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Abstract

Previous research has demonstrated cognitive-enhancing effects of modafinil in humans and generated evidence for its therapeutic potential in psychiatric disorders. The neurochemical basis of these effects remains unresolved although a role for $\alpha 1$ -adrenoceptors has been hypothesised. In this within-subject, double-blind, placebo-controlled study, 12 healthy male adults received modafinil (300 mg), the $\alpha 1$ -adrenoceptor antagonist prazosin (3 mg), both together and placebo on separate occasions at least 5 days apart. Cognitive effects were assessed using a well-validated testing battery focusing on executive and working memory functions. Blood pressure, heart rate and salivary α -amylase (sAA) were measured at hourly intervals. Cognitive effects of modafinil and prazosin were identified at the difficult levels of the One-Touch Stockings of Cambridge (OTSOC) planning task. Prazosin antagonized the error-reducing effect of modafinil when the agents were given together. In contrast, the combined agents

acted synergistically to increase time taken to complete OTSOC problems compared with placebo. The tachycardic and sAA-elevating effects of prazosin were also potentiated by concurrent modafinil administration. The current data suggest that the cognitive effects of modafinil on performance accuracy and latency are dissociable in terms of their neurochemical mechanisms. Our findings support the hypothesised involvement of $\alpha 1$ -adrenoceptors in some of the cognitive-enhancing effects of modafinil and warrant further investigation.

Key words

attention deficit hyperactivity disorder (ADHD); cognition; executive function; human; modafinil; noradrenaline; physiological effects; prazosin; prefrontal cortex; salivary α -amylase

Introduction

The wake-promoting agent modafinil has attracted considerable interest in recent years following recognition of its cognitive-enhancing potential in humans (Chamberlain, *et al.*, 2007; Minzenberg and Carter, 2008; Rugino and Samscock, 2003; Turner, *et al.*, 2003; Turner, *et al.*, 2004a; Turner, *et al.*,

2004b). A well-defined biological mode of action for modafinil, however, remains to be elucidated. Computerised cognitive tasks such as those in the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition, <http://www.camcog.com>) have proven to be effective tools for assessing the domain-specific influence of modafinil on cognitive performance in healthy volunteers and patient groups. By these means, beneficial effects of modafinil have been

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demonstrated on discrete aspects of cognition including mnemonic function [Digit Span tasks, delayed matching to sample tasks, Pattern Recognition Memory (PRM)], planning (Stockings of Cambridge task) and response inhibition (Stop-Signal task) (Müller, *et al.*, 2004; Turner, *et al.*, 2004a; Turner, *et al.*, 2004b; Turner, *et al.*, 2003). Increased performance accuracy has been observed in conjunction with a slowing of response latency on several tasks relative to placebo (Turner, *et al.*, 2004a; Turner, *et al.*, 2003), prompting suggestions that modafinil may act to increase vigilance. The influence of modafinil may be subtle, restricted to challenging tasks (Müller, *et al.*, 2004) and limited in healthy, non-sleep-deprived or high-performing volunteers (Randall, *et al.*, 2004; Randall, *et al.*, 2003). However, the demonstrable pro-cognitive properties and high-tolerability of modafinil make it a promising candidate for the treatment of cognitive dysfunction associated with a range of neuropsychiatric disorders. Indeed, modafinil has recently demonstrated efficacy in the treatment of attention-deficit hyperactivity disorder (ADHD), a condition often characterized by impairments in 'executive functions', which include planning, working memory and inhibitory control (Chamberlain, *et al.*, 2007; Taylor and Russo, 2000; Turner, 2006).

The emerging therapeutic indications for modafinil encourage attempts at elucidating its presently unknown mechanism of action as an atypical psychomotor stimulant (reviewed in Minzenberg and Carter, 2008). The proposed interaction of modafinil with arousal and attentional circuitry is well substantiated, given the clinical efficacy of this agent in the treatment of narcolepsy (Banerjee, *et al.*, 2004). Various neurotransmitter systems have been implicated in the actions of modafinil, and a permissive role for the noradrenergic system has been demonstrated. For example, modafinil inhibits the noradrenaline transporter (Madras, *et al.*, 2006) and elevates extracellular noradrenaline levels in various brain regions including the pre-frontal cortex, a heterogeneous brain region that forms part of the neural circuitry underlying the executive functions (de Saint Hilaire, *et al.*, 2001). It is further posited that modafinil confers adaptive shifts in cortical gain and thus optimises information processing by modulation of the ascending locus-coeruleus noradrenergic system (Minzenberg, *et al.*, 2008). This is consistent with other evidence from tests of pharmacological antagonism and receptor knock-out studies that indicates a requirement for intact $\alpha 1$ -adrenoceptors in the actions of modafinil (Duteil, *et al.*, 1990; Lin, *et al.*, 1992; Stone, *et al.*, 2002).

