European Neuropsychopharmacology (2015) **25**, 1865–1881

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REVIEW

Modafinil for cognitive neuroenhancement in healthy non-sleep-deprived subjects: A systematic review

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Received 29 January 2015; received in revised form 27 July 2015; accepted 30 July 2015

KEYWORDS
Neuroenhancement;
Modafinil;
Cognitive;
Psychometric;
Enhancement;
Nootropic

Abstract
Modafinil is an FDA-approved eugeroic that directly increases cortical catecholamine levels, indirectly upregulates cerebral serotonin, glutamate, orexin, and histamine levels, and indirectly decreases cerebral gamma-amino-butrytic acid levels. In addition to its approved use treating excessive somnolence, modafinil is thought to be used widely off-prescription for cognitive enhancement. However, despite this popularity, there has been little consensus on the extent and nature of the cognitive effects of modafinil in healthy, non-sleep-deprived humans. This problem is compounded by methodological discrepancies within the literature, and reliance on psychometric tests designed to detect cognitive effects in ill rather than healthy populations. In order to provide an up-to-date systematic evaluation that addresses these concerns, we searched MEDLINE with the terms "modafinil" and "cognitive", and reviewed all resultant primary studies in English from January 1990 until December 2014 investigating the cognitive actions of modafinil in healthy non-sleep-deprived humans. We found that whilst most studies employing basic testing paradigms show that modafinil intake enhances executive function, only half show improvements in attention and learning and memory, and a few even report impairments in divergent creative thinking. In contrast, when more complex assessments are used, modafinil appears to consistently engender enhancement of attention, executive functions, and learning. Importantly, we did not observe any preponderances for side effects or mood changes. Finally, in light of the methodological discrepancies encountered within this literature, we conclude with a series of recommendations on how to optimally detect valid, robust, and consistent effects in healthy populations that should aid future assessment of neuroenhancement.

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http://dx.doi.org/10.1016/j.euroneuro.2015.07.028
0924-977X/

1. Introduction

"Neuroenhancement" refers to the targeted enhancement and extension of cognitive and affective abilities based on an understanding of their underlying neurobiology, and is increasingly represented by the media as an eventuality, usually in a desirable context. In reality, most contemporary strategies for neuroenhancement – comprising invasive and non-invasive brain stimulation and pharmacological manipulation – remain in their infancy. However, one agent, the FDA-approved eugeroic modafinil, has been extensively evaluated for cognitive modulation in healthy humans, and appears safe for widespread use. Unfortunately, discrepancies in methodology and outcomes within the literature have precluded consensus on the nature and degree of modafinil's effects on cognition, and continue to undermine discussions on the suitability of its off-label use as a cognitive enhancer, which is already thought to be extensive (Franke et al., 2013; Maher, 2008). In particular, studies using simple psychometric assessments derived from assessments of animal cognition or clinical populations have tended to report variable outcomes following modafinil intake (see, for example, Randall et al. (2003, 2004, 2005a, 2005b)), whereas more recent studies using complex testing paradigms have tended to report beneficial effects (see, for example, Finke et al. (2010)). Thus, we aim to provide an evaluation of modafinil as a neuroenhancement agent that addresses these discrepancies. To do so, we first introduce modafinil's molecular actions in the context of its pharmacological contemporaries, as well as the basic psychometric tests commonly employed to detect any alteration of cognition by these agents, before reporting the results of a systematic review on the cognitive effects of modafinil. We then follow this with methodological criticism of study designs employed to date, and offer a set of criteria that builds these observations into guidance for future study of neuroenhancement.

