on each testing day. The single dose of 200 mg was considered to be a compromise between efficacy, cost-effectiveness and safety when the study was submitted for application. Each subject was tested on 2 days separated by 1 week. Cognitive testing was performed between 90 and 180 min after drug intake, i.e. at ascending or maximal plasma concentrations of modafinil (t_{max}) as reported in the literature (McClellan and Spencer 1998; Wong et al. 1999) and confirmed by plasma level measurements in five randomly selected subjects (Fig. 1). Blood pressure and heart rates were monitored every 30 min. Two psychopathological self-rating scales for state anxiety (state trait anxiety inventory part 1, STAI-1) and subjective well being (Befindlichkeitsskala, Bf-S) were administered at baseline and after cognitive testing as previously described (Müller et al. 1998).

Cognitive tasks Manipulation processes were investigated with a numeric working memory task that requires short-term maintenance and manipulations of four-digit sequences (Bublak et al. 2000, 2002). During each trial, four digits are presented sequentially, followed by a delay of about 4 s and a cue that indicates if the sequence has to be recognised in the original order or re-ordered. In the "easy" manipulation condition the middle two numbers have to be switched (positions 1-2-3-4 to 1-3-2-4) and in the "difficult" manipulation condition all four digits are re-ordered (positions 1-2-3-4 to 3-1-4-2). Trials end with a sequential recognition of the original (no manipulation) or re-ordered sequence (i.e. after "easy" or "difficult" manipulation). In each trial, four consecutive dual-choice responses (left or right) have to be performed with the correct item on randomised positions, right or left to the middle of the screen. Reactions times (RTs) of the first response (initiation times) and of the following three responses (execution times) were analysed separately, because initiation times are more indicative for the duration of the manipulation process (Lewis et al. 2003a, b). Subjects with more than 25% of errors in a preceding practice session were excluded. A total of 96 randomised trials, 32 per manipulation condition (no, easy, difficult manipulation), had to be performed in eight blocks. The task duration was about 35 min.

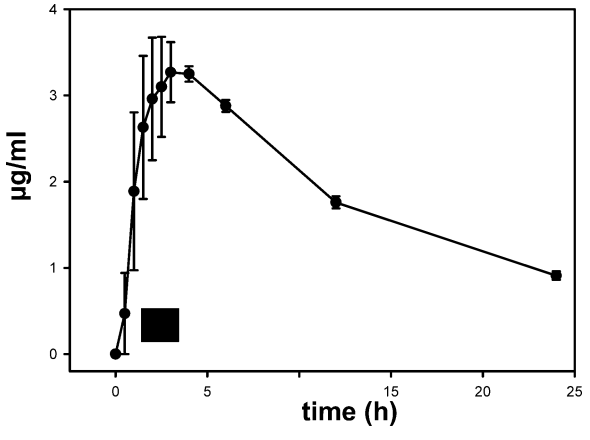

Fig. 1 Plot of mean plasma concentration-time curves (mean±SD) after single oral administration of modafinil 200 mg in five subjects

Maintenance processes were tested using visuo-spatial delayed matching to sample task with three different delay lengths. The task was developed with the intention to (a) be homologue to delay tasks that have been extensively used in monkey research (Goldman-Rakic 1996; Robbins 1998; Arnsten and Robbins 2002), (b) to require only minimal finger movements (button press) instead of difficult pointing or grasping movements, and (c) to be suitable for later application in a neuroimaging experiment. It was implemented using the ERTS software package (Experimental Run Time System, BeriSoft Cooperation, Frankfurt/Main, Germany), which provides millisecond accuracy in stimulus presentation and response registration. Subjects sat in front of a 17-inch monitor (1024×768 resolution) in dim room light; the eye-to-screen distance was 100 cm as controlled by a chin rest. They had to memorize the location of a 2×2 mm yellow square (sample) and compare it after a delay of 1, 4, or 8 s with a second stimulus (match) that appeared on one of five possible positions (−10°, −5°, 0°, +5° or +10°) on an invisible circle (150 mm diameter) around the crosshair fixation (3×3 mm). There were 52 possible locations since the 12 digit positions of the analogue clock were omitted. The subject has to decide whether the match is at the same or a different position by pressing one of two buttons. There was a trial-wise performance feedback: With a correct response the fixation cross changes its colour from yellow to green and with a wrong answer to red (Fig. 2). Each block consisted of 24 randomised trials and two catch trials. Catch trials served to control for fixation of the hair cross and to avoid eye movements; they consisted of a short (250 ms) shrinkage of the fixation cross during the main delay that had to be responded to with a button press. Subjects who missed more than 30% of the catch trials were excluded. A maximum of 240 randomised trials, up to 80 per delay condition, were presented and the task duration was about 30 min.

