# Effects of modafinil on cognitive performance in healthy individuals, substance-dependent individuals and patients with dementia

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Bachelorarbeit Psychologie

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# 1. Introduction

The subject of this bachelor thesis is, broadly speaking, cognitive enhancement. Bostrom and Roache (2010, p. 1) define cognitive enhancement as "the amplification or extension of core capacities of the mind through improvement or augmentation". The focus of this thesis is on neurocognitive enhancement, i.e. cognitive enhancement through drugs. The use of prescription drugs like e.g. methylphenidate or modafinil as study aids is receiving considerable media attention and becoming ever more widespread (Greely et al., 2008; Sahakian & Morein-Zamir, 2007; Farah et al., 2004), not only in the USA but also in Europe (Eickenhorst et al., 2012). The issue of cognitive enhancing substances is of considerable importance because many small individual improvements in cognitive performance could have profound effects at a societal level (Bostrom & Sandberg, 2009).

To be more precise, the main research question of this thesis is if and to what extent modafinil has positive effects on cognitive performance (operationalized as performance improvements in a variety of cognitive tests) in healthy, non-sleep deprived individuals, substance-dependent individuals or patients with dementia. The abuse liability and adverse effects of modafinil are also discussed. A literature research of all available, randomized, placebo-controlled, double-blind studies which examined those effects was therefore conducted.

Chapter 2 begins with a short overview of the history and mechanism of action of modafinil, followed by methodological remarks. Thereafter, a summary of the effects of modafinil on several measures of cognitive functioning in healthy individuals is given. Chapter 2.4 contains detailed descriptions of the methods and results of the reviewed studies. Following the same structure, chapter 2.5 and 2.6 analyze the effects of modafinil on cognitive performance in substance-dependent individuals. Due to the lack of relevant studies, a very brief chapter about the effects of modafinil on cognitive performance in patients with dementia follows. Chapter 2 ends with a discussion of adverse effects and the abuse liability of modafinil.

Subsequently, two studies on the effects of d-amphetamine and donepezil on cognitive performance in healthy individuals are analyzed. Due to the limited scope of this bachelor thesis a comprehensive review of the effects of those drugs was not possible, but the two studies can serve as a point of comparison.

The thesis ends with a short conclusion, discussions of its limitations and suggestions for further research.

# 2. Modafinil

## 2.1 History and mechanism of action

Modafinil, along with amphetamine and methylphenidate, is probably one of the most well-known and widely used cognitive enhancers (Greely et al., 2008; Maher, 2008). Modafinil is an atypical psychostimulant and used as a treatment for narcolepsy. Despite extensive research its precise mechanism of action is not yet fully understood but modafinil seems to effect serotonin, glutamate, GABA, orexin, histamine and especially noradrenaline and dopamine systems (Minzenberg & Carter, 2008).

According to Laffont et al. (1994) peak plasma concentrations of modafinil occur 2-3 h after ingestion. Similarly, Wong et al. (1999) found that peak plasma concentrations of d-modafinil and l-modafinil occur around 2 h and 2,5 h post ingestion. The same authors also state that the plasma half-life of d-modafinil is 14-17 h and of l-modafinil 13-16 h.

## 2.2 Methodological remarks

Searching the Cochrane Database for "modafinil" results in 9 reviews. Unfortunately, none of those studies examines the cognitive effects of modafinil in healthy individuals but rather its potential benefits for e.g. schizophrenia (Scoriels et al., 2010), depression (Candy et al., 2008) or fatigue associated with advanced disease (Peuckmann-Post et al., 2010).
Therefore, Google Scholar and other databases were used.

## 2.3 Overview of the effects in healthy individuals

Altogether 19 randomized, double-blind, placebo-controlled studies about the effects of modafinil on cognitive functioning in healthy, non sleep-deprived individuals were reviewed. One of them (Randall et al., 2005b) was a retrospect analysis of 2 other studies (Randall et al., 2002 and 2005a), so 18 independent studies remain.
Out of the 19 studies, 14 found performance improvements in at least one of the administered cognitive tests through modafinil in healthy volunteers.
Modafinil significantly improved performance in 26 out of 102 cognitive tests, but significantly decreased performance in 3 cognitive tests.

Modafinil seems to have beneficial effects on visual memory, especially on pattern recognition memory, where performance improvements were found in 3 of 4 studies (Randall et al., 2005a; Turner et al., 2003; Müller et al., 2012). However, in the delayed matching to sample task (DMTS), also a test of visual memory, no positive effects of modafinil were found in 3 studies. In one study (Turner et al., 2003) modafinil even decreased performance in the DMTS.
Modafinil also had positive effects on spatial planning ability. Performance improvements were found in 3 of 6 tests of spatial planning ability (Turner et al., 2003, Winder-Rhodes et al., 2010; Müller et al., 2012).
The effects on working memory were also notable. Modafinil increased performance in one test of spatial working memory (Müller et al., 2012), in one test of numeric working memory (Müller et al., 2004) and in one test of visuo-spatial working memory (Müller et al., 2004). Modafinil also improved performance in one test of visual short-term memory storage capacity, but only in subjects with low baseline performance (Finke et al., 2010). Additionally, modafinil had beneficial effects on performance in the digit span task in 2 of 4 studies (Turner et al., 2003; Randall et al., 2005a).
In 3 of 5 studies (Turner et al., 2003; Baranski et al., 2004; Schmaal et al., 2012) modafinil led to reduced reaction times in stop-signal and serial reaction time tasks which measure inhibitory control.
3 of 6 studies (Randall et al., 2004; Randall et al., 2005a; Schmaal et al., 2013) found performance enhancements on versions of the Stroop test in subjects on modafinil.
In 1 of 3 studies (Randall et al., 2004) modafinil led to an improved performance in the Clock Drawing Test which measures visuospatial and constructional ability.
In only 1 out of 5 studies (Randall et al., 2005a) modafinil increased performance in the RVIP, a test of sustained attention. However, modafinil improved performance in 3 other tests of sustained attention, namely in the Continuous performance test (Dean et al., 2011), the Mackworth clock test (Theunissen et al., 2009) and the Detection of repeated numbers test (Baranski et al., 2004).

3 studies employed the Controlled Word Association test which examines word production ability. In none of those studies significant performance differences between modafinil and placebo emerged. Modafinil also led to no performance enhancements in the Trail-Making Test of visual attention and mental flexibility which was used in 3 studies.
Notably, modafinil appears to have detrimental effects on mental flexibility. Although 4 studies employed the Intra/Extradimensional Set Shift task (ID/ED), no performance improvements could be detected. Performance was even reduced in a study by Randall et al. (2004). Furthermore, Müller et al. (2012) found that subjects on modafinil had lower flexibility scores in the Abbreviated Torrance task for adults.
Modafinil also led to performance improvements in other cognitive tests, e.g. in a version of an attention shift task (Marchant et al., 2009) and in a logical reasoning task (Baranski et al., 2004).

However, these tests were only employed in those studies and the results are therefore difficult to compare and interpret.

Several studies suggest that modafinil is only effective in subjects with lower IQ or lower baseline performance (Randall et al., 2005b; Müller et al., 2004; Finke et al., 2010). Significant differences between modafinil and placebo also often only emerge in the most difficult conditions of cognitive tests (Müller et al., 2004; Müller et al., 2012; Winder-Rhodes et al., 2010; Marchant et al., 2009).

## 2.4 Detailed descriptions of the reviewed studies

### 2.4.1 Cognitive enhancing effects of modafinil in healthy volunteers

Turner et al. (2003) examined the effects of modafinil on a wide range of cognitive functions. Subjects receiving modafinil had a significantly increased performance on tests of digit span, visual memory, spatial planning and stop-signal reaction time. There were no significant differences between drug and placebo on fast visual information processing, attention performance, spatial memory span or working memory.

**Methods:**
A double-blind, between-subjects design was employed and 60 healthy male volunteers were randomly assigned to 3 different groups and either received a lactose placebo, 100 mg modafinil or 200 mg modafinil.
Cognitive performance was measured with tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB), a computer-based test battery which has been validated by several studies (Elliott et al. 1995; Owen et al. 1997) and shown to be highly sensitive to fluctuations of cognitive functioning caused by neurochemical manipulations (Coull et al. 1995).

**Results:**
*Visual memory:*
Three subtests from the CANTAB battery tested visual memory, namely PRM, PAL and DMTS. There were no significant differences in the PAL between the three groups, but on the PRM subjects receiving modafinil had a significantly ($p=0,01$) higher performance than subjects receiving placebo (placebo: 92% correct answers vs. 100 mg modafinil: 98% vs. 200mg modafinil: 97%). Although there were no significant differences in accuracy on the DMTS, modafinil increased the time to select the correct response.

*Spatial working memory and planning:*

Spatial working memory and planning was also examined by three subtests from the CANTAB battery: The SWM, the SSP and the NTOL. There were no significant performance differences between drug and placebo on the SWM and the SSP. On the NTOL subjects given modafinil required significantly fewer attempts (p=0,002) to find the correct answer than those in the placebo group (placebo: 7,7 mean attempts vs. 100 mg modafinil: 6,61 vs. 200 mg modafinil: 6,55).

*Attentional set-shifting:*

Two further subtests, the RVIP and the IDED, examined attention performance. No significant differences between placebo and modafinil were observed.

*Digit span:*

On the Digit span task, taken from the Wechsler Adult Intelligence Scale the drug groups had significant improvements in performance, in both the forwards (p=0,026) and the backwards (p=0,046) condition. For more details see figure 1.

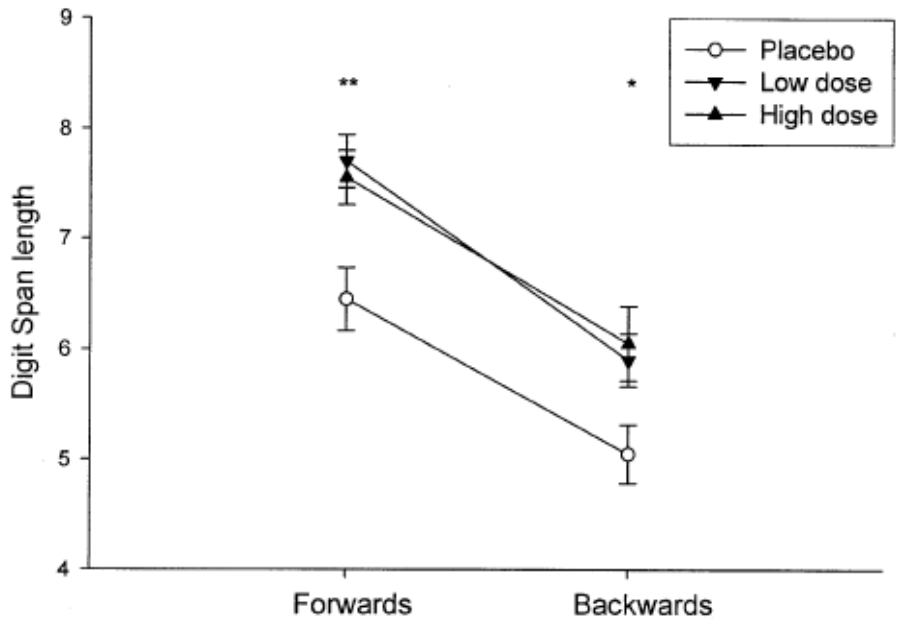


**Fig. 1** Digit span performance. The mean performance for each group, with standard error bars, for both the forwards and backwards conditions is shown. The graphs clearly illustrate the improvement seen in span length in the drug groups. $*P<0.05$, $**P\leq0.01$

N=20 for each group. Reprinted from Turner et al. (2003) without permission.

*Stop-signal reaction time:*

The last test, the stop-signal task (SSRT), measures response-inhibition, reaction time and

attention. There were significant differences in reaction time between placebo and the 200 mg modafinil group (p<0,01) and between the 100 mg and the 200 mg modafinil group (p<0,01). Thus, the effectiveness of modafinil on the SSRT seems to be dose-dependent.
Modafinil also reduced the mean number of errors on go-trials. For more details see figure 3a,b.

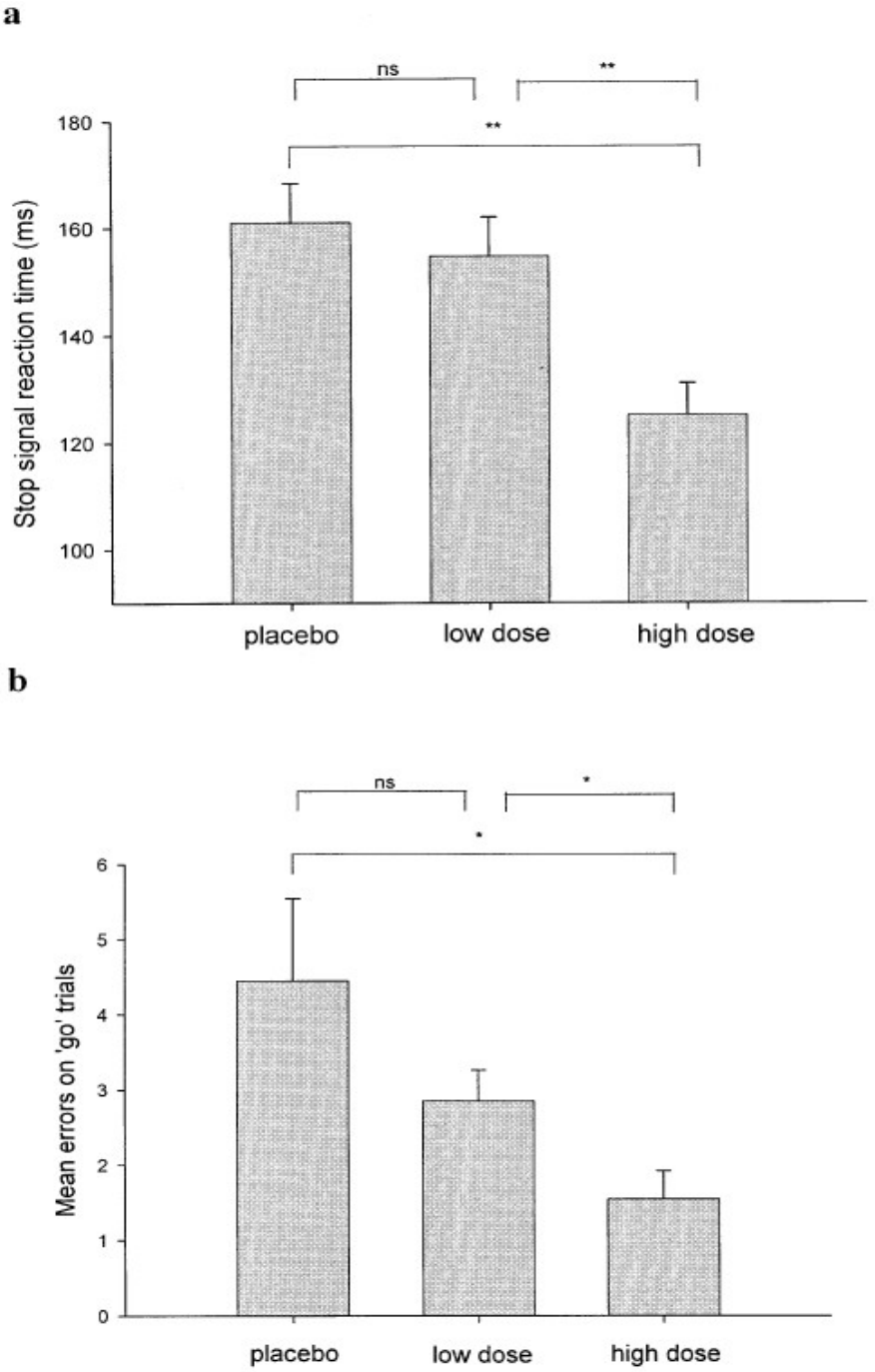


**Fig. 3a, b** Stop errors and stop-signal reaction time (SSRT). There was a highly significant decrease in the SSRT on drug (**a**), with subjects on drug also making significantly fewer errors on 'go' trials than those on placebo (**b**), particularly at the highest dose. *$P$<0.05, **$P$≤0.01

N=20 for each group. Reprinted from Turner et al. (2003) without permission.