1.1. Modafinil and other pharmacological neuroenhancement agents

Pharmacological neuroenhancement agents may target online cognitive processes, such as attention and executive function, offline processes, such as memory consolidation, or a combination of the two. The stimulant methylphenidate (Ritalin©), which increases central catecholamine levels, appears to mainly target *online* processes, with some studies observing improvements in working memory, speed of processing, verbal learning and memory, and various attentional functions including vigilance (see Linssen et al. (2014); but see Repantis et al. (2010)). Despite the extensive attention that methylphenidate has received for cognitive enhancement, the significant side effect profile and high abuse potential that accompanies its use have curtailed discussions about wider societal use (Linssen et al., 2014). Conversely, piracetam, a racetam drug that may ameliorate cognitive decline in clinical populations (Waegemans et al., 2002), appears to target *offline* properties via modulation of acetylcholinergic and glutamatergic systems and increases in membrane permeability (Winblad, 2006), but appears to have limited effects in healthy humans (Dimond and Brouwers, 1976; Mindus et al., 1976). In addition, several herbal substances – namely *Panax ginseng*, *Ginkgo biloba*, and *Bacopa monneri*, all of which contain a mixture of neuroactive compounds attributed with pleiotropic molecular and cognitive effects – have been investigated for their potentiation of both online and offline processes (Aguiar and Borowski, 2013; Farooqui, 2012; Lü et al., 2009; Neale et al., 2013). However, methodological and evidential inconsistency within this *corpus* of research has obviated the demonstration of any robust effects on cognition.

Modafinil shares features with all of these agents: it is a stimulant drug, like methylphenidate; and, like the herbal substances and piracetam, exerts a complex neurochemical profile affecting both online and offline processes. Modafinil was first marketed in France in the 1990s as a eugeroic treatment for narcolepsy, and has since been FDA-approved for the treatment of excessive somnolence in narcolepsy, obstructive sleep apnoea, and shift work sleep disorder (Kumar, 2008). Modafinil directly inhibits central dopamine and noradrenaline uptake transporters, causing an elevation in catecholamine levels (Qu et al., 2008); these effects in turn elevate extracellular concentrations of serotonin, glutamate, histamine, and orexin, and reduce concentrations of gamma-amino-butrytic acid. Arousal- and wakefulness-promoting actions are thought to arise from these increases in dopaminergic and adrenergic transmission, and interactions with the orexin/hypocretin axis (Minzenberg and Carter, 2008). Although modafinil effects are thought to arise primarily from alterations in cortical neurotransmitter systems, similar neurochemical modulations have been reported in the hippocampus, thalamus, hypothalamus, amygdala, caudate, and midbrain (see Scoriels et al. (2013)).

1.2. Imaging studies

Modafinil does not appear to diffusely increase cortical activation (Ellis et al., 1999); rather, selective brain networks and inter-areal functional connectivity are altered. Resting-state imaging studies have shown that modafinil intake increases regional blood flow in bilateral precentral gyri, left hippocampus, left fusiform gyrus, bilateral lingual gyri, and cerebellum in narcoleptic and healthy participants (Joo et al., 2008). When Esposito and colleagues examined the activity of seven resting-state cortical networks, they found that in the absence of structural changes modafinil intake increases activity in the Dorsal Attention Network – thought to modulate externally-directed attention by amplifying or attenuating the saliency of relevant and irrelevant cues – and increased connectivity in the anterior cingulate cortex (ACC) node of the left Frontal Parietal Control network (Esposito et al., 2013) – which may mediate planning across domains (Spreng et al., 2010). On further analysis, this group found that although overall activity in the Saliency Network – which orients attention towards key environmental stimuli and helps guide behaviour – was unchanged, functional coupling between the right posterior insula, a key network node, and the rest of the network was strengthened (Cera et al., 2014).

1.3. Psychometric assessment of neuroenhancement

Research groups typically rely on two types of psychometric tests to assess altered neuropsychiatric states and provide

cognitive information to complement the type of biochemical changes outlined above: 1) simple tasks, which involve basic cognitive exercises targeting discrete sub-components of cognitive functions; and, 2) more complex tasks, which incorporate multiple difficulty levels and test more integrated features of cognition. The former are typically developed for single-dose studies examining many subjects, and have been well-validated for the detection of specific cognitive deficits in clinical populations (tests presented in glossary form in Table 2). In particular, sub-tasks of the CANTAB test battery – a test series developed at the University of Cambridge in 1986 from popular tests of non-human primate cognition (Owen et al., 1990) – dominate this literature. Conversely, the latter tend to be designed by individual groups in order to assess more global functions. Although more sensitive at detecting the cognitive changes of specific interventions, they are more tasking to design and administer, and, as they are less standardised, impose difficulties on the comparison of results between studies.