A well-defined biochemical action of modafinil will be informed by a clearer profile of its physiological effects. Various animal and human studies have reported modafinil-associated hypertension and tachycardia, in addition to elevations in plasma noradrenaline and adrenaline indicative of elevated adrenomedullary discharge (Makris, *et al.*, 2004; Müller, *et al.*, 2004; Taneja, *et al.*, 2005). However, other studies have reported no effect of the drug on cardiovascular, salivary regulation or peripheral adrenoceptor activity (Heitmann, *et al.*, 1999; Hou, *et al.*, 2005).

This study sought to investigate the mechanism of action of modafinil by assessing its effects in combination with the centrally acting α -adrenoceptor antagonist prazosin in healthy male volunteers. Prazosin is primarily classified as an $\alpha 1$ -adrenoceptor antagonist; however, it also demonstrates a high affinity for α -2B and α -2C adrenoceptors (Bylund, 1992). Used in the treatment of hypertension and benign prostatic hyperplasia, it has more recently been associated with impairment of motor learning (Sawaki, *et al.*, 2003) and reduction of emotional arousal (reviewed in Chamberlain, *et al.*, 2006), with demonstrable efficacy in the treatment of post-traumatic stress disorder (PTSD) – a condition characterized by persistent emotional memories and associated with detrimental elevations in noradrenaline (Dierks, *et al.*, 2007; Miller, 2008; Taylor, *et al.*, 2006; Taylor, *et al.*, 2008).

A collection of previous studies reported that prazosin counteracted the increases in arousal and activity induced by modafinil in various non-human species (Duteil, *et al.*, 1990; Hermant, *et al.*, 1991; Lin, *et al.*, 1992). This study aimed to extend these findings to humans, with a focus on cognitive and physiological parameters. We used a validated testing battery to assess drug-induced variations in memory, planning and attention and thereby further define the putative agonist–antagonist relationship between the two agents. We hypothesized that a single dose of modafinil would improve aspects of cognitive performance in healthy human volunteers and that this effect would be blocked by concurrent administration of a single dose of prazosin.

Methods

Participants

Twelve healthy male volunteers aged 18–40 years (mean age \pm SD = 26.3 \pm 6.6 years, range = 18–39) were recruited by newspaper advertisement in the local community. Before enrolment, all potential participants undertook a clinical interview, which included the revised Beck Depression Inventory (Steer, *et al.*, 1999). Exclusion criteria included any psychiatric history including substance abuse, cardiovascular/neurological/metabolic disease, intake of medication contra-indicated with prazosin or modafinil, consumption of more than five cigarettes a day and consumption of more than 24 units of alcohol per week. Volunteers were requested to abstain from alcohol for 12 h as well as from caffeine and nicotine for 3 h before the test sessions. Verbal IQ estimates were calculated with the National Adult Reading Test (Nelson, 1982), and participants were excluded from the study if they scored <90 (mean score for the group \pm SD = 115.1 \pm 4.7; range = 103.3–122.6). Each participant received a financial compensation of £60 per visit. The study protocol was approved by the Cambridge Research Ethics Committee (CamREC reference number 06/Q0106/47) and Addenbrooke's Research and Development (R&D) office and was formally exempted from clinical trial status by the Medicines Healthcare Regulatory Agency (MHRA), London. All participants gave written informed consent.

Experimental design

This study followed a within-subject, double-blind, placebo-controlled design. Each volunteer participated in four sessions at the Wellcome Trust Clinical Research Facility at Addenbrooke's Hospital, Cambridge. Visits were a minimum of five days apart, and each was of approximately 5-h duration. On each occasion, participants received any one of the following: 1) 300 mg of modafinil, 2) 300 mg of modafinil plus 3 mg of prazosin 3) 3 mg of prazosin or 4) a placebo. Medications were randomised by the supplying pharmacy and were administered orally in identical capsules. The drugs were counterbalanced using a half-randomisation grid across three testing sessions and randomized for the fourth. The chosen doses were within the standard clinical ranges for modafinil and prazosin (British National Formulary, <http://www.bnf.com>) and selected on the basis of the available literature to achieve a compromise between efficacy and tolerability. The dose of modafinil was consistent with that used in certain previous studies that have demonstrated significant cognitive effects of this agent in healthy volunteers (Minzenberg and Carter, 2008; Müller, *et al.*, 2004). The prazosin dose was chosen to be within the effective dosing range for PTSD and therefore relevant to current psychiatric research, without being so high as to unduly increase the risk of adverse effects (Dierks, *et al.*, 2007; Miller, 2008; Taylor, *et al.*, 2006; Taylor, *et al.*, 2008). Neuropsychological testing was conducted 2 h after capsule administration based on previous neuropsychological studies (Müller, *et al.*, 2004; Turner, *et al.*, 2003), and given that peak-plasma levels of the two drugs were anticipated to occur around this time (Robertson and Hellriegel, 2003). The half-lives of modafinil and prazosin are 12–15 h (Robertson and Hellriegel, 2003) and 2.5 h (Jaillon, 1980), respectively. By testing volunteers at least five days apart, we allowed a substantive wash-out period of more than five half-lives for each agent.