### 2.4.2 Effects of modafinil on working memory processes in humans

Müller et al. (2004) examined the effects of modafinil on working memory processes. Healthy volunteers either received modafinil or placebo. Modafinil significantly reduced error rates in the long delay condition of a visuo-spatial task and in the difficult condition of a numeric working memory task, especially in lower performing subjects. Subjects on modafinil also had significantly faster reaction times in the shorter delay conditions of the visuo-spatial task.

**Methods:**

16 healthy students (mean age: 24 years) were recruited for this double-blind, randomized crossover design study. Subjects received either 200 mg modafinil or placebo on the first session and the opposite medication on the second session. Each participant was tested on 2 days separated by at least 1 week. Cognitive testing started between 90 and 180 minutes after drug ingestion.

Two cognitive tests were employed to measure the effects of modafinil on working memory processes. Firstly, a numeric working memory task with two conditions ("easy" and "difficult") examined manipulation processes. Secondly, the visuo-spatial delayed matching to sample task with three different delay conditions, examined maintenance processes.

**Results:**

*Manipulation processes*

Subjects on modafinil made significantly fewer errors ($p<0,03$) than subjects receiving placebo in the difficult condition of the numeric working memory task. However, a median split based on performance on the placebo day showed that only the relatively poor-performing subjects increased their performance on modafinil (improving from 9,8% to 5,7% errors). There were no significant differences in good-performing subjects between modafinil and placebo (3,9% vs. 3,7% errors). See also figure 1.

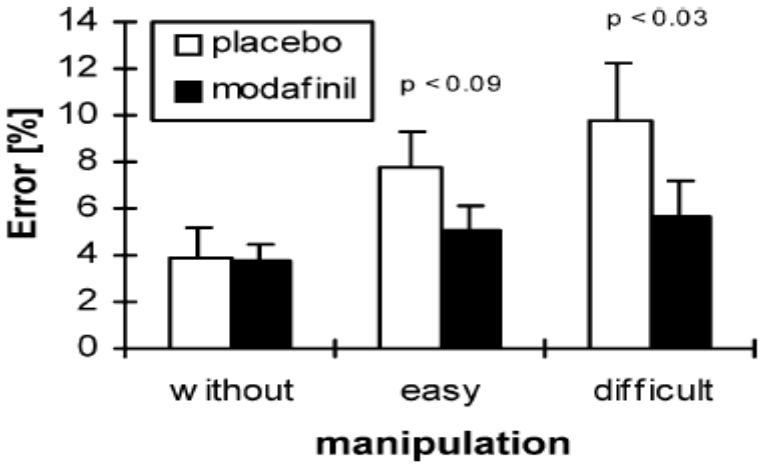


Fig. 1. Error rates in the numeric working memory task (mean and SEM) after 200 mg modafinil or placebo. N=16.
Reprinted from Müller et al. (2004) without permission.

*Maintenance processes*

Modafinil led to a significant reduction of errors (p=0,01) in the long delay condition of the visuo-spatial working memory task. However, no significant differences in accuracy were observed in the short delay conditions.

Reaction times were significantly faster in subjects receiving modafinil in the 1s and 4s delay conditions. See also table 1.

**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 |

*$P<0.05$; **$P\leq0.01$

N=16. Reprinted from Müller et al. (2004) without permission.

### 2.4.3 Effects of modafinil on cognitive and meta-cognitive performance

Baranski et al. (2004) analyzed the effects of modafinil on cognitive and meta-cognitive performance in healthy, non-sleep deprived individuals. In comparison to placebo, modafinil improved mental and physical fatigue levels, motivation, vigilance and reaction time. Modafinil induced no detrimental effects in cognitive performance or subjective measures. On some tasks subjects on modafinil showed a non-significant tendency towards overconfidence for self-assessments of performance.

**Methods:**

The study used a double blind, fully within-subjects design and 18 participants were randomly assigned to the order of drug condition (placebo or 4mg/kg modafinil, i.e. around 300 mg on average). Testing phases were separated by a drug ‘washout’ period (at least 1 week). Cognitive testing sessions were conducted 90 min prior to drug ingestion as well as 90 min and 3 h after drug ingestion.

The cognitive test battery examined a wide range of fundamental cognitive processes and included the following tasks: Four-choice serial reaction time, Mental addition, Detection of repeated numbers (DRN) vigilance task, Logical reasoning task, Visual perceptual comparison and Self-monitoring.

**Results:**

*Serial reaction time*

The four choice serial reaction time task (SRT) examines response time as well as accuracy of response. There were no differences in response accuracy. However, 90 minutes after drug ingestion subjects receiving modafinil had significantly ($p<0,04$) faster reaction times than subjects on placebo. See also figure 1.

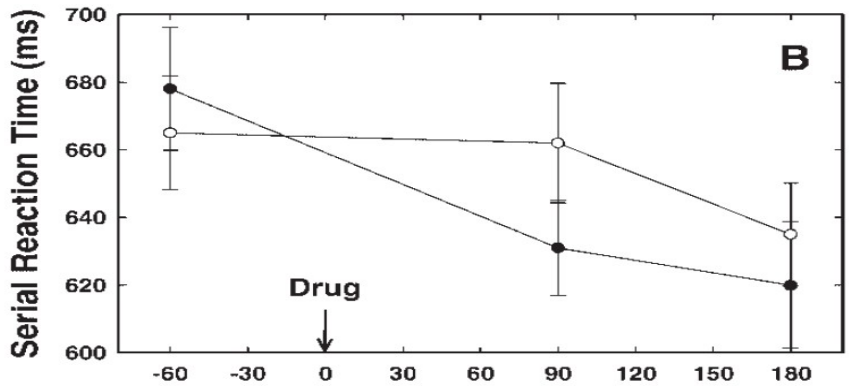


Fig. 1. Serial reaction time for modafinil (black) and placebo (white). Error bars denote the standard error of the mean across subjects. N=18. Reprinted from Baranski et al. (2004) without permission.

*Mental addition:*

This task measured accuracy of mental arithmetic. Subjects were also asked to give a confidence rating which should reflect their subjective probability of a correct response. There were no significant differences in accuracy or judgment confidence between the modafinil and the placebo condition.

*Detection of repeated numbers:*

The detection of repeated numbers task (DRN), based on an extensively used, similar variation by Smith and Miles (1986), measures mainly vigilance. Figure 2 shows that subjects on modafinil detected significantly more repeated numbers than subjects receiving placebo on session 2 ($p<0,003$) and 3 ($p<0,05$).

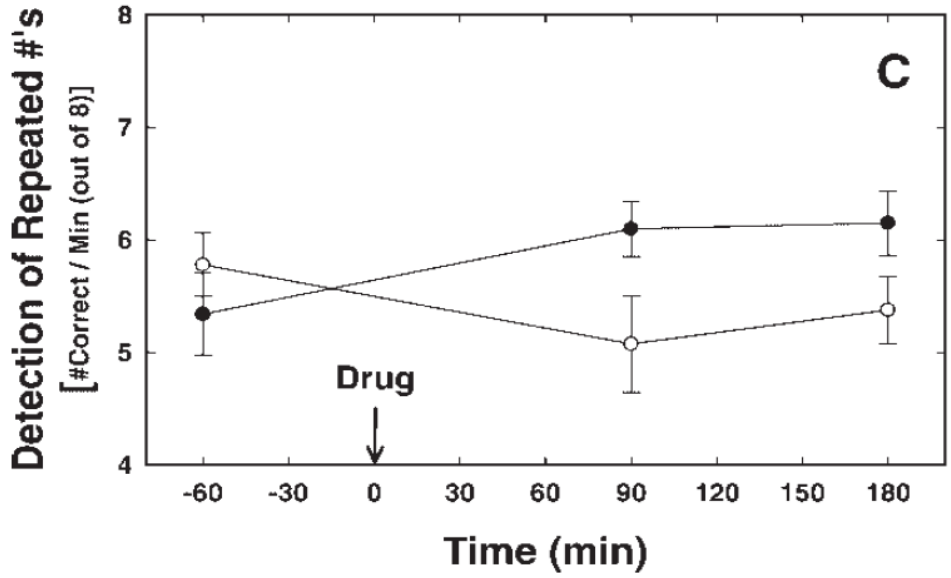


Fig. 2. Vigilance scores for modafinil (black) and placebo (white). Error bars denote the standard error of the mean across subjects. N=18.
Reprinted from Baranski et al. (2004) without permission.

*Logical reasoning:*

In the logical reasoning task (LRT), based on Baddeley (1968), response time and accuracy were measured. Subjects receiving modafinil had a significantly higher accuracy than subjects receiving placebo (88,5% vs. 86,7%, p<0,05). Response times in the modafinil condition were faster, but the difference was not significant (3083 ms vs. 3219 ms; p=0,056).

*Visual comparison:*

The comparison task is a variation of the forced choice line-length discrimination task by Henmon (1911). Response accuracy, response time and subjective confidence rating were measured. No significant differences between the modafinil and the placebo condition were observed.

### 2.4.4 The cognitive-enhancing properties of modafinil are limited in non-sleep-deprived middle-aged volunteers

Randall et al. (2004) studied the effects of modafinil in healthy, middle-aged volunteers. Subjects were randomly assigned to placebo, 100 mg or 200 mg modafinil. There were no significant differences on most cognitive tests. However, the 200 mg modafinil group was significantly faster in color naming of dots and also had a significantly improved performance in the Clock Drawing Test. Subjects receiving 200 mg modafinil also made significantly more errors in the Intra/Extradimensional Set Shift task than subjects in the other groups.

**Methods:**

For this randomized, double-blind, parallel group design study 45 healthy volunteers (aged 50-67 years) were recruited. The subjects received either placebo, 100 mg modafinil or 200 mg modafinil. Cognitive testing started 3 hours after drug intake.

The cognitive testing battery consisted of computerised tests taken from the CANTAB, namely Delayed Matching to Sample (DMTS), a test of visual episodic memory, Intra/Extradimensional Set Shift (ID/ED), which measures mental flexibility, Stockings of Cambridge (SOC), a test of spatial planning ability and Rapid Visual Information Processing (RVIP) which measures sustained attention. The following pen and paper Tests were also administered: Logical Memory, a test of verbal memory, the Stroop Test, which examines perceptual-set-shifting ability, the Trail-Making Tests (Part A and B) of mental flexibility and speed of attention, Controlled Word Association Test (COWAT) of word production ability and the Clock Drawing test, which measures visuospatial and constructional ability.

**Results:**

*Stroop Test*

Subjects receiving 200 mg modafinil needed significantly less time ($p<0,02$) to complete the color naming part of the Stroop Test than subjects receiving placebo, as can be seen in figure 1a.

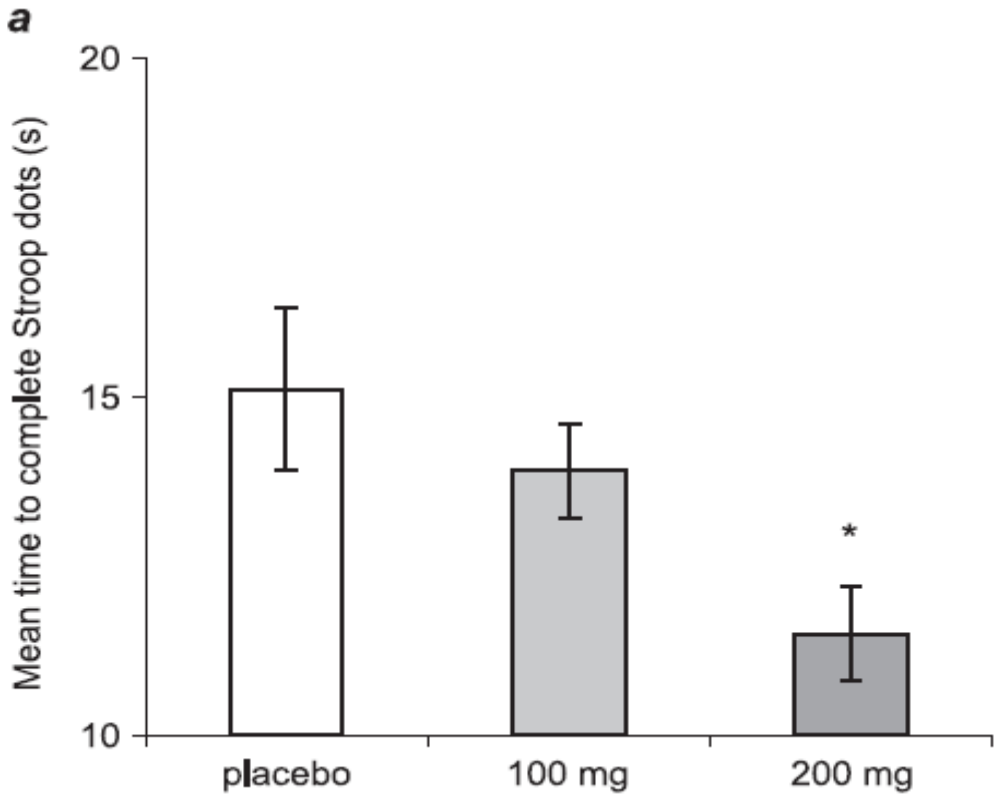


Fig. 1a. Mean (±SEM) time taken by each treatment group to complete the color naming part of the Stroop Test. * P < .05 compared with placebo. N=15 for each group.
Reprinted from Randall et al. (2004) without permission.

*Clock Drawing*

The 200 mg modafinil group had a significantly better (p<0,05) performance in the Clock Drawing test than the placebo group. See figure 1b.

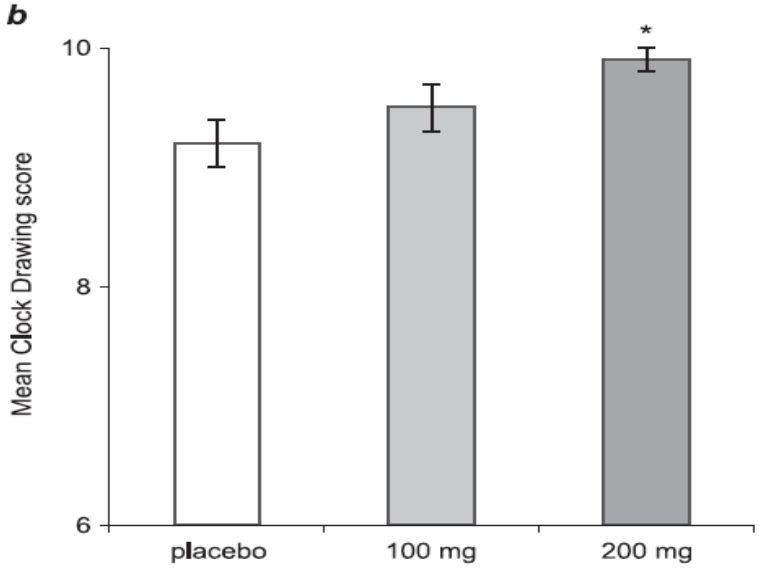


Fig. 1b Mean (±SEM) score obtained on the Clock Drawing task by each treatment group. * P < .05 compared with placebo. N=15 for each group.
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*Intra/Extradimensional Set Shift*

Participants in the 200 mg modafinil condition made significantly more errors in the ID/ED than participants in the placebo and the 100 mg modafinil condition, as is evident in figure 2.