2. Procedure

In order to evaluate the cognitive effect of modafinil on healthy adults, we conducted a systematic review of relevant literature by searching MEDLINE with the terms "modafinil" and "cognitive" from January 1990 until December 2014, and reviewed all resultant eligible studies. We included studies for analysis if they were written in English, prospective, conducted on healthy humans that were not sleep-deprived, compared performance on modafinil to placebo, included randomisation protocols, and contained at least one cognitive test (see Figure 1).

3. Results

Our search of the literature and subsequent selection process resulted in 24 eligible studies, including both parallel and cross-over designs. Within these studies, several cognitive domains were well-represented, namely, attention, executive function, learning and memory, and creativity. The results of studies that employed simple psychometric assessments to analyse these functions are presented in Table 1, and reviewed by cognitive domain below; a brief description of the tasks themselves may be found in Table 2. The results of studies using more complicated testing paradigms spanning multiple domains are also presented in Table 1, and described at the end of this section.

3.1. Attention

Attention is the cognitive function that allocates cognitive resources to space, time, sense, and task (Posner, 2012): it drives enhancement and suppression of relevant and irrelevant sensory information, respectively, with the goal of processing relevant information more accurately. The most basic attentional sub-component is arousal, which is associated to the intensity of attention (Berlyne, 1960), and given modafinil is licensed for its arousal-promoting properties, it is unsurprising that many studies have investigated its ability to promote or sustain various attentional functions. Simple psychometric assessments isolate and test *alertness* – reaction toward isolated stimuli either without (tonic alertness) or with (phasic alertness) a preceding warning stimulus; *selective attention* – the ability to detect specific stimuli within an environment containing distractors; *sustained attention* – the maintenance of a consistent behavioural response during continuous or repetitive activity; and, *divided attention* – the ability to allocate cognitive resources to two or more stimulus features or separate tasks (see Table 2; Sohlberg and Mateer, 1987).

Although two studies demonstrated increased alertness following modafinil intake (Baranski et al., 2004; Randall et al., 2005a, 2005b), in the majority of studies no effect on this sub-function was found (Baranski et al., 2004; Gilleen et al., 2014; Liepert et al., 2004; Minzenberg et al., 2011; Randall et al., 2003). Modafinil intake had no effect on most simple measures of *selective* attention (Marchant et al., 2009; Müller et al., 2004; Randall et al., 2003, 2004, 2005a, 2005b), with the exception of one small study that showed decreased reaction time with similar accuracy on the digit-symbol substitution task (Makris et al., 2007). In terms of *sustained* attention, again the majority of studies failed to detect any improvement (Liepert et al., 2004; Müller et al., 2004; Randall et al., 2003, 2004; Theunissen et al., 2009; Turner et al., 2003; Winder-Rhodes et al., 2010), with only two studies reporting an improvement in performance with modafinil: one using the detection of repeated numbers task (Baranski et al., 2004), and one the rapid visual information processing task (Randall et al., 2005a, 2005b). Finally, no benefits were found for *divided* attention following modafinil intake (Theunissen et al., 2009). In summary, studies relying on simple tests of attention did not find consistent benefits to modafinil intake.