To control drug effects on attention two well-established paper–pencil tasks, the d2-Test (a letter cancellation task) and ZVT (Zahlenverbindungstest, a German variant of the trail-making task) were administered as previously described (Müller et al. 1998).

Pharmacokinetics In five randomly selected subjects blood samples were taken at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 12 and 24 h after drug administration. When placebo was given on the second day blood sampling was stopped after cognitive testing and debriefing; blood samples were centrifuged immediately at 4°C and serum was stored at −80°C until the end of the study. Modafinil serum concentrations were analysed after solid phase extraction on a Bond Elut C18 reverse phase cartridge by high

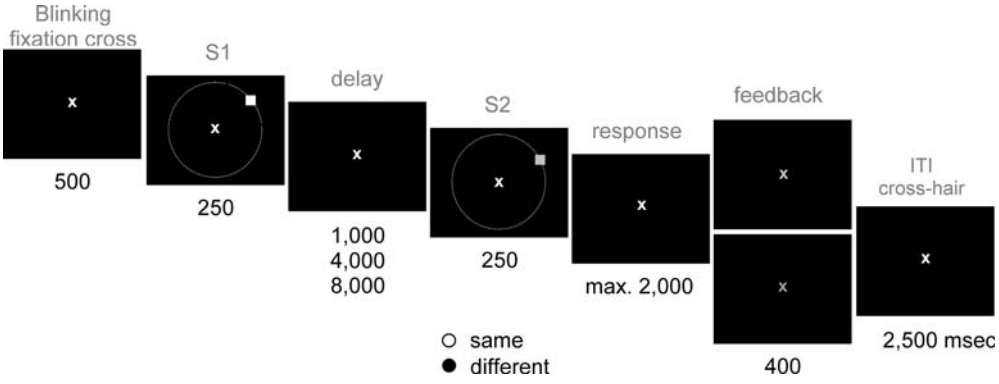

Fig. 2 Visuo-spatial delayed matching task (the *dotted circle* is not shown in the real experiment, feedback stimuli are either *green* or *red*)

performance liquid chromatography (HPLC) and UV detection at 235 nm wave length, according to the method described by Burnat et al. (1998).

Data analysis All data were analysed using windows versions of SPSS (Statistical Package for the Social Sciences). Repeated measures ANOVAs were calculated for the planned main effects and interactions. Sphericity was assessed and the Greenhouse-Geisser conservative *F*-test was used to interpret the ANOVA where necessary. Post hoc contrasts were evaluated by *t*-tests to evaluate drug effects on the different conditions of the working tasks and other selected parameters.

Results

Manipulation processes Performance in the manipulation task was influenced by modafinil. There was a significant main effect for drug [$F(1,15)=5.6$; $P=0.032$] with fewer errors after modafinil; however, no significant drug by manipulation interaction [$F(2,30)=1.2$; $P>0.10$]. Planned post hoc analyses of the modafinil effects revealed no difference ($P>0.10$) for the "no" manipulation condition, a trend ($P<0.09$) for fewer errors in the "easy" manipulation and significantly ($P<0.03$) less errors in the "difficult" manipulation condition (Fig. 3). The mean error rates of both manipulation conditions:

$$\text{error rate}_{\text{manipulation}} = \left[\text{error rate}_{\text{easy manipulation}} + \text{error rate}_{\text{difficult manipulation}}\right]/2$$

were significantly ($P=0.01$) lower after modafinil (3.4 ±2.7% as compared to 5.6±4.1% after placebo). A median split based on the performance on the placebo day revealed that only the relatively "poor manipulators" benefited from modafinil treatment ($P<0.03$) improving from 9.8 to 5.7% of errors, whereas the good manipulators remained good (3.9 versus 3.7%) indicating a floor effect. There were no relationships between performance and state anxiety. As shown before in other studies there was a main effect of manipulation on both errors [$F2,30=5.0$; $P<0.013$] and mean RTs [$F(2,30)=32.2$; $P<0.001$] with increasing manipulation costs. There were no significant drug or drug×manipulation effects on RTs, either on the mean of all four RTs or on the first reaction. Post hoc analyses of RT distributions ("vincentization", see Schubert et al. (2002) for methodological aspects) showed a trend for a decile by drug interaction [$F(8,135)=1.77$; $P=0.089$] with drug-related differences only for the slower RTs, indicating less attention lapses (Fig. 4).