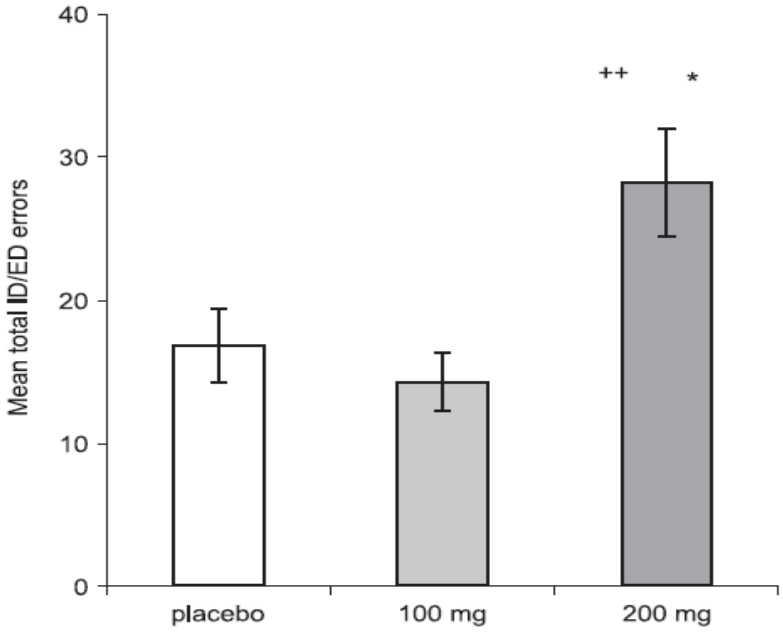


Fig. 2. Mean (±SEM) total errors made by each treatment group in the ID/ED test. + + P < .005 compared with 100 mg. * P < .05 compared with placebo. N=15 for each group. Reprinted from Randall et al. (2004) without permission.

There were no significant performance differences between modafinil and placebo in the remaining cognitive tests.

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

Randall et al. (2002) investigated the effects of modafinil in healthy, non sleep-deprived students. There were no significant differences in cognitive performance between the modafinil conditions and placebo on any test. Of note, the modafinil groups showed significantly higher ratings of somatic anxiety as well as psychological anxiety and aggression after the testing phase.

**Methods:**

In this placebo-controlled, double-blind study 30 healthy young individuals (19 men and 11 women, aged 19–23 years) were randomly assigned to placebo, 100 mg or 200 mg modafinil. Cognitive testing began 3 hours after ingestion of the drug.
The cognitive test battery examined memory, attention, mental flexibility, planning verbal fluency and constructional ability. The computerized tests, taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB), have been widely used and shown to be sensitive to neurochemical modulations, e.g. to the effects of methylphenidate (Elliott et al., 1997). Pen and Paper versions were also employed and have also been shown to be sensitive to the effects of e.g. d-amphetamine (Taylor & Russo, 2001).

**Results:**

*Computerized tests*

Delayed matching to sample (DMTS), a test of visual episodic memory, Intra/extra dimensional set shift (IED), a test of mental flexibility, Stockings of Cambridge (SOC), a test of spatial planning and Rapid visual information processing (RVP), a test of vigilance were administered. There were no significant differences between modafinil and placebo on any of these tests.

*Pen and Paper tests*

The Logical Memory test which examines verbal memory, the Stroop test which examines interferences of reaction time, the Trail-Making test which measures speed of attention and mental flexibility, the Controlled oral word association test (COWAT) which examines the spontaneous production of words and Clock drawing, which examines visuospatial and constructional ability were administered. There were also no significant differences on any of these tests between the three groups.

### 2.4.6 Does modafinil enhance cognitive performance in young volunteers?

In this randomized, placebo-controlled, double-blind, parallel groups study by Randall et al. (2005a) healthy student volunteers received 100 mg, 200 mg modafinil or placebo. The 200 mg group was significantly faster at simple color naming of dots and had an increased performance in the Rapid Visual Information Processing test of sustained attention. The 100 mg group performed significantly better on the digit span test. Both modafinil groups had significantly improved pattern recognition. There were no significant differences between placebo and drug condition on several tasks of working memory, reaction time and attention.

**Methods:**

Because of the previous conflicting findings on the cognitive-enhancing potential of modafinil (Turner et al., 2003; Randall et al., 2002) the authors increased the length of cognitive testing to 2,25 hours as well as the sample size to 60. Two hours after ingestion extensive cognitive tests were conducted. Several tests were taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB), namely the RVIP, IDED, PRM, SOC and SWM. The COWAT, the Clock Drawing test, the Stroop Task, the Trail-Making Test A and B, Logical Memory, the Paced Auditory Serial Addition Task, the Digit Span Task, Digit Cancelation, Digit Symbol Substitution and Symbol Copying were also administered.

**Results:**

*Stroop Task:*

Subjects receiving 200 mg Modafinil needed significantly less time ($p<0,05$) to complete the Stroop Task as is evident in Figure 1a. However, there were no significant differences in accuracy between drug and placebo.

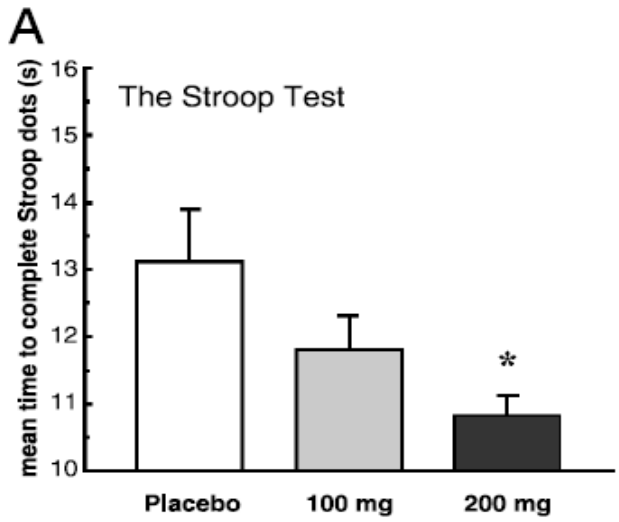


Fig. 1a. Mean (±SEM) time taken by each treatment group to complete the control condition of the Stroop test (A); *P < 0.05 compared with placebo. N=20 for each group.
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*Rapid Visual Information Processing test (RVIP)*

Participants in the 200 mg Modafinil group also had significantly greater target sensitivity (p<0,05) and missed significantly fewer targets (p<0,05) in the RVIP than the placebo group. See also figures 1b and c.

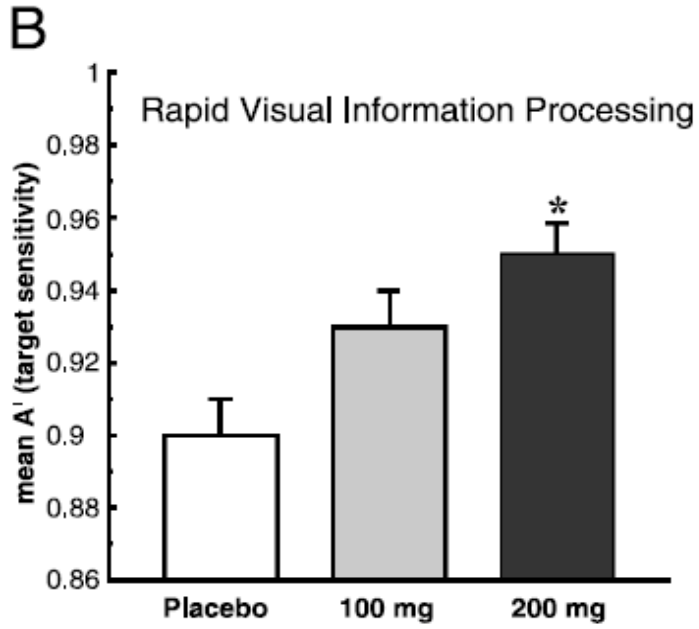


Fig. 1b. Mean (±SEM) A0 (target sensitivity). *P < 0.05 compared with placebo. N=20 for each group. Reprinted from Randall et al. (2005a) without permission.

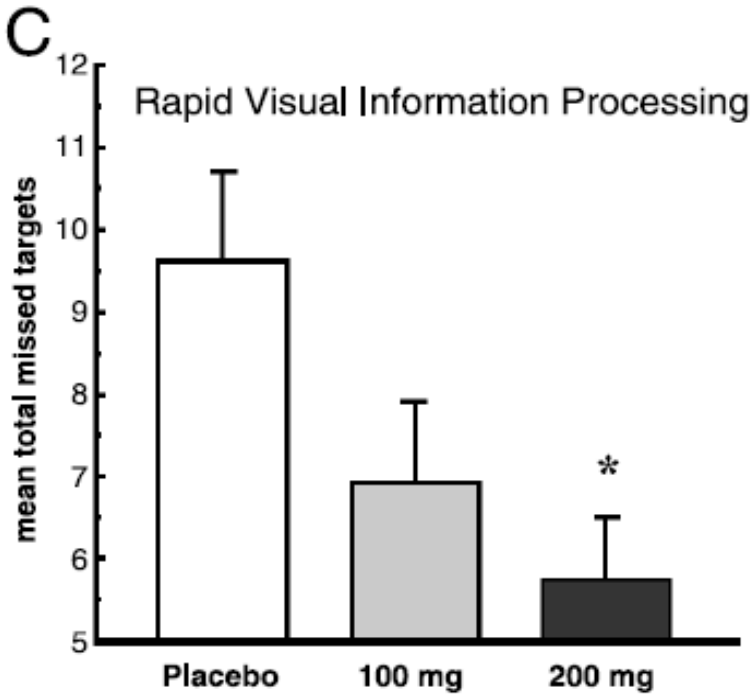


Fig. 1c. Total missed targets (±SEM) for each treatment group in the RVIP task. *P < 0.05 compared with placebo. N=20 for each group. Reprinted from Randall et al. (2005a) without permission.

*Digit Span test*

Subjects in the 100 mg Modafinil condition also had significantly better scores (p<0,05) and longer span length (p<0,01) than placebo in the forward part of the Digit Span test of immediate verbal recall, as figure 2a and 2b show.

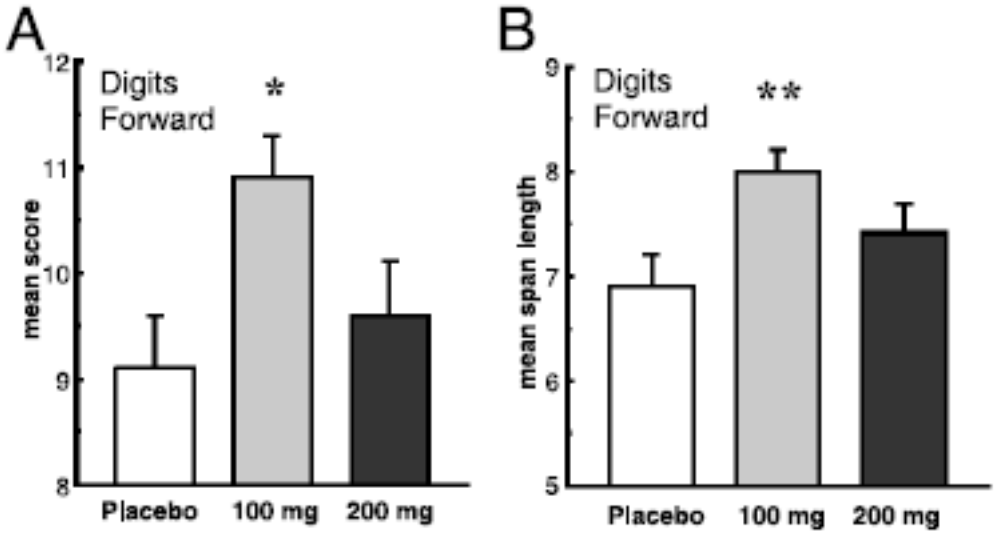


Fig. 2a and 2b. Mean (±SEM) score obtained by each treatment group in the forward part of the Digit Span test (A); mean (±SEM) span length for each treatment group in the forward part of the Digit Span test (B). *P < 0.05 compared with placebo; **P < 0.01 compared with placebo. N=20 for every group.
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In the backward part of the Digit Span test the 100 mg group also had significantly longer span length (p<0,05) than placebo, as is evident in figure 2c.

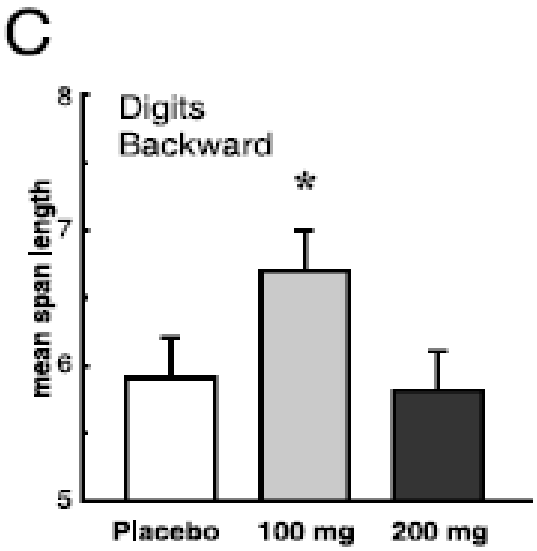


Fig. 2c. Mean (±SEM) span length for each treatment group in the backward part of the Digit Span test.
*P < 0.05 compared with placebo. N=20 for every group.
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*Pattern Recognition Memory*

In the PRM, a test of visual short-term recognition memory, both modafinil groups recognized significantly more patterns than the placebo group (p<0,05), as can be seen in figure 2d. However, subjects receiving 200 mg modafinil needed significantly longer (p<0,05) than subjects in the placebo group to select the right answer. See figure 2e.

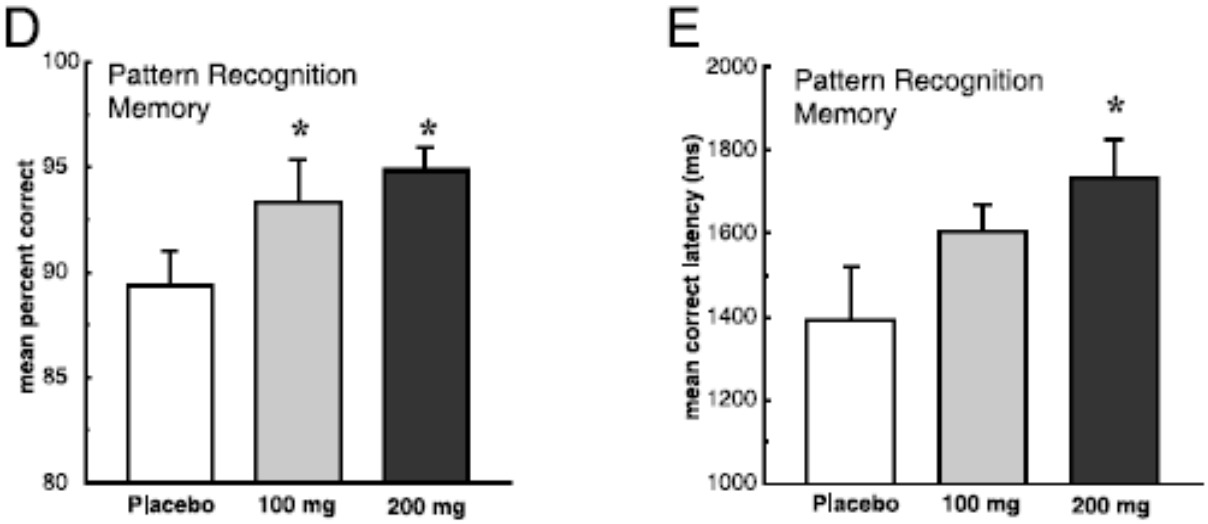


Fig. 2d and e. Mean (±SEM) percent correct (D) and correct latency (E) for each treatment group in the PRM task. *P < 0.05 compared with placebo. N=20 for every group.
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*Remaining cognitive tasks*

There were no significant differences between the modafinil groups and placebo in the remaining cognitive tasks.

### 2.4.7 Cognitive effects of modafinil in student volunteers may depend on IQ

In this review Randall et al. (2005b) analyzed the data of their two previous studies (Randall et al., 2002, 2005a) about modafinil in healthy students in order to find out if the effects of modafinil were dependent on IQ. In the combined sample modafinil significantly reduced the number of missed targets in the RVIP. Modafinil significantly improved target sensitivity in the RVIP, but only in the group with 'lower' IQ (mean=106) and not in subjects with 'higher' IQ (mean=115,5). Modafinil also significantly reduced speed of responding in color naming of dots and clock drawing, however only in the 'lower' IQ group. Therefore, modafinil seems to be particularly effective in tests of vigilance and speed, especially in subjects with lower IQ.