3.2. Executive function

Executive functions mediate the selection and manipulation of incoming information, use of that information to construct and initiate action plans, and enlistment of other cognitive functions and brain regions into complex task-oriented networks (Diamond, 2013). Enhancement of executive functions is the primary aim of many people seeking and developing neuroenhancement, and modafinil has anecdotally been thought to exert the largest effect on them. Three core executive functions have been proposed, namely, the inhibition of irrelevant information (*inhibitory control*), the ability to alternate the focus of attention in order to meet shifting task demands (*cognitive flexibility*), and the ability to hold and manipulate external and internal information (*working memory*). Higher order executive functions such as adaptive reasoning, problem solving, planning, and decision making are hypothesised to evolve from the interactions of these systems, as is fluid intelligence (Au et al., 2014).

3.2.1. Inhibitory control

In terms of simple tasks, Rycroft and colleagues (2007) found that modafinil intake improved inhibitory control on an anti-saccade task, and one large between-subjects trial demonstrated a beneficial effect on the stop signal task

Table 1 Results of literature review on cognitive effects of modafinil in healthy non-sleep-deprived subjects.

Authors	Number of Participants	Study Design	Dose	Side effects	Mood changes	Cognitive domains assessed	Effects observed
Baranski et al., 2004	18M	PC; DB; R; WS	4 mg/kg	-	-	Attention (DRN); executive function: logical reasoning (LR) and mental addition (MA); motor: (SRT); visuomotor/arousal; self-monitoring.	Improved accuracy on DRN; faster reaction time on SRT. No effect on other domains.
Esposito et al., 2013	26M	PC; DB; R; BS	100 mg	None	-	Executive function: fluid intelligence (RAPM).	No effect of group. Individuals taking modafinil demonstrated significant improvement on medium difficulty trials, whereas those on placebo did not.
Finke et al., 2010	18 (9M)	PC; DB; R; WS	400 mg	-	Yes	Attention (complex-TVA task).	Improvement in visual attention of low baseline performers: more objects processed, and increased visual short-term memory storage capacity.
Geng et al., 2013	26 (10M)	PC; DB; R; WS	200 mg	-	-	Spatial attention and cognitive control.	Increased successful selective spatial attention in low probability conditions; increased attention/vigilance in combination with enhanced cognitive control mechanisms.
Gilleen et al., 2014	33 (13M)	PC; DB; R; BS.	200 mg (12 days)	Yes	No	Memory: language/implicit learning (complex multi-day task, involving 10 days of cognitive training) and short-term verbal memory (LM); transfer to measures of general cognitive performance; motor: reaction time (CCI).	Faster improvements in early training period of language learning task; superior performance maintained over ten day training period and at two week follow up. Performance of high IQ group improved to a greater extent than low IQ. No effect on other measures.
Liepert and Weiller, 2004	10 (10M)	PC; DB; R; WS	200 mg	-	-	Attention (DC); motor: reaction time, dexterity (NPH) and excitability (TMS-based).	No effect found.
Makris et al., 2007	11(5M)	PC; DB; R; WS	1.75/3.5/7 mg/kg	-	Yes	Attention (DSS); memory: short-term verbal memory (SNR) and learning and rule acquisition (RA).	Improved performance on DSS and RA. Decreased reaction time on SNR.
Marchant et al., 2009	24 (7M)	PC; DB; R; BS	200 mg	-	Yes	Attention (DSS); executive function: cognitive flexibility and working memory (complex task); memory: prospective memory (PM) and short-term verbal memory (FR).	Increased accuracy on complex attentional set shifting task. No effect on DSS, PM, or FR.
Minzenberg et al., 2008	21 (12M)	PC; DB; R; WS	200 mg	None	Yes	Executive function: inhibitory control (POP).	No effect on POP when whole group analysed; sub-group with sub-ceiling performance exhibited improved accuracy.
Minzenberg et al., 2011	18 (10M)	PC; DB; R; WS	200 mg	None	No	Visuomotor/arousal.	Trend towards faster reaction time on arousal task.
Minzenberg et al., 2014	22 (12M)	PC; DB; R; WS	200 mg	-	-	Executive function: inhibitory control (POP).	No effect.
Mohamed, 2014	64 (31M) (same		200 mg	-	Yes		Marginally significant improvement on GEF. No main effect on ReA (but participants low in creativity