Maintenance processes Error rates in the visuo-spatial delayed matching task were around 35% (Table 1), which is quite high but would have prevented ceiling effects in a study with predicted cognitive enhancement. There were some effects of modafinil on performance: when considering error rates the primary ANOVA showed a drug by delay length interaction on trend level [$F(2,30)=2.9$; $P=0.068$]. Planned post hoc comparisons revealed no differences in error rates after short (1 and 4 s) delays; however, a significant ($P=0.01$) error reduction of 13.7% after modafinil in the long delay condition. The comparison of error rates adjusted for the 1 s control condition

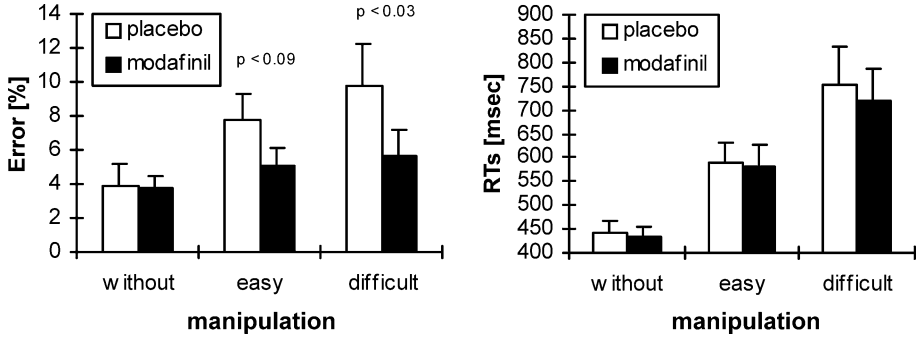

Fig. 3 Error rates and reaction times (*RTs*) in the numeric working memory (manipulation) task (mean±SEM) after modafinil 200 mg or placebo

Table 1 Error rates and reaction times (*RTs*) in the visuo-spatial working memory (maintenance) task (mean±SD) after modafinil 200 mg or placebo

	Drug	Delay length (ms)		
		1,000	4,000	8,000
Errors (%)	Placebo	35.8±7.8	32.5±5.0	37.9±7.1
	Modafinil	34.8±7.0	33.6±7.7	32.7±6.3**
RTs (ms)	Placebo	937±207	889±197	873±183
	Modafinil	894±193*	860±187*	854±172

*P<0.05; **P≤0.01

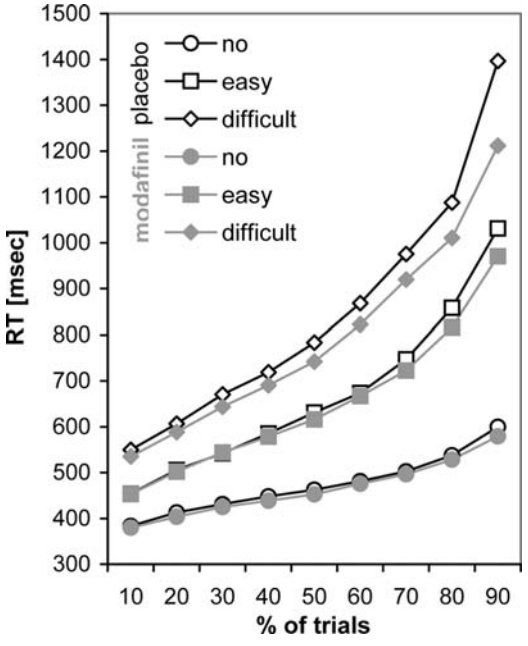

Fig. 4 Reaction time (*RT*) distributions for the no, easy and difficult manipulation conditions in the numeric manipulation task after modafinil 200 mg or placebo

(error rate$_{4\ or\ 8\ s}$ − error rate$_{1\ s}$) showed a marginally significant drug effect [F(1,15)=4.4, P=0.053], but no significant delay effect or drug by delay interaction. A further post hoc comparison revealed a significant (P<0.03) decrease of adjusted errors in the 8 s condition after modafinil (Fig. 5). RTs were significantly faster after modafinil in all delay conditions [F(1,15)=5.5; P=0.033]; however, there was no significant drug by delay length interaction. Further analysis revealed no significant effects of modafinil on RTs in the long delay condition. There was no significant main effect of delay length, either for errors [F(1,30)=2.9; P=0.069] or for RTs [F(1,30)=1.2; P>0.10]. Catch trials were detected correctly in 81.5±15.1% after placebo versus 85.8±15.8% after modafinil; the difference was not significant.