**Methods:**

In this retrospective analysis the data of 89 healthy students were examined. The larger sample size made it possible to detect more cognitive effects of modafinil. Verbal IQ was estimated with the National Adult Reading Test-II (NART-II). Subjects were divided into to two groups: 'Lower' IQ (mean IQ=106,1; SEM=0,6; n=42) and 'higher' IQ (mean IQ=115,5; SEM=0,5; n=47). The cognitive testing methods and remaining procedures are described in detail above.

**Results:**

*Rapid Visual Information Processing*

Subjects in the 200 mg modafinil condition missed significantly less targets (p<0,05) than subjects in the placebo condition in the RVIP. See also figure 1a.

There was also a significant effect (p<0,05) of modafinil on target sensitivity in subjects in the 'lower' IQ-group, as can be seen in figure 1b.

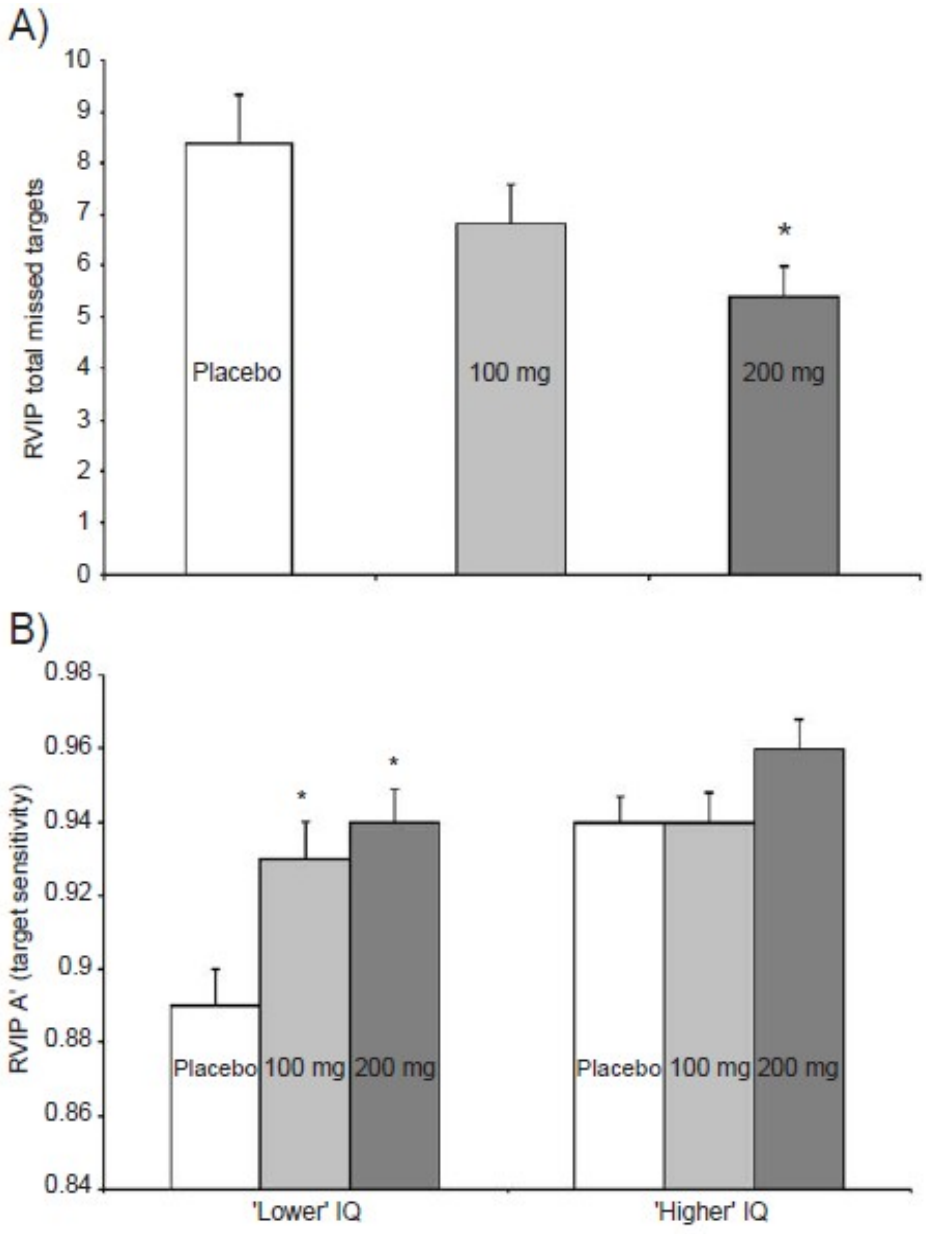


Fig. 1. (A) Mean (±SEM) total missed targets in the RVIP test; $*p < 0.05$, compared with placebo; (B) Mean (±SEM) A′ (target sensitivity[#]) in the RVIP test; $*p < 0.05$, compared with placebo.

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*Stroop Test*

Subjects in the 'lower' IQ group on modafinil needed significantly less time (p<0,05) to name colored dots in the control condition of the Stroop test than 'lower' IQ subjects receiving placebo, as can be seen in figure 2a.

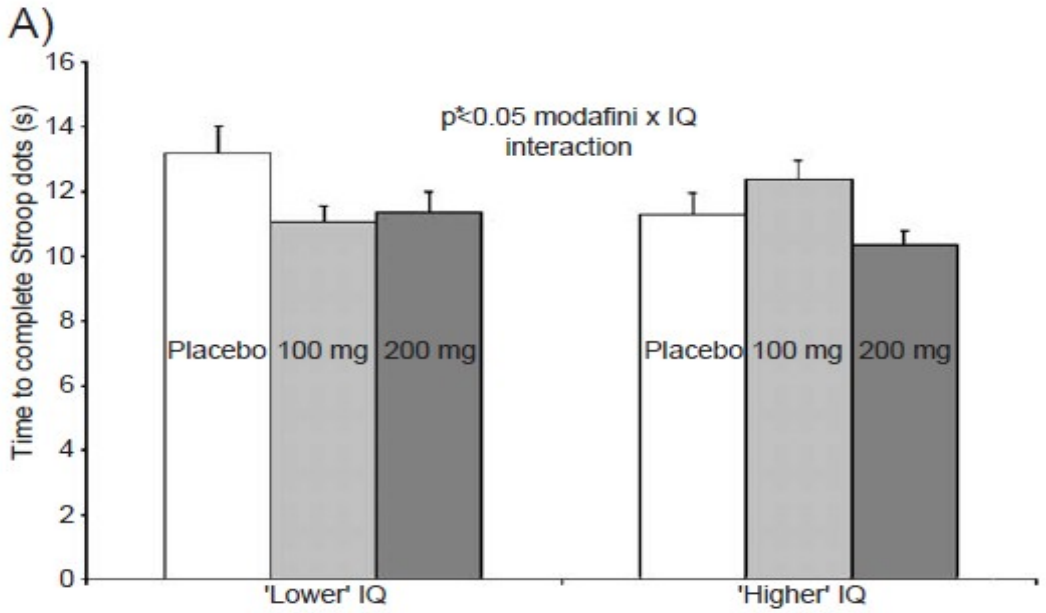


Fig. 2A. Mean (±SEM) time taken to complete the color naming of dots from the Stroop Test; *p <0.05. Reprinted from Randall et al. (2005b) without permission.

*Clock Drawing*

On the clock drawing task, participants in the 'lower' IQ group receiving modafinil were significantly faster (p<0,05) in comparison to placebo. See also figure 2b.

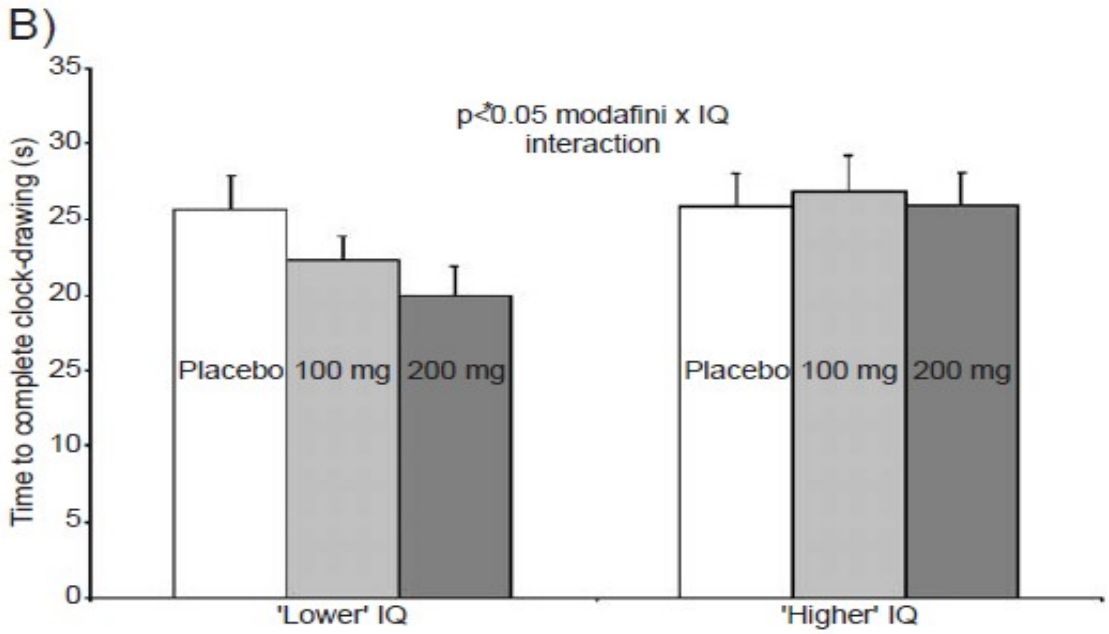


Fig 2b. Mean (±SEM) time taken to complete the Clock Drawing test; *p <0.05.
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There were no significant differences between modafinil and placebo on the remaining cognitive tests.

### 2.4.8 Disrupted sleep-wake rhythm and performance: advantages of modafinil

Lagarde and Batejat (1995) used a cross-over design in order to examine the effects of modafinil on sleep-deprived, otherwise healthy soldiers. After ingestion of modafinil performance on several cognitive tests remained mainly constant, even with increasing sleep-deprivation. Performance after the administration of placebo decreased almost regularly with increasing sleep-deprivation. However, there were no significant differences in performance in the control phase of the study, i.e. when subjects were not sleep-deprived.

**Methods:**
8 healthy men from the French Air Force were recruited. Subjects in the drug condition received 200 mg modafinil three times per day (every $8^{th}$ hour), for a total of 6 administrations. Participants were tested for 1 week with modafinil and for 1 week with placebo during this cross-over design experiment. Testing phases were separated by a 2-week washout-period. A double-blind protocol was used and subjects were randomly assigned to each group.

Performance was measured with the Standardized Tests for Research with Environmental Stressors (STRES) battery. The following subtests of the STRES battery were used: The Reaction Task which examines vigilance and attention, the Mathematical Processing Task which measures arithmetical ability, the Memory Search Task, which tests working and short time memory, the Spatial Processing Task which examines spatial memory, the Unstable Tracking Task which measures hand-eye-coordination, the Grammatical Reasoning Task which examines the processing of complex mental procedures and the Tracking and Concurrent Memory Search Task which tests vigilance and short time memory.

**Results:**
There were no significant differences among response times or for error scores on the first three control testing sessions between the drug and the placebo condition in any of the aforementioned tests. Only on the fourth testing session, which began after 20 hours of sleep deprivation, the modafinil group had a significantly better ($p<0,05$) performance on the Mathematical Processing Task, the Memory Search Task and the Tracking and Concurrent Memory Search Task.

### 2.4.9 Effects of modafinil and prazosin on cognitive and physiological functions in healthy volunteers

Winder-Rhodes et al. (2010) examined the effects of modafinil and prazosin on cognitive functions in healthy volunteers. Subjects receiving modafinil alone had a significantly improved performance in the difficult conditions of the One-Touch Stockings of Cambridge planning task.

**Methods:**

12 healthy male volunteers participated. Verbal IQ was estimated with the National Adult Reading Test and participants were excluded if they had a score of less than 90. In this randomized, double-blind, placebo-controlled, within-subject design study each subject participated in four sessions which were at least 5 days apart. On each testing session participants received either 300 mg modafinil, 300 mg modafinil plus 3 mg prazosin, 3 mg prazosin or placebo. Cognitive testing started 2 hours after ingestion.

The cognitive tests were taken from the CANTAB and consisted of the following tasks: Digit Span, Digit Ordering Span, Pattern Recognition Memory, Rapid Visual Information Processing, One-Touch Stockings of Cambridge (SOC) and Stop-Signal Task.

**Results:**

*One-Touch Stockings of Cambridge:*

Subjects on modafinil needed significantly fewer attempts (p=0,027) to achieve the correct solution than subjects receiving placebo in the most difficult condition of the SOC. See also figure 1.

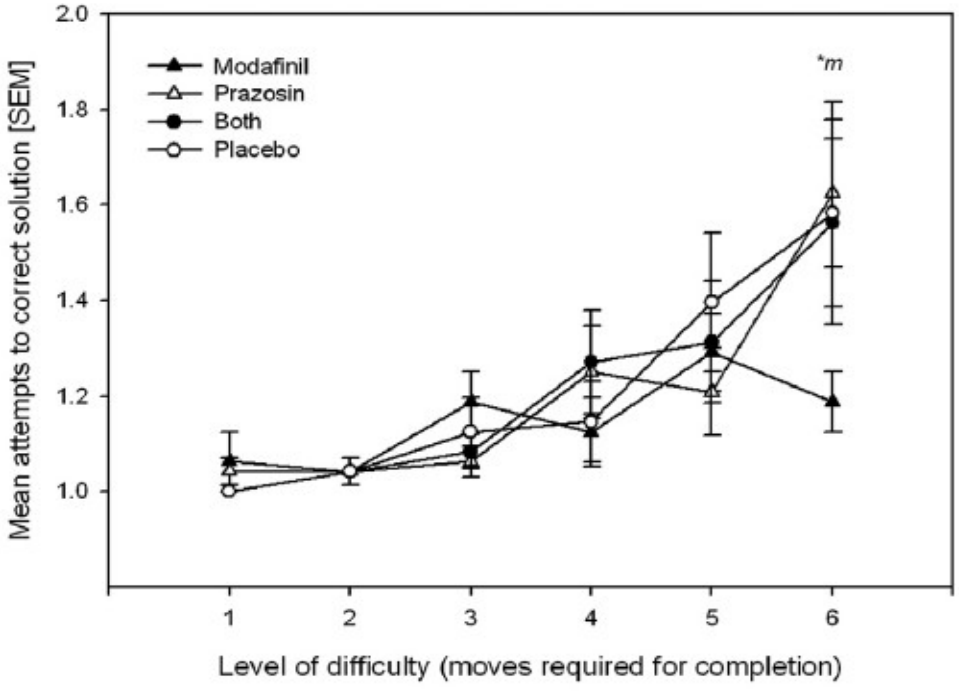


Fig. 1. The effects of modafinil (300 mg), prazosin (3 mg), both [modafinil (300 mg) + prazosin (3 mg)] and placebo on the number of attempts required to correctly complete the One-Touch Stockings of Cambridge Task of spatial planning. Means are plotted ± error bars of 1 SEM. Asterisk indicates deviation from placebo under drug condition where m=modafinil. *P < 0.05. N=12. Reprinted from Winder-Rhodes et al. (2010) without permission.

There were no significant performance differences between modafinil and placebo in any of the remaining cognitive tasks.