	population as below)	PC; DB; R; BS				Short-term verbal (fDS) and visual (PAL) memory; creativity: convergent (GEF, ReA) and divergent (AT, LD, PM).	personality trait scored significantly higher than those high in creativity personality trait in modafinil group only). Reduced performance on flexibility scores on the AT. No effect on other tasks.
Mohamed and Lewis, 2014	64 (31M)	PC; DB; R; BS	200 mg	None	None	Executive function: inhibitory control (HSC); convergent thinking (HSC).	No effect on accuracy of HSC (slower reaction times in inhibition section).
Müller et al., 2004	16 (10M)	PC; DB; R; WS	200 mg	None	No	Attention (TMT-A, DC); numeric manipulation/working memory (NWM); short-term visual memory (DMTS).	Fewer errors on NWM when difficult manipulation required only; "poor" baseline manipulators benefitted more than "good". Decrease in error rates after long delays only in DMTS. No effect on DC or TMT-A.
Müller et al., 2013	64 (31M)	PC; BD; R; BS	200 mg	Yes	Yes	Executive function: planning (SOC) and working memory (SWM, bDS); short-term memory (fDS, PAL); creative thinking: convergent (LD, GEF) and divergent (AT).	Improved performance on SOC, SWM, and PRM (delayed only). No effect on other tasks.
Pringle et al., 2013	34 (17M)	PC; DB; R; BS	100 mg	-	Yes	Executive function: working memory and cognitive flexibility (complex task), working memory (bDS); short-term verbal memory (fDS).	Enhanced learning rate in complex learning task (rule acquisition and set shifting): reflects executive function (working memory and cognitive flexibility). No effect on DS.
Randall et al., 2003	30 (19M)	PC; DB; R; BS	100/ 200 mg	-	No	Attention (TMT-A); executive function: inhibitory control (Stroop), cognitive flexibility (TMT-B), and planning (SOC); short-term verbal (LM) and visual memory (DMTS); clock drawing (CD); creativity (COWA).	No effect found on any task.
Randall et al., 2004	45 (20M)	PC; DB; R; BS	100/ 200 mg	-	No	Attention (TMT-A, RVIP); executive function: inhibitory control (Stroop), cognitive flexibility (TMT-B, IEDSS), and planning (SOC); short-term verbal (LoM) and visual (DMTS) memory; clock drawing (CD); creativity (COWA).	200 mg group scored better on CD. 200 mg were faster on congruent Stroop task (i.e., to name colour); No effect on TMT-A, RVIP, SOC, TMT B, DMTS.), LoM, or COWA. 200 mg scored worse on IEDSS.
Randall et al., 2005a, 2005b	60 (29M)	PC; BD; R; BS	100/ 200 mg	-	No	Attention (TMT-A, DSS, DC, PASAT, RVIP); executive function: inhibitory control (Stroop), cognitive flexibility (TMT-B, IEDSS), working memory (DST, SWM), and planning (SOC); short-term verbal (fDS, LM) and visual (PRM) memory; clock drawing (CD); creativity (COWA); motor (RT).	Improved performance on PRM (200 mg were slower during accurate trials). 200 mg more accurate and sensitive on RVIP. 100 mg showed improved digit span. 200 mg group faster on congruent Stroop trials. No effect on other trials, although drug group were faster on easy trials, and slower on harder trials in the SOC.
Rasetti et al., 2010	38 (18M)	PC; DB; R; WS	100 mg (7 days)	None	No	Attention (complex VAC task); executive function: working memory (2-Back); visuomotor (VPC); emotion (FMT).	No effect.
Rycroft et al., 2007	44 (44M)	PC; DB; R; BS	200 mg	None	No	Executive function: inhibitory control (antisaccade task).	Faster correct movements on an antisaccade task, did not decrease (incorrect) prosaccades.
Theunissen et al., 2009	16 (5M)	PC; DB; R; WS	200 mg	-	-	Attention (CT, MC, DA); executive function: inhibitory control (SST).	Faster reaction time on MC. No effect on other tests.

