Review

Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review

Dimitris Repantis [a,*], Peter Schlattmann [b,1], Oona Laisney [a], Isabella Heuser [a]

[a] Department of Psychiatry, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Eschenallee 3, 14050 Berlin, Germany
[b] Department of Biometry and Medical Statistics, Charité-Universitätsmedizin Berlin, Campus Charité Mitte, Charitéplatz 1, 10098 Berlin, Germany

ABSTRACT

The term neuroenhancement refers to improvement in the cognitive, emotional and motivational functions of healthy individuals through, inter alia, the use of drugs. Of known interventions, psychopharmacology provides readily available options, such as methylphenidate and modafinil. Both drugs are presumed to be in widespread use as cognitive enhancers for non-medical reasons. Based on a systematic review and meta-analysis we show that expectations regarding the effectiveness of these drugs exceed their actual effects, as has been demonstrated in single- or double-blind randomised controlled trials. Only studies with sufficient extractable data were included in the statistical analyses. For methylphenidate an improvement of memory was found, but no consistent evidence for other enhancing effects was uncovered. Modafinil on the other hand, was found to improve attention for well-rested individuals, while maintaining wakefulness, memory and executive functions to a significantly higher degree in sleep deprived individuals than did a placebo. However, repeated doses of modafinil were unable to prevent deterioration of cognitive performance over a longer period of sleep deprivation though maintaining wakefulness and possibly even inducing overconfidence in a person's own cognitive performance.

© 2010 Elsevier Ltd. All rights reserved.

Contents

* Corresponding author. Tel.: +49 30 8445 8293; fax: +49 30 8445 8726.
  E-mail addresses: dimitris.repantis@charite.de (D. Repantis), peter.schlattmann@charite.de (P. Schlattmann).

URLs: http://www.charite-psychiatrie.de (D. Repantis), http://www.charite.de/biometrie/de/index.html (P. Schlattmann).
[1] Tel.: +49 30 450 562007.

1. Introduction

The term *neuroenhancement* has been coined to denote interventions by which healthy people improve their cognitive, emotional and motivational functions [1,2]. If psychopharmaceutical substances are used to achieve such improvements, it is called pharmaceutical neuroenhancement. Apparently, psychostimulants are popular among healthy people seeking neuroenhancement [3]. In this article, we examine possible neuroenhancement properties of two substances that have often been in the spotlight of both the scientific [4,5] and popular press [3,6], namely methylphenidate (MPH) and modafinil. The first, a stimulant used to treat attention-deficit hyperactivity disorder (ADHD), is known to have been extensively misused, especially by college students as a "study aid" [7]. The second, a wakefulness promoting agent licensed for the treatment of excessive daytime sleepiness associated with narcolepsy, sleep apnoea and shift-work sleep disorder, is already used by military personnel, as depicted for instance in the Memorandum of the United States Air Force "Modafinil and management of aircrew fatigue" (2nd December 2003), which approves the use of modafinil for missions of great duration, and in the Internet site of the United States Air Force Laboratory, who conducted the relevant research (http://www.hep.afrl.af.mil/HEPF/Research/index.html, accessed 12th April 2010). It also seems to become increasingly popular, both in business and in academia. In an online poll conducted by Nature magazine [8], 20% of the 1400 responding readers reported use of MPH, modafinil or beta-blockers (drugs prescribed for cardiac arrhythmia, that can also have an anti-anxiety effect) for non-medical reasons: 62% of users reported taking MPH and 44% modafinil. Their main reasons for doing so were to improve concentration, focus for a specific task or counteract sleep deficit or jetlag Indirect evidence for the non-medical use of MPH and modafinil can also be gained by comparing their disproportionately high prescription and sales numbers to the numbers of patients suffering from the disorders for which these substances are approved or used off-label [9,10].

This systematic review, which has been conducted according to a pre-defined protocol, aims to collect and analyse the available evidence about the effects of MPH and modafinil in healthy individuals. If these drugs can be shown to have positive effects in healthy individuals, then this adds urgency to the question how to regulate their potential use for neuroenhancement purposes. If no evidence of neuroenhancement effects can be found in the existing literature, then this fact should be made known to those healthy people who are ready to accept the risk of consuming MPH or modafinil [11,12] because of their belief in such not empirically supported benefits.

2. Objectives

The aim of this review was to assess the effect of MPH and modafinil on emotional, cognitive and motivational processes and the safety of their use by healthy individuals. Although these drugs are supposed to mainly affect cognition, the widespread neurochemical systems they implicate suggest that they might also have an impact on emotional and motivational functions [1]. MPH is a dopamine reuptake blocker that also enhances dopamine and norepinephrine release with pharmacologic mechanisms similar to those of amphetamines [13]. The mechanisms of action of modafinil are not well understood but are believed to differ from those of methylphenidate and amphetamines. Although there is mounting evidence that the effects on dopamine and norepinephrine are primary, effects on γ-aminobutyric acid, glutamate, histamine and orexin/hypocretin are also theorised [14–16]. Both substances are being investigated or already in use for ameliorating the cognitive impairment in several psychiatric disorders [5], but since their effects in these diseases are not the scope of this review refer for more details to [15,16].

3. Methods

3.1. Criteria for considering studies for this review

3.1.1. Types of studies

Included were all published single- or double-blind randomised or quasi-randomised controlled clinical trials, including cross-over clinical trials, which compare MPH or modafinil with placebo.

3.1.2. Types of participants

Eligible studies were those involving individuals of any age and either sex who show no evidence of psychiatric disorder, cognitive decline or other diseases. The studies were divided into those enrolling sleep deprived individuals and those with participants in a normal state of wakefulness.

3.1.3. Types of interventions

All interventions with MPH or modafinil in all doses and dosing schedules (single dose or repeated doses) for any duration and by any route of administration in comparison with placebo.

3.1.4. Types of outcome measures

The primary outcomes of interest were measures for emotional, cognitive or motivational parameters. Specifically: mood, wakefulness, motivation, attention, concentration, memory, learning and executive functions. The outcomes were not pre-defined any further. Secondary outcomes of interest were adverse effects and acceptability of the medication, measured by the number of people dropping out during the trials and post-randomisation exclusions due to the drugs' effects.

3.2. Search methods for identification of studies

Supported by a professional librarian an author (DR) developed search strategies (available upon request) including terms such as "methylphenidate", "modafinil", "healthy volunteers" and their variants, synonyms, acronyms and the relevant medical subject headings (MeSH) to identify potentially relevant studies. The MEDLINE and EMBASE databases were searched using the WebSPIRS® 5.12 search engine from OVID. No language restriction was applied. The search was performed in the second week of August 2007 (MEDLINE: 1950 to 2007/08-week 2, EMBASE: 1989 to 2007/07). Reference lists from relevant primary and review articles were examined so as to identify additional studies.

3.3. Methods of the review

3.3.1. Selection of studies

The studies obtained through the search strategy were screened and those being clearly irrelevant were discarded on the basis of their title and abstract. The remaining references were retrieved in hard copy and compared against the review's inclusion criteria. If there was any doubt whether an article should be included or not, the article was assessed by one of the other authors (OL) and disagreements were resolved by discussion.

3.3.2. Quality assessment

Methodological quality and quality of reporting of each trial was assessed using the criteria of the three-item, five-point Oxford Scale (Jadad scale) which assigns a numerical score of 1–5 (5 being the best score; [17]). The score in the Jadad scale was not used as cut off to justify inclusion in the meta-analysis or not, but rather as a practical tool for quality assessment by the descriptive reporting of the studies.

3.3.3. Data extraction

Four types of data were extracted from the published reports onto a pre-tested, standardised abstraction form in a spreadsheet: (1) study characteristics, design and quality (randomisation, blinding, method of randomisation and blinding, all-cause dropouts), (2) population characteristics (number, age and gender of participants, sleep deprived or not), (3) study interventions (drug, dosage, frequency, duration of trial, duration of sleep deprivation prior and after drug taking), and (4) primary outcomes: results for relevant tests, with all their parameters, for instance both time and accuracy in a reaction time test. For data processing, these tests were grouped into test clusters according to the predominant neuropsychological domain that they were assessing [18,19] and these clusters were aggregated for further analyses into the main factors, namely outcomes. Adverse events were used as a secondary outcome. Studies from which the data could not be extracted (out of tables or diagrams) were included in the systematic review if they fulfilled the inclusion criteria, but their results could not be integrated in the meta-analyses. Their findings however were taken into account in the descriptive presentation of the results of the systematic review. The data were extracted and summarised by two investigators (DR and OL) not blinded to the studies' authors.

For continuous data, the summary statistics required for each trial and each outcome were the mean, the standard deviation and the number of participants for each treatment group at each time point. If available, the mean change from baseline was considered in each group. The baseline assessment was defined as the latest available assessment prior to randomisation, but no longer than two months prior to it. For binary data, the number of people in each treatment group and the number of people experiencing the outcome of interest were sought. If only the treatment effects and their standard errors were reported, these were extracted.

The outcomes measured in clinical trials often arise from ordinal rating scales. Whenever the rating scales used in the trials had a reasonably large number of categories, the data were treated as continuous outcomes arising from a normal distribution.

3.3.4. Data analysis

Based on the means and standard deviations of each group, a standardised effect difference, namely Cohen's d, was calculated for the relevant test parameters of each study. Additionally, the variance of Cohen's d was calculated. Cohen's d was chosen since it allows comparing results measured with different psychometric scales. In order to take heterogeneity and correlation within studies into account, a linear mixed model was used for data analysis. Based on this linear mixed model, a meta-analysis and a meta-regression were performed. The results report the heterogeneity variance, which measures structural variability between studies, together with regression coefficients for fixed effects such as time. An effect size was computed for each outcome and in all cases, positive effect sizes give the difference in improvement between drug and placebo adjusted for the scale and accuracy of the measurements used in each study. For interpreting the results we use the widely accepted guidelines of Cohen [20]. For research in the behavioural sciences, he defined 0.2 as small, 0.5 as medium and 0.8 as large effects. All analyses were performed with PROC MIXED of the statistical package SAS 9.1.

Most studies included several assessment points. For our analysis, the results from the different studies of the assessments that were near to one another were summed up to form the results for the first, second, etc. assessment's time points. On the contrary, the fine gradation of sleep deprivation as a covariate, allowed for a continuous analysis of its effects. For our analyses, a significance level of <0.05 was applied.