Cognitive assessment

Each participant undertook a 1-h battery of well-validated neuropsychological tests during each visit. Tasks were specifically chosen to assess the effects of the agents across different cognitive domains and included a selection of tests from the CANTAB (Sahakian and Owen, 1992; <http://www.camcog.com>). There was no practice prior to the first experimental session, and all participants received the tests in the same order. Parallel versions of the digit span and pattern recognition tasks with novel number sequences and patterns were used between visits so that variants of the task were randomised within each drug condition. Computerised tasks were run on the Paceblade tablet personal computer, and responses were registered either via the touch-sensitive screen or via a response key, depending on the task. The testing battery is outlined (in order) below.

Digit Spans Participants were asked to listen to sequences of numbers that were read aloud by the assessor and then to repeat them back verbally, either in forward or in backward order as instructed. The sequences got progressively longer

(extending from two digits to a maximum of nine), and there were two tests at each level. One point was awarded for each sequence repeated correctly. Failure at the second attempt of any particular level terminated the test (Wechsler, 1981).

Digit Ordering Span Participants were asked to listen to sequences of numbers that were read aloud by the assessor, then to rearrange the numbers in their head and to repeat them back in ascending numerical order. As in Digit Span, this was repeated for sequences up to nine digits (Müller, *et al.*, 2005).

CANTAB Pattern Recognition Memory: immediate In this test of abstract visual PRM, participants were presented with 12 patterns, which appeared one after another in the centre of the screen. Following this, pairs of patterns were displayed; for each pair, participants were asked to discriminate the pattern which they had already seen from that which was novel. This was repeated in a second stage with 12 new patterns. A record was made of the percentage of correct choices.

CANTAB Rapid Visual Information Processing: extended version In this test of sustained attention (with a small working-memory component), participants were asked to focus on a box in the centre of the screen in which single numerical digits appeared one after the other pseudo-randomly at a rate of 100 digits per minute. Participants were instructed to signal the detection of target sequences that consisted of three specified digits appearing consecutively (e.g., 3-5-7) by pushing the button on the press-pad. A record was made of a measure relating to the proportion of accurately detected sequences [Rapid Visual Information Processing (RVIP) A], and the tendency to respond regardless of whether or not the target was present (RVIP B).

CANTAB One-Touch Stockings of Cambridge In this test of spatial planning and working memory, participants were presented with two displays on the computer screen. Each showed three coloured balls arranged within three columns ('stockings'). In the practice trial, participants were asked to rearrange the balls in the lower display (taking balls from the top of each column only) so that it mimicked the upper (template) display and to aim to achieve this in the least possible number of moves. Tests were at a range of difficulty levels, requiring between 1 and 6 moves for completion. In the tested version, participants were not required to move the balls, but instead, they were requested to select the number of moves that they thought the solutions to these problems required from a list of seven possibilities at the bottom of the screen. Participants were allowed as many attempts as required to solve each problem in the task, and there were a total of 24 problems. A record was made of the number of attempts made and the time taken (ms) to correctly solve the task at each level.

CANTAB Stop-Signal task This task measured the ability to inhibit prepotent responses. On each trial, a left- or right-pointing arrow appeared within a fixation circle on the

screen. The participant was asked to respond as quickly as possible by pressing the button on the press-pad, which corresponded with the direction of the arrow, that is, left-hand or right-hand (Go task). On a quarter of the trials, a beep was randomly sounded. On hearing the beep, subjects had to refrain from responding (Stop task). In the Stop task, an estimate of stop signal reaction time was generated using staircase functions. During trials, no feedback was given as to whether there was correct or failed stopping, but discrimination errors (e.g., pressing the left key following presentation of a right-pointing arrow) generated the message "Wrong!" Participants performed a practice block of 16 Go trials, before completing 5 blocks of 64 trials, with 16 stop trials per block. They were encouraged to respond as quickly as possible and to avoid anticipating the beep. A record was made of the median reaction time during Go task trials (ms) and the stop-signal reaction time (SSRT), a key measure of inhibitory control.

Physiological assessment

Blood pressure and heart rate were measured at baseline and at 1, 2 and 3 h following capsule administration using a Dinamap system (GE Healthcare, UK). Saliva samples were also obtained from participants at hourly intervals using the Salivette system (Sarstedt AG, Nürnberg, Germany). This non-invasive technique required participants to chew on a cotton roll for 3 min. Samples were then centrifuged to obtain saliva and stored at -20°C . The samples were later analysed for levels of

α -amylase, a neuroendocrine marker thought to reflect noradrenergic activity (Rohleder, *et al.*, 2004; van Stegeren, *et al.*, 2006).

