Neuropharmacology 64 (2013) 490–495

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

# Effects of modafinil on non-verbal cognition, task enjoyment and creative thinking in healthy volunteers

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ARTICLE INFO

*Article history:*
Received 8 May 2012
Received in revised form
2 July 2012
Accepted 4 July 2012

*Keywords:*
Modafinil
Executive functions
Memory
Creative thinking
Motivation
Cognitive enhancer

ABSTRACT

*Background:* Modafinil, a putative cognitive enhancing drug, has previously been shown to improve performance of healthy volunteers as well as patients with attention deficit disorder and schizophrenia, mainly in tests of executive functions. The aim of this study was to investigate the effects of modafinil on non-verbal cognitive functions in healthy volunteers, with a particular focus on variations of cognitive load, measures of motivational factors and the effects on creative problem-solving.
*Methods:* A double-blind placebo-controlled parallel design study evaluated the effect of 200 mg of modafinil ($N = 32$) or placebo ($N = 32$) in non-sleep deprived healthy volunteers. Non-verbal tests of divergent and convergent thinking were used to measure creativity. A new measure of task motivation was used, together with more levels of difficulty on neuropsychological tests from the CANTAB battery.
*Results:* Improvements under modafinil were seen on spatial working memory, planning and decision making at the most difficult levels, as well as visual pattern recognition memory following delay. Subjective ratings of enjoyment of task performance were significantly greater under modafinil compared with placebo, but mood ratings overall were not affected. The effects of modafinil on creativity were inconsistent and did not reach statistical significance.
*Conclusions:* Modafinil reliably enhanced task enjoyment and performance on several cognitive tests of planning and working memory, but did not improve paired associates learning. The findings confirm that modafinil can enhance aspects of highly demanding cognitive performance in non-sleep deprived individuals.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.



## 1. Introduction

Modafinil (Provigil, 1997) is a wake promoting agent of largely unknown mechanism with demonstrable efficacy in the treatment of daytime sleepiness associated with narcolepsy (Benerjee et al., 2004) and shift-work (Czeisler et al., 2005). Modafinil has been shown to significantly improve performance on tests of executive cognition such as working memory, cognitive flexibility and planning in non sleep-deprived healthy volunteers (Turner et al., 2003; Müller et al., 2004; Minzenberg and Carter, 2008; Finke et al., 2010; Repantis et al., 2010; Mohamed and Sahakian, 2012) and in patients with neuropsychiatric disorders (Turner et al., 2004; Turner, 2006; Minzenberg and Carter, 2008). These pro-cognitive effects of modafinil are of possible therapeutic importance given its low liability for abuse (Deroche-Gamonet et al., 2002), lower risk of adverse effects on the cardiovascular system (Makris et al., 2004; Lynch et al., 2009) and lack of anxiogenic effects that may occur with typical stimulant drugs such as dexamphetamine (Simon et al., 1994).

Turner et al. (2003) originally showed that a single oral dose of modafinil (100 mg or 200 mg) significantly improved performance on tests of digit span, visual recognition memory, visuospatial planning, and stop-signal reaction time (SSRT), but not self-ordered spatial working memory (SWM) in healthy volunteers. The same doses also lengthened response times in tests of decision making, delayed matching to sample, and visuospatial planning, suggesting

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http://dx.doi.org/10.1016/j.neuropharm.2012.07.009

some effects on speed-error trade-offs. However, other findings are inconsistent with this interpretation, whilst still obtaining reliable cognitive enhancing effects (Müller et al., 2004; Marchant et al., 2009; Winder-Rhodes et al., 2010). Some studies have failed to find robust cognitive enhancing effects on performance of modafinil using similar tests, although some of these were flawed due to insufficient statistical power (see Randall et al., 2005).

In order to address these issues, the present study used a single dose of modafinil 200 mg (Turner et al., 2003; Minzenberg et al., 2008) in a placebo-controlled double-blind design with non sleep-deprived healthy volunteers.

There were three key advances on previous work: First, variations of the cognitive tests which utilised a wider range of cognitive load or task difficulty were employed, in the case of three 'CANTAB' tests: self-ordered spatial working memory (SWM); one-touch 'Stockings of Cambridge' (SoC) test of planning; and the test of visuospatial paired-associates learning (PAL). Performance improvements in the more difficult task conditions were predicted. Second, we investigated if previously established effects on non-verbal on memory and executive functions could be extended to non-verbal 'creative' reasoning, using tasks similar to those adopted in a study of effects of amphetamine by Farah et al. (2009). Finally, we also employed subjective measures of performance, as well as standard analogue mood and cardiovascular indices, because of suggestions that modafinil might influence cognition in part through possible effects on motivation or arousal. Our cognitive tasks were selected so that we could test the hypothesis of cognitive enhancing effects of a single dose of modafinil in healthy participants without sleep deprivation.

## 2. Methods

### 2.1. Participants

Sixty four healthy male ($n$ = 31) and female ($n$ = 33) volunteers (mean age ± SD = 25.34 ± 3.95, range 19–36 years) were identified via the University of Cambridge Behavioural and Clinical Neuroscience Institute subject panel and via local advertisements. All participants were screened by an experienced psychiatrist (UM) or neurologist (JBR). Subjects were excluded if they had any significant psychiatric history, visual or motor impairment or the concurrent use of any psychotropic medications or any medication contra-indicated with modafinil. In addition, participants with a history of hypertension, cardiac disorders, epilepsy, drug or alcohol abuse were also excluded. All subjects were advised not to consume alcohol or caffeine for 12 h before the testing sessions. All participants were questioned about compliance with alcohol and caffeine restrictions before inclusion into the study. Smoking history was not recorded but as subjects were randomly allocated to the two groups, there should have been no difference between groups. A light breakfast or snack and juice were allowed before, but not during, the experimental session. Each participant gave a written consent prior to testing and received monetary compensation of £25 plus local transport expenses.