4. Results

4.1. Results of the search

Our research yielded 288 relevant titles for MPH and 130 for modafinil from MEDLINE and EMBASE databases (including some duplicate records, where the two databases overlapped). The selection process is illustrated in Figs. 1 and 2. We retrieved 80 and 56 publications respectively for full-text evaluation together with those found through references. From these articles, 46 about MPH and 45 about modafinil met our inclusion criteria and their results are considered here. In the statistical analyses however, only those with sufficient extractable data were included. Generally, each study looked at and provided data only for some of the outcomes at question and therefore a different number of studies was included in the meta-analysis of each outcome (Figs. 1 and 2). Two of the included studies were only published as abstracts [21,22]. All the
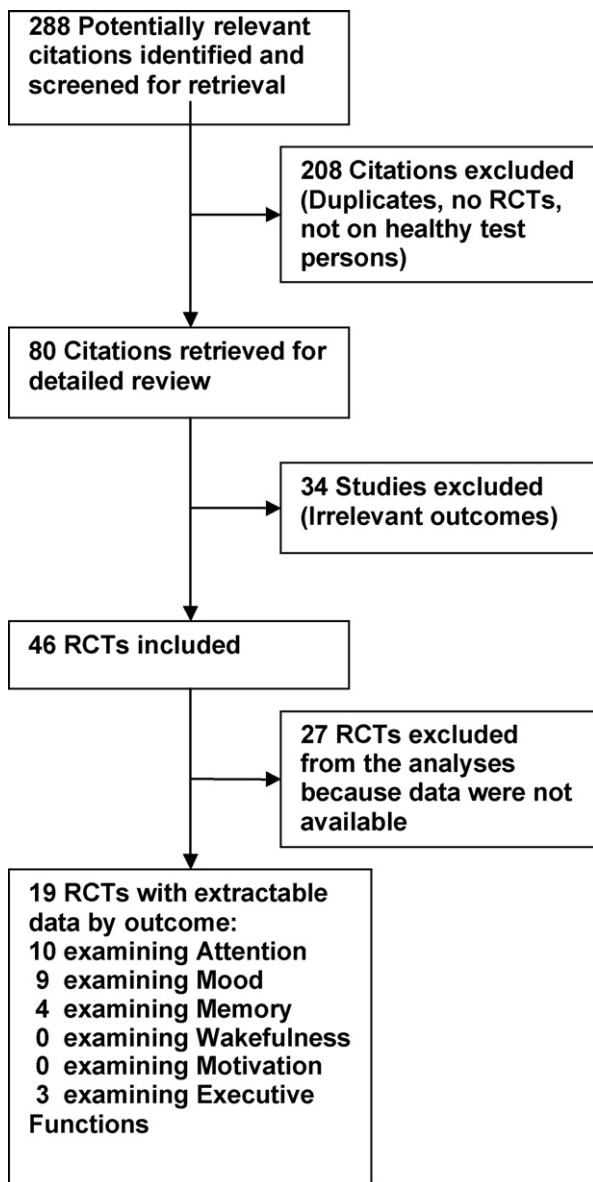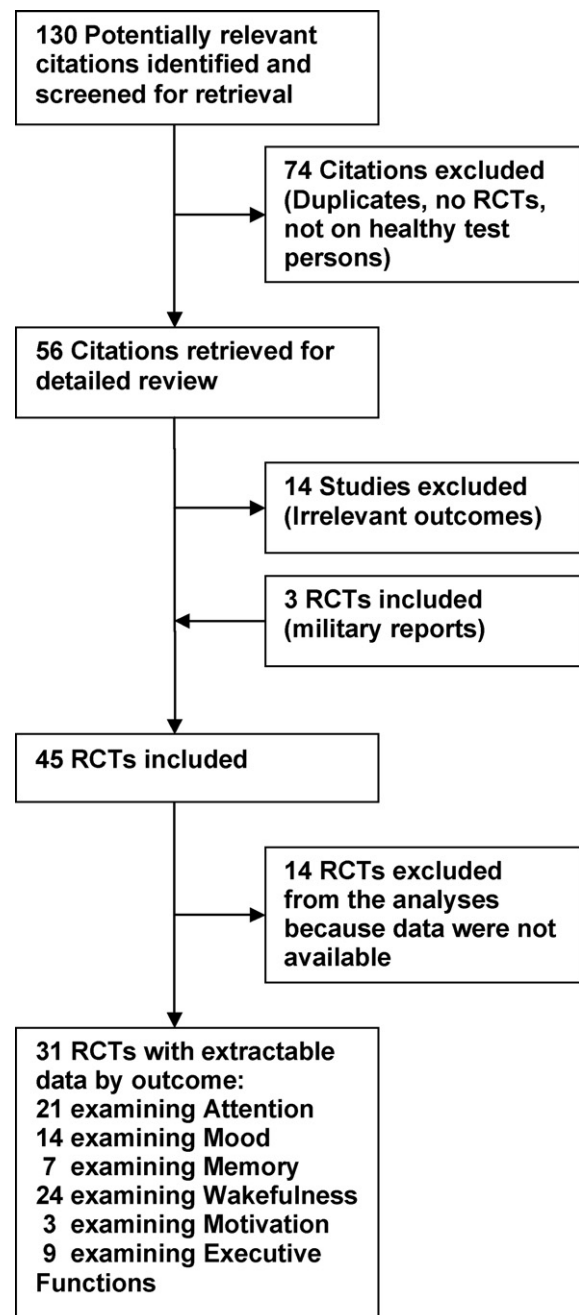
Fig. 1. Trials identification and selection process (QUOROM Flow Chart) for methylphenidate. Several studies examined more than one outcome (RCT = randomised controlled trial).

relevant publications were in English, except an article published in Chinese, which, although it was indexed in a database, was not retrievable [23]. Through cross-references we also came across published reports of military studies. The results of some of them were also partially presented in already found publications [24,25]. In these cases only the additional, unpublished results were considered. Other reports were not published elsewhere and therefore they were included as such in the systematic review [26–28]. For detailed information about the included studies and their results refer to Tables 1–4. (Because of space limitation, studies included in the systematic review, but not cited in the text, are not listed in the reference list.)

4.2. Description and methodological quality of included studies

Before proceeding to the statistical analyses of the results, a short description of all the articles, including those yielding qualitative, but no quantitative information follows. In order to evaluate the results, a first crucial point is the duration of the trials, or else if

Fig. 2. Trials identification and selection process (QUOROM Flow Chart) for modafinil. Several studies examined more than one outcome (RCT = randomised controlled trial).

the drug was given only once (single dose trial) or more than once, for a period of time (repeated doses trial). Furthermore, it is a known fact that stimulants have wakefulness promoting properties [29], and therefore several studies have tested the effect of these drugs in sleep deprived individuals. Hence, a further a-priori subgroup analysis was performed: trials with non-sleep deprived individuals and trials with sleep deprived individuals, including people that were completely sleep deprived, those that were allowed to nap for a few hours in the course of the study and those that were tested in a simulated shift-workers condition.

Among the 46 studies of MPH, four were repeated dose trials [30–33] two of which were with non-sleep deprived volunteers, who received MPH once per day for one [33] and six weeks [32] respectively. The third was a sleep deprivation study where MPH

Table 1

Included studies—methylphenidate (MPH).

First author (year)	Study design (Jadad score)	N, sex (mean age)	Dose (mg/d) (Ndrug)	Domains tested	Significant effects of MPH vs. placebo (p < 0.05)	Remark
Aman, M.G. (1984)	Crossover DB,RCT (2)	12 M + F (28.3)	0.3/kg (~20)	Mood, wakefulness, memory, attention	Decreased commission errors in CPT (but due to ceiling effect, no effect in omission errors or in performance in a memory task).	Change occurred on 1 of 13 measures; a trend for improved attention was found.
Anderer, P. (2002)	Crossover DB,RCT (2)	20 M + F (28.5)	20	Mood, wakefulness	Increased high spirits and reduced dizziness under MPH.	Limited subjective effects.
Bishop, C. (1997)	Crossover DB,CT (2)	9 M + F (28)	20	Mood, wakefulness, attention	Subjective effects of decreased fatigue, sedation and increased high, euphoria. No effect on attention.	Some stimulant-like subjective effects. Testing also under sleep deprivation.
Booij, J. (1997)	Parallel DB,RCT (3)	12 M (24)	Not reported (N = 6)	Mood	Increased scores in the positive and general psychopathology scales. (items: excitement, anxiety, tension, and mannerisms and posturing.)	Behavioural effects measured by an interview (single-photon emission computed tomography (SPECT) study).
Brignell, C.M. (2006)	Parallel DB,RCT (4)	32 M + F (23.5)	40 (N = 16)	Mood	No effect on fear conditioning.	Study on fear conditioning using skin conductance. No effect of MPH.
Brown, W.A. (1977)	Crossover DB,CT (2)	17 M (25)	10, 20	Mood, wakefulness	Increased subjective ratings of well-being/euphoria, vigor and elation (20 mg: also for concentration).	Improved subjective mood and arousal.
Brown, W.A. (1978)	Parallel DB,CT (2)	32 M + F (24.2)	10 (N = 20), 20 (N = 12)	Mood, wakefulness	Increased subjective ratings of well-being/euphoria and trend for increased ratings in vigor and elation.	MPH appeared equally effective with dextroamphetamine in eliciting euphoria.
Brumaghim, J.T. (1998)	Crossover DB,RCT (2)	22 M + F (20.9)	0.3/kg (~20)	Mood, wakefulness, memory	Increased ratings on mood, but not on concentration, vigor. No change in a paired-associate learning task.	Improved subjective mood. No improvement in memory.
Bullmore, E. (2003)	Crossover DB,RCT (3)	12 M + F (69.8)	20	Memory	No change in an object-location learning task (same study as in Müller, U., 2005).	No effect on spatial memory (part of an fMRI study).
Camp-Bruno, J.A. (1993)	Parallel DB,RCT (3)	31 M + F (23)	20 (N = 15)	Attention, memory	Decreased RT in a vigilance task and improvement in 1 out of 2 verbal memory tasks.	An improvement of attention and memory was found.
Clark, C.R. (1986)	Crossover DB,RCT (2)	10 M (24)	0.65/kg	Wakefulness, attention	Increased response rate, but no change in RT or target discrimination in a dichotic attention task.	Some improvement in attention and in spontaneous behaviour (talkative, etc.).
Clark, C.R. (1986)	Crossover DB,RCT (3)	18 M (24)	0.65/kg	Mood, wakefulness, attention	No change in a dichotic attention task. Increased subjective ratings of elation and alertness and decreased lethargy, depression and concentration.	No change in divided or focused attention, but increased subjective arousal and distractibility of attention.
Coons, H.W. (1980) (1st)	Crossover B, RCT (1)	13 M (23.8)	20	Mood, wakefulness, attention, memory	No difference in working memory found (CPT).	No difference found; maybe due to floor effect.
Coons, H.W. (1980) (2nd)	Crossover B, RCT (2)	23 M (19.7)	20	Mood, wakefulness, attention, memory	Improved performance in CRT and 2 difficult CPT versions. Increased concentration and aggression.	Improved attention/working memory and some subjective effects was found.
de Haes, J.I.U. (2006)	Crossover SB,CT (0)	7 M + F (22)	0.25/kg	Mood, wakefulness, memory	No difference in CPT found. Oral report of increased happiness on analogue rating scales. (PET study).	No change in attention and 11 out of 12 oral subjective measurements.
Elliott, R. (1997)	Crossover DB,CT (0)	28 M (21.3)	20 (N = 8) 40 (N = 20)	Wakefulness, attention, memory, executive function	Increased alertness and performance in a planning task and decreased subjective tiredness. In spatial working memory tasks, improved performance when the drug was taken 1st and decreased accuracy (but also RT) when taken 2nd. Practise effect on some CANTAB tasks did not allow for clear results.	Some cognitive enhancing effects. Some results supporting the hypothesis that MPH enhances spatial memory on novel tasks, but impairs previously established performance (induces impulsive response before the processing of the information).
Fitzpatrick, P. (1988)	Crossover DB,CT (1)	10 M (19.7)	0.3/kg (~20)	Mood, wakefulness, memory	No difference between the 2 groups in a Sternberg task due to practise effect. Increased mood ratings.	Improved subjective mood.
Gilbert, J.G. (1973)	Parallel DB,RCT (5)	53 M + F (>60)	5–30 **(for 6w)** (N = 27)	Mood, wakefulness, memory	Test after 3 and 6w: reduced fatigue. No difference on VAS on anxiety, hostility, depression, cognitive disturbance, carefree or friendliness. No difference on any of the six scales of the Guild memory test.	After 3w and 6w no effect on memory was found. Out of the 6 behavioural measures MPH reduced fatigue, but had no other effect on mood.
Gobbi, G. (2003)	Parallel DB,RCT (3)	12 M (25)	20 (for 1w) (SR)(N = 6)	Mood, wakefulness	Increased anxiety, but no other change in the other subjective measures (subscales of POMS) after 7 d of MPH treatment.	Little effect of MPH on mood, besides an increase in anxiety (Little was reported as the focus of the paper was on bupropion).
Hermens, D.F. (2007)	Crossover DB,RCT (2)	32 M (22.3)	5/15/45	Mood, wakefulness, attention, memory, executive function	MPH dose-dependently reduced RT in 3 tasks and reduced total and omission errors in 2 of them. No effect on memory, executive function and on subjective measures.	Improved sustained attention (MPH induced faster and more correct responses in attentional tasks).
Hink, R.F. (1978)	Crossover DB,CT (1)	12 M (23.5)	10	Attention, executive function	No difference in a selective attentional task and a time estimation task. Subjective effects of arousal.	No effect on selective attention.
Hink, R.F. (1978)	Crossover DB,CT (2)	16 M (24)	10	Attention	Performance increased in a divided attention task; trend to increase in a focused attention task.	Improved divided (and focused) attention.
Kollins, S.H. (1999)	Crossover DB,CT (3)	10 M + F (30.7)	20/40 IR/20/40 SR	Mood, wakefulness, attention	The IR formulation produced stimulant-like drug effects in time- and dose-dependent manner, while the SR had only transient effects.	This study showed that the abuse potential of MPH can be reduced by slowing the rate of onset of drug effect.
Kupietz, S.S. (1980)	Crossover SB,CT (0)	9 M + F (28.7)	5, 10	Memory	5 mg: Better performance in learning a nr. of Chinese characters simultaneously in a PAL task.	Better memory for symbols learned simultaneously (but not progressively).