Control parameters Letter cancellation (d2 task) and trail-making (ZVT) were not affected by modafinil (Table 2); there were practice effects when comparing the first and the second day, as previously observed. Modafinil had no significant effects on state anxiety (STAI-1) and mood (Bf-S); self-rated mood did not differ before and after cognitive testing.

Table 2 Effects of modafinil 200 mg or placebo on attentional control tasks and mood ratings (mean±SD, no significant differences). *d2* letter cancelation (high score=good performance); *ZVT* trail-making-A (low time [s]=good performance); *Bf-S* well being (low score=good mood); *STAI-1* state anxiety (low score=low anxiety)

	Attention		Mood	
	d2	ZVT	Bf-S	STAI-1
Placebo	198±48	57.9±12.7	11.6±10.3	30.8±7.3
Modafinil	202±56	57.0±14.5	11.0±8.5	31.9±8.6

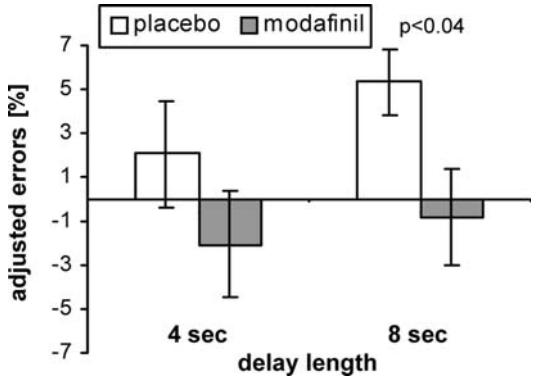

Fig. 5 Error rates (mean±SEM) in the visuo-spatial working memory (maintenance) task adjusted for performance in the short (1 s) delay control condition after modafinil 200 mg or placebo

Systolic (114.8±10.7 versus 119.8±10.7 mmHg) and diastolic (71.5±8.5 versus 74.1±6.9 mmHg) blood pressure as well as heart rate (61.4±6.4 versus 65.5±9.4 per min) were significantly (P<0.05) increased by modafinil when comparing the mean of the last two ("on drug") measurements (135 and 180 min after drug administration); there was no drug effect on sublingual temperature. Cognitive testing was performed at a time of maximal plasma levels of modafinil, as confirmed in a subgroup of five subjects (Fig. 1). The single dose of modafinil 200 mg was generally well tolerated and no unpleasant side effects were observed. In the debriefing at the end of the second day 75% of all subjects attributed the drug to the correct day, which is above chance level but also indicating a reasonable blinding.

Discussion

We have shown that a single dose of modafinil results in subtle improvement of performance in the difficult conditions of two working memory tasks, independent from stimulus modality. After 200 mg of modafinil, young healthy adults without sleep deprivation made fewer errors in the difficult manipulation condition of a numeric task and in the long delay condition of a visuo-spatial maintenance task. The drug did not influence attentional control tasks and mood ratings.

These results confirm and extend findings from previous studies with modafinil in healthy volunteers (Turner et al. 2003) and animals (Béracochéa et al. 2001). Turner et al. (2003) found no effects on attentional (rapid visual information processing), executive (attentional set-shifting) and spatial working memory tasks of the CANTAB, however, there were positive effects of modafinil on performance in the digit span (forward and backward) and pattern recognition memory tasks. Significant effects on RTs in the delayed matching tasks can be explained by speed-accuracy trade-off, i.e. better performance at the expense of slower RTs, whereas in our study reduced errors were accompanied by faster or unchanged RTs. The small cardiovascular effects observed in our study are consistent with the finding of increased systolic blood pressure after modafinil observed by Turner et al. (2003). Randall et al. (2003) found no cognitive or cardiovascular effects of modafinil in a similar, albeit underpowered study. In pharmacological studies with a comparable design working memory performance of healthy volunteers was improved by noradrenaline (Coull et al. 1995; Jäkälä et al. 1999) and dopamine agonists (Müller et al. 1998; Mehta et al. 2001), by conventional psychostimulants like methylphenidate or amphetamine (Mattay et al. 2000) and impaired by noradrenaline and dopamine antagonists (Mehta et al. 1999); these findings are, however, not consistent across all studies, tasks and drugs (Ellis and Nathan 2001; Arnsten and Robbins 2002; Müller 2002).