### 2.4.10 Effects of modafinil and methylphenidate on visual attention capacity

Finke et al. (2010) investigated the effects of modafinil and methylphenidate on visual attention and how these effects depend on baseline performance and blood-plasma levels. Participants either received 40 mg methylphenidate, 400 mg modafinil or placebo. Modafinil and methylphenidate improved perceptual processing speed in low-performing participants. Additionally, modafinil enhanced short-term memory in low-performing subjects. Higher plasma levels led to an enhancement in low-performing participants and to performance decreases in high-performing participants.

**Methods:**
18 healthy participants, aged between 20 and 35 years, were recruited for this randomized, double-blind, counterbalanced cross-over designed study. 400 mg modafinil, 40 mg methylphenidate or placebo were administered each testing day. Each Subject was tested on 3 days separated by a minimum of 1 week. Cognitive testing started between 150 min and 210 min after ingestion.

Two parameters of visual attention, based on the Theory of Visual Attention by Bundesen (1990), were measured with the whole-report task: Visual perceptual processing speed and visual short-term memory storage capacity. Low-performing subjects were defined as those whose placebo baseline performance was below the groups median.

**Results:**
*Visual perceptual processing speed:*
Low-performing participants receiving modafinil processed significantly more objects ($p<0,05$) than low-performing participants in the placebo condition (mean=42,9 vs. mean= 34,3). There were no significant differences in high-performing participants between drug and placebo. See also figure 3.

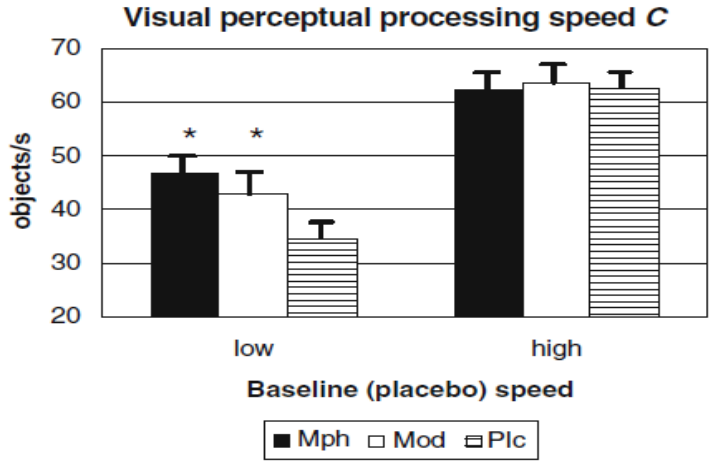


**Fig. 3** Visual perceptual processing speed *C* in the methylphenidate, modafinil and placebo condition. Mean TVA parameter estimates, separately for participants with slow (*left*) and high (*right*) baseline speed (under placebo). The error bars indicate the standard errors. Abbreviations: Mph, methylphenidate; Mod, modafinil; Plac, placebo. *Asterisk*: $p<0.05$

N=18. Reprinted from Finke et al. (2010) without permission

*Visual short-term memory storage capacity*

Modafinil significantly increased (p<0,05) the visual short-term memory storage capacity of low-performing participants as compared to placebo (mean=4,0 vs. mean=3,5 objects). There were no significant differences between drug and placebo in the high-performing group. See also figure 6.

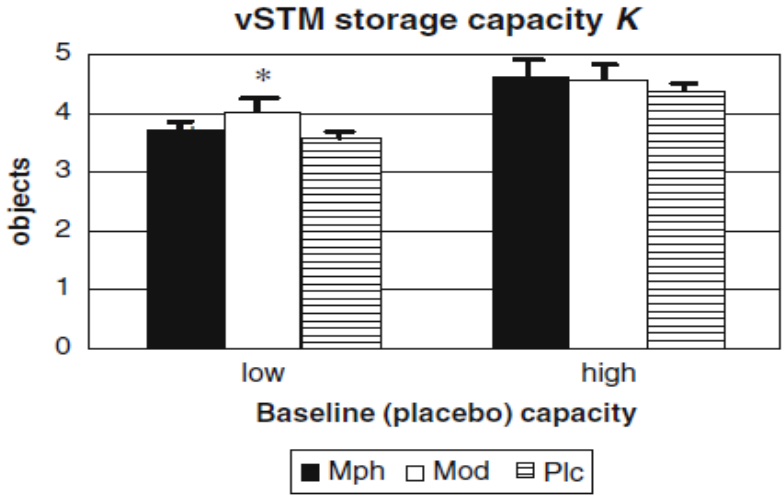


**Fig. 6** Visual short-term memory storage capacity *K* in the methylphenidate, modafinil and placebo condition. Mean TVA parameter estimates, separately for participants with relatively low (*left*) and relatively high (*right*) baseline storage capacity (under placebo). Error bars indicate standard error. Abbreviations: Mph, methylphenidate; Mod, modafinil; Plac, placebo. (*$p<0.05$)

N=18. Reprinted from Finke et al. (2010) without permission.

### 2.4.11 Motor excitability and motor behavior after modafinil ingestion

In this randomized, double-blind, cross-over designed study Liepert et al. (2004) investigated the effects of modafinil on motor performance and attention in healthy participants. Reaction time tasks, the nine-hole peg test and the d2 attention test were administered. There were no significant performance differences in any of the aforementioned tasks between modafinil and placebo.

**Methods:**

10 healthy male volunteers (mean age: 27 years) participated. A cross-over design was employed, thus each subject took either 200 mg modafinil or placebo on the testing day. Testing sessions were separated by a minimum of 2 weeks and testing occurred 2-3 hours after drug ingestion. The cognitive testing battery consisted of reaction time taks (with and without a prior acoustic warning stimulus), the d2 attention test and the nine-hole-peg test, which measures dexterity.

**Results:**

There were no significant performance differences in any of these tests. See also table 2.

**Table 2.** Motor performance data obtained before ("pre") and after ("post") and 24 hours after ("24 h post") intake of either a single dose of modafinil (MO) or placebo (PL)

| | Pre | | Post | | 24 h post | |
|---|---|---|---|---|---|---|
| | MO | PL | MO | PL | MO | PL |
| D 2 | 62.1 ± 38.9 | 70.3 ± 28.7 | 37.7 ± 30.9 | 47.9 ± 23.6 | 28.5 ± 28.6 | 32.7 ± 19.9 |
| 9HPT | 12.9 ± 1.4 | 13.15 ± 1.5 | 12.05 ± 1.3 | 12.85 ± 1.4 | 12.35 ± 1.4 | 12.7 ± 1.5 |
| RT without warning | 215.1 ± 32.6 | 215.7 ± 27.9 | 209.5 ± 29.1 | 213.6 ± 25.6 | 224.7 ± 34.5 | 214.1 ± 30 |
| RT with warning | 201.2 ± 29.7 | 203.9 ± 26.8 | 194.9 ± 28.8 | 197 ± 24.2 | 203.1 ± 26.9 | 202.2 ± 26.9 |

*D 2* the number of omissions is indicated. *9HPT* Nine-hole-peg test, measured in sec. *RT* reaction time task, measured in msec. Data are shown as mean ± standard deviation

N=10. Reprinted from Liepert et al. (2004) without permission.

### 2.4.12 Modafinil improves rapid shifts of attention

Marchant et al. (2009) examined the effects of modafinil on attention shifting ability and prospective memory in healthy volunteers. 200 mg modafinil improved performance in one condition of an attention-shifting task, but only in the most challenging trials. No significant differences in prospective memory, short-term verbal memory or processing speed between drug and placebo were found.

**Methods:**

For this double-blind, placebo-controlled, between-subjects design study 24 healthy volunteers (mean age: 22 years) were recruited. Subjects received either 200 mg modafinil or placebo. Participants completed several cognitive tasks 2-3 hours after drug-ingestion: Immediate Verbal Free Recall of short-term verbal memory and the Digit Symbol Substitution Task which measures processing speed. Furthermore, an attention shift task, adapted from Ravizza and Ivry (2001) was administered in two conditions. The 'constant' condition of this task examines attentional switching ability. The 'alternating' condition tests working memory, additionally.

Lastly, subjects had to complete a lexical decision task which also entailed an embedded prospective memory task.

IQ was estimated with the National Adult Reading Test. Based on these scores, participants were divided into lower and higher IQ groups and cognitive tasks were analyzed using a median split of IQ.

**Results:**

*Attention shift task ('constant' condition)*

Subjects on modafinil detected significantly more targets ($p<0,05$) in the 950 ms inter-stimulus interval (ISI) condition than subjects receiving placebo, as can be seen in figure 2. No other significant differences between drug and placebo were detected.

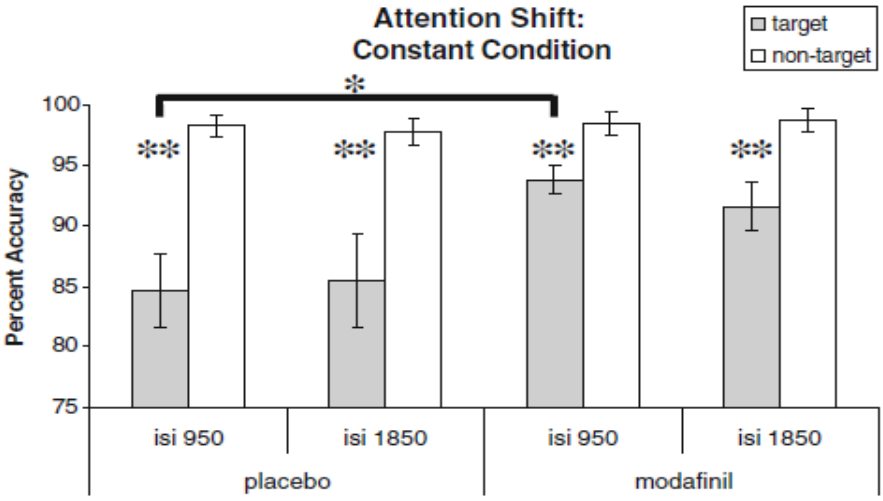


**Fig. 2** Percent accuracy for targets and non-targets in the constant attention-shifting condition as a function of ISI (950 vs. 1,850 ms) and drug (placebo vs. modafinil). Participants were more accurate at responding to non-targets than targets for both ISIs and in both drug conditions. Additionally, the modafinil group was more accurate at responding to targets with shorter ISIs (950 ms) than the placebo group. $*p<0.05$; $**p<0.01$

N=12 for both groups. Reprinted from Marchant et al. (2009) without permission.

*Attention shifting task ('alternating' condition)*

There were no significant differences between modafinil and placebo in this condition of the attention shifting task.

There were also no significant performance differences between drug and placebo in the word recall task, the Digit Symbol Substitution Task, the lexical decision task or the prospective memory task.

### 2.4.13 Modafinil modulation of the default mode network

Minzenberg et al. (2011) investigated the effects of 200 mg modafinil in 18 healthy volunteers using fMRI and a visual sensorimotor task. There was a trend toward faster reaction time with modafinil, which was not significant.

**Methods:**
18 healthy volunteers (mean age: 37 years) were recruited for this double-blind, placebo-controlled, cross-over designed study. Participants received either 200 mg modafinil or placebo. Each participant was tested on two days, separated by at least 3 days. Cognitive testing occurred around 3-4 hours after drug ingestion. Each subject completed a visual sensorimotor processing task.

**Results:**
There was a trend towards faster reaction times on modafinil in comparison to placebo (mean: 421 ms vs. 476 ms). However, this trend was not significant (p=0,08).

### 2.4.14 Effects of modafinil on non-verbal cognition, task enjoyment and creative thinking

Müller et al. (2012) investigated the effects of modafinil on non-verbal cognitive functions and motivation in healthy volunteers. Modafinil significantly improved spatial working memory, planning and decision making in the most difficult conditions and visual pattern recognition memory.

**Methods:**
For this randomized, double-blind placebo-controlled parallel design study 64 healthy volunteers (mean age: 25,3) were recruited. Participants were randomly allocated to either 200 mg modafinil or placebo. Cognitive testing started 2 hours after drug ingestion.
Many of the cognitive tests were taken from the CANTAB battery, however novel, more difficult versions were sometimes used. The following tasks were administered: Amended versions of the CANTAB paired associates learning task and the Pattern Recognition Memory task measured non-verbal, visuospatial, declarative memory. Forward and backward digit span from the Wechsler Adult Intelligence Scale and the SWM task from CANTAB examined verbal and non-verbal working memory. The Stockings of Cambridge task tested spatial planning ability. Non-verbal creative problem solving was examined with the group-embedded figure task, the line drawing task and the Abbreviated Torrance task for adults.

**Results:**

*One touch Stockings of Cambridge (SOC)*

Subjects on modafinil needed significantly fewer attempts (p=0,007) to achieve a correct solution in comparison to subjects receiving placebo. This improvement was especially large at six moves, see also figure 1.

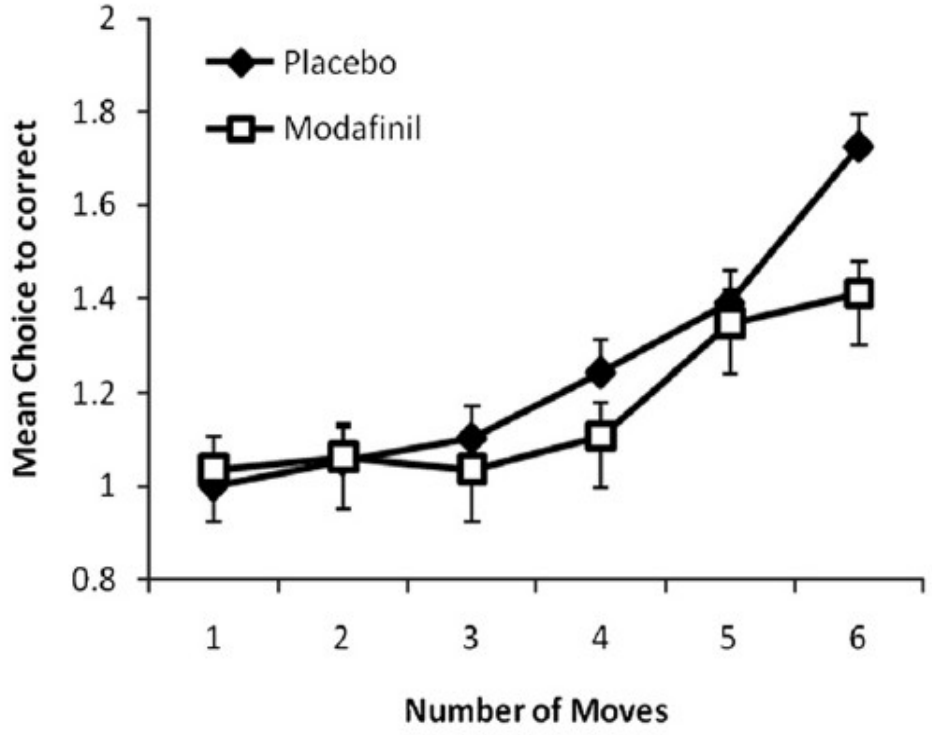


**Fig. 1.** One-touch Stockings of Cambridge (SOC) spatial planning task mean choice to correct. Subjects on modafinil made significantly fewer choices ($p = 0.002$) to achieve the correct answer than those on placebo, particularly at the harder (6 moves). Error bars represent the SEM.

N=32 for every group. Reprinted from Müller et al. (2012) without permission.

*Spatial working memory*

Subjects in the modafinil condition made significantly fewer errors (p<0,05) than subjects in the placebo condition as is evident in figure 2.