Table 1 (*Continued*)

First author (year)	Study design (Jadad score)	N, sex (mean age)	Dose (mg/d) (Ndrug)	Domains tested	Significant effects of MPH vs. placebo ($p < 0.05$)	Remark
Mehta, M.A. (2000)	Crossover DB,CT (2)	10 M (34.8)	40	Mood, wakefulness, memory	Decreased between errors, but not within errors in the Spatial Working Memory task.	Some improvement in spatial memory. No change in subjective measurements.
Müller, U. (2005)	Crossover DB,RCT (2)	12 M + F (69.8)	20	Attention	No effect on a cued or uncued choice RT. (same study as in Bullmore, E., 2003).	No effect on attention (part of an fMRI study).
Naylor, H. (1985)	Crossover DB,CT (2)	8 M (34.5)	5/10/20	Memory, attention	Decreased RT for both the easy and the hard stimulus in a Sternberg task.	Improved attention regardless of the complexity of the stimulus.
Oken, B.S. (1995)	Crossover DB,RCT (3)	23 M + F (25)	0.2/kg	Mood, wakefulness, attention	Increased subjective arousal and decreased RT in 1 out of 3 RT tasks. No change in the Digit Span Memory Task.	Subjective effects of arousal, but limited, non attentional specific, effects on the objective tasks.
Peloquin, L.J. (1986)	Crossover DB,CT (1)	18 M + F (11.4)	0.3/kg (~12)	Mood, memory, attention	Decreased: errors and RT variability (but not RT) in a memory task; errors, RT and RT variability in CPT; dysphoria in subjective ratings.	Improved mood (without eliciting euphoria), memory and attention in children.
Roehrs, T. (1999)	Crossover DB,RCT (3)	6 M + F (25.5)	30	Mood, wakefulness, attention	Subjective effects of decreased fatigue and increased tension, vigor, stimulation and mental efficiency. Decreased RT in one attentional task.	Subjective stimulating effects and some effects on tasks of attention. Testing also under sleep deprivation.
Roehrs, T. (2004)	Crossover DB,RCT (3)	7 M + F (33)	5/10/20	Mood	5 mg: Increased stimulated, feeling friendly, anxiety, feeling down, dysphoria. Decreased alertness.	Stimulant-like subjective effects. The effects on an attentional task are not reported. Testing also under sleep deprivation.
				Wakefulness	10 mg: Increased liking, euphoria, stimulation, good drug effect, alertness, anxiety, hostility.	
				Attention	20 mg: Increased arousal, stimulation, euphoria, dysphoria, mental efficiency, bad drug effect, good drug effect, liking. Both 10 and 20 mg decreased tired.	
Rogers, R.D. (1999)	Parallel DB,CT (2)	32 M (20.5)	40 (N = 16)	Attention	ID/ED task: increased errors at the ID-shift, smaller increases in errors at the ED-shift and increased RT.	Disrupted attentional control.
Smith, R.C. (1977)	Crossover DB,RCT (2)	16 M + F (28)	10, 20	Mood, wakefulness	Increase in the subscales talkative, active, cheerful, euphoric, speeding and confident. 10 mg increased and 20 mg decreased ratings of anxiety.	MPH had an intermediate efficacy in producing subjective effects.
Stoops, W.W. (2005)	Crossover DB,CT (2)	7 M + F (24), 2: prior use of cocaine	10/20/40	Executive function	MPH dose dependently increased the % of arithmetic problems solved and ratings at the Stimulant subscale and of: Restless, Alert, Any Effect, Good Effects, Like Drug, Rush, Shaky/Jittery, Stimulated, Talkative/Friendly, Willing to pay for and to take again.	Reinforcing effects of MPH found. Participants dose-dependently self-administered more MPH before performing an arithmetic task, but not before relaxation.
Strauss, J. (1984)	Crossover DB,CT (1)	22 M (19.2)	20	Mood, wakefulness, attention, memory	Better performance in a difficult CPT version and subjective rating on mood. No change in a PAL task.	Improved attention and mood. In a memory test, no difference maybe due to ceiling effect.
Turner, D.C. (2002)	Parallel DB,RCT (2)	60 M (61,6)	20 (N = 20), 40 (N = 20)	Mood, arousal, attention, memory, executive function	Increased alertness with 40 mg. Decreased RT in the ID/ED and a gambling task. No effect on the other tasks of the CANTAB.	No cognitive enhancing effects (on working memory, sustained attention and response inhibition) found in elderly participants.
Unrug, A. (1997)	Crossover DB,CT (1)	2 × 12 M + F (24)	20	Mood, wakefulness, memory	Decreased deactivation. No change in activation, or immediate and delayed verbal recall.	Increased subjective arousal, but no change in memory found.
van Luijtelaar, G. (2002)	Crossover DB,RCT (3)	12 M + F (24)	20	Mood, wakefulness	No subjective effect or effect on the acoustic startle reflex.	No effect on the acoustic startle reflex.
Volkow, N.D. (1998)	Crossover SB,CT (0)	7 M + F (24)	5/10/20/40/60	Mood, wakefulness	On oral report of high, rush, anxiety or restlessness on analogue rating scales no effect found.	No subjective effects (part of a PET study).
Volkow, N.D. (1999)	Crossover SB,RCT (1)	14 M + F (33)	0.025/0.1/0.25/0.5/kg	Mood, wakefulness	Increased restlessness. 0.25/kg, 0.5/kg: increased high and rush. 0.5/kg: showed a trend to increase anxiety and alertness.	Subjective effects of high and rush was found (part of a PET study).
Volkow, N.D. (1999)	Crossover SB,CT (0)	8 M + F (32)	0.025/0.1/0.25/0.5/kg	Mood, wakefulness	0.25/kg, 0.5/kg: increased high and rush on oral reports on analogue rating scales.	Subjective effects of high and rush was found (part of a PET study).
Volkow, N.D. (2004)	Crossover SB,CT (1)	16 M + F (35)	20	Motivation, executive function	No effect on solving mathematical tasks, but increased rating of the task as interesting, motivating, exciting and tiresome.	A mathematical, but not a passive task (looking at pictures) was rated as more interesting and motivating.(PET study).
Wang, G.J. (1997)	Crossover SB,RCT (1)	20 M (35.2)	0.5/kg	Mood, wakefulness	Increased alertness, restlessness, loss of control and sexual desire in VAS.	A subjective effect of arousal was found.
Wang, G.J. (1999)	Crossover SB,CT (0)	7 M + F (31.4)	0.5/kg	Mood, wakefulness	Increased anxiety, rush, stimulation, high, restlessness, tiredness and talkativeness in VAS.	Most of the subjective measurements were reproduced in this twofold trial (part of a PET study).
Wetzel, C.D. (1981)	Crossover DB,CT (1)	12 M + F (27.5)	0.1/kg, 0.25/kg, 0.5/kg	Memory	High dose impaired retention (immediate and after 24 h) in 2 out of 3 memory tests when given before learning, but not when given after.	High dose impaired facilitation of new memories, but not of memories acquired before the drug was given.

The studies included in the analysis of at least one domain are marked with bold. *Abbreviations*: B = blind, CANTAB = Cambridge Neuropsychological Test Automated Battery, CPT = continuous performance task, CRT = choice reaction time task, CT = controlled trial, DB = double blind, F = female participants, fMRI = functional magnetic resonance imaging, ID/ED = intra- and extra-dimensional shift task, IR = immediate-release, M = male participants, MPH = methylphenidate, N = number of participants, Ndrug = number of participants that took drug in parallel design trials, PAL = paired-associate learning task, POMS = profiles of mood states, PET = positron emission tomography, RCT = randomised controlled trial, RT = reaction time, SB = single blind, SR = sustained-release, VAS = visual analogue scale

Table 2
Included studies—MPH in sleep deprived individuals.

First author (year)	Study design (Jadad score)	N, sex (mean age)	Dose (mg) (Ndrug)	Hours of sleep deprivation	Domains tested	Significant effects of MPH vs. placebo ($p < 0.05$)	Remark
Babkoff, H. (1992)	Parallel DB,RCT (3)	24 M (20.9)	8 × 10 (every 6 h) (N = 12)	64	Mood, wakefulness, attention, executive function	No effect in subjective measurements or cognitive tests.	MPH was not effective in reducing sleepiness neither on the subjective nor on the objective measures.
Bishop, C. (1997)	Crossover DB,CT (2)	9 M + F (28)	2 × 10 (after 24 h)	36	Mood, wakefulness, attention	Subjective effects of decreased fatigue, sedation, depression and increased vigor, high, euphoria, mental efficiency. Improved attention (RT).	Subjective stimulating effects. Reversed attention to predeprivation levels.
Bray, C.L. (2004)	Parallel DB,RCT (5)	20 M + F (24.1)	20 (N = 10)	24	Memory, attention, self-monitoring	No changes in a battery of four cognitive tests (Digit Span, Trail making, modified Stroop, Hopkins Verbal learning (HVL). In the most challenging of them (HVL) participants receiving MPH perceived their verbal memory performance as higher than it actually was.	No cognitive enhancing effects. Higher performance estimation in one out of four tests.
Roehrs, T. (1999)	Crossover DB,RCT (3)	6 M + F (25.5)	10 (after 4 h nap)	Partial sleep deprivation 32/4 h nap	Mood, wakefulness, attention	Subjective effects of decreased fatigue and increased tension, vigor, stimulation, mental efficiency. Decreased RT in one attentional task.	Subjective stimulating effects. Attention was more improved in this group than in the group without sleep deprivation.
Roehrs, T. (2004)	Crossover DB,RCT (3)	7 M + F (33)	5, 10, 20 (after 4 h nap)	Partial sleep deprivation 32/4 h nap	Mood, wakefulness, attention	5 mg: Increased alertness, stimulated, feeling friendly, dysphoria and decreased feeling down, anxiety. 10 mg: Increased positive mood, vigor, arousal, alertness, elation, stimulation, good drug effect, liking. Decreased anxiety, hostility, fatigue, tired. 20 mg: increased depression, arousal, stimulation, mental efficiency, euphoria, dysphoria, bad drug effect, good drug effect, liking. Decreased sedation, tired.	Stimulant-like subjective effects. The effects on an attentional task are not reported.

The studies included in the analysis of at least one domain are marked with bold. *Abbreviations*: CT = controlled trial, DB = double-blind, F = female participants, M = male participants, *N* = number of participants, Ndrug = number of participants that took drug in parallel design trials, RCT = randomised controlled trial, RT = reaction time.

Table 3
Included studies–modafinil.

First author (Year)	Study design (Jadad score)	N, sex (mean age)	Dose (mg) (Ndrug)	Testing points	Domains tested	Tests	Significant effects of modafinil vs. placebo ($p < 0.05$)	Remark
Baranski, J.V. (2004)	Crossover DB,RCT (4)	18 M (24.2)	4/kg (~300)	Baseline, 1 1/2, 3 h	Mood, motivation, wakefulness	VAS, questionnaire, global vigour affect scale	Improved motivation, fatigue, RT and logical reasoning and sustained performance in the vigilance task. Non-significant trend towards 'overconfidence' in one out of six self-monitoring tasks of the performance in the tests.	Cognitive enhancing effects with 'well calibrated' confidence judgements of the performance on the various tests.
					Attention	CRT, Detection of repeated numbers vigilance task		
					Executive function	Line-length discrimination, mental addition (MA), logical reasoning		
					Self-monitoring	Self estimation in MA		
Hou, R. (2005)	Crossover DB,CT (2)	16 M (27.9)	200	Baseline 2 h	Mood, anxiety	VAS	Reduced anxiety	Comparison of modafinil with clonidine.
					Wakefulness	VAS		
Hou, R. (2007)	Crossover DB,CT (2)	16 M (25.3)	200	Baseline (25.3)	Mood	VAS	n.s.	Comparison of modafinil with diphenydramine.
					Arousal	VAS		
Liepert, J. (2004)	Crossover DB,RCT (2)	10 M (26.7)	200	Baseline, 3, 24 h	Attention	RT, d2 test	n.s.	TMS study. No effect on attention or coordination.
					Coordination	Pegboard test		
Makris, A.P. (2007)	Crossover DB,RCT (2)	11 M + F (26.3)	1.75/kg, 3.50/kg, 3.50/kg	Baseline, 1/2, 1, 2, 3, 4, 5 h	Mood, Wakefulness	POMS, ARCI, VAS	POMS: increased vigor arousal, elation, total positive. ARCI: increased stimulated, decreased sedation scale. VAS: increased high, decreased sleepy. DSST: increased correct trials.	Modafinil produced subjective effects similar to d-amp., improved attention on one test and sustained performance that deteriorated across time on a memory test.
					Attention, Memory	DSST, RA task, Sternberg number recognition task temporal discrimination task		
					Executive Function			
Müller, U. (2004)	Crossover DB,RCT (3)	16 M + F (24.1)	200	Baseline, 1 1/2 h	Mood	Befindlichkeits Scale (BFS), STAI-SAI	DMTS: reduced error rates in the long delay condition and decreased RT. Numeric task: fewer errors in the manipulation condition	Subtle improvement (in the difficult conditions only) in two working memory tasks. No speed-accuracy trade-off.
					Attention, Memory	d2 Test, Trail making test DMTS, numeric working memory task		
Randall, D.C. (2003)	Parallel, DB,RCT (3)	30 M + F (20.6)	100 (N = 10), 200 (N = 10)	3 h VASs: 3, 4 1/2 h	Mood	VAS	Increased 'somatic anxiety and bodily symptoms'. Greater increases in 'psychological anxiety' and 'aggressive mood' after the stress of cognitive testing.	No cognitive enhancing effects on the CANTAB (and other tests) found. Some subjective effects of increased anxiety and aggression.
					Wakefulness, Memory	DMTS, COWAT, SOC, logical memory test		
					Attention	RVIP, ID/ED, Stroop CWT Trail making test A & B		
					Executive Function	Clock drawing task		
Randall, D.C. (2004)	Parallel, DB,RCT (3)	45 M + F (57)	100 (N = 15)	3 h VASs: 3, 4 1/4 h	Mood	VAS	200 mg: Decreased the time of the dots colour naming part of the Stroop test and improved performance in the Clock drawing task, but increased the number of errors in the ID/ED.	Limited cognitive enhancing effects in middle aged on the CANTAB (and other tests). (Improvements in 2 and impairment in 1 out of 9 tests found).
			200 (N = 15)		Wakefulness, Memory	DMTS, COWAT, SOC, logical memory test		
					Attention	RVIP, ID/ED, Stroop CWT Trail making test A & B		
					Executive Function	Clock drawing task		