### 2.2. Research governance

The protocol was approved by the Cambridge Local Research and Ethics Committee (LREC No. 10/H0305/39) and exempted from clinical trial status by the Medicines and Health Care Products Regulatory Agency (MHRA), London, the national drug licensing agency.

### 2.3. Pharmacological design

This was a randomised, placebo controlled and double-blind study with a parallel group design, deliberately chosen to avoid problems with practice effects that are common in studies with crossover subjects design on tasks of executive and memory functions.

Participants were randomly allocated to one of two blinded medications: modafinil or placebo. This allowed us to control the matching of parallel groups in the course of the study. In order to balance drug conditions for gender, males and females were separately randomised for medications. Unblinding of the medication followed after the data analysis. All volunteers were asked to spend the waiting time with low arousing activities (reading, watching TV or napping) in a day room and were monitored by research nurses. Cognitive testing stated 2 h after drug administration in a silent consultation room at the Wellcome Trust Clinical Research Facility at Addenbrooke's Centre for Clinical Investigation.

### 2.4. Procedure

Subjects completed questionnaires assessing mood and creativity (Visual Analogue Scale, Bond and Lader, 1974; Gough, 1979) and were tested for verbal IQ (National Adult Reading Test, Nelson and Willison, 1991). Following that, a baseline blood pressure and pulse was taken and a single oral dose of 200 of modafinil (Provigil) or placebo (lactose) hidden in identical opaque gelatin capsules was administered with a small glass of water. Dose selection was based on previous cognitive studies in healthy volunteers (Turner et al., 2003) and clinical studies in patients with ADHD (Turner et al., 2004) as well the best recommended therapeutic dose by the British National Formulary 2010 (www.bnf.org). Peak plasma concentrations of modafinil have been obtained 2–3 h after oral administration with an elimination half-life of 10–12 h (Wong et al., 1998; Müller et al., 2004). Therefore, 2 h post-drug administration subjects completed the digit span, a reliable battery of computerised neuropsychological tasks measuring executive function and working memory, and objective creativity and motivational saliency tasks (see Table 1). The test battery was performed in fixed order.

### 2.5. Physiological measures

Blood pressure and pulse measurements were taken using a Criticare Systems Inc. Comfort Cuff (Model 507NJ) at baseline (0 h), during waiting time (+1 h), immediately prior to testing (+2 h), during a short break (+3 h) and after completion of the cognitive test battery (+4 h).

### 2.6. Mood rating and task motivation scale

Participants completed visual analogue scales (VAS, Bond and Lader, 1974) before administration of the drug (baseline) and at intervals during the testing session: immediately prior to testing (2 h post dosing), 1 h into testing (3 h post dosing) and on completion of testing (discharge). At each time point subjects were asked to rate their feeling in terms of 16 dimensions. The measures used in this study were alert–drowsy, calm–excited, strong–feeble, muzzy–clear headed, well coordinated–clumsy, lethargic–energetic, contented–discontented, troubled–tranquil, mentally slow–quick witted, tense–relaxed, attentive–dreamy, incompetent–proficient, happy–sad, antagonistic–amicable, interested–bored and withdrawn–gregarious. The dimensions were presented as 100-mm lines, the two extremes of the emotion (e.g. 'alert' and 'drowsy') written at each end, and subjects marked where they felt they ranked on each line. Factors of "alertness", "contentedness", "calmness" and "tranquility" were calculated as proposed by Bond and Lader (1974) and Herbert et al. (1976).

Task motivation and pleasure was measured using a computerised VAS. After each task participants were asked "Please rate your feelings on the task you took today" and had to slide a pointer accordingly on a scale from "0 = not unpleasant" to "10 = very pleasurable" using a computer mouse.

### 2.7. Neuropsychological measures

Many of the cognitive measures in this study were drawn from the CANTAB battery (www.camcog.com) (Sahakian and Owen, 1992; Robbins et al., 1998), but using novel versions of some of these tasks which included more difficult levels. All computerised tasks were run on an Advantech personal computer (Model PPC-120T-RT), and responses were registered either via the touch-sensitive screen or a response key, depending on the task. A brief description of the key measures for each of the tasks is presented in Table 1. For full details of each outcome measure see CANTABeclipse™ (2011) Test Administration Guide.

To measure non-verbal (visuospatial) declarative memory, we used a version of the CANTAB PAL with an additional level of 12 pattern/location associations ('Duke no ceiling', 12 patterns), and an amended version of the Pattern Recognition Memory (PRM) task, which included an additional delayed recognition test after 20 min. For assessment of verbal and non-verbal working memory, we used forward and backward digit span from the Wechsler Adult Intelligence Scale (Wechsler, 1981) and the SWM task from CANTAB with an additional 10-box level. Executive function was tested by a novel variant of CANTAB tower of London task, the 'one-touch' version of the Stockings of Cambridge (SOC) spatial planning task (Owen et al., 1995) which included a choice of from one to seven; there were, however, no seven move problems, the most difficult problems were six move.

### 2.8. Statistical analysis

All data were analysed using the Windows versions of SPSS (Version 15, SPSS, Chicago). To investigate the effect of experimental treatment on test performance, differences between group mean performances for single measures were analysed using one-way analysis of variance (ANOVA) or the equivalent non-parametric Kruskal–Wallis ANOVA. Repeated measures ANOVA were used to test the effects of relevant independent within- and between-subjects variables. To clarify the