Some limitations of our study have to be considered. (a) We used a single dose of modafinil and did not investigate dose-related effects. The dose of 200 mg showed cognitive enhancing effects in other studies with non-sleep deprived healthy volunteers. The focus of our study was on the nature of cognitive processes modulated by modafinil rather than dose-dependency of the effects. In the light of recent publications, we would recommend to use at least two doses of 200 and 400 mg modafinil in future studies with healthy volunteers. (b) Crossover designs allow the detection of modest drug effects within a relative small number of subjects; however, practice effects may confound intervention effects. We reduced possible practice effects by training all subjects up to a stable level of performance. Due to problems with consent and blood sampling, plasma levels could only be evaluated in five subjects and no correlations between individual modafinil levels and cognitive parameters could be calculated. (c) Unlike findings with our previous task with more complex visuo-spatial stimuli (Müller et al. 1998) and a pilot study with this task (Müller et al., unpublished data), there were no increases in errors and even a decrease of RTs with increasing delay-length. The trials with the shortest delays were probably too much attention-loaded and the trial-wise (often negative) feedback may have distracted the subjects. Our modafinil effect can, nevertheless, be regarded as maintenance-specific, because it was only observed in the long-delay condition of the task. In a subsequent behavioural study with this task we used block-wise feedback with more consistent results (Müller 2002). (d) The modafinil effect on slower RTs in the manipulation task is hampered by a preceding exclusion of the slowest 10% of reactions in order to control for outliers.

The subtle effects on manipulation performance together with the finding that the benefit of modafinil was mainly observed in the poorer manipulators is compatible with findings in other cognitive drug studies in healthy students; in relatively high performing subjects without brain pathology or experimentally induced impairment it is difficult to improve cognitive performance with any given drug (ceiling effect). Most studies that report cognitive enhancement in healthy volunteers administered modafinil after sleep deprivation (Bensimon et al. 1991; Baranski and Pigeau 1997; Stivalet et al. 1998; Caldwell et al. 2000; Wesensten et al. 2002), a condition with down regulated noradrenergic and/or hypocretin systems (Aston-Jones et al. 1999; Sutcliffe and de Lecea 2002). In non-sleep deprived subjects, pharmacological enhancement of cognitive functions can only be detected with "high resolution" tasks that are difficult enough to avoid ceiling (or floor) effects. Higher doses of psychostimulants may even result in cognitive impairment according to the inverted-U model that predicts optimal cognitive functioning at intermediate cortical catecholamine levels and impairments at both too low and too high levels (Arnsten and Robbins 2002). Neither our study nor any other published study has observed impairment of cognitive performance by higher doses of modafinil. This supports clinical observations of relatively safe use and broad "therapeutic window" in patients with various neuropsychiatric diseases (Jasinski 2000; Taylor and Russo 2000; Rugino and Copley 2001; Högl et al. 2002; Rammohan et al. 2002; DeBattista et al. 2003; Talbot et al. 2003; Thorpy et al. 2003).

The mechanism of action of modafinil remains controversial. Data from animal experiments suggest direct activation of the tuberomammillary nucleus and the hypocretin neurons of the perifornical area (Scammell et al. 2000). Several brain regions are targets of extensive hypocretin projections; in rats and monkeys the most dense arborization of hypocretin axons in the brainstem was detected in the locus coeruleus complex (Horvath et al. 1999; Sutcliffe and de Lecea 2002). Animal models and patient studies suggest that the hypocretin system is dysfunctional in narcolepsy (Nishino 2003), which is the primary indication for modafinil treatment (McClellan and Spencer 1998). An indirect stimulation of noradrenaline and other arousal enhancing neurotransmitters (serotonin, histamine, acetylcholine) seems to be the most plausible mechanism of action of modafinil, at the moment. Glutamate enhancing and GABA inhibiting effects are favoured by other researchers (Ferraro et al. 1999), and there are conflicting studies about the effects of modafinil on dopamine release (Wisor et al. 2001). Further pharmacological studies with various antagonists are necessary to investigate the noradrenergic specificity of modafinil, especially the proposed involvement of the α_1-receptor (Lin et al. 1992).