Randall, D.C. (2005)	Parallel, DB,RCT (2)	60 M + F (20.5)	100 (N = 20), 200 (N = 20)	2 h VASs: 2, 4 1/2 h (tesing occurred in the early evening)	Mood	VAS	100 mg: Improved performance in Digit span (forward & backward) and PRM	Limited cognitive enhancing effects on the CANTAB (and other tests) found. Testing was performed in the evening (with the existence presumably of 'day fatigue').
					Wakefulness		200 mg: Decreased the time of the dots colour naming part of the Stroop test, improved performance in the RVIP and the PRM (but slowed the response latency in the PRM)	
					Memory	DMTS, COWAT, SOC, PRM, SWM, logical memory test, Digit span		
					Attention	RVIP, ID/ED, Stroop CWT, CRT, RT, Digit Cancellation, DSST, DSST-SCT, PASAT, Trail making test A & B		
					Executive Function	Clock drawing task		
Randall, D.C. (2005)	Meta-analysis of Randall, D.(2002,2005)	89 M + F (21)			Same as in Randall, D.C. (2003, 2005)		The meta-analysis did not reveal any more effects than those previously reported.	IQ correlation showed that high IQ limit detection of modafinil's positive effects.
Saletu, B. (1989)	Crossover, DB,RCT (2)	10 M + F (68.3)	100 Evening	After a nights sleep	Mood, Motivation	BFS, VAS	n.s.	No effect found on the sleep and morning behaviour (mood and cognition) in elderly volunteers.
			200 Evening		Wakefulness Attention Memory Coordination	VAS RT, alphabetical cross-out numeric memory test fine motor activity test		
Saletu, B. (1989)	Crossover DB,RCT (3)	10 M + F (29.8)	100 Evening	After a nights sleep	Mood, Motivation	BFS, VAS	n.s.	No effect found on the sleep and morning behaviour (mood and cognition) in young volunteers.
			200 Evening		Wakefulness Attention Memory Coordination	VAS RT, alphabetical cross-out numeric memory test fine motor activity test		
Samuels, E. (2006)	Crossover DB,CT (2)	16 M (20.9)	200	Baseline 2 h	Mood	VAS	n.s.	Comparison of modafinil with pramipexole
					Wakefulness	VAS		
Smith, D. (2004)	Crossover DB,RCT (2)	6 M (27.2)	2 × 100 Eveningmorning	3 h post morning dose	Attention	CRT, Simple RT, Stroop CWT	n.s.	No effect found on participants in euglycaemic status.
					Coordination	Tapping task		
Stoops, W.W. (2005)	Crossover DB,CT (1)	6 M + F (24), 1 with prior use of amp., cocaine	100, 200, 400	Baseline, 1, 2, 3, 4, 5, 6 h	Wakefulness Executive Function	Drug Effects Questionnaire Adjective rating scale Arithmetic Performance Task	All doses increased rating on Active/Alert/ Energetic, Rush, Any Effect, Good Effects, Like Drug, Shaky/Jittery, Stimulated and the Stimulant Adjectives subscale.	Reinforcing effects found. Participants dose-dependently self-administered more modafinil before performing a task, but not before relaxation.
Taneja, I. (2007)	Crossover DB,RCT (2)	12 M + F (30)	400/d for 3 d	Baseline, 1, 2, 3 d	Mood Wakefulness	Positive and Negative Affect Scale, Bipolar adjective ratings	Increased positive and negative affect. Higher score on 'energised', 'overalert', 'concentrated', 'quick-witted' and lower on 'calm'.	General mood-elevating effects, but with increased negative affect (anxiety).

Table 3 (*Continued*)

First author (Year)	Study design (Jadad score)	N, sex (mean age)	Dose (mg) (Ndrug)	Testing points	Domains tested	Tests	Significant effects of modafinil vs. placebo ($p < 0.05$)	Remark
Turner, D.C. (2002)	Parallel DB,RCT (2)	60 M (24.4)	100 (N=20), 200 (N=20)	2 h	Mood	VAS	Increased ratings on alert, attentive and energetic	Cognitive enhancing effects on the CANTAB. Independent of drug dose, improved memory, visual memory, spatial planning and RT found. The slowing of response latency suggests reduced impulsive responses.
					Wakefulness	VAS		
					Memory	Digit Span, PRM, PAL, DMTS, SWM, SSP, NTOL	Improved performance in Digit span, PRM, NTOL, SSRT.	
					Attention	RVIP, ID/ED		
					Executive Function	Gamble (decision making) task	Reduced latency in DMTS, gamble task (trend for reduced latency in NTOL).	
					Coordination	Stop-signal RT		
Warot, D. (1993)	Crossover DB,RCT (5)	16 M+F (23.9)	300	Baseline, 1, 2, 4, 8 h	Mood	POMS, VAS	n.s.	No subjective stimulant-like effects found. Modafinil does not possess abuse liability.
					Wakefulness	ARCI		

The studies included in the analysis of at least one domain are marked with bold. *Abbreviations*: Amp = amphetamine, ARCI = Addiction Research Center Inventory, CANTAB = Cambridge Neuropsychological Test Automated Battery, CRT = choice reaction time task, COWAT = controlled oral word association test, CT = controlled trial, DB = double-blind, DMTS = delayed matching to sample task, DSST = Digit Symbol Substitution Test, DSST-SCT = Digit Symbol Substitution Test-Symbol Copying task, F = female participants, ID/ED = intra- and extra-dimensional shift, M = male participants, *N* = number of participants, Ndrug = number of participants that took drug in parallel design trials, NTOL = One-Touch Tower of London Task, n.s. = non significant, PAL = paired associates learning task, PASAT = Paced Auditory Serial Additions Test, POMS = Profile of Mood States, RA task = Repeated Acquisition of Response Sequences task, RCT = randomised controlled trial, PRM = pattern recognition task, RT = reaction time, RVIP = rapid visual information processing task, SOC = Stockings of Cambridge (based on the Tower of London), STAI-SAI = State Trait Anxiety Inventory–State Anxiety Inventory, SSP = spatial memory span task, Stroop CWT = Stroop Colour Word Test, SWM = Spatial working memory task, TMS = transcranial magnetic stimulation, VAS = visual analogue scales

was given every 6 h for a total of 64 h without sleep [30] while in the fourth the drug was given twice after a night of either normal sleep or no sleep [31]. Regarding the studies on the effect of MPH in sleep deprived individuals, five studies were found. In addition to the two repeated dose studies mentioned above, the other three single dose studies were one 24 h sleep deprivation study [34] and two studies on partial sleep deprivation, where the drug was given after 4 h of sleep [35,36].

For modafinil the following was found: of the 45 studies there were 17 on non-sleep deprived individuals that were administrated 100–400 mg of modafinil. In only two of those modafinil was given more than once, in one case twice, in the evening and in the morning before the testing [37] and in the other case in a dose of 400 mg/d for three consecutive days [38]. There were 28 studies with sleep deprived individuals and in 17 of them the drug was given more than once with or without napping between the doses. In general, one of two different protocols had been used. In the *recovery paradigm* the volunteers were administered a (typically large) dose of 200–400 mg of modafinil after they had become extremely fatigued by sleep deprivation to determine if, and to what extend the drug could restore cognitive performance to baseline levels. In the maintenance studies (*preventive paradigm*), participants were given smaller (16.7–300 mg), more frequent doses in an attempt to maintain cognitive performance at, or near, baseline levels throughout a period of sleep deprivation [39,40]. Exact doses can be found in Tables 3 and 4. One of the studies examined the effects of armodafinil, the levorotatory R-enantiomer of modafinil, which is a racemic compound containing equal amounts of R-modafinil and S-modafinil [41].

4.3. Outcomes

In order to evaluate the neuroenhancing effects of MPH and modafinil, we focused in this review on relevant objective and subjective ratings and neuropsychological tests. A common limitation in neuropsychological research is that performance in most tests is influenced by more than one cognitive process. Details of the cognitive processes intervening in the performance of neuropsychological tests are not completely known, since cognitive functions are not isolated compartments, but related to each other [42]. Thus, different tests were categorised into several cognitive domains by clustering those tests that putatively tap similar cognitive functions. This was done mainly according to a standard textbook of neuropsychology [19]. In total, the assessments were grouped into (a) mood, (b) motivation, (c) wakefulness, (d) attention and vigilance, (e) memory and learning, and (f) executive functions and information processing. This categorisation was based also, to some extent, on previous research on the surrogate markers for the effects of drugs in healthy people [18] and was used in a similar systematic review on the effects of antidepressants in healthy individuals as well [43]. A brief description of the domains and the most commonly applied tests follows.

4.3.1. Mood

One of the primary outcomes in our research question was the change in mood after drug administration. Several instruments have been applied to measure mood. A first major distinction should be made between objective ratings (observer-rated instruments applied by a mental health care professional) and subjective self-ratings. The former were applied only occasionally, whereas the latter were used in the majority of the cases. Nevertheless, before inclusion in the trial, in almost all of the studies the participants were screened by a health care expert such as a psychiatrist or a psychologist for past or current psychiatric disorders. The standard testing procedure was a self-reporting instrument used at baseline and after drug or placebo application. Then the mean

Table 4
Included studies—modafinil in sleep deprived individuals.

First author (year)	Study design (Jadad score)	N, sex (mean age)	Dose (mg) (Ndrug)	Hours of sleep deprivation	Domains tested	Significant effects of drug vs. placebo ($p < 0.05$)	Remark
Baranski, J.V. (1997)	Parallel DB,CT (2)	27 M + F (33)	3 × 300 (N = 14)	64 h, Doses at 18, 48, 58 h	Executive function, self-monitoring	Performance in a visual perception comparison task and a mental addition task was sustained after the first two doses. In a retrospective (but not in a prospective) estimation of the actual cognitive performance an overestimation of the performance was found. Part of the study of Pigeau et al. [56].	Cognitive performance was sustained, but modafinil had a disruptive effect on self-monitoring. ("overconfidence" effect).
Baranski, J.V. (1998)	Crossover DB,RCT (3)	6 M (22)	6 × 16.7, 6 × 50, 6 × 100	64 h, Dose every 8 h (after the 12th hour)	Mood Motivation Wakefulness Attention Memory Executive Function	In a dose finding study, modafinil dose-related improved subjective measures of fatigue, motivation, subjective performance, alertness following 4 min with eyes closed and objective measures of serial RT, complex mental addition, and short-term memory.	300 mg/d maintained performance at or near baseline levels, 150 mg/d provided some maintenance of performance, and 50 mg/d had no difference to placebo
Baranski, J.V. (2002)	Crossover DB,RCT (3) (in 30 °C climate chamber)	6 M (24.7)	7 × 100	40 h, Dose every 6 h (one less at 2nd day)	Mood Motivation Wakefulness Attention Executive Function Self-monitoring	Sustained performance in a logical reasoning task, an attentional task, serial RT and subjective measures of motivation and mental fatigue, but not in a memory task, mental addition, a visual perception comparison task and measures of mood and fatigue. The actual cognitive performance was not under- or overestimated.	Cognitive performance deteriorated from sleep deprivation in a warm environment was largely but not completely restored by modafinil. No effect on self-monitoring was found.
Bard, E.G. (1996)	Parallel DB,CT (2)	27 M + F (33)	3 × 300 (N = 14)	64 h, Doses at 18, 48, 58 h	Executive function	Spontaneous dialogue in reproducing a map over radio was studied. Participants on modafinil produced less speech per dialogue and over time became less accurate. Part of the study of Pigeau et al. [56].	Performance declined to a less precise communication type. The placebo and amp groups compensated for that with more speech.
Batéjat, D.M. (1999)	Crossover DB,RCT (2)	8 M (37.3)	1 × 200 (6 h sleep between drug and placebo)	27 h, 1 dose at 18 h	Attention Memory Executive Function	Improved short-term memory (Sternberg memory task), divided attention and tracking performance, but no change in performance in complex RT, mathematical processing, spatial processing and grammatical reasoning.	The design does not allow a head to head placebo-modafinil comparison. Modafinil was effective especially after the 6 h nap.
Batéjat, D.M. (2006)	Crossover DB,RCT (2)	8 M (30.4)	1 × 200	18 h, dose at 9 h	Mood Wakefulness Attention Memory	Sustained ratings in subjective measures of sedation (alertness, clearheaded, etc.) and performance in attentional tasks (Complex RT, Divided attention task, DSST, Stroop) and memory tasks (Sternberg test).	Cognitive performance and alertness was maintained throughout 18 h of sleep deprivation.