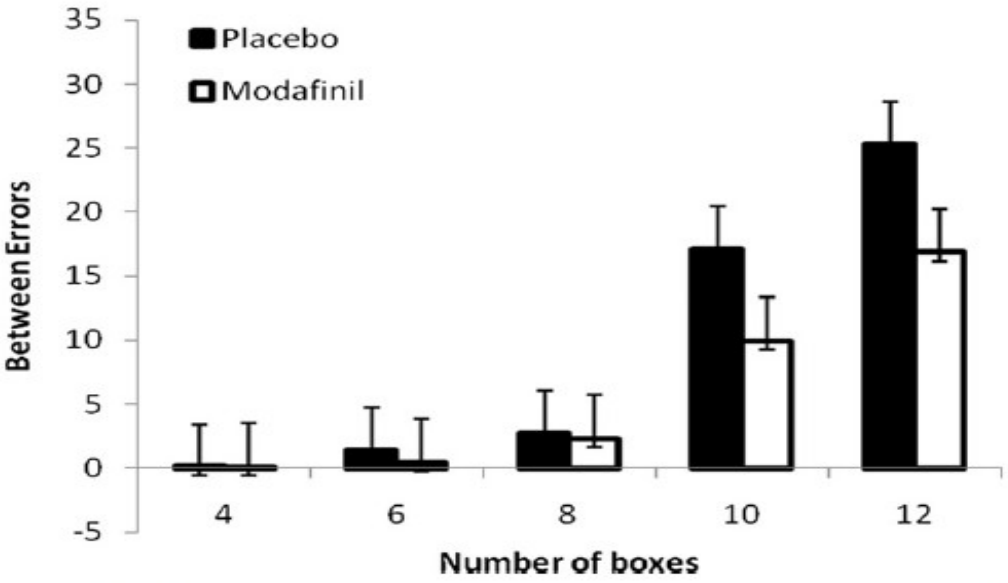


**Fig. 2.** Effect of drug on spatial working memory. Subjects on placebo made significantly more between search errors on the difficult 10-box problems ($p < 0.05$). Error bars represent the SEM.

N=32 for every group. Reprinted from Müller et al. (2012) without permission.

*Pattern recognition memory*

The modafinil group made significantly fewer errors (p<0,05) in the delayed version of the pattern recognition memory task than the placebo group. There were no significant differences in the immediate version between modafinil and placebo.

*Abbreviated Torrance task for adults*

Subjects receiving modafinil had significantly lower flexibility scores (p=0,036) as compared to subjects on placebo.

There were no significant performance differences in the digit span tasks, the paired associates learning task, group embedded figures tasks and the line drawing task.

### 2.4.15 Comparing the stimulant effects of fexofenadine, modafinil and methylphenidate

Theunissen et al. (2009) compared the stimulant effects of fexofenadine, modafinil and methylphenidate in healthy volunteers. Cognitive functions were measured with critical tracking, divided attention, motor impulsivity and vigilance tasks. Subjects on modafinil had significantly faster reaction times in the vigilance task. Modafinil produced no other significant effects.

**Methods:**

For this placebo-controlled, double blind, cross-over design study 18 healthy volunteers (mean age: 22 years) were recruited. Participants received 360 mg fexofenadine, 200 mg modafinil, 20 mg methylphenidate or placebo. Cognitive testing started 2 hours after drug ingestion.
The following cognitive tests were administered: The critical tracking task which measures the ability to control a displayed error signal, the divided attention task which measures the ability to divide attention, the Mackworth clock test which examines sustained attention and the stop signal task which measures motor impulsivity.

**Results:**

*Mackworth clock test*

Participants in the modafinil group had significantly faster reaction times ($p<0,016$) than participants in the placebo group (624,6 ms vs. 666,6 ms). There were no significant differences in accuracy between modafinil and placebo.
No significant performance differences between modafinil and placebo were found in the other remaining cognitive tasks.

### 2.4.16 Acute modafinil effects on attention and inhibitory control

Dean et al. (2011) examined the effects of modafinil on attention, working memory and inhibitory control in methamphetamine-dependent and healthy individuals. Modafinil significantly improved performance in a test of sustained attention in healthy and methamphetamine-dependent participants. No other significant performance differences between modafinil and placebo were found.

**Methods:**

24 methamphetamine-dependent and 17 healthy participants were recruited for this randomized, double-blind, placebo-controlled, crossover study. Subjects either received 200 mg modafinil or placebo and, followed by an at least 2-day washout period, received the alternate compound on the second testing day. Each time, cognitive testing began 3.5 hours after drug ingestion.
Cognitive functioning was measured with tests of inhibitory control (Stroop Color-Word Inhibition and Swicthing Test, Continuous Performance Test, Attention Networks Task), processing speed and attention (Digit Symbol Coding, Trailmaking-Number Sequencing, Stroop Color-Naming Test, Stroop Word-Reading Test, Continuous Performance Test) working memory/attention switching (Letter/Number Sequencing Test, Spatial Capacity Delayed Response Test, Trailmaking-Letter/Number Switching) and motor speed (Finger Tapping Test).

**Results:**
On the Continuous performance test, which measures attentional vigilance, modafinil significantly improved the variability of reaction time in comparison to placebo in healthy subjects ($p<0.05$). There were no performance differences in healthy subjects between modafinil and placebo on the other cognitive tests.

### 2.4.17 Effect of modafinil on learning and task-related brain activity

Ghahremani et al. (2011) examined the effects of modafinil on learning in methamphetamine-dependent and healthy individuals. Modafinil improved performance in an associative learning task in methamphetamine-dependent participants, but not in the control group.

**Methods:**
22 methamphetamine-dependent and 28 healthy individuals participated in this randomized, double-blind, placebo-controlled, cross-over study. Subjects either received 200 mg modafinil or placebo and cognitive testing started 2 hours after ingestion. The participants had to complete a deterministic associative learning task with reversal components.

**Results:**
There were no significant performance differences in the control group between modafinil and placebo.

### 2.4.18 Effects of modafinil on neural correlates of response inhibition

Schmaal et al. (2012) examined the effects of modafinil on response inhibition in abstinent alcohol-dependent individuals and healthy control subjects. Modafinil significantly improved response inhibition in alcohol-dependent subjects with poor baseline response inhibition, whereas response inhibition was decreased in better performing participants.

**Methods:**
For this randomized, double-blind, placebo-controlled, within-subjects, crossover designed study 20 male alcohol-dependent subjects and 18 healthy control subjects were recruited. Each participant was examined in two sessions separated by 1 week. In the first session participants were either given 200 mg modafinil or placebo and in the second session subjects received the opposite medication. Cognitive performance was measured using a stop signal task with go and stop trials.

**Results:**
In the control group modafinil significantly decreased reaction time (p=0,05) on go-trials (mean: 532,9 ms, SD: 81,6 on modafinil vs. mean: 565,2 ms; SD: 77,5 on placebo). No other significant group, drug, or drug by group interaction effect on any of the performance measures could be detected.

### 2.4.19 Modafinil modulates resting-state functional network connectivity and cognitive control

Another study by Schmaal et al. (2013) examined the effects of modafinil on cognitive control functions in alcohol-dependent patients and healthy controls. Modafinil significantly improved cognitive control in alcohol-dependent subjects.

**Methods:**
For this randomized, double-blind, placebo-controlled, crossover designed study 20 male alcohol-dependent individuals and 18 healthy control subjects were recruited. Each participant was tested in two sessions separated by 1 week. In the first session subjects either received 200 mg modafinil or placebo. In the second session subjects received the opposite medication. 2 hours after drug administration cognitive performance was measured with a classic Stroop task (color-word paradigm). The difference in mean reaction time between incongruent and congruent stimuli, i.e. the interference score, was calculated to obtain a measure of cognitive control.

**Results:**
A significant main effect of treatment (p=0,02) was found on the Stroop task. Healthy controls had a mean interference score of 112,3 ms (SEM: 15,8 ms) on modafinil and 174,4 ms (SEM: 21,8 ms) on placebo. No main effect of group or treatment by group interaction effect was found. There were also no significant differences between modafinil or placebo with regard to accuracy on the Stroop task.

## 2.5 Overview of the effects in substance-dependent individuals

Altogether 9 randomized, double-blind, placebo-controlled studies about the effects of modafinil on cognitive functioning in substance-dependent individuals were reviewed (4 studies in methamphetamine-, 2 in cocaine-, 2 in alcohol- and 1 in nicotine-dependent individuals).
All of the 9 studies found significant performance improvements in at least one of the administered cognitive tests in substance-dependent individuals receiving modafinil.
Modafinil significantly improved performance in 11 of 53 measures of cognitive functioning.

In substance-dependent individuals modafinil appears to have beneficial effects on sustained attention. On the Continuous Performance Test methamphetamine-dependent (Dean et al., 2011) and cocaine-dependent (Kalechstein et al., 2012) individuals performed significantly better on modafinil than on placebo.
Modafinil led to performance improvements on the Stroop Task in nicotine-dependent (Sofuoglu et al., 2008) and in alcohol-dependent individuals (Schmaal et al., 2013). However, Dean et al. (2011) found no significant performance differences between modafinil and placebo in methamphetamine-dependent individuals on several versions of the Stroop Task.
Working memory processes were also improved by modafinil in cocaine-dependent (Kalechstein et al., 2012) individuals and methamphetamine-dependent subjects with low baseline performance (Kalechstein et al., 2010).
Modafinil had beneficial effects on inhibitory control (measured with go-stop-signal tasks) in cocaine-dependent individuals (Vansickel et al., 2008) and in alcohol-dependent individuals with low baseline performance (Schmaal et al., 2012).

One study by Hester et al. (2010) found positive effects of modafinil on verbal memory in methamphetamine-dependent individuals. However, Kalechstein et al. (2010) and Kalechstein et al. (2012) found no such positive effects.
Information processing speed (Hester et al., 2010; Kalechstein et al., 2010; Kalechstein et al., 2010; Dean et al., 2011) and episodic memory (Kalechstein et al., 2010; Kalechstein et al., 2012) were not affected by modafinil.

2 studies indicate that modafinil is especially effective in subjects with lower baseline performance (Schmaal et al., 2012; Kalechstein et al., 2010) and even appears to have detrimental effects in subjects with higher baseline performance (Schmaal et al., 2012).

## 2.6 Detailed descriptions of the reviewed studies

### 2.6.1 Methamphetamine

4 randomized, placebo-controlled, double-blind studies about the effects of modafinil on cognitive performance in methamphetamine-dependent individuals are analyzed below. Two of them (Dean et al., 2011; Ghahremani et al., 2011) are described in more detail in part 2.4.16 and 2.4.17.

#### 2.6.1.1 Acute Modafinil Effects on Attention and Inhibitory Control in Methamphetamine-Dependent Humans

The design of the study by Dean et al. (2011) is already described in detail above. Here the focus lies on the results for the methamphetamine-dependent subjects.

Methamphetamine-dependent subjects on modafinil showed significantly less reaction time variability and therefore better attentional vigilance ($p=0.02$) on the Continuous Performance Test than subjects receiving placebo. No other significant differences between modafinil and placebo were found.

#### 2.6.1.2 Effect of Modafinil on Learning and Task-Related Brain Activity in Methamphetamine-Dependent and Healthy Individuals

The design of this study by Ghahremani et al. (2011) is described in more detail above. Here the focus lies on the results for the methamphetamine-dependent subjects.

Modafinil significantly improved performance ($p<0,01$) in methamphetamine-dependent subjects in the associative learning task (see figure 1a for a short description of the learning task). See figure 1b for more details.

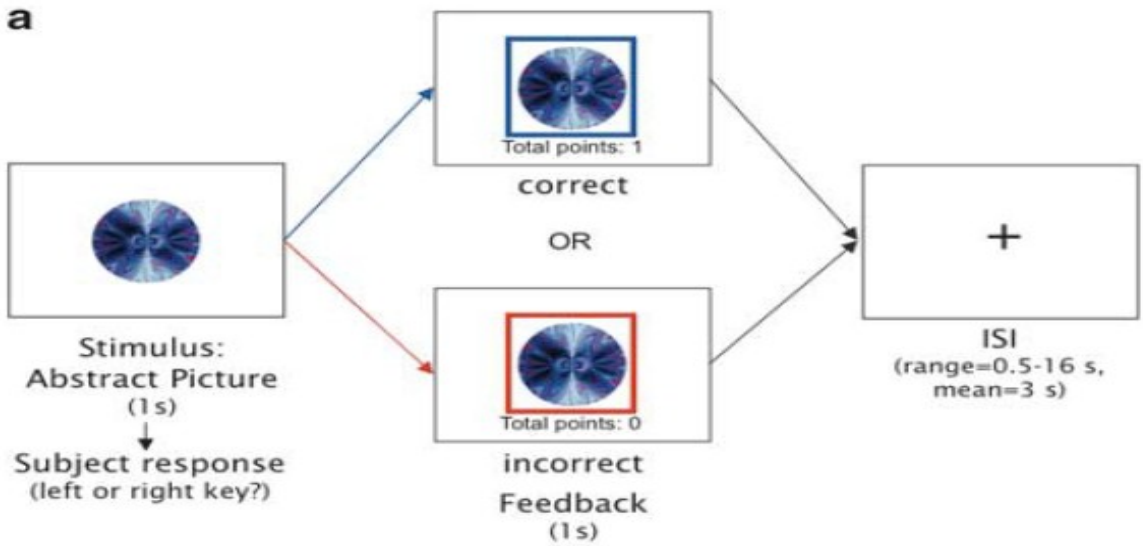


Fig. 1a Trial structure of the reversal learning task. Subjects were presented with an abstract picture and were required to select the appropriate key (left or right) within 1s. A total of 16 images were repeated 12 times. After 6 trials the stimulus-response contingencies were altered.
Reprinted from Ghahremani et al. (2011) without permission.

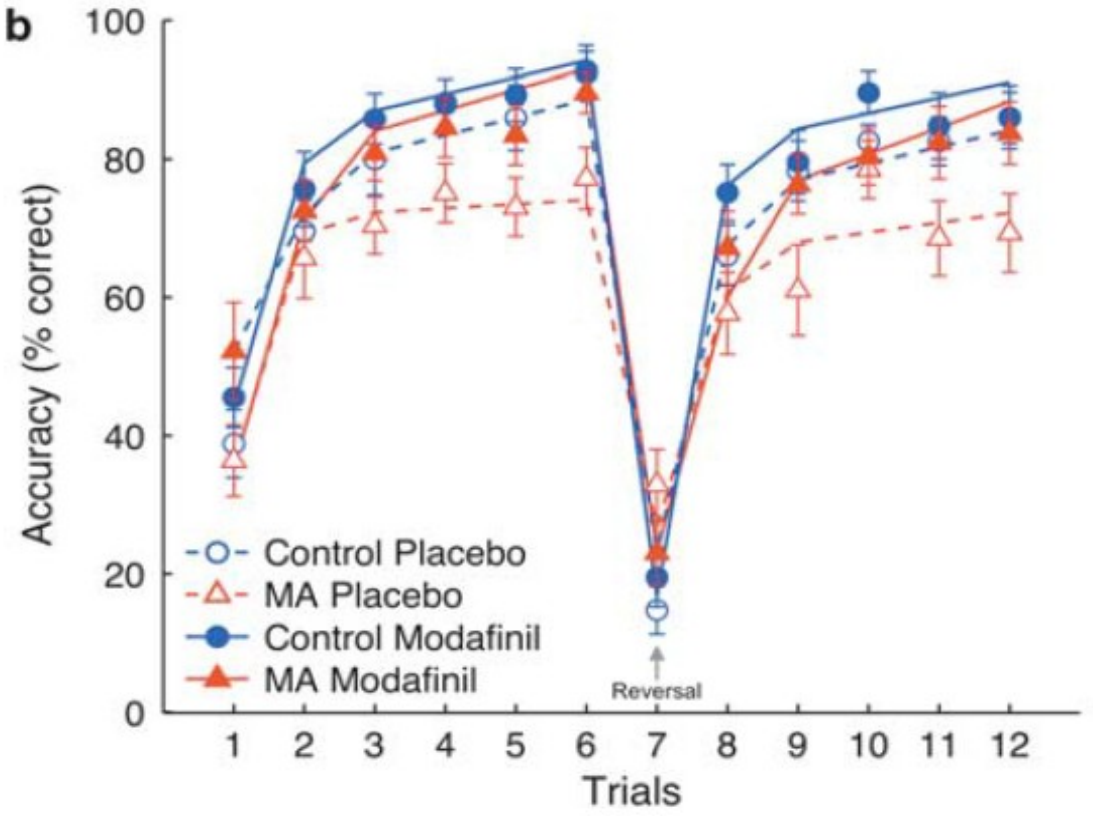


Fig. 1b Effect of modafinil on accuracy in the reversal learning task. Numbers on the x-axis indicate repeated trials for each of the 16 stimuli presented. The y-axis indicates percent correct responses at each of the 12 repeated trials. Triangles and circles represent mean values, and error bars each show one standard error of the mean.
N=22 for the methamphetamine-dependent group, and N=28 for the healthy control group.
Reprinted from Ghahremani et al. (2011) without permission.