Statistical analysis

Data were subjected to within-subjects repeated-measures analysis of variance (ANOVA) with four treatment factors (prazosin, modafinil, both together, and placebo). Where Mauchly's test indicated that the assumption of sphericity had been violated and degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity. Significant treatment/time/level of difficulty effects or interactions was explored further using *post hoc* tests. In such instances, simple (within-subject) contrasts and paired *t*-tests (two-tailed) were used to compare performance between treatment conditions and placebo, between time-points and baseline (i.e., $t = 0$ h) and between difficulty levels and easiest levels. Given the exploratory nature of this study, we report significant differences as $P < 0.05$ and trends as $0.05 < P < 0.10$. Data collected were compiled in a relational database (Microsoft Excel 2000) and analysed using Statistical Package for the Social Sciences (SPSS) version 15.

Results

Cognitive measures

Mean performance data under each drug condition for the volunteers are displayed in Table 1. There were significant

Table 1 Summary of test results

	Placebo	Modafinil	Prazosin	Both	Treatment effect, <i>P</i> value
PRM					
% correct	93.1 \pm 6.7	90.3 \pm 10.7	89.3 \pm 13.2	90.3 \pm 9.5	0.469
SST					
Median correct RT Go trials (ms)	312.6 \pm 60.9	309.2 \pm 41.4	311.8 \pm 33.4	314.1 \pm 51.1	0.954
SSRT (ms)	172.7 \pm 42.0	167.9 \pm 91.0	184.2 \pm 41.20	176.9 \pm 41.6	0.719
Digit Span/Ordering					
Forward	9.67 \pm 1.50	9.58 \pm 2.19	9.33 \pm 2.35	9.08 \pm 2.64	0.755
Backward	8.00 \pm 1.35	8.33 \pm 2.19	7.91 \pm 2.31	8.17 \pm 2.33	0.910
Ordering	9.10 \pm 1.37	8.20 \pm 2.15	9.00 \pm 1.82	8.10 \pm 2.77	0.463
RVIP					
RVIP A	0.97 \pm 0.04	0.97 \pm 0.23	0.97 \pm 0.02	0.97 \pm 0.04	0.981
RVIP B	0.54 \pm 0.77	0.55 \pm 0.78	0.89 \pm 0.77	0.74 \pm 0.59	0.317
OTSOC					
Mean latency (ms) (all levels) [level 6]	17240 \pm 19087 [46502 \pm 19209]	18508 \pm 19617 [48677 \pm 19975]	16587 \pm 17411 [44566 \pm 19186]	22739 \pm 29178 [64689 \pm 39845]	0.047 [0.057]
Mean attempts (all levels) [level 6]	1.21 \pm 0.46 [1.58 \pm 0.81]	1.15 \pm 0.23 [1.19 \pm 0.22]	1.21 \pm 0.35 [1.63 \pm 0.54]	1.21 \pm 0.39 [1.56 \pm 0.61]	0.686 [0.027]

PRM, Pattern Recognition Memory; SST, Stop-Signal task; SSRT, stop-signal reaction time; RVIP, Rapid Visual Information Processing; OTSOC, One-Touch Stockings of Cambridge.

Values shown for each variable are the mean and standard deviation for each treatment condition. The reported *P* values are derived from within-subjects repeated measures ANOVAs with four treatment groups (modafinil, prazosin, both and placebo). For OTSOC mean latency to correct and mean attempts at obtaining the correct solution, values reflect performance across all levels of difficulty; values in brackets are specific to performance at the hardest level (6) of task difficulty.

drug-related effects on performance accuracy (number of attempts required to correctly solve the task) and response times (latency to correct response) on the One-Touch Stockings of Cambridge (OTSOC) task (Figure 1).

As anticipated, there was a main effect of task-difficulty level on performance accuracy during the Stockings of Cambridge task [$F(1.75, 19.20) = 8.35, P = 0.003$], with participants requiring significantly more attempts to achieve the correct solution at level 6 than level 1 [simple contrasts: $F(1,11) = 10.95, P = 0.007$]. There was a significant treatment \times the level of difficulty interaction [$F(4.90, 53.81) = 2.41,$

$P = 0.049$]. Paired t -tests confirmed a significant decrease in performance accuracy between easy (1) and hard (6) levels of difficulty in all conditions except under modafinil treatment when given alone (modafinil, $P = 0.166$; prazosin, $P = 0.004$; both, $P = 0.009$; placebo, $P = 0.029$). At the hardest level of the task (6), there was a significant effect of treatment [$F(3,33) = 3.47, P = 0.027$]; paired t -tests showed a tendency towards increased performance accuracy under modafinil compared with placebo ($P = 0.065$).