Table 4 (*Continued*)

First author (year)	Study design (Jadad score)	*N*, sex (mean age)	Dose (mg) (Ndrug)	Hours of sleep deprivation	Domains tested	Significant effects of drug vs. placebo ($p < 0.05$)	Remark
Bensimon, G. (1991)	Crossover DB,CT (2)	12 M (24)	1 × 200	36 h, dose at 14 h	Wakefulness	Modafinil attenuated for 6 h after dose the sleep deprivation deficits on arousal, attention (RT) and short-term memory, but not on long-term memory. 18 h after administration, only an effect on arousal was found.	A single 200 mg dose was effective in sustaining performance for 6 h, but not for 18 h.
					Attention Memory		
Brun, J. (1998)	Crossover DB,RCT (3)	8 M (21.5)	2 × 300	36 h, Doses at 15, 25 h	Attention	Performance (RT) in a grammatical reasoning task was worst under placebo and there was a trend for increased errors. No difference in a RT task was found.	Mental performance (but not attention) was sustained after one night of sleep deprivation.
Caldwell, J.A. (2000) [also USAARL Report 99-17]	Crossover DB,CT (3)	8 M (37,3)	3 × 200	40 h Doses at 16, 20, 24 h	Executive Function Mood	In a helicopter simulator, the effects of sleep deprivation on 4 of 6 flight maneuvers were attenuated. Decrements in RT and tracking performance and self-reported mood, vigour, energy, sleepiness, confidence and talkativeness, were diminished.	Improved flight simulation, performance in some of the tests and subjective measures of mood in helicopter pilots.
					Wakefulness Attention Executive Function		
Caldwell, J.A. (2004) [also Report AFRL-HE-BR-TR-2004-0003]	Crossover SB,CT (0) (data from a no-treatment study as "placebo")	10 M (36.6) (5 pilots took only drug)	3 × 100	37 h, Doses at 17, 22, 27 h	Mood	In an F-117 flight simulator, decrement of performance on 6 of 8 maneuvers was attenuated. Improved RT, tracking performance and subjective measures of vigor, alertness, energy and confidence and decreased ratings of depression and anger. No effect on a mathematical processing task.	Improved flight simulation, performance in some cognitive tests and subjective measures of mood in pilots.
					Wakefulness Attention Executive Function		
Dagan, Y. (2006)	Crossover DB,RCT (3)	25 M (28)	1 × 200	29 h, dose at 16 h	Mood	In a flight simulator, decrement of performance on 2 of 3 measures was attenuated. Subject-estimated sleepiness (SSS) and ratings on exhaustion were reduced and ratings on vigilance were increased.	Improved flight simulation, and some subjective measures and ratings of sedation.
					Wakefulness Executive Function		
Dinges, F. (2006)	Parallel DB,RCT (5)	107 M (26.9)	200, Armodafinil, 100,150, 200, 300 (*N* = 18 × 5)	28 h, dose at 12 1/2 h	Sedation	All doses of armodafinil and modafinil improved wakefulness (MWT) and sustained attention (PVT). No effect on subject-estimated sleepiness was found (KSS)	Armodafinil (the R-enantiomer of modafinil) improved wakefulness and sustained attention for a longer period post-dose.
					Attention		

Eddy, D. (2005) (report)	Crossover, DB,CT (2)	17 M (31.3)	1 × 200, 1 × 400	~24 h, dose at ~12 h	Mood	Sustained performance in two attentional (PVT, CRT) a memory and a tapping task, without induced "overconfidence". Subject-estimated sleepiness (SSS) and ratings of fatigue and drowsiness were reduced. 400 mg increased ratings of nervousness.	Cognitive performance was positively affected, and still correctly self-estimated.
					Wakefulness Attention Self-monitoring		
Gill, M. (2006)	Crossover DB,RCT (5)	27 M + F (30)	1 × 200	~24 h after night shift	Wakefulness	Improved performance in some of the aspects of two attentional tests (DSST, CPT) and subjective ratings of the ability to attend post-night shifts didactic sessions in sleep deprived physicians.	Improved attention and subjective measures after night shift in emergency physicians.
					Attention Memory		
Hart, C.L. (2005)	Crossover DB,CT (3)	11 M + F (25.2)	3 × 200-day	Simula-ted day and night shifts	Mood	In the 3 night-shifts, improved performance in 2 memory tests, 3 attentional tests and ratings of alertness. In the 3 day-shifts, the effect was analogues but with less significant effects and the large dose produced also mood disruption effects (e.g., anxiety)	Modafinil attenuated in a dose related manner most of the night-shift impairments, with a less robust effect on the day-shift.
			3 × 200-night 3 × 400-day 3 × 400-night		Wakefulness Attention Memory		
Killgore, W.D. (2006)	Parallel DB,RCT (3)	25 M + F (23.5)	1 × 400 (*N* = 11)	66 h, dose at 44 h	Wakefulness	Improved attention (PVT) and visual (but not verbal) humor appreciation. Trend for decreased subject-estimated sleepiness (SSS).	Appreciation of humor in cartoons (but not of verbal humor) was improved.
					Attention Executive Function		
Lagarde, D (1995)	Crossover DB,RCT (4)	8 M (27)	6 × 200	60 h, dose every 8 h (after the 15th)	Attention	Sustained performance in logical reasoning, an arithmetic task, a spatial processing task, a tracking task, attention tasks (Complex RT, Divided attention) and a short-term memory task.	Performance was sustained at pre sleep deprivation levels for 44 h and was still better than placebo until the 60th h.
					Memory Executive Function		
Lagarde, D (1995)	Crossover DB,RCT (4)	8 M (27)	6 × 200	60 h, dose every 8 h (after the 15th)	Mood	As part of a bigger study (Lagarde, D., 1995) subjective rating of mood anxiety and vigilance were sustained in the pre sleep deprivation levels. Sleep latency (MSLT) was significantly longer than after placebo.	Vigilance was maintained as seen in both subjective ratings and objective measures.
					Wakefulness		
Li, Y.F. (2003) [abstract: article in Chinese]	Crossover B,CT (?)	6 M	3 × 200	48 h, Doses at 17, 33, 41 h	Wakefulness	Reduced subjective fatigue and sleepiness levels (SSS) and increased arousal in the Critical Flicker Fusion Frequency test (CFF). No effect on two tests of attention.	Reduced subjective fatigue and sleepiness levels, but no effect on attention.
					Attention		

Table 4 (*Continued*)

First author (year)	Study design (Jadad score)	N, sex (mean age)	Dose (mg) (Ndrug)	Hours of sleep deprivation	Domains tested	Significant effects of drug vs. placebo ($p < 0.05$)	Remark
Pigeau, R. (1995)	Parallel DB,CT (2)	27 M + F (33)	3 × 300 (N = 14)	64 h, Doses at 18, 48, 58 h	Mood	Consistent pattern of results in favour of modafinil for positive and negative mood, fatigue, sleepiness as well as performance in serial RT, logical reasoning and short-term memory tasks (for the latter, the Digit Span task, only a trend was found).	Mood, arousal and performance were sustained during the 1st and were better than placebo during the 2nd night of sleep deprivation.
					Wakefulness Attention Memory Executive Function		
Rogers, N.L. (2004) [abstract]	Parallel DB,RCT (?)	24 M + F	200/d (N = 11)	~88 h (with 2 h nap/d)	Wakefulness	Reduced impairment in sustained attention and working memory tests for up to 14 h post-drug and improved subjective ratings of vigour.	Performance decrement was attenuated. Modest effects on subjective ratings found.
					Attention Memory		
Stivalet, P. (1998)	Crossover DB,RCT (2)	6 M (25)	7 × 100	60 h, dose every 8 h	Attention	Error rates and RT of serial (but not parallel) process in a visual search task were sustained during 60 h of sleep deprivation.	Positive effect on attention with maintenance of performance.
					Executive Function		
Walsh, J.K. (2004)	Parallel DB,RCT (3)	32 M + F (29.7)	4 × 200 (N = 16)	"Night shift" (dose at 22:00)	Wakefulness	Attention (PVT), wakefulness (MWT) and performance in 3 executive function tests were sustained. No effect on a memory test, an attentional test (DSST), 4 executive function tests and subject-estimated sleepiness (SSS, KSS).	In a simulated night-shift, alertness and performance in some executive function tests was sustained.
					Attention Memory Executive Function		
Wesensten, N.J. (2002)	Parallel DB,CT (2)	40 M + F (22.4)	100, 200, 400 (N = 10 × 3)	54 1/2 h, dose at 41 1/2 h	Mood	200 mg and 400 mg improved attention (PVT, CRT, SRT) and decreased subject-estimated sleepiness (SSS). 400 mg also improved wakefulness (MWT)	Improved alertness and attention from a dose during the 2nd night of sleep deprivation.
					Wakefulness Attention Memory		
Wesensten, N.J. (2005)	Parallel DB,CT (2)	24 M + F (25.1)	1 × 400 (N = 12)	85 h, dose at 64 h	Mood, wakefulness	Improved attention (PVT) and cognitive estimation, increased subjective excitation. Trend for decreased subject-estimated sleepiness (SSS) and improved wakefulness (MWT).	Sustained executive function (1 of 2 tests) and attention (1 of 2 tests) but not memory.
					Attention Memory Executive Function		

Study	Design	Participants	Drug dose	Duration	Domain	Results	
Wesnes, K.A. (2004) [abstract]	Crossover DB,RCT (?)	36 M (29)	1 × 200 (N=18)	28 h, 1 dose at ~11 h	Attention	In attentional tasks, RT was decreased. Correct responses increased, while incorrect responses decreased.	Performance was sustained for 24 h in 3 attentional and 1 memory tests and remained better than placebo for 28 h.
Whitmore, J. (2004) (report)	Parallel DB,RCT (4)	20 M (26)	6 × 100	65 h (with 2 2 h naps)	Memory Wakefulness	Improvement in arithmetic task, and trend for improvement in logical reasoning and CRT. No effect (due to ceiling effect) on CPT. Subject-estimated sleepiness (SSS) was reduced	A trend for attenuated sleep deprivation performance decrements was found in a military, field environment study.
Batéjat, D.M. (2006)	Crossover DB,RCT (4)	12 M (30.5)	5 × 100 and 2 × 200 (high dose at midnight)	72 h, dose every 7 1/2 h	Attention Executive Function Wakefulness Attention Executive Function	Improvement in arithmetic task and subjective ratings of vigor. No effect on grammatical reasoning, attention (PVT), subject-estimated sleepiness (SSS) or other subjective ratings.	Sleep deprivation performance decrements were only partially attenuated in a military, field environment study.

The studies included in the analysis of at least one domain are marked with bold. *Abbreviations:* amp = amphetamine, B = blind, CPT = continuous performance task, CRT = choice reaction time test, CT = controlled trial, DB = double-blind, DSST = Digit Symbol Substitution Task, F = female participants, KSS = Karolinska Sleepiness Scale, M = male participants, MSLT = Multiple Sleep Latency Test, MWT = Maintenance of Wakefulness Test, N = number of participants, Ndrug = number of participants that took drug in parallel design trials, PVT = Psychomotor Vigilance Task, RCT = randomised controlled trial, RT = reaction time, SRT = four-choice serial reaction time test, SSS = Stanford Sleepiness Scale.

change from baseline for all participants under medication and placebo was measured and compared. In some cases there was no baseline assessment and the mean value after drug intake was compared with the mean value after placebo intake. The most commonly used instrument was a visual analogue scale (VAS) (or a derived factor of several VAS or scales of ascending numbers), on which participants reported their current state of mood. Most individual scales corresponded to (the individual VAS lines of) the sub-scale "contentment" proposed by Norris and validated for central nervous system drug evaluation by Bond and Lader [18]. These included instruments such as the von Zerssen Befindlichkeits Scale, scales from the Profile Of Mood States (POMS) and the Positive And Negative Affect Scale (PANAS). Specific mood states were measured by similar instruments. For example, anxiety was measured by scales such as the Spielberger State Trait Anxiety Inventory (STAI) and the POMS Anxiety scale. All of them corresponded to the sub-scale "calmness" of Bond and Lader [18] Aggression was mostly assessed by the Buss-Durkee Hostility Inventory (BDHI), but also by other subjective ratings such as VAS and the POMS sub-scales on irritability, assertiveness, hostility and anger.