### 2.6.1.3 The Effects of modafinil treatment on neuropsychological and attentional bias performance during 7-day inpatient withdrawal from methamphetamine dependence

Hester et al. (2010) examined the effects of modafinil on cognitive functioning in patients undergoing a 7-day withdrawal from methamphetamine. Modafinil led to significant improvements in immediate verbal memory recall. No significant differences between modafinil and placebo were found in executive functioning, delayed memory tasks, verbal learning, visual memory, processing speed or verbal fluency.

**Methods:**
20 participants (mean age: 34 years) were recruited for this randomized, double-blind, placebo-controlled study. During the first 5 days of inpatient treatment subjects received 200 mg modafinil or placebo once daily in the morning. On day 6 and 7 the modafinil dose was lowered to 100 mg. 17 participants completed the study.

The following neuropsychological tests were conducted on the day of admission (prior to receiving modafinil or placebo) and on the day of discharge: The Rey Auditory Verbal Learning test (RAVLT) and the Rey Complex Figure test (RCFT) which measure verbal and visual memory, the Digit Span test which measures working memory, the Digit-Symbol Substitution test which examines psychomotor speed, the Controlled Oral Word Association test (COWAT) and the Trail-Making test which measure executive function.

**Results:**
Only one subtest of the Rey Auditory Verbal Learning (RAVLT Recall B) test showed significant differences between modafinil and placebo ($p<0,05$). Participants receiving modafinil achieved a mean score of 5,9 (SEM: 0,5) on the day of discharge, whereas participants on placebo had a mean score of 4,6 (SEM: 0,5). For comparison, on the day of admission the mean scores were 3,7 (SEM: 0,4) for the modafinil group and 4,4 (SEM: 0,4) for the placebo group.

No significant differences between modafinil and placebo were found in any of the other aforementioned tests.

### 2.6.1.4 Modafinil administration improves working memory in methamphetamine-dependent individuals who demonstrate baseline impairment

Kalechstein et al. (2010) examined the effects of modafinil on cognitive functions in methamphetamine-dependent individuals. Modafinil led to significant improvements on tests of working memory, but only in subjects with low baseline performance. Episodic memory and information processing speed were not affected.

**Methods:**
For this randomized, double-blind, placebo-controlled, cross-over designed study 14 methamphetamine-dependent participants were recruited. 11 completed the study. The participants completed a 3-day washout period, after which baseline neuropsychological tests were administered. Then each subject either received 400 mg modafinil or placebo for the first 3 days and underwent cognitive testing. After the first 3 days subjects receiving modafinil were given placebo and vice versa for the next 3 days and underwent cognitive testing again.

The neuropsychological testing battery included the following tasks: The Simple Reaction Time Task which assesses information processing speed, a variation of a N-back task which measured working memory and the Hopkins Verbal Learning Test-Revised (HVLT-R) which examined verbal learning and memory.

Furthermore, the sample was divided into high and low performing subjects based on performance at baseline using median split.

**Results:**
In comparison to baseline and placebo, low performers at baseline (n=6) were significantly more accurate on modafinil in the 1-back ($p<0,05$) and the 2-back condition ($p<0,01$) of the working memory test. For high performing subjects (n=7) there were no significant differences between modafinil and placebo. See also figure 1.

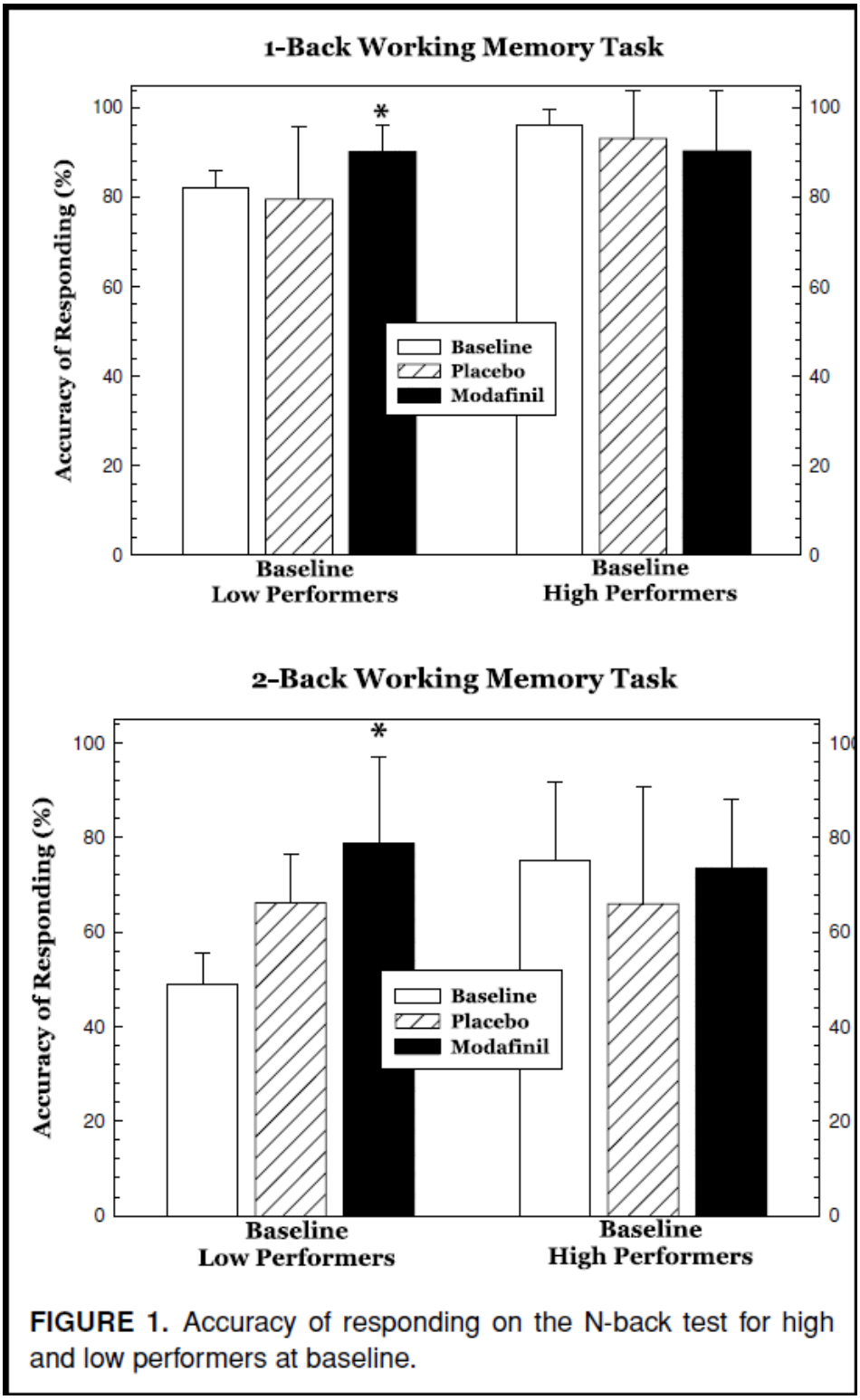


**FIGURE 1.** Accuracy of responding on the N-back test for high and low performers at baseline.

Baseline Low Performers (n=6). Baseline High Performers (n=7). Error bars represent one standard error of the mean.
Reprinted from Kalechstein et al. (2010) without permission.

There were no significant differences between modafinil and placebo in the Simple Reaction Time Task or the HVLT-R.

### 2.6.2 Cocaine

2 randomized, placebo-controlled, double-blind studies about the effects of modafinil on cognitive performance in cocaine-dependent individuals are analyzed below.

#### 2.6.2.1 Modafinil, but not escitalopram, improves working memory and sustained attention in long-term, high-dose cocaine users

Kalechstein et al. (2012) examined the effects of modafinil and escitalopram on cognitive functions in long-term, high-dose cocaine users. Subjects receiving modafinil and escitalopram had a significantly improved performance on one measure of working memory. Subjects on modafinil alone performed significantly better on two measures of sustained attention. No other significant differences were found.

**Methods:**
For this randomized, double-blind, placebo-controlled study 61 cocaine-dependent individuals were recruited. The subjects were randomly assigned to receive placebo (n=14), 200 mg modafinil (n=16), 20 mg escitalopram (n=16) or modafinil and escitalopram (n=16) once daily for 5 days. At day one participants had been abstinent from cocaine for 4-6 days.

The following neurocognitive tests were administered on day one (baseline) and day five (post-treatment): The continuous performance test-II which measures sustained attention, the Hopkins verbal learning test-Revised which examines verbal learning and episodic memory and the Dual n-back task which measures working memory.

**Results:**
Participants receiving modafinil and escitalopram performed significantly better (p=0,026) on one of four measures of working memory, namely auditory block accuracy, post-treatment (mean: 0,65; Standard deviation: 0,08) than on baseline (mean: 0,45; SD: 0,27). Subjects on modafinil alone performed significantly better on two measures of sustained attention. The mean score on Sensitivity post-treatment was 46,7 (SD: 14,1) compared to 50,9 (SD: 11,6) on baseline (p=0,034; higher scores reflect poorer performance). Post-treatment, the mean Hit rate reaction time interstimulus interval was 57,2 ms (SD: 13 ms) compared to 65,3 ms (SD: 17,5 ms) on baseline (p=0,044).

There were no significant differences on all of the remaining measures of working memory and sustained attention. Modafinil did also not affect episodic memory or information processing speed.

### 2.6.2.2 Effects of Potential Agonist-Replacement Therapies for Stimulant Dependence on Inhibitory Control in Cocaine Abusers

Vansickel et al. (2008) examined the effects of modafinil and methylphenidate on reaction time and inhibitory control in cocaine-dependent individuals. Modafinil significantly decreased reaction time in a cued go-no-go reaction time task.

**Methods:**

11 participants were recruited and were randomly given one of four doses of modafinil (0, 150, 300 or 450 mg). Cognitive testing began 2-3 hours after drug ingestion.

Participants performed a cued go-no-go reaction time task. The two outcome measures were failure to inhibit response on no-go trials and speed of responding on go trials, i.e. reaction time.

**Results:**

Reaction time scores significantly decreased as a function of dose in participants receiving modafinil (p=0,04). See also figure 1.

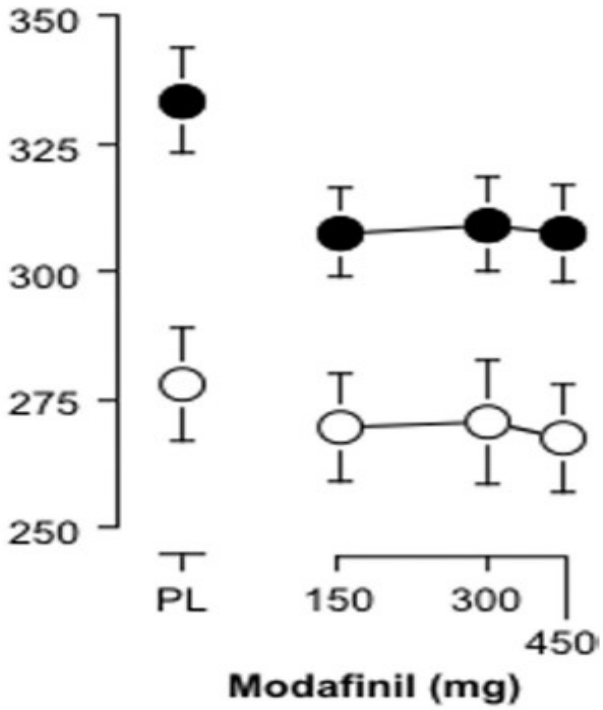


Fig. 1 Y-axis: The mean reaction time in milliseconds required to execute a response. X-axis: dose (mg). Empty symbols indicate trials in which a Go cue was presented prior to the target and filled symbols indicate trials in which a No-Go cue was presented prior to the target.
Reprinted from Vansickel et al. (2008) without permission. Meaning of error bars unknown.

Modafinil had no significant effects on response inhibition.

### 2.6.3 Nicotine

Only one relevant study about the effects of modafinil on cognitive performance in nicotine-dependent individuals could be found.

#### Modafinil and nicotine interactions in abstinent smokers

In this randomized, double-blind, placebo-controlled, crossover-designed study Sofuoglu et al. (2008) examined the effects of modafinil alone and with nicotine on cognitive variables in overnight abstinent smokers. Subjects on modafinil had significantly faster reaction times on a modified Stroop task.

**Methods:**
19 participants were recruited. The three testing sessions were separated by at least 2 days to minimize carryover effects from study medications. Participants were instructed to refrain from smoking after midnight on the testing days and their compliance was verified. 2 hours and 10 minutes after drug ingestion (modafinil or placebo) participants took 2 mg nicotine lozenge. 2 hours after drug ingestion cognitive performance was measured with the Sustained Attention to Response Test (SART) and a modified Stroop task.

**Results:**
On the Stroop task, participants responded significantly faster ($p<0,05$) in the 400 mg (mean: 598,7 ms; standard error: 39,5) and the 200 mg conditions (mean: 604,7 ms; SE: 39,6) than in the placebo condition (mean: 643,6 ms; SE: 39,6). There were no significant effects of word type.

On the SART there were no significant performance differences between modafinil and placebo.

### 2.6.4 Alcohol

Two randomized, placebo-controlled, double-blind studies about the effects of modafinil on cognitive performance in alcohol-dependent individuals are analyzed below. Detailed descriptions of the study designs are already given in part 2.4.18 and 2.4.19.

#### 2.6.4.1 Effects of Modafinil on Neural Correlates of Response Inhibition in Alcohol-Dependent Patients

Schmaal et al. (2012) examined the effects of modafinil on response inhibition in abstinent alcohol-dependent individuals and healthy control subjects. Modafinil significantly improved response

inhibition in alcohol-dependent subjects with poor baseline response inhibition, whereas response inhibition was decreased in better performing participants.

**Results:**
In the alcohol-dependent group modafinil significantly (p=0,02) improved the performance in subjects with low baseline response inhibition (based on a median split), whereas subjects with better baseline response inhibition performed worse on modafinil.
No other significant group, drug, or drug by group interaction effect on any of the performance measures could be detected.

#### 2.6.4.2 Modafinil Modulates Resting-State Functional Network Connectivity and Cognitive Control in Alcohol-Dependent Patients

Another study by Schmaal et al. (2013) examined the effects of modafinil on cognitive control in alcohol-dependent patients and healthy controls. Modafinil significantly improved cognitive control in alcohol-dependent subjects.

**Results:**
A significant main effect of treatment (p=0,02) was found on the Stroop task. Alcohol-dependent subjects receiving modafinil had a mean interference score of 118,9 ms (SEM: 16,1 ms), compared to 141,4 ms (SEM: 13,9 ms) on placebo. Thus modafinil led to significant improvements in cognitive control in alcohol-dependent. No main effect of group or treatment by group interaction effect was found. There were also no significant differences between modafinil or placebo with regard to accuracy on the Stroop task.

## 2.7 Patients with Dementia

Unfortunately, no randomized, placebo-controlled studies about the effects of modafinil on cognitive performance in patients with dementia could be found.
Available studies of modafinil in patients with dementia did examine the effects on e.g. fatigue (Cochran, 2000), apathy (Padala et al., 2007) or increased agitation (Prado et al., 2012). Of note, most of these studies were also not randomized or placebo-controlled.
A review by Dolder et al. (2010) also found no relevant studies about the effects of modafinil on cognitive functioning in patients with dementia.