Table 1 (*continued*)

Authors	Number of Participants	Study Design	Dose	Side effects	Mood changes	Cognitive domains assessed	Effects observed
Turner et al., 2003	60 (60M)	PC; DB; R; BS	100/ 200 mg	-	Yes	Attention (RVIP); executive function: inhibitory control (SS), cognitive flexibility (IEDSS), working memory (bDS, SWM); short-term verbal (fDS) and visual (PAL, DMTS, SpS) memory; creative problem solving (CGT).	Improved performance on SOC, SST, and DS, PRM. Longer latency/deliberation time in DMTS and CGT, with similar accuracy. No effect on other tests.
Winder-Rhodes et al., 2010	12 (12M)	PC; DB; R; WS	300 mg	-	-	Attention (RVIP); executive function: inhibitory control (SS), planning (SOC) and working memory (DO); short-term visual memory (PRM); noradrenergic activity (salivary alpha-amylase).	Fewer moves required on hardest difficulty of SOC. No difference on other measures.

Studies are single-dose unless otherwise indicated. Abbreviations: M=male; PC=placebo-controlled; DB=double-blind; R=randomised; WS=within-subjects (i.e., crossover); BW=between-subjects; TVA=theory of visual attention; IQ=intelligence quotient; TMS=transcranial magnetic stimulation; VAC=variable attentional control. For all other task abbreviations see Table 2.

Table 2 Glossary of simple psychometric tests used in the assessment of modafinil in healthy non-sleep-deprived humans.

Domain and Task	Description
Attention	
Selective attention	
Trail-making task A (TMT-A)	Participants sequentially connect 25 encircled numbers distributed on a sheet of paper by drawing straight lines between them.
Digital-symbol substitution task (DSS)	Participants use a table showing pairs of digits and hieroglyphic-like symbols to 'translate' a series of symbol strings.
Symbol copying task (SC)	Participants are presented with a sheet with 200 randomised symbols from the DSS (see above), and must copy as many symbols as possible in the space and time provided.
Digit cancellation task (DC)	The time taken to score out a given digit from random digit sequences is recorded, with errors.
Sustained attention	
Critical tracking task (CT)	Participants must reverse the horizontal deviation of a cursor from the midpoint of a horizontal line segment with compensatory joystick movements.
Mackworth clock task (MC)	Participants must detect a skip in the clockwise illumination of 60 grey dots on a computer screen.
Rapid visual information processing task (RVIP)	Participants must detect letters/numbers and then determine whether they are immediately followed by another, related, letter or number.
Detection of repeated numbers task (DRN)	Participants must detect repeated numbers in a sequence of three-digit numbers, and write down the appropriate number.