4.3.2. Motivation

Motivation refers to the initiation, direction, intensity and persistence of human behaviour [44]. In the context of neuroenhancement it could be desirable to improve one's motivation, probably through enhancing primarily the persistence of behaviour. Unfortunately, the methods of measuring motivation by the simple means that are typically used in pharmacological studies are limited and in the studies included in our systematic review consisted mainly of a VAS assessing the interest or motivation of performing a particular task after drug or placebo intake. Moreover these testing procedures existed in only a few studies.

4.3.3. Wakefulness

One of the main effects of stimulants, and one of the most desirable when it comes to modafinil, is wakefulness, since they are known to have wake promoting properties. The several assessments of wakefulness were usually done by means of VAS measuring arousal (and equivalents, e.g., alertness) or the opposite, namely sedation (and equivalents, e.g., drowsiness), or else with corresponding parts of subjective ratings, such as the POMS fatigue, vigor scales, or the energy sub-scale of the Befindlichkeits Scale. Especially in studies where sleep deprivation was applied there has also been extensive use of equivalent sleepiness scales, such as the Stanford and the Karolinska Sleepiness Scales (SSS and KSS respectively) and tests that measure the ability of a person to stay awake, such as the Maintenance of Wakefulness Test (MWT) or the Multiple Sleep Latency Test (MSLT). In these tests the person sits in a comfortable position in a dark, quite room for a period of several minutes and is instructed to close his or her eyes but try to stay awake. The time to first 10 s of sleep and the time to unequivocal sleep latency, i.e., minutes to three consecutive epochs of stage 1 or one epoch of stages 2, 3, 4 or rapid eye movement sleep) are scored and serve as a measure of the effect of the drug on arousal during sleep deprivation [41].

4.3.4. Attention and vigilance

Improving one's attention is a key ability in several fields of human life. As these drugs might enhance the attention span, the interest in taking them is not surprising [7]. Attention is defined as the appropriate allocation of processing resources to relevant stimuli [45] and several tests have been developed to evaluate the effect of drugs on this cognitive process. Most of them demand a rapid but simple motor response to a stimulus, usually a light. Scoring is done by measuring the reaction time (RT), which can be separated into two components: the recognition reaction time

(or the time taken to spot the stimulus and move the finger from a starting position) and the motor reaction time (the time taken from lifting the finger to pressing the appropriate response button that extinguishes the stimulus) [46]. Simple reaction time tests (SRT) measure the response to one sensory cue, while in choice reaction time tests (CRT) the person is required to extinguish one of several equidistant lights, illuminated at random. Selective attention (giving attentional priority to a relevant stimulus while ignoring distracting or competing irrelevant information) can also be tested by asking the person to only respond to one stimulus out of many (e.g., Stroop Colour Word Test) or to a specific cue combination (e.g., red light and high tone). Often a RT task is combined with a tracking task in order to assess divided attention, which is the ability to respond simultaneously to two or more different stimuli. In this case, one must, for instance, keep a joystick-controlled cursor in line with a moving target, while responding to a random stimulus, such as a light. Both the RT and the tracking error are recorded (Compensatory Tracking Task—CTT, Divided Attention Task—DAT). Moreover, vigilance or sustained attention (the ability to maintain a consistent behavioural response to a particular stimulus during continuous and repetitive activity over a prolonged period of time) was usually measured with the Mackworth Clock Test, a 45-min long task. In this test there is a circular arrangement of 60 dots simulating the second marks on a clock and they are briefly illuminated in clockwise rotation proceeding with a 6 dots jump. At rare irregular intervals the target proceeds with a 12 dots jump by skipping one of the dots in the normal sequence and this jump has to be detected.

The above-mentioned attention-measuring tasks were classified under this domain although many of them, such as the RT tasks, were more broadly defined as measuring "psychomotor performance" in the original studies. Under this term, the researchers tried to encapsulate the co-ordination of sensory and motor systems through the integrative and organizational processes of the central nervous system. The distinction between cognitive and psychomotor functions is artificial, but nevertheless the relevant cognitive components of the psychometric tests have been classified here (e.g., recognition RT). However, there were also a number of commonly used standardised psychometric tests, which mostly relied on coordination and had a predominant motor component. These included tracking tasks, but also covered a broad spectrum of tasks such as tapping tests, for which the person was required to tap his or her finger as fast as possible. These tests are irrelevant to the objectives of this review and therefore their results are not mentioned here.

4.3.5. Memory and learning

Even without a manifest loss of memory there is a tremendous interest for memory enhancement [47]. The effects of MPH and modafinil have been investigated with a number of memory tests. They were all classified in this category although they varied considerably in terms of information types, temporal characteristics and specific processes that were targeted. List learning tests were often used and typically consisted of one or more acquisition trials in which the items were presented, followed by recall and recognition trials to assess retrieval and storage respectively. Varying the time interval between presentation and assessment allowed for a differentiation between short- and long-term memory functioning [48]. Besides these assessments, this outcome comprised tests that measure changes in visual memory, spatial memory and learning capacities, and tests measuring working memory.

4.3.6. Executive functions and information processing

Finally, there is the domain of tests assessing information processing and executive functions. Obviously several of the memory- or attention-measuring tests are also capturing to some extent cognitive flexibility and the information processing capacities. However, some more complex test procedures have been assessed the results of which do not rely merely on memory or attention. These tests examine executive functions, which refers to abilities that enable flexible, task-appropriate responses in the face of irrelevant competing inputs or more habitual but inappropriate response patterns [49]. They extend from calculation tasks and logical reasoning tests to maneuvers in flight simulators. Other examples are gambling and probabilistic learning tasks, tests on verbal fluency and humour appreciation and perceptual tasks such as tests where the relative length of a line or a tone has to be judged. The majority of these tests, especially the most complicated ones such as the flight simulators, were applied in military research in order to evaluate the use of the drugs in question (usually modafinil) in operational settings.

5. Results of the analyses

5.1. Methylphenidate

5.1.1. Single drug administration

Through our analyses we found that a single dose of MPH had a distinguishable effect in one outcome, namely memory: a large positive effect was shown, with 1.4 (standard error, SE = 0.48, $p < 0.007$) at the first assessment time point and 1.37 (SE = 0.6, $p < 0.03$) at the second. No statistically significant effect was found in the outcomes attention, mood and executive functions, while for wakefulness, the lack of baseline measurements did not allow for a statistical analysis. Only one study examined the effects of MPH on motivational parameters [50] and therefore no further analysis was performed. In this study, the authors reported that a single dose of MPH significantly increased subjective ratings of a mathematical task as being interesting, exciting, motivating and less tiresome, while such an effect was not found in ratings of a passive task (looking at pictures).

5.1.2. Repeated drug administration studies

With only two studies performing repeated dose trials, statistical analyses of the results were not possible [32,33]. On these two repeated drug administration studies the following results were reported: Gobbi et al. [33] reported that one week of MPH significantly increased subjective feelings of energy, but did not have any other effects on the POMS. Unfortunately, since the focus of this study was on another drug (bupropion) and MPH was only used as psychoactive control, little was reported on the exact effects of MPH. In an other study with a cohort of 27 elderly healthy volunteers, after 6 weeks of daily intake, MPH significantly reduced ratings on a VAS on fatigue, but had no effect on five other VAS and no difference on a memory test could be measured [32].

5.1.3. Methylphenidate in sleep deprived individuals

From the five studies testing people in sleep deprivation [30,31,34–36] two were on partial sleep deprivation (with 4 h nap before the drug administration) [35,36] and two on repeated drug administration [30,31]. The differences between the studies did not allow for an aggregation of their results and hence no further analysis was performed. Again, for the sake of completeness, the results of these studies are reported: a single dose after a night of sleep deprivation did not have cognitive enhancing effects and in contrast a negative effect on self-monitoring was observed, with people estimating their performance in a task as better than it actually was [34]. Repeated intake of MPH during a sustained sleep deprivation period of 64 h [30] did not effectively reduce sleepiness, while in a study with 36 h of sleep deprivation [31] and in two partial sleep deprivation studies with only 4 h of sleep [35,36], subjective stimulating effects and only a mediocre improvement of attention was found.

5.2. Modafinil

5.2.1. Single drug administration studies

In the meta-analyses, following effects on the outcomes attention and wakefulness were found after a single dose of modafinil in non-sleep deprived individuals: with regard to attention, a moderate, positive effect was found at the latter of two assessment points (0.56, SE = 0.27, $p < 0.05$). Wakefulness was analysed for four assessment points at the third of which a negative impact of modafinil was observed (−0.88, SE = 0.41, $p < 0.05$). The outcomes mood, memory and motivation remained without any significant systematic changes whatsoever. Statistical analysis on the effects on executive functions could not be performed due to the lack of numerical data for baseline measurements.

5.2.2. Repeated drug administration studies

Only two studies with repeated administration have been performed and hence a statistical analysis was not feasible [37,38]. In the shorter of the two, no effect of an evening and a morning dose of 100 mg on attentional tasks was found [37]. In the other study, which focused on mood, modafinil was given in a 400 mg dose per day for three consecutive days and increased the scores in both the Positive and Negative Affect Scales [38], results which speak for a general mood elevating effect, but with simultaneous increase of negative affect, namely anxiety.

5.2.3. Modafinil in sleep deprived individuals

5.2.3.1. Single drug administration studies. Modafinil in sleep deprived individuals had in the meta-analyses distinctive effects after a single drug administration. The impact on executive function was very strong and persistent over time. The analysis yielded large positive effects at all five time points. The effect was smallest at the first and second assessment points (1.95, SE = 0.31, $p < 0.0001$ and 2.4, SE = 0.4, $p < 0.0001$ respectively), had a peak with 3.3 (SE = 0.45, $p < 0.0001$) at the third, and then lessened slightly at the fourth (2.25, SE = 0.54, $p < 0.0003$) and fifth (2.3, SE = 0.54, $p < 0.0003$).

On memory, a significant positive effect became apparent in both of the assessment points of the meta-analysis. At the first time point a large effect of 1.22 (SE = 0.41, $p < 0.009$) was found, which declined somewhat (0.89, SE = 0.42, $p < 0.05$) at the second time point. The strength of the drug effect was continuously reduced the longer the sleep deprivation lasted. This effect tended towards significance without quite reaching it ($p = 0.0583$).

Wakefulness was significantly and strongly improved by one single dose of modafinil in sleep deprived individuals throughout five of the six analysed time points. The effect was very large at the first three time points: 2.12 (SE = 0.30, $p < 0.0001$), 2.6 (SE = 0.54, $p < 0.0001$) and 2.08 (SE = 0.52, $p < 0.0003$) respectively. At the fourth (1.89, SE = 0.52, $p < 0.0006$) and fifth (1.34, SE = 0.51, $p < 0.02$) time points the effect remained quite large and at the sixth time point there was a trend towards a similarly large, positive effect (1.01, SE = 0.51, $p = 0.0528$). With prolongation of sleep deprivation the effect of modafinil became continuously stronger: an increase of effect strength by 0.046 per hour of sleep deprivation was clearly significant (SE = 0.02, $p < 0.009$).

The analysis showed no significant effects in the outcomes attention and mood and none of the studies examined the effects on motivation.

5.2.3.2. Repeated drug administration studies. The effect of modafinil on healthy people undergoing sleep deprivation after repeated drug administration could be analysed only for the outcomes executive functions, attention and wakefulness, since only for these outcomes enough studies yielded extractable data. From these three outcomes, only wakefulness was significantly changed by modafinil. Six out of seven assessment time points

showed very large positive effects: 2.35 (SE = 0.91, $p < 0.02$) at the first, 2.36 (SE = 0.91, $p < 0.02$) at the second, 2.44 (SE = 0.91, $p < 0.02$) at the third, 2.27 (SE = 0.91, $p < 0.02$) at the fourth, 2.34 (SE = 0.91, $p < 0.02$) at the fifth and a maximum of 4.86 (SE = 1.47, $p < 0.003$) at the sixth time point, though at the seventh and last time point the effect was not significant. For the outcomes attention and executive functions the analyses showed no statistically significant effects. No analyses were performed for memory, mood or motivation.