The following study by Blackwell et al. (2008) which examined the effects of modafinil on mood and cognition in patients with Huntington's disease, a disorder which often leads to dementia, may be of some interest. 20 patients with mild Huntington's disease participated in this double-blind, randomized, placebo-controlled, cross-over design study and received a single dose of 200 mg modafinil.
There were no significant performance differences in the digit span task, ID/ED, NTOL or tasks of reaction time. Surprisingly, subjects on modafinil recognized significantly fewer visual patterns in the PRM ($p=0.047$) and had a significantly poorer strategy score in a task of spatial working memory ($p=0.039$) in comparison to subjects on placebo. Consequently, these findings reduce the prospects of success for modafinil as a treatment for cognitive decline in patients with dementia.

## 2.8 Adverse effects and abuse liability

### 2.8.1 Adverse effects

A study by Wong et al. (1999) of 32 healthy, male volunteers showed that the most frequently observed adverse effects among modafinil subjects were headache (34%), followed by insomnia, palpitations and anxiety (each occurring in 21% of participants). Adverse events were clearly dose-dependent: 50%, 83%, 100% and 100% of the participants in the 200 mg, 400 mg, 600 mg, and 800 mg dose groups respectively experienced at least one adverse event. According to the authors of this study the maximal safe dosage of modafinil is 600 mg.

In another randomized, double-blind, placebo-controlled study by Heinzerling et al. (2010) 71 treatment-seeking methamphetamine-dependent participants were administered 400 mg modafinil or placebo once daily for 12 weeks. The most frequently reported adverse events were headache (32% for modafinil vs. 19% for placebo), insomnia (29% for modafinil vs. 19% for placebo), nausea (21% vs. 11%) and upper respiratory infection symptoms (21% vs. 8%).

Although modafinil increased cognitive performance in sleep-deprived individuals in a study by Baranski and Pigeau (1997) it also induced an overestimation of actual cognitive performance. In the same study, subjects receiving d-amphetamine also showed increased subjective estimates of performance but these were matched by an appropriately large increase in actual performance. However, a more recent study by Baranski et al. (2002) found no such overconfidence when modafinil was administered to sleep-deprived individuals.

### 2.8.2 Abuse liability

Using a randomized, double-blind, placebo-controlled design Rush et al. (2002) examined subjective and behavioral effects of cocaine (100, 200 or 300 mg), modafinil (200, 400 or 600 mg) and placebo in cocaine users. Drug effects were assessed through the Drug Effect Questionnaire, performance measures, and physiological indices. Whereas all 3 doses of cocaine could be discriminated from placebo, there were no significant differences between modafinil and placebo on the Drug Effect Questionnaire. Modafinil and cocaine both increased heart rate and blood pressure, but the elevations caused by modafinil were clinically insignificant. Of note, while subjects taking cocaine were willing to pay $3 for 100 mg, $6 for 200 mg and $10 for 300 mg cocaine, participants on modafinil were willing to pay $2, regardless of the dose. These results suggest that modafinil has a low abuse liability, but the rather small sample size (n=9) limits the validity of this study.

The study by Marchant et al. (2009) which is discussed in more detail in part 2.4.12 found that subjects receiving modafinil were significantly less ($p<0,05$) content than subjects receiving placebo which indicates a low abuse potential of modafinil. In contrast, in a study by Müller et al. (2012) which is also discussed in more detail above, modafinil significantly increased ($p<0,05$) ratings of "task-enjoyment" which may suggest a moderate potential for abuse.

Warot et al. (1993) compared the subjective, behavioral and physiological effects of modafinil (300 mg) with those of d-amphetamine (15 mg), caffeine (300 mg) and placebo in a randomized, double-blind, placebo-controlled, cross-over study. Participants were 8 males and 8 females with no history of drug abuse. Subjective drug effects were examined with the Addiction Research Center Inventory (ARCI), Profile of Mood States (POMS) and a variety of visual analog scales at baseline, and at 1, 2, 4 and 8 hours after drug ingestion. Participants reported modafinil and caffeine to be similar on all addiction discrimination scales. Subjects receiving d-amphetamine had significantly higher ($p<0,05$) addiction scores than subjects on modafinil, caffeine or placebo. Participants taking modafinil felt significantly ($p<0,05$) less "alert", "energetic" and "happy" than subjects on d-amphetamine indicating that modafinil does not induce euphoria or well-being. These results suggest that modafinil has a relatively low abuse liability for healthy volunteers.

In a randomized, double-blind, placebo-controlled cross-over study by Jasinski and Kovacevic-Ristanovic (2000) 24 male, non-treatment seeking volunteers with histories of stimulant abuse received methylphenidate (45 or 90 mg), modafinil (200, 400 or 800 mg) or placebo. Physiological measures and the ARCI were employed. No significant differences between placebo and modafinil emerged on the Amphetamine Subscale of the ARCI. Subjects reported only the highest dose of modafinil (800 mg) to be stimulant-like.

Another randomized, double-blind, placebo-controlled study by Jasinski (2000) compared the effects of modafinil (200 mg, 400 mg or 800 mg), methylphenidate (45 mg or 90 mg) and placebo in 24 male volunteers with histories of polysubstance abuse. Subjective effects were measured with 4 Drug Questionnaires each consisting of visual analog scales. A short version of the ARCI was also used. On the Drug Rating Questionnaire subjects could generally discriminate modafinil as well as methylphenidate from placebo. Stimulant ratings for methylphenidate were significantly greater ($p<0,05$) than those for modafinil. On the ARCI modafinil did not produce any increases in the Amphetamine score, while both doses of methylphenidate led to significant increases ($p<0,05$) in the Amphetamine score. However, modafinil resulted in less observed and reported sleep.

Overall, these results indicate that although modafinil promotes wakefulness, its effects are distinct from those of more typical stimulants like amphetamine and methylphenidate and more similar to the effects of caffeine which suggests a relatively low abuse liability.

A review of abuse liability issues of modafinil by Myrick et al. (2004) also concludes that modafinil has limited potential for abuse.

# 3. Amphetamine

## 3.1 History and mechanism of action

The psychostimulant amphetamine is a widely used performance (Yesalis & Bahrke, 2005) and cognitive enhancer (Greely et al., 2008) and used by the U.S. Army for fatigue management (Kelley et al., 2012). Amphetamines are prescribed for the treatment of ADHD, narcolepsy and as appetite suppressants. It is clear that amphetamine effects mainly dopamine, noradrenaline and serotonin, although the precise mechanisms involved are not yet fully understood (Sulzer et al., 2005).

## 3.2 Effects in healthy individuals

The limited scope of this bachelor thesis did not allow for a comprehensive review of the effects of amphetamine on cognitive performance in healthy individuals. However, one exemplary study is described in more detail below.

### Amphetamine improves cognitive function in medicated individuals with schizophrenia and in healthy volunteers

Barch and Carter (2005) examined the effects of d-amphetamine on cognitive functions in patients with schizophrenia and in healthy individuals. For healthy controls d-amphetamine reduced reaction times on spatial working memory tasks and on the Stroop task. Language production ability and accuracy on the dual Stroop task were also improved by d-amphetamine.

**Methods:**
Subjects were 22 healthy controls and 10 DSM-IV schizophrenics (data of the schizophrenics will be ignored in the following). The authors used a randomized, double-blind, placebo controlled design. Each participant was tested on two different days, separated by at least 2 and maximally 7 days. On one day, subjects received a placebo and on the other day 0,25 mg/kg of d-amphetamine. After receiving either placebo or drug the subjects rested for 2,5 h and then completed a cognitive test battery which consisted of Stroop tasks, spatial working memory tasks and structured interviews.

**Results:**

*Spatial Working memory*

Accuracy did not change for healthy individuals with d-amphetamine on the single and the dual spatial working memory task. However, subjects receiving d-amphetamine had significantly faster reaction times (p<0,05) than subjects receiving placebo on both versions.

*Language production*

Participants completed structured interviews in order to assess language production ability. For healthy volunteers d-amphetamine significantly increased (p<0,05) the number of words produced, decreased the number of filled pauses (e.g. "ah", "um") and poverty of speech, on both the single- and the dual task interview. See also table 3.

Language production

| Variable | Group | | | |
|---|---|---|---|---|
| | Healthy controls | | | |
| | Placebo | | D-Amphetamine | |
| | Mean | S.D. | Mean | S.D. |
| *Single task interview* | | | | |
| Formal thought disorder | 0 | 0 | 0.05 | 0.2 |
| Number of words | 246.4 | 128.7 | 362.8 | 237.1 |
| Poverty of speech | 0.23 | 0.4 | 0.1 | 0.3 |
| Syntactic complexity | 0.30 | 0.15 | 0.31 | 0.14 |
| Filled pauses per word | 0.06 | 0.04 | 0.04 | 0.03 |
| *Dual task interview* | | | | |
| Formal thought disorder | 0.08 | 0.28 | 0.08 | 0.28 |
| Number of words | 202.7 | 131.6 | 251.2 | 150.0 |
| Poverty of speech | 0.59 | 0.67 | 0.36 | 0.50 |
| Syntactic complexity | 0.20 | 0.11 | 0.32 | 0.17 |
| Filled pauses per word | 0.07 | 0.03 | 0.05 | 0.03 |

Table 3 N=22 for healthy controls for d-amphetamine and placebo. Reprinted from Barch and Carter (2005) without permission.

*Stroop Task*

Participants were significantly faster (p<0,05) on d-amphetamine compared to placebo on both the single and the dual task Stroop. Subjects in the drug condition also made significantly fewer (p<0,05) errors on the dual task Stroop. See also Table 4.

Stroop task errors and RT

| Variable | Group | | | |
|---|---|---|---|---|
| | Healthy controls | | | |
| | Placebo | | D-Amphetamine | |
| | Mean | S.D. | Mean | S.D. |
| *Single task Stroop* | | | | |
| Congruent errors (%) | 1 | 2 | 1 | 2 |
| Neutral errors (%) | 1 | 1 | 1 | 2 |
| Incongruent errors (%) | 4 | 5 | 3 | 4 |
| Congruent RT (ms) | 652.3 | 127.8 | 618.0 | 128.5 |
| Neutral RT (ms) | 694.3 | 115.8 | 655.5 | 102.2 |
| Incongruent RT (ms) | 804.2 | 148.3 | 768.8 | 128.2 |
| *Dual task Stroop* | | | | |
| Congruent errors (%) | 5 | 7 | 2 | 4 |
| Neutral errors (%) | 3 | 4 | 2 | 2 |
| Incongruent errors (%) | 10 | 11 | 8 | 8 |
| Congruent RT (ms) | 724.9 | 135.7 | 698.5 | 122.4 |
| Neutral RT (ms) | 761.3 | 149.1 | 721.6 | 120.4 |
| Incongruent RT (ms) | 850.7 | 155.9 | 844.8 | 163.3 |

Table 4. N=22 for healthy controls for d-amphetamine and placebo. Reprinted from Barch and Carter (2005) without permission.

# 4. Donepezil

## 4.1 History and mechanism of action

The main therapeutic use of donepezil is the treatment of mild to moderate Alzheimer's disease (Birks & Harvey, 2006). Donepezil inhibits the enzyme acetylcholinesterase and thereby leads to an accumulation of the neurotransmitter acetylcholine and thus increased stimulation of cholinergic receptors (Pope et al., 2005).

## 4.2 Methodological remarks

Searching the Cochrane Database Review for "donepezil" generated 41 results. Almost all of the studies examine the efficacy of donepezil in the treatment of dementia and none of them directly examines possible cognitive enhancing properties of donepezil in healthy individuals. However, one of the studies (Birks & Flicker, 2006) concludes that donepezil does not improve cognitive function in people with mild cognitive impairment which suggests that donepezil probably also has little beneficial cognitive effects for healthy individuals.

## 4.3 Effects in healthy individuals

As is already mentioned above, the limited scope of a bachelor thesis did not allow for a comprehensive review of the effects of donepezil on cognitive performance in healthy individuals. One exemplary study is described in more detail below.

### Neuropsychological test performance in healthy volunteers before and after donepezil administration

Beglinger et al. (2004) examined the effects of donepezil on neuropsychological test performance in healthy volunteers. Subjects receiving donepezil had slight but statistically significant performance decreases on tests of processing speed, attention and memory compared to the non-drug groups.

**Methods:**
28 healthy, normally intelligent adults (mean age: 37 years) were recruited. 27 participants completed the study. For this 6-week, double-blind study subjects were randomly assigned on day 14 to one of three groups (8 donepezil 5 mg daily, 9 placebo and 10 no treatment). Neuropsychological tests were administered on days 0, 7, 14 (begin of treatment), 21, 28 (end of

treatment) and 42 (washout). The neuropsychological test battery consisted of tasks measuring attention, memory, executive functioning, language and motor ability. The following tests were employed: Finger tapping (FT), verbal fluency (VF), Rey Auditory Verbal Learning Test (AVLT), Digit Symbol (Dsy), Trail-Making Test: Parts A and B, Letter-Number-Sequencing (LNS), Stroop Colour and Word Test (Stroop) and Paced Auditory Serial Additions Test (PASAT).

**Results:**

*Placebo and no treatment*

There were no statistically significant performance differences between placebo and no-treatment. By implication, no evidence for a placebo effect was found in this study.

*Donepezil*

Donepezil didn't improve performance in any of the aforementioned tests. However, the no-treatment and the placebo group performed significantly better ($p<0,05$) than the donepezil group after 1 week of treatment (on day 21) on the Stroop Word, the AVLT trial 1 free-recall and the AVLT short delay free-recall. Furthermore, subjects in the placebo condition performed significantly better ($p<0,05$) than subjects on donepezil on the AVLT long delay. After 2 weeks of treatment (day 28) the no-treatment group was significantly better ($p<0,05$) than the donepezil group on the Trail-Making Test, Part B.

# 5. Conclusion

The main aim of this thesis was to provide an analysis of the effects of modafinil on cognitive performance in healthy individuals, substance-dependent individuals and patients with dementia. For this purpose a literature research of all available and relevant randomized, double-blind, placebo-controlled studies was conducted.

In healthy individuals modafinil seems to improve cognitive performance, especially on the Stroop Task, stop-signal and serial reaction time tasks and tests of visual memory, working memory, spatial planning ability and sustained attention. However, these cognitive enhancing effects did only emerge in a subset of the reviewed studies. Additionally, significant performance increases may be limited to subjects with low baseline performance. Modafinil also appears to have detrimental effects on mental flexibility.
In substance-dependent individuals modafinil also led to performance improvements, especially on the Stroop Task, stop-signal reaction time tasks and tests of sustained attention and working memory. These performance enhancements were particularly large in subjects with low baseline performance.
No studies on the effects of modafinil on cognitive performance in patients with dementia could be found.

The abuse liability of modafinil seems to be small, particularly in comparison with other stimulants such as amphetamine and methylphenidate. Headache and insomnia are the most common adverse effects of modafinil.

There are several limitations to this thesis. First of all, no meta-analysis on the Cochrane Database or elsewhere could be found. Thus, only normal studies could be analyzed at all. Moreover, the effects of modafinil on cognitive performance were examined only by few studies, as little as 9 in the case of substance-dependent individuals. Additionally, many of the reviewed studies had small sample sizes of less than 30. Furthermore, only few studies used identical cognitive tests which reduces the findings' comparability.
The most severe limitation is that due to the limited scope of this thesis the effects of other drugs on cognitive performance were not evaluated. Therefore possibly illuminating comparisons between the effects of modafinil and those of other drugs on cognitive performance are lacking. Future studies should therefore analyze and compare the effects of modafinil and those of more traditional wake-promoting agents like amphetamine or caffeine on relevant subparts of cognitive functioning and the associated effect sizes.
Future research on the effects of modafinil on cognitive performance in patients with dementia is needed since currently no such studies exist.

Because several studies suggest that modafinil may only provide substantial beneficial effects to individuals with low baseline performance, ultimately the big question remains if modafinil can really improve the cognitive performance of already high-functioning, healthy individuals. Only in the latter case modafinil can justifiably be called a genuine cognitive enhancer.

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