There was an expected overall effect of task difficulty on time taken to complete the OTSOC task [$F(1.35, 14.87) = 56.43, P < 0.001$] with significantly more time spent completing level 6 than level 1 in all groups [simple contrasts: $F(1,11) = 65.00, P < 0.001$]. There was also a significant main effect of treatment [$F(3,33) = 2.94, P = 0.047$]; simple contrasts showed that combined modafinil plus prazosin yielded an overall effect which differed on trend level from placebo [$F(1,11) = 4.14, P = 0.067$] consistent with a systematic increase in the time taken to complete the task.

No significant effects of drug were identified on the other neurocognitive tasks examined.

Physiological measures

Blood pressure There was a significant main effect of time on blood pressure [diastolic: $F(3,24) = 3.55, P = 0.005$; systolic: $F(3,24) = 6.86, P = 0.002$]. In addition, a main treatment effect on systolic blood pressure [$F(3,24) = 4.99, P = 0.008$] and a significant treatment \times time interaction on diastolic blood pressure [$F(3.87, 30.96) = 2.79, P = 0.045$] were observed. Simple contrasts showed that prazosin exerted an overall effect on blood pressure relative to placebo [diastolic: $F(1,8) = 3.90, P = 0.084$; systolic: $F(1,8) = 6.29, P = 0.036$] consistent with a reduced blood pressure under prazosin compared with placebo (paired t -tests at $t = 3$ h: diastolic: $P = 0.011$; systolic: $P = 0.006$). Despite a significant rise in blood pressure in the modafinil group between the $t = 1$ h and $t = 3$ h sampling points (diastolic: $P = 0.003$; systolic: $P = 0.029$), there were no time-point specific deviations from placebo (Figure 2A).

Heart rate There was a significant main effect of treatment on heart rate [$F(3,24) = 6.24, P = 0.003$]. Simple contrasts showed that prazosin and combined prazosin plus modafinil exerted significant overall effects relative to placebo [both, $F(1,8) = 21.84, P = 0.002$; prazosin, $F(1,8) = 13.02, P = 0.007$]. A significant treatment \times time interaction was also observed [$F(2.98, 23.88) = 3.07, P = 0.047$]. Paired t -tests showed that there was a significant reduction in heart rate between baseline and $t = 3$ h in the placebo group ($P = 0.001$) but not in the other groups (modafinil, $P = 0.118$; prazosin, $P = 0.985$; both, $P = 0.105$) and confirmed that from the $t = 2$ h sampling point onwards, heart rate was significantly raised under prazosin ($t = 2$ h; $P = 0.012$) and combined prazosin plus modafinil ($t = 2$ h; $P = 0.002$) compared with placebo (Figure 2B).

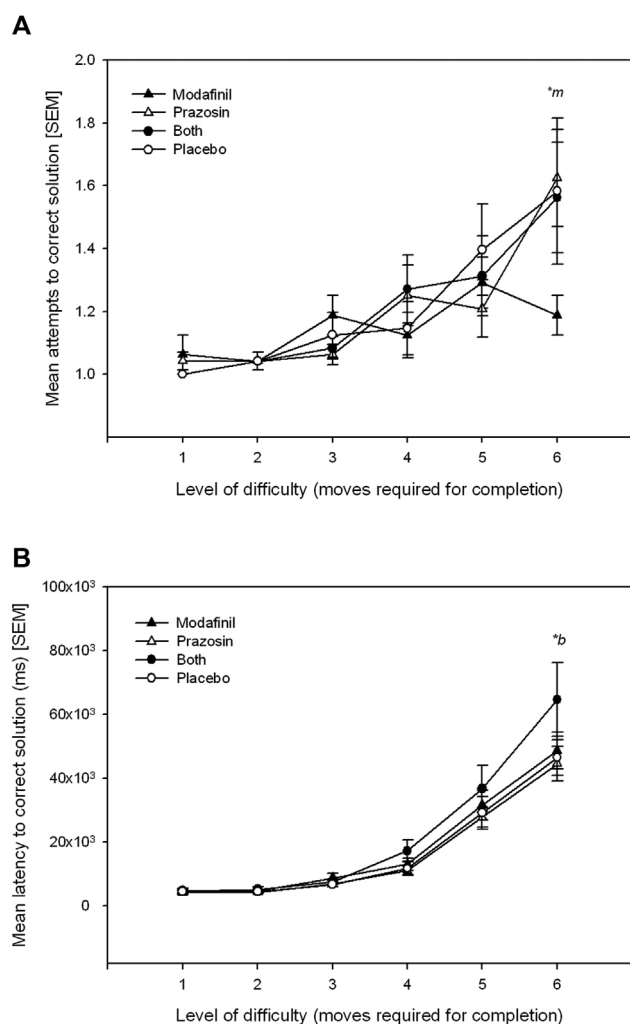


Figure 1 The effects of modafinil (300 mg), prazosin (3 mg), both [modafinil (300 mg) + prazosin (3 mg)] and placebo on (A) the number of attempts required and (B) time taken (latency) to correctly complete the One-Touch Stockings of Cambridge Task of spatial planning. Means are plotted \pm error bars of 1 SEM. Asterisk indicates deviation from placebo under drug condition where m, modafinil; b, both (combined modafinil plus prazosin). * $P < 0.1$.