Divided attention	
Divided attention task (DA)	Participants perform the CT (see above) with the difficulty level fixed at 50% of their maximum, but must remove their foot from a pedal if a target number (e.g., "2") appears as one of 24 single digits (0 to 9) that change asynchronously every 5 seconds in the 4 corners of the computer screen (6 digits per corner).
Executive function	
Inhibitory control	
Stroop task	Participants must press a button signalling a colour named by a visually presented word. In the experimental condition, the colour of the letters making up the name differs from the colour the word describes, and participants typically take longer to react appropriately.
Stop-signal task (SST)	Participants must respond rapidly to visually-presented "go" signals with a key stroke, and inhibit any response when a "stop" signal is suddenly presented.
Preparing to overcome prepotency task (POP)	Participants must overcome instinctive or trained responses to various aspects of stimuli, in order to make a choice that is incongruent to these features.
Antisaccade task	Participants must fixate on a small red circle in the centre of a computer screen. When the circle disappears, a peripherally located red circle appears after 200 milliseconds, simultaneous with a tone. Participants must look and quickly and accurately to the mirror location of the circle, whilst their eye movements are monitored automatically.
Variable attentional control task	Participants must indicate the direction of a subset of arrows within an image (small, medium, or big). In low-control conditions, non-salient arrows face the same direction as salient. In high control conditions, non-salient arrows act as distractors, and face the opposite direction.
Working memory – verbal	
Digit span task (backward) (bDS)	Participants are required to immediately repeat a list of digits in reverse order, presented visually or verbally.
Digit ordering task (DO)	Participants are read a string of numbers by an examiner, and then must repeat them, but in ascending order.
2-Back task	Participants must identify the digit that occurred 2 digits ago in a series of sequentially presented digits.
Paced auditory serial addition task (PASAT)	Participants must sum the two most recent digits from a serially presented set of single digits.
Numeric working number task (NWM)	Participants must recognise if a four digit test sequence is ordered the same as a previously presented four digit sequence. In the "easy" manipulation condition the middle two numbers have to be switched (positions 1-2-3-4 to 1-3-2-4) and in the "difficult" manipulation condition all four digits are re-ordered (positions 1-2-3-4 to 3-1-4-2).
Mental addition (MA)	Participants must add a random sequence of eight numbers (between 1 and 16), presented serially.
Working memory – non-verbal	
Spatial working memory task (SWM)	Participants must search an increasing number of boxes (3–8) to locate hidden tokens, which were each located in the same box per trial. Searching any box more than once each trial results in a 'within search error,' while returning to search an already emptied box incurs a 'between search error.'
Spatial span task (backward) (SpS)	Participants must touch an irregularly arranged series of boxes in the reverse order that they are touched by the examiner.
Cognitive flexibility	
Intra/extra dimensional set shift task (IEDSS)	The participant sees two colour-filled shapes, and must learn which is correct by touching them. After six correct responses, the stimuli and/or rules are changed. These shifts are initially intra-dimensional (e.g., colour filled shapes remain the only relevant dimension), then later extra-dimensional (white lines become the only relevant dimension).
Trail-making test B (TMT-B)	Participants must draw lines sequentially connecting 25 encircled numbers and letters alternating between numbers and letters.
Higher executive function	
Logical reasoning task (LR)	Participants must identify whether a statement displayed below two letters, A and B, truthfully describes their relationship.
One-Touch Stockings of Cambridge/Tower of Hanoi/Tower of London (SOC)	In the Stockings of Cambridge task, participants must rearrange coloured balls in vertical columns ("socks") to match a desired final arrangement in a specified minimum number of moves. In the Tower of London version, participants must instead move coloured balls between three "pegs" ("towers").

Table 2 (*continued*)