As indicated by the vincentized RT data, modafinil seems to speed up the slowest responses in the difficult manipulation condition that can be taken as an indication for attention lapses and a noradrenergic mechanism of action (Smith and Nutt 1996). Although our two working memory tasks are not explicitly matched for sensitivity, the findings of this study suggest an underlying attentional mechanism for the facilitating effects of modafinil on both spatial and numerical working memory processes. General fastening of RTs in the maintenance task, selective effects on RT outliers in the manipulation task together with mild increases of blood pressure and heart rate can be taken as evidence for an enhancement of arousal and the speeding of RTs in one task and the lack of process-specific RT or performance effects (no significant interaction of drug and task condition) are indicating complex interactions between arousal and working memory processes. Both in the study of Turner et al. (2003) and in our study, traditional measures of attentional functions like the rapid visual information processing (RVIP), a trail-making task (ZVT), a letter cancellation task and the detection of catch trials were not influenced by modafinil. Enhancement of arousal or vigilance may affect performance in the more difficult conditions of any given cognitive task (Eysenck 1982). High performing subjects might be more able to allocate attentional resources to perform difficult cognitive tasks. This idea is, however, not directly supported by our data and has to be investigated in future studies.

The functional neuroanatomy of maintenance and manipulation processes in working memory has been elucidated by a series of recent neuroimaging studies with event-related fMRI (D'Esposito et al. 1999; Postle et al. 1999; Barde and Thompson-Schill 2002; Glahn et al. 2002; Lewis et al. 2003b). Depending on stimulus modality and task complexity these tasks activate extended neuronal networks. The (dorso)lateral prefrontal cortex is critically involved in more difficult and effort demanding conditions. Future behavioural and neuroimaging studies will investigate the effects of modafinil and other stimulants on maintenance and manipulation processes in working memory and task-related brain activity in order to disentangle the contribution of ascending neurotransmitter systems to the cognitive enhancing effects of modafinil and the overlap of underlying attentional and working memory processes.

In conclusion, the results of this study suggest that modafinil, possibly via hypocretin mediated activation of the locus coeruleus/noradrenaline system, has a potential to enhance difficult and effort demanding working memory processes. These findings are relevant for the treatment of subjects with attention deficit disorders and daytime sleepiness of different etiology.

Acknowledgements The authors are indebted to Dr. Luke Clark and an anonymous reviewer for comments on an earlier version of this paper, to Sandra Brattge and Bettina Johst for programming the delayed matching task, to Anke Pitzmaus for laboratory assistance and to all volunteers for participation. The study was supported by the Max Planck Society and the Alexander von Humboldt-Foundation (Feodor Lynen-Fellowship awarded to U.M.).

References

Arnsten AFT (1998) Catecholamine modulation of prefrontal cortical cognitive function. Trends Cognit Sci 2:436–447

Arnsten AFT, Robbins TW (2002) Neurochemical modulation of prefrontal function in humans and animals. In: Stuss DT, Knight RT (eds) Principles of frontal lobe function. Oxford University, New York, pp 51–84

Aston-Jones G, Rajkowski J, Cohen J (1999) Role of locus coeruleus in attention and behavioral flexibility. Biol Psychiatry 46:1309–1320

Baranski JV, Pigeau RA (1997) Self-monitoring cognitive performance during sleep deprivation: effects of modafinil, D-amphetamine and placebo. J Sleep Res 6:84–91

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. Mol Psychol 10:173–193

Barde LH, Thompson-Schill SL (2002) Models of functional organization of the lateral prefrontal cortex in verbal working memory: evidence in favor of the process model. J Cognit Neurosci 14:1054–1063

Becker PM, Schwartz JR, Feldman NT, Hughes RJ (2004) Effect of modafinil on fatigue, mood, and health-related quality of life in patients with narcolepsy. Psychopharmacology 171:133–139

Bensimon G, Benoit D, Lacomblez L, Weiller E 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

Béracochéa D, Cagnard B, Célérier A, le Merrer J, Pérès M, Piérard C (2001) First evidence of a delay-dependent working memory-enhancing effect of modafinil in mice. Neuroreport 12:375–378

Bublak P, Schubert T, Matthes-von Cramon G, von Cramon Y (2000) Differential demands on working memory for guiding a simple action sequence: evidence from closed-head-injured subjects. J Clin Exp Neuropsychol 22:176–190

Bublak P, Müller U, Grön G, Reuter M, von Cramon DY (2002) Difficult manipulation of working memory information is impaired in Parkinson's disease and related to working memory capacity. Neuropsychology 16:577–590

Buguet A, Moroz DE, Radomski MW (2003) Modafinil: medical considerations for use in sustained operations. Aviat Space Environ Med 74:659–663

Burnat P, Robles F, Do B (1998) High-performance liquid chromatographic determination of modafinil and its two metabolites in human plasma using solid-phase extraction. J Chromatogr B 706:295–304