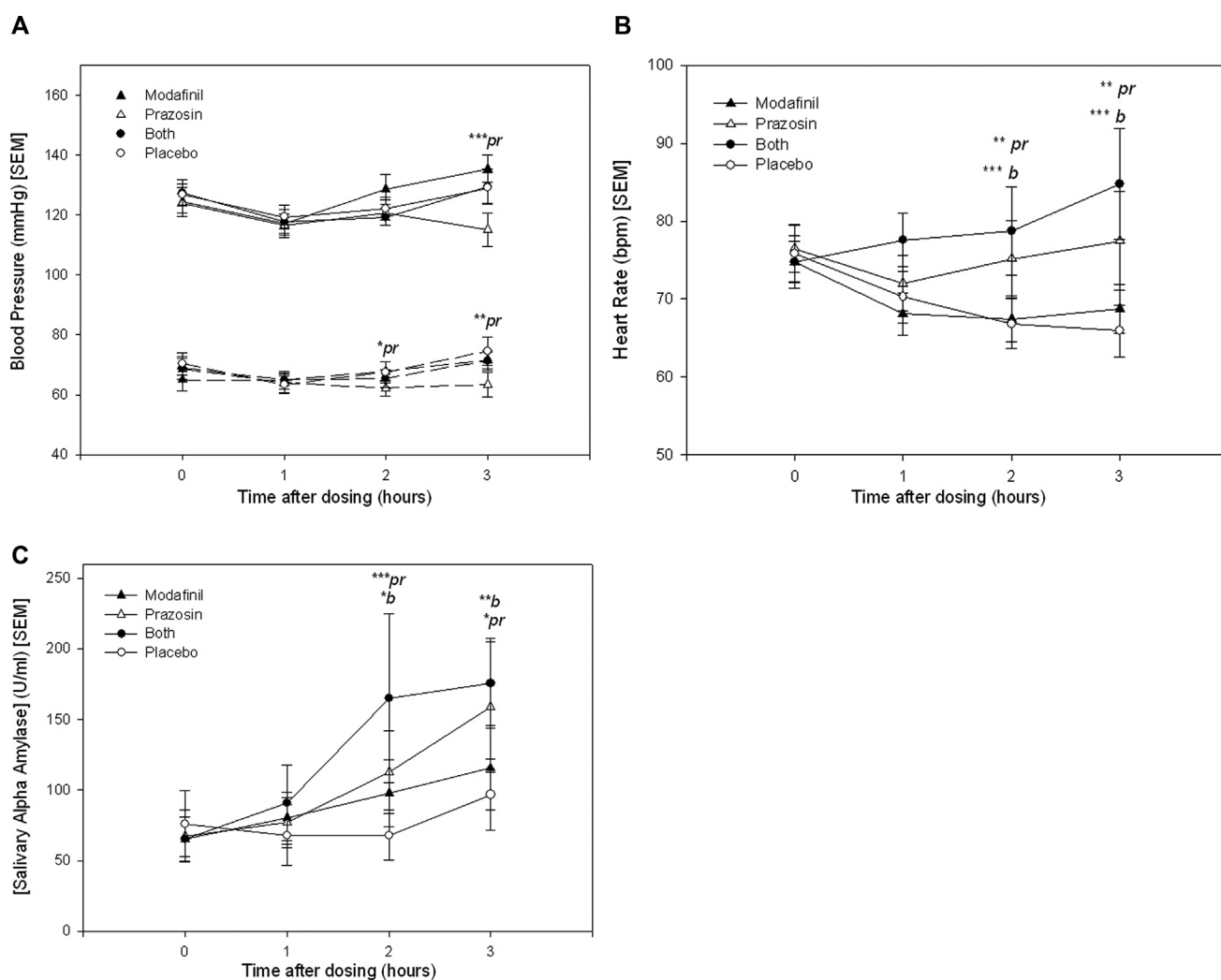


Figure 2 The effects of modafinil (300 mg), prazosin (3 mg), both [modafinil (300 mg) + prazosin (3 mg)] and placebo on physiological parameters measured at hourly intervals: (A) systolic (solid line) and diastolic (dashed line) blood pressure, (B) heart rate and (C) salivary α -amylase levels. Means are plotted + error bars of 1 SEM. Asterisk indicates deviation from placebo under drug condition where pr, prazosin; m, modafinil and b, both.