Domain and Task	Description
Raven's advanced progressive matrices (RAPM)	Participants must choose the correct visuospatial pattern from a set of fixed alternatives, in order to complete a set of six patterns that are related according to various logical principles.
Cambridge Gambling Task (CGT)	Participants are presented with a row of ten red and blue boxes, and must guess in which colour a randomly-hidden yellow token is hidden by pressing the red or blue button. Participants are offered ascending or descending bets based on their colour choice, and must attempt to increase their "score" by betting on their choice being correct. The ratio of red and blue boxes is varied between trials to examine a subject's decision-making behaviour.
Clock drawing task (CD)	Participants must indicate the positions of the minute and hour hand according to a set of test-times on pre-drawn clock faces.
Memory	
Visual short-term memory	
Spatial span task (forward) (SpS)	Participants must copy the sequence with which an irregularly arranged series of boxes are highlighted.
Pattern recognition memory task (PRM)	Participants are presented with a series of visual patterns, and must select the pattern that has been previously presented.
Paired associates learning task (PAL)	Participants are shown a set of boxes, which are opened at random to reveal a unique pattern. Participants are then shown a cue pattern, and must select the box that contains it.
Delayed matching to sample task (DMTS)	Participants are shown a complex visual pattern (the sample) and then, after a brief delay, four similar patterns. Participant musts touch the pattern that matches the sample. Various adaptations of this test are in use.
Prospective memory task (PM)	Participants must indicate whether letter strings presented on a computer screen are real English words or not. In addition, participants must withhold their response and press the spacebar key if they saw a "PM" target (a letter string containing only a single "P" or "Q")*.
Repeated acquisition of response sequences (RA)	Participants must learn a novel 10-response sequence, only using trial and error with four keys on a keypad. If the correct key is pressed, a counter in the corner increases by one. Incorrect keystrokes cause the screen to turn blank for one second, but do not alter the step counter.
Verbal short-term memory	
Letter memory task (LM)	Participants are told to mentally update a set of four most recent letters from a continuously presented stream of letters and recall the last four when the stream is stopped.
Digit span task (forward) (fDS)	Participants must immediately repeat a list of digits, presented visually or verbally. If they fail, a second list of the same length is presented.
Sternberg number recognition task (SNR)	Participants view a series of letters. Following a delay, participants are shown a probe letter and must indicate if it was present in the series of letters. Various other versions of this task exist.
Immediate verbal free recall task (FR)	Participants must write as many items as they remember from 20 serially-presented words.
Logical memory task (LoM)	Participants are asked to recall a short story immediately after they hear it, and then 20 minutes later.
Creative thinking	
Convergent thinking	
Group embedded figures task (GEFT)	Participants must identify a simple shape within a more complex figure.
Remote associate task (RA)	Participants must give a word that has an associative linkage with three other given words.
Divergent thinking	
Line drawing task (LD)	Participants must list all the things they can think of when shown a series of line drawings.
Pattern meaning task (PaM)	Participants must list all the things they can think of when shown a series of patterns.
Abbreviated Torrance task for adults – figure subtask (AT)	

	Participants must complete a series of figures by adding lines and interesting shapes to them. They are instructed to try to create unique objects and scenes, and attempt to create a picture or narrative that no other participant would think of. Participants then have to name their drawing.
Alternative uses task (AU)	Participants must state as many alternative uses as possible for a named object.
Hayling sentence completion test (HSC)	Participants must listen to a sentence, then complete it by supplying the most appropriate last missing word (automatic completion section) or by an unrelated word (inhibition section) as quickly as possible.
Motor	
Nine-Hole-Peg task (NHP)	Participants must place nine pegs into nine holes, and then remove them as fast as possible.
Four-choice serial reaction time (SR)	Participants must move a visual pointer with a mouse to select one of four displayed letters, based on the identity of serially presented probe letters.
CogState card identification (CCI)	Participants must indicate as quickly as possible whether a card is red or not as soon as it is revealed.
Emotion	
Face matching task (FM) – emotional processing	Participants must indicate which of two simultaneously presented matches the emotion displayed on a third face.

*Only one study within this review uses a prospective memory task, and so its details are given here under this abbreviation. However, the reader should note that there are many tasks that assess prospective memory, and the description given here refers only to one specific example of these tasks, and does not receive this abbreviation as standard elsewhere.

(Turner et al., 2003); although notably two smaller crossover studies using similar doses did not (Theunissen et al., 2009; Winder-Rhodes et al., 2010). By contrast, no effect was observed on Stroop task (Randall et al., 2004, 2005a, 2005b). In two studies using two preparing-to-overcome-pre-potency paradigms, Minzenberg and colleagues failed to detect an effect of modafinil on task performance; however, they both reported differences in brain activity accompanying modafinil intake. In the first study, participants exhibited increased pre-frontal cortex (PFC) activity (task-dependent), a decrease in locus coeruleus activity (task-independent), and an increase in functional connectivity between the locus coeruleus and the PFC (Minzenberg et al., 2008). In the second, increases in theta, alpha, and beta power in frontal and parietal electroencephalography (EEG) electrode subgroups during high-control subtasks were seen (Minzenberg et al., 2014). Finally, Rasetti and colleagues conducted a seven-day daily-dose trial in which functional magnetic resonance imaging