Caldwell JA Jr, Caldwell JL, Smythe NK III, 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

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

DeBattista C, Doghramji K, Menza MA, Rosenthal MH, Fieve RR, Modafinil in Depression Study Group (2003) Adjunct modafinil for the short-term treatment of fatigue and sleepiness in patients with major depressive disorder: a preliminary double-blind, placebo-controlled study. J Clin Psychiatry 64:1057–1064

Duteil J, Rambert FA, Pessonnier J, Hermant JF, Gombert R, Assous E (1990) Central alpha$_1$-adrenergic stimulation in relation to the behaviour stimulating effect of modafinil; studies with experimental animals. Eur J Pharmacol 180:49–58

D'Esposito M, Postle BR, Ballard D, Lease J (1999) Maintenance versus manipulation of information held in working memory: an event-related fMRI study. Brain Cognit 41:66–86

Ellis KA, Nathan PJ (2001) The pharmacology of human working memory. Int J Neuropsychopharmacol 4:299–313

Ellis CM, Monk C, Simmons A, Lemmens G, Williams SC, Brammer M, Bullmore E, Parkes JD (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

Eysenck MW (1982) Attention and arousal: cognition and performance. Springer, Berlin

Ferraro L, Antonelli T, Tanganelli S, O'Connor WT, Perez de la Mora M, Mendez-Franco J, Rambert FA, Fuxe K (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

Fuster JM (1995) Memory in the cerebral cortex: an empirical approach to neural networks in the human brain and nonhuman primate. MIT Press, Cambridge

Glahn DC, Kim J, Cohen MS, Poutanen VP, Therman S, Bava S, Van Erp TG, Manninen M, Huttunen M, Lonnqvist J, Standertskjold-Nordenstam CG, Cannon TD (2002) Maintenance and manipulation in spatial working memory: dissociations in the prefrontal cortex. Neuroimage 17:201–213

Goldman-Rakic PS (1996) Regional and cellular fractionation of working memory. Proc Natl Acad Sci USA 93:13473–13480

Gruber O, Bublak P, von Cramon DY (1999) The neural correlates of working memory components: a functional magnetic resonance imaging study at 3 Tesla [abstract]. J Cognit Neurosci 11:32–33

Honey RA, Turner DC, Honey GD, Sharar SR, Kumaran D, Pomarol-Clotet E, McKenna P, Sahakian BJ, Robbins TW, Fletcher PC (2003) Subdissociative dose ketamine produces a deficit in manipulation but not maintenance of the contents of working memory. Neuropsychopharmacology 28:2037–2044

Horvath TL, Peyron C, Diano S, Ivanov A, Aston-Jones G, Kilduff TS, van Den Pol AN (1999) Hypocretin (orexin) activation and synaptic innervation of the locus coeruleus noradrenergic system. J Comp Neurol 415:145–159

Högl B, Saletu M, Brandauer E, Glatzl S, Frauscher B, Seppi K, Ulmer H, Wenning G, Poewe W (2002) Modafinil for the treatment of daytime sleepiness in Parkinson's disease: a double-blind, randomized, crossover, placebo-controlled polygraphic trial. Sleep 25:905–909

Jäkälä P, Riekkinen M, Sirviö J, Koivisto E, Kejonen K, Vanhanen M, Riekkinen P Jr (1999) Guanfacine, but not clonidine, improves planning and working memory performance in humans. Neuropsychopharmacology 20:460–470

Jasinski DR (2000) An evaluation of the abuse potential of modafinil using methylphenidate as a reference. J Psychopharmacol 14:53–60

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

Lewis SJ, Cools R, Robbins TW, Dove A, Barker RA, Owen AM (2003a) Using executive heterogeneity to explore the nature of working memory deficits in Parkinson's disease. Neuropsychologia 41:645–654

Lewis SJ, Dove A, Robbins TW, Barker RA, Owen AM (2003b) Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. J Neurosci 23:6351–6356

Lin JS, Roussel B, Akaoka H, Fort P, Debilly G, Jouvet M (1992) Role of catecholamines in the modafinil and amphetamine induced wakefulness, a comparative pharmacological study in the cat. Brain Res 591:319–326

Mattay VS, Callicott JH, Bertolino A, Heaton I, Frank JA, Coppola R, Berman KF, Goldberg TE, Weinberger DR (2000) Effects of dextroamphetamine on cognitive performance and cortical activation. Neuroimage 12:268–275