* $P < 0.1$, ** $P < 0.05$, *** $P < 0.01$.

Salivary α -amylase There was a significant main effect of time on levels of salivary α -amylase (sAA) [$F(1,175, 19.20) = 8.93$, $P = 0.002$] consistent with a general increase in sAA between baseline and $t = 3$ h [simple contrasts: $F(1,11) = 19.45$, $P = 0.001$] under all conditions except for placebo (paired t -tests: prazosin, $P = 0.022$; modafinil, $P = 0.036$; both, $P < 0.001$; placebo, $P = 0.178$). Simple contrasts showed that prazosin and combined prazosin plus modafinil exerted significant and near-significant overall effects, respectively, relative to placebo [prazosin, $F(1,11) = 10.27$, $P = 0.008$; both, $F(1,11) = 3.66$, $P = 0.082$]; paired t -tests confirmed that sAA levels were elevated under prazosin ($P = 0.010$ at $t = 2$ h) and

combined modafinil and prazosin ($P = 0.018$ at $t = 3$ h) compared with placebo (Figure 2C).

Discussion

This study investigated the effects of 300 mg of modafinil and 3 mg of prazosin on cognitive and physiological measures in healthy male volunteers. To the authors' knowledge, this is the first study to combine these two agents in humans and the first to explore the effects of prazosin by itself on executive cognition. The key finding was that prazosin antagonised the

improvement in performance associated with modafinil at the most difficult levels of the OTSOC planning task, consistent with prior hypotheses of an $\alpha 1$ -adrenoceptor involvement in some of the cognitive enhancing effects of this atypical stimulant drug. Another important yet contrasting observation was that prazosin synergized with modafinil in terms of its effect to slow response latency on this task; thus, the previous suggestion that the improvement in planning was in part the result of a speed-accuracy trade-off is compromised (Turner, *et al.*, 2003, Turner, *et al.*, 2004a). A similar synergy was found for the effects of the drugs in combination on autonomic indices. This study, despite the higher than usual dose of modafinil and high baseline performance of the participants, replicates previous observations relating to the positive effects of modafinil on performance of the OTSOC planning task (Turner, *et al.*, 2004a, Turner, *et al.*, 2004b). We thereby generate support for the cognitive-enhancing effects of a single dose of modafinil in healthy individuals (Müller, *et al.*, 2004; Randall, *et al.*, 2004; Randall, *et al.*, 2003; Turner, *et al.*, 2003). The findings were, however, limited to the OTSOC task, where modafinil negated the significant decrease in performance accuracy (attempts required to obtain the correct solution) associated with increasing task difficulty seen under all other conditions. We observed no significant effects of 3 mg of prazosin on any measure of cognitive performance when given alone.

The finding that prazosin antagonized the error-reducing effects of modafinil bears parallels with previous animal studies, which reported antagonistic effects of these two drugs, albeit in terms of locomotor activity and arousal (Duteil, *et al.*, 1990; Hermant, *et al.*, 1991; Lin, *et al.*, 1992) and may reflect a bi-directional modulation of the noradrenergic system by modafinil and prazosin. Remarkably, the cognitive slowing previously associated with modafinil only emerged on the OTSOC task when modafinil was combined with prazosin. Our data therefore suggest that the effects of modafinil on accuracy and latency are somewhat dissociable and that improved accuracy is not contingent on response slowing as previously proposed (Turner, *et al.*, 2004a; Turner, *et al.*, 2003). The slowing effect may be mediated by other factors, potentially including those which act peripherally given the similar pattern of effects of modafinil and prazosin on physiological parameters such as heart rate and sAA.

Previous studies have reported beneficial effects of modafinil on mnemonic function (Digit Spans, Digit reordering and PRM) (Müller, *et al.*, 2004; Turner, *et al.*, 2003) and on response inhibition (SSRT) in healthy volunteers (Turner, *et al.*, 2003), patients with ADHD (Turner, *et al.*, 2004a) and experimental animals (Eagle, *et al.*, 2008). The failure to replicate these findings and the more modest effect of modafinil on performance of the OTSOC task observed in the current study may have been a consequence of the higher dose of modafinil used (300 mg compared with 100–200 mg). The 300 mg dose of modafinil was expected to yield cognitive effects that replicated or surpassed those observed in previous studies in healthy volunteers (Minzenberg and Carter, 2008; Müller, *et al.*, 2004) yet may actually have proved less efficacious. According to the