5.3. Adverse effects of MPH or modafinil

Since most of the included papers reported small experimental studies (see Tables 1–4) and not large scale clinical trials, in the majority of the cases, no standardised method of assessing adverse reactions and reporting drop-outs due to adverse effects was used. In a number of studies (26 for MPH and 26 for modafinil) no comment on side effects was made, which leaves us to assume that no severe adverse effects appeared that would deserve a comment in the limited space of a publication. Therefore no further analysis was performed and the results are presented here in a descriptive manner. In the majority of the trials, the drugs were well tolerated. There were some side effects reported, but these were normally benign and only in few cases lead to drop-outs. For modafinil [24–26,28,41,51–57], adverse reactions were primarily headache, dizziness, gastrointestinal complains (e.g., nausea, abdominal pain, dry mouth), increased diuresis, tachycardia and palpitations, nervousness, restlessness, and sleep disturbances and especially in studies with non-sleep deprived individuals, insomnia. For MPH a frequently reported side effect (reported in 13 out of 14 trials reporting side effects [34,58–69]) was slightly increased heart rate, while increase in blood pressure was not consistently found. Besides these, typical complains were headache, anxiety, nervousness, dizziness, drowsiness and insomnia. In total, these drugs seem to be well tolerated even by this population where the trade-off between side effects and improvement may be less clear. Finally, since the majority of the studies that have been performed were short term and single dose studies, no comment can be made on the reinforcing effects, dependence development, and drug tolerance (and tachyphylaxis) of MPH or modafinil in healthy individuals.

6. Discussion

This systematic review focused on studies of MPH and modafinil in healthy individuals. A first finding was that some studies did not report their raw data and therefore, although included in the systematic review, their results could not be used for the meta-analyses. This is a well-known weakness in reporting controlled trials [70,71], especially those failing to find any significant result. However, for the general conclusions discussed here, the findings of all studies included in the systematic review were considered.

Regarding the use of MPH by healthy individuals, the available data and the analyses performed do not allow for a firm conclusion to be drawn. A major drawback in the analyses was the lack of information on baseline measurements. For some outcomes, such as wakefulness, there was no measurement at all available, making any further analysis impossible. For other outcomes, the few existing measurements that were used as reference values had a strong impact on the results, such as for mood and executive functions where only one baseline measurement was available. Therefore, through these analyses only cautious conclusions can be drawn.

The analyses of the existing studies provide no consistent evidence for neuroenhancement effects of MPH, though evidence for

a positive effect on memory of healthy individuals was found. The most prominent positive effect was on spatial working memory, which was also found in studies that could not be included in the analysis [72]. However, the popular opinion that MPH enhances attention was not verified through the meta-analysis. This result is in concordance with most of the individual studies, which reported either no effects [73], or even negative effects, such as a disruption of attentional control [64]. The positive, albeit solitary result for memory enhancement seems at first insufficient to explain the reported high prevalence of use of MPH for non-medical reasons [7]. One can speculate that there are other motives besides genuine neuroenhancement that propel this illicit use [74], such as subjective enhancing effects and recreation, which were not captured neither here nor in the original data. Furthermore, studies on repeated doses are scarce and the few studies in sleep deprivation reported only subjective positive effects. Finally, in most of the studies mainly doses of 10–20 mg of MPH were used and this might also be a reason why no consistent effects or side effects were found. MPH, like other stimulants, may follow an inverted U-shape function, whereby too much or too little of the drug may impair performance and a moderate dose may be optimal. Unfortunately, not enough studies with a range of different doses have been conducted, so we could not test this hypothesis or include dose as a covariate in our analyses. The exact doses used in the individual studies can be found in Tables 1 and 2. There it can also be seen that only two studies [33,75] reported explicitly on the effects of extended or controlled release formulations of MPH, which leaves at to believe that all other studies were conducted with immediate release formulations. This could be of relevance considering the different effects of the two types of formulations, by producing a pulsatile or a slow-dose effect on dopamine and norepinephrine release and thereby being associated with distinct effects.

For modafinil, evidence of enhancing effects could be found. Modafinil had some positive, though moderate, enhancing effects on individuals who were not sleep deprived, namely on attention. No effect was found on memory, mood or motivation. Contrary to our expectations, a negative effect on wakefulness was seen at a late time point after drug administration. However, post hoc inspection of the original data revealed that this result is not valid, because it is derived from only one study [76]. In sleep deprived individuals the effects were more global: there was a positive effect of a single dose on wakefulness, executive functions and memory. No evidence of effects on mood was found.

Also, during sustained sleep deprivation over several days, repeated intake of modafinil was shown to maintain wakefulness in higher levels than placebo and this effect lasted for up to four days. However, attention and executive functions were not sustained with repeated doses.

Another issue deserves special notice, namely the effect of modafinil on self-monitoring. In well rested individuals, Baranski and colleagues reported a trend towards overconfidence in one of six tasks [39]. Yet, in individuals who had been sleep deprived for 64 h they found an actual "overconfidence" effect [51]. The participants had to estimate their performance in a number of tests, before and after the task. Modafinil led to an overrating of the actual cognitive performance, although this was found only in the retrospective and not in the prospective estimations. In contrast, in a further study of 40 h of sleep deprivation [77] and a military study of 24 h of sleep deprivation [26] no such effect was found. Nevertheless, it remains a question of great importance whether modafinil, besides its cognitive enhancing effect, interferes with one's ability to accurately self-assess one's own cognitive performance.

To sum up, a single dose of modafinil seems to have a cognitive enhancing effect in cases of moderate sleep deprivation. In repeated doses it does not seem to boost cognitive performance over a longer period of sleep deprivation, but only maintains wakefulness. This, together with a possible effect of overconfidence on one's cognitive performance, makes it questionable whether repeated doses of modafinil in long lasting sleep deprivation could be of help in a practical way for someone who wants to stay alert and preserve performance at pre-sleep deprivation level.

As to MPH, the existing research summarised in this systematic review provides insufficient evidence for or against any effect of MPH in healthy people. This applies not only to the results of our meta-analysis, but also to the findings of the studies that, due to inadequate result reporting were not included in our meta-analyses. Therefore, the question whether MPH has a potential to enhance the performance of healthy people can only be answered by further studies. These future studies need to report results in greater detail, e.g., provide numerical data and state precisely dosage and rate and extent of adverse effects.

As to modafinil, the effects were not unequivocal for people in a normal state of wakefulness; therefore, more studies are also necessary. There is evidence that the effect of modafinil depends to some extent on the individual baseline performance, e.g., Randall et al. [78] found that it was correlated with the IQ of the volunteers. It would be of great interest in future studies to look specifically for such interactions or interactions to particular characteristics of each individual such as genetic profile. This could also provide further useful information on the neuropharmacological basis of the effects in healthy individuals. Studies in sleep deprived individuals showed a clear neuroenhancing effect after one dose of modafinil and moderate sleep deprivation. Repeated dose administration, especially after a prolonged sleep deprivation, had a positive effect only on wakefulness. It is therefore necessary to examine whether the ability to stay awake beyond the normal limits is contradicting with the ability to maintain normal cognitive performance. Furthermore, since the majority of these trials had military personnel as participants, further research that would reproduce these results in the general population is needed. If mentally competent adults are to be able to engage in neuroenhancement using drugs, their decision to do so should be based on the known effects of the drugs [79]. For that we need conclusive data on the risks and benefits, knowledge which can only be derived from research.

7. Reviewers' conclusion

In an April fools' prank, Jonathan Eisen, evolutionary biologist at the University of California, Davis faked a press release of the National Institute of Health (NIH) announcing the creation of the World Anti-Brain Doping Authority. This hoax might not be too far from reality though; only one month later, the Academy of Medical Sciences in the UK, after thorough consideration of the issue, recommended the establishment of regulating authorities for cognitive enhancers [80]. Whether such regulating bodies are actually necessary at this point in time depends to some extent on whether "brain doping" is currently feasible. Just recently a number of experts called for an evidence-based approach to the evaluation of the risks and benefits of cognitive enhancement [81]. Our systematic review contributes to this quest by analysing data for two of the most cited neuroenhancement drugs. With regard to MPH, we were not able to provide sufficient evidence of positive effects in healthy individuals from objective tests. This is in contrast to a number of reports on the misuse of MPH for non-medical purposes particular in US Colleges [7,74], but one has to keep in mind that it is the subjective effects that motivate people to take a certain drug, not the seemingly objective results of neuropsychological assessments. Neuroenhancement is but one kind of non-medical use of MPH. People who use it for recreational purposes may not be impressed by the fact that MPH does not seem to be an efficient neuroenhancement drug. Yet, the lack of positive objective effects of

MPH found in this review should be propagated so as to discourage people who consider using it to achieve an enhancement of cognitive capacities. Regarding the other candidate drug – modafinil – the aggregated results show a clear enhancing effect, especially on people undergoing sleep deprivation. With this in mind, it is not surprising that modafinil is increasingly gaining popularity. Further research on questions about the equity, the ethics and the social aspects of modafinil use is urgently needed. The demand for a drug like modafinil has to be understood against the backdrop of a growing pressure on people in modern societies to live and work, often continuously disregarding their biological rhythms. Besides the question of whether and how we are to regulate their use [79,82], we should engage in public debate on the social factors creating the need for such drugs.

Acknowledgments

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.phrs.2010.04.002.

References

[1] Schöne-Seifert B, Talbot D. (Neuro-)enhancement. In: Helmchen H, Sartorius N, editors. Textbook of Psychiatry. New York: Springer; 2009.

[2] Larriviere D, Williams MA, Rizzo M, Bonnie RJ. Responding to requests from adult patients for neuroenhancements: guidance of the Ethics, Law and Humanities Committee. Neurology 2009;73:1406–12.

[3] Talbot M. Brain gain. The New Yorker; 2009.

[4] de Jongh R, Bolt I, Schermer M, Olivier B. Botox for the brain: enhancement of cognition, mood and pro-social behavior and blunting of unwanted memories. Neurosci Biobehav Rev 2008;32:760–76.

[5] Sahakian B, Morein-Zamir S. Professor's little helper. Nature 2007;450:1157–9.

[6] The Economist. All on the mind. The Economist 2008;.

[7] McCabe SE, Knight JR, Teter CJ, Wechsler H. Non-medical use of prescription stimulants among US college students: prevalence and correlates from a national survey. Addiction 2005;100:96–106.

[8] Maher B. Poll results: look who's doping. Nature 2008;452:674–5.

[9] DAK-Gesundheitsreport. Schwerpunktthema Doping am Arbeitsplatz 2009;37–91.

[10] Mehlman M. Cognition-enhancing drugs. Milbank Quart 2004;82:483–506.

[11] Physicians' desk reference. Physicians' desk reference. 63rd ed. Montvale, NJ: Thomson Reuters; 2009.

[12] Gould MS, Walsh BT, Munfakh JL, Kleinman M, Duan N, Olfson M, et al. Sudden death and use of stimulant medications in youths. Am J Psychiatry 2009;166:A16.

[13] Sulzer D, Sonders MS, Poulsen NW, Galli A. Mechanisms of neurotransmitter release by amphetamines: a review. Prog Neurobiol 2005;75:406–33.

[14] Volkow ND, Fowler JS, Logan J, Alexoff D, Zhu W, Telang F, et al. Effects of modafinil on dopamine and dopamine transporters in the male human brain: clinical implications. JAMA 2009;301:1148–54.

[15] Minzenberg MJ, Carter CS, Modafinil:. A review of neurochemical actions and effects on cognition. Neuropsychopharmacology 2008;33(7):1477–502.

[16] Ballon JS, Feifel D. A systematic review of modafinil: potential clinical uses and mechanisms of action. J Clin Psychiatr 2006;67:554–66.

[17] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996;17:1–12.

[18] Dumont GJ, de-Visser SJ, Cohen AF, van-Gerven JM. Biomarkers for the effects of selective serotonin reuptake inhibitors (SSRIs) in healthy subjects. Br J Clin Pharmacol 2005;59:495–510.

[19] Spreen O, Strauss E. A compendium of neuropsychological tests; administration, norms, and commentary. 2nd ed. New York: Oxford University Press, Inc.; 1998.

[20] Cohen J. Statistical power analysis for the behavioral sciences. New York: Academic Press; 1988.

[21] Rogers NL, Maislin G, Van Dongen HP, Dinges DF. Neurobehavioural and physiological outcomes from modafinil during severe sleep loss (abstract). Int Med J 2004;34:A19.

[22] Wesnes KA, Macher JP. Modafinil reverses the marked attentional deficits produced by acute sleep deprivation in healthy volunteers. Eur Neuropsychopharm 2004;14:S380.

[23] Li YF, Zhan H, Xin YM, Tang GX, Wei SH, et al. Effects of modafinil on visual and auditory reaction abilities and subjective fatigue level during 48 h sleep deprivation. Space Med Med Eng (Beijing) 2003;16:277–80.