McClellan KJ, Spencer CM (1998) Modafinil: a review of its pharmacology and clinical efficacy in the management of narcolepsy. CNS Drugs 9:311–324

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

Mehta MA, Swainson R, Ogilvie AD, Sahakian J, Robbins TW (2001) Improved short-term spatial memory but impaired reversal learning following the dopamine D(2) agonist bromocriptine in human volunteers. Psychopharmacology 159:10–20

Müller U (2002) Die katecholaminerge Modulation präfrontaler kognitiver Funktionen beim Menschen (MPI Series in Cognitive Neuroscience 26). Max-Planck-Institut für neuropsychologische Forschung, Leipzig

Müller U, von Cramon DY, Pollmann S (1998) D_1- versus D_2-receptor modulation of visuospatial working memory in humans. J Neurosci 18:2720–2728

Müller U, Mottweiler E, Bublak P (2004) Noradrenergic blockade and numeric working memory in humans. J Psychopharmacol (in press)

Nishino S (2003) The hypocretin/orexin system in health and disease. Biol Psychiatry 54:87–95

Pigeau R, Naitoh P, Buguet A, McCann C, Baranski J, Taylor M, Thompson M, Mack II (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

Postle BR, Berger JS, D'Esposito M (1999) Functional neuroanatomical double dissociation of mnemonic and executive control processes contributing to working memory performance. Proc Natl Acad Sci USA 96:12959–12964

Rammohan KW, Rosenberg JH, Lynn DJ, Blumenfeld AM, Pollak 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

Randall DC, Shneerson JM, Plaha KK, File SE (2003) Modafinil affects mood, but not cognitive function, in healthy young volunteers. Hum Psychopharmacol Clin Exp 18:163–173

Robbins TW (1998) Homology in behavioural pharmacology: an approach to animal models of human cognition. Behav Pharmacol 9:509–519

Robbins TW (2000) Chemical neuromodulation of frontal-executive functions in humans and other animals. Exp Brain Res 133:130–138

Robbins TW, James M, Owen AM, Sahakian BJ, Lawrence AD, McInnes L, Rabbitt PM (1998) A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: implications for theories of executive functioning and cognitive aging. Cambridge neuropsychological test automated battery. J Int Neuropsychol Soc 4:474–490

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

Scammell TE, Estabrooke IV, McCarthy MT, Chemelli RM, Yanagisawa M, Miller MS, Saper CB (2000) Hypothalamic arousal regions are activated during modafinil-induced wakefulness. J Neurosci 20:8620–8628

Schubert T, Volkmann J, Müller U, Sturm V, Voges J, Freund HJ, Von Cramon DY (2002) Effects of pallidal deep brain stimulation and levodopa treatment on reaction-time performance in Parkinson's disease. Exp Brain Res 144:8–16

Smith A, Nutt D (1996) Noradrenaline and attention lapses. Nature 380:291

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

Sutcliffe JG, de Lecea L (2002) The hypocretins: setting the arousal threshold. Nat Rev Neurosci 3:339–349

Talbot K, Stradling J, Crosby J, Hilton-Jones D (2003) Reduction in excess daytime sleepiness by modafinil in patients with myotonic dystrophy. Neuromuscul Disord 13:357–364

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

Thorpy MJ, Schwartz JR, Kovacevic-Ristanovic R, Hayduk R (2003) Initiating treatment with modafinil for control of excessive daytime sleepiness in patients switching from methylphenidate: an open-label safety study assessing three strategies. Psychopharmacology 167:380–385

Turner DC, Robbins TW, Clark L, Aron AR, Dowson J, Sahakian BJ (2003) Cognitive enhancing effects of modafinil in healthy volunteers. Psychopharmacology 165:260–269

Turner DC, Clark L, Dowson J, Robbins T, Sahakian B (2004) Modafinil improves cognition and response inhibition in adult attention-deficit/hyperactivity disorder. Biol Psychiatry 55:1031–1040

US Modafinil in Narcolepsy Multicenter Study Group (2000) Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. Neurology 54:1166–1175

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

Wisor JP, Nishino S, Sora I, Uhl GH, Mignot E, Edgar DM (2001) Dopaminergic role in stimulant-induced wakefulness. J Neurosci 21:1787–1794

Wong YN, King SP, Simcoe D, Gorman S, Laughton W, McCormick GC, Grebow P (1999) Open-label, single-dose pharmacokinetic study of modafinil tablets: influence of age and gender in normal subjects. J Clin Pharmacol 39:281–288