putative inverted-U dose-response curve, whilst a modest amount of $\alpha 1$ -receptor stimulation is beneficial to prefrontal cortex function (McCormick, *et al.*, 1993), higher levels – such as occur during stress and potentially at high doses of modafinil – may have limited or even detrimental effects (Birnbaum, *et al.*, 2004). It remains to be elucidated whether the high dose of modafinil also engaged $\alpha 2$ -adrenoceptors, which are situated as autoreceptors on locus-coeruleus dendrites, and thereby sub-optimising locus-coeruleus neuronal discharge. The possibility exists that the expected latency-increasing effects of modafinil at the relatively high dose used were facilitated or ‘released’ only when the limitations imposed by $\alpha 1$ and $\alpha 2C$ adrenoceptors were removed by concurrent prazosin administration. This concept is analogous with the proposed mechanism of prazosin in the treatment of PTSD (Dierks, *et al.*, 2007; Miller, 2008; Taylor, *et al.*, 2006; Taylor, *et al.*, 2008) and would be compatible with previous reports that pre-treatment with low doses of yohimbine, a highly potent and selective $\alpha 2C$ -adrenoceptor antagonist (Bylund, 1985), potentiated the wake-promoting and activity enhancing effects of modafinil in animals (Duteil, *et al.*, 1990; Lin, *et al.*, 1992). A within-subject dose-response curve (200–400 mg) and the use of more specific $\alpha 2C$ -adrenoceptor antagonists may provide future clarification of these issues.

In terms of the physiological effects, modafinil in isolation did not produce any convincing deviation from placebo in either blood pressure or heart rate over the course of the study, to some extent concordant with previous literature describing inconsistent/ambiguous cardiovascular effects of this agent (e.g., Taneja, *et al.*, 2005; Turner, *et al.*, 2003). Modafinil tended to increase sAA levels over time compared with placebo although this effect was limited in magnitude. sAA levels have been endorsed as an indirect marker of sympatho-adreno-medullar (SAM) system activity, independent of variability in salivary flow rate (Rohleder, *et al.*, 2006). In humans, sAA rises in response to physiological stress and psychological stressors (Rohleder, *et al.*, 2004; van Stegeren, *et al.*, 2006), and direct measurements have shown that sAA reflects plasma noradrenaline levels (Chatterton, *et al.*, 1996). Our results thus suggest that modafinil may have some sympathomimetic effects, whether or not these are centrally mediated, and appear to challenge suggestions that modafinil may activate noradrenergic neurones in the locus coeruleus, without affecting extra-coerulear noradrenergic neurones involved in cardiovascular and salivary regulation (Hou, *et al.*, 2005). Prazosin exerted blood pressure-lowering effects over time, coupled with a compensatory increase in heart rate, consistent with its peripheral vasodilatory properties and established efficacy in the treatment of hypertension. Contrary to expectations, prazosin increased sAA over time, an observation that warrants further exploration. When the agents were combined, modafinil negated the hypotensive effects of prazosin, but the effects of prazosin on heart rate and sAA were sustained, if not potentiated, suggesting some over-arching influence between the latter two systems. Some of these effects of both modafinil and prazosin may have been mediated by $\alpha 2C$ -adrenoceptors, which

are located as pre-synaptic autoreceptors on sympathetic ganglia neurons and modulate the regulated release of noradrenaline from sympathetic neurons (Brum, *et al.*, 2006). The affinity of prazosin for these receptors may explain why the current study found evidence of increased SAM activity with prazosin and why, as with the cognitive effects, some physiological measures were actually additive rather than antagonistic with modafinil treatment.

Although this is the first study to have explored the effects of concurrent prazosin and modafinil administration in humans, it is nonetheless important to consider several limitations. Firstly, we used a randomized, within-subject, cross over design, which generally has the benefit of allowing the detection of drug effects within a small sample – in this case, 12 male adults. Based on the data of Turner, *et al.* (2003), a sample size of $n = 12$ per condition would yield approximately 90% power to detect a significant beneficial effect of modafinil on stop-signal response inhibition assuming similar magnitude of effect (DSS Research: researcher's toolkit, http://www.dssresearch.com/toolkit/spcalc/power_a2.asp). Therefore, we feel that the study, though small, was not underpowered to test the cognitive effects of such agents.

The participants, however, were healthy, non-sleep-deprived and relatively high-performing individuals (mean verbal IQ score = 115.5), who became highly practised given the total of four testing sessions and in whom the effects of modafinil may have thus been limited (Randall, *et al.*, 2005). As described above, the study used a relatively high dose of modafinil and did not evaluate dose-dependent effects of modafinil and prazosin, limiting interpretation of the combined effects of these agents. Future studies in healthy, sleep-deprived and patient populations using a range of doses of the agents, alternative adrenoceptor antagonists and more direct measurements of SAM activity, are recommended to facilitate investigation of the mechanisms underlying the cognitive-enhancing effects of modafinil.

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