[24] Caldwell JA, Caldwell JL, Smythe III NK, Hall KK. A double-blind, placebo-controlled investigation of the efficacy of modafinil for sustaining the alertness and performance of aviators: a helicopter simulator study. Psychopharmacology (Berl) 2000;150:272–82.

[25] Caldwell JA, Caldwell JL, Smith JK, Brown DL. Modafinil's effects on simulator performance and mood in pilots during 37 h without sleep. Aviat Space Environ Med 2004;75:777–84.

[26] Eddy D, Storm W, French J, Barton E, Cardenas R. An assessment of modafinil for vestibular and aviation-related effects. AFRL-HE-BR-TR-2005-0129 ed. United States Air Force Research Laboratory; 2005.

[27] Whitmore J, Doan B, Heintz T, Hurtle W, Kisner J, Smith JK. The efficacy of modafinil as an operational fatigue countermeasure over several days of reduced sleep during a simulated escape and evasion scenario. AFRL-HE-BR-TR-2004-0021 ed. United States Air Force Research Laboratory; 2004.

[28] Whitmore J, Hickey P, Doan B, Harrison R, Kisner J, Beltran T, et al. A double-blind placebo controlled investigation of the efficacy of modafinil for maintaining alertness and performance in sustained military ground operations. AFRL-HE-BR-TR-2006-0005 ed. United States Air Force Research Laboratory; 2006.

[29] Bonnet MH, Balkin TJ, Dinges DF, Roehrs T, Rogers NL, Wesensten NJ. The use of stimulants to modify performance during sleep loss: a review by the sleep deprivation and Stimulant Task Force of the American Academy of Sleep Medicine. Sleep 2005;28:1163–87.

[30] Babkoff H, Kelly T, Matteson L, Gomez S, Lopez A, Hauser S, et al. Pemoline and methylphenidate: interaction with mood, sleepiness, and cognitive performance during64 hours of sleep deprivation. Mil Psychol 1992;4:235–65.

[31] Bishop C, Roehrs T, Rosenthal L, Roth T. Alerting effects of methylphenidate under basal and sleep-deprived conditions. Exp Clin Psychopharm 1997;5:344–52.

[32] Gilbert JG, Donnelly KJ, Zimmer LE, Kubis JF. Effect of magnesium pemoline and methylphenidate on memory improvement and mood in normal aging subjects. Int J Aging Hum Dev 1973;4:35–51.

[33] Gobbi G, Slater S, Boucher N, Debonnel G, Blier P. Neurochemical and psychotropic effects of bupropion in healthy male subjects. J Clin Psychopharm 2003;23:233–9.

[34] Bray CL, Cahill KS, Oshier JT, Peden CS, Theriaque DW, et al. Methylphenidate does not improve cognitive function in healthy sleep-deprived young adults. J Invest Med 2004;52:192–201.

[35] Roehrs T, Papineau K, Rosenthal L, Roth T. Sleepiness and the reinforcing and subjective effects of methylphenidate. Exp Clin Psychopharm 1999;7:145–50.

[36] Roehrs T, Meixner R, Turner L, Johanson CE, Roth T. Reinforcing and subjective effects of methylphenidate: dose and time in bed. Exp Clin Psychopharm 2004;12:180–9.

[37] Smith D, Pernet A, Rosenthal JM, Bingham EM, Reid H, Macdonald IA, et al. The effect of modafinil on counter-regulatory and cognitive responses to hypoglycaemia. Diabetologia 2004;47:1704–11.

[38] Taneja I, Haman K, Shelton RC, Robertson D. A randomized, double-blind, crossover trial of modafinil on mood. J Clin Psychopharm 2007;27:76–9.

[39] Baranski JV, Pigeau R, Dinich P, Jacobs I. Effects of modafinil on cognitive and meta-cognitive performance. Hum Psychopharmacol Clin Exp 2004;19:323–32.

[40] Babkoff H, Krueger G. Use of stimulants to ameliorate the effects of sleep loss during sustained performance. Mil Psychol 1992;4:191–205.

[41] Dinges DF, Arora S, Darwish M, Niebler GE. Pharmacodynamic effects on alertness of single doses of armodafinil in healthy subjects during a nocturnal period of acute sleep loss. Curr Med Res Opin 2006;22:159–67.

[42] Balanza-Martinez V, Rubio C, Selva-Vera G, Martinez-Aran A, Sanchez-Moreno J, Salazar-Fraile J, et al. Neurocognitive endophenotypes (endophenocognitypes) from studies of relatives of bipolar disorder subjects: A systematic review. Neurosci Biobehav Rev 2008;32:1426–38.

[43] Repantis D, Schlattmann P, Laisney O, Heuser I. Antidepressants for neuroenhancement in healthy individuals: a systematic review. Poiesis Prax 2009;6:139–74.

[44] Geen R. Human motivation: a psychological approach. Belmont: Wadsworth Publishing; 1994.

[45] Coull JT. Neural correlates of attention and arousal: insights from electrophysiology, functional neuroimaging and psychopharmacology. Progr Neurobiol 1998;55:343–61.

[46] Amado-Boccara I, Gougoulis N, Littre MFP, Galinowski A, Loo H. Effects of antidepressants on cognitive functions: a review. Neurosci Biobehav Rev 1995;19:479–93.

[47] Rose SP. 'Smart drugs': do they work? Are they ethical? Will they be legal? Nat Rev Neurosci 2002;3:975–9.

[48] Schmitt JAJ, Wingen M, Ramaekers JG, Evers EAT, Riedel WJ. Serotonin and human cognitive performance. Curr Pharmaceut Des 2006;12:2473–86.

[49] Farah MJ, Illes J, Cook-Deegan R, Gardner H, Kandel E, King P, et al. Neurocognitive enhancement: what can we do and what should we do? Nat Rev Neurosci 2004;5:421–5.

[50] Volkow ND, Wang GJ, Fowler JS, Telang F, Maynard L, et al. Evidence that methylphenidate enhances the saliency of a mathematical task by increasing dopamine in the human brain. Am J Psychiat 2004;161:1173–80.

[51] Baranski J, Pigeau RA. Self-monitoring cognitive performance during sleep deprivation: effects of modafinil, d-amphetamine and placebo. J Sleep Res 1997;6:84–91.

[52] Caldwell JA, Smythe NK, Caldwell JL, Hall KK, Norman DN, et al. The effects of modafinil on aviator performance during 40 hours of continuous wakefulness: a UH-60 helicopter simulator study. United States Air Force Research Laboratory 1999; USAARL Report No. 99-17:.

[53] Gill M, Haerich P, Westcott K, Godenick KL, Tucker JA. Cognitive performance following modafinil versus placebo in sleep-deprived emergency physicians: a double-blind randomized crossover study. Acad Emerg Med 2006;13:158–65.

[54] Hart CL, Haney M, Vosburg SK, Comer SD, Gunderson E, Foltin RW. Modafinil attenuates disruptions in cognitive performance during simulated night-shift work. Neuropsychopharmacol 2006;31:1526–36.

[55] Lagarde D, Batejat D, Van-Beers P, Sarafian D, Pradella S. Interest of modafinil, a new psychostimulant, during a sixty-hour sleep deprivation experiment. Fund Clin Pharmacol 1995;9:271–9.

[56] Pigeau R, Naitoh P, Buguet A, McCann C, Baranski J, Taylor M, et al. Modafinil, d-amphetamine and placebo during 64 hours of sustained mental work. I. Effects on mood, fatigue, cognitive performance and body temperature. J Sleep Res 1995;4:212–28.

[57] Wesensten NJ, Belenky G, Kautz MA, Thorne DR, Reichardt RM, Balkin TJ. Maintaining alertness and performance during sleep deprivation: modafinil versus caffeine. Psychopharmacology 2002;159:238–47.

[58] Brumaghim JT, Klorman R. Methylphenidate's effects on paired-associate learning and event-related potentials of young adults. Psychophysiology 1998;35:73–85.

[59] Clark CR, Geffen GM, Geffen LB. Role of monoamine pathways in attention and effort: effects of clonidine and methylphenidate in normal adult humans. Psychopharmacology (Berl) 1986;90:35–9.

[60] Fitzpatrick P, Klorman R, Brumaghim JT, Keefover RW. Effects of methylphenidate on stimulus evaluation and response processes: evidence from performance and event-related potentials. Psychophysiology 1988;25:292–304.

[61] Hink RF, Fenton Jr WH, Pfefferbaum A, Tinklenberg JR, Kopell BS. The distribution of attention across auditory input channels: an assessment using the human evoked potential. Psychophysiology 1978;15:466–73.

[62] Mehta MA, Owen AM, Sahakian BJ, Mavaddat N, Pickard JD, Robbins TW. Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. J Neurosci 2000;20:RC65.

[63] Peloquin LJ, Klorman R. Effects of methylphenidate on normal children's mood, event-related potentials, and performance in memory scanning and vigilance. J Abnorm Psychol 1986;95:88–98.

[64] Rogers RD, Blackshaw AJ, Middleton HC, Matthews K, Hawtin K, Crowley C, et al. Tryptophan depletion impairs stimulus-reward learning while methylphenidate disrupts attentional control in healthy young adults: implications for the monoaminergic basis of impulsive behaviour. Psychopharmacology 1999;146:482–91.

[65] Strauss J, Lewis JL, Klorman R, Peloquin LJ, Perlmutter RA, Salzman LF. Effects of methylphenidate on young adults' performance and event-related potentials in a vigilance and a paired-associates learning test. Psychophysiology 1984;21:609–21.

[66] Volkow ND, Wang GJ, Fowler JS, Gatley SJ, Logan J, Ding YS, et al. Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. Am J Psychiatry 1998;155:1325–31.

[67] Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Wong C, et al. Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D2 receptors. J Pharmacol Exp Therapeut 1999;291:409–15.

[68] Volkow ND, Wang GJ, Fowler JS, Gatley SJ, Logan J, Ding Y, et al. Blockade of striatal dopamine transporters by intravenous methylphenidate is not sufficient to induce self-reports of 'high'. J Pharmacol Exp Therapeut 1999;288:14–20.

[69] Wetzel CD, Squire LR, Janowsky DS. Methylphenidate impairs learning and memory in normal adults. Behav Neural Biol 1981;31:413–24.

[70] Egger M, Smith GD, Altman DG. Systematic reviews in health care: meta-analysis in context. London: BMJ Books; 2001.

[71] Higgins J, Green S, editors. Cochrane handbook for systematic reviews of interventions 4. 2. 6 [updated September 2006]. Chichester, UK: The Cochrane Library, John Wiley & Sons, Ltd; 2006. Issue 4.

[72] Elliott R, Sahakian BJ, Matthews K, Bannerjea A, Rimmer J, Robbins TW. Effects of methylphenidate on spatial working memory and planning in healthy young adults. Psychopharmacology 1997;131:196–206.

[73] Turner DC, Robbins TW, Clark L, Aron AR, Dowson J, Sahakian BJ. Relative lack of cognitive effects of methylphenidate in elderly male volunteers. Psychopharmacology 2003;168:455–64.

[74] Babcock Q, Byrne T. Student perceptions of methylphenidate abuse at a public liberal arts college. J Am Coll Health 2000;49:143–5.

[75] Kollins SH, Rush CR, Pazzaglia PJ, Ali JA. Comparison of acute behavioral effects of sustained-release and immediate-release methylphenidate. Exp Clin Psychopharmacol 1998;6:367–74.

[76] Warot D, Corruble E, Payan C, Weil JS, Puech AJ. Subjective effects of modafinil, a new central adrenergic stimulant in healthy volunteers: a comparison with amphetamine, caffeine and placebo. Eur Psychiat 1993;8:201–8.

[77] Baranski J, Gil V, McLellan TM, Moroz D, Buguet A, Radomski MW. Effects of modafinil on cognitive performance during 40 hr of sleep deprivation in a warm environment. Military Psychol 2002;14:23–47.

[78] Randall DC, Shneerson JM, File SE. Cognitive effects of modafinil in student volunteers may depend on IQ. Pharmacol Biochem Behav 2005;82:133–9.

[79] Chatterjee A. Is it acceptable to take methylphenidate to enhance performance? No. BMJ 2009;338:b1956.

[80] Horn G. Brain science, addiction and drugs. An Academy of Medical Sciences working group report. Acad Med Sci 2008.

[81] Greely H, Sahakian B, Harris J, Kessler RC, Gazzaniga M, Campbell P, et al. Towards responsible use of cognitive-enhancing drugs by the healthy. Nature 2008;456:702–5.

[82] Harris J. Is it acceptable for people to take methylphenidate to enhance performance? Yes. BMJ 2009;338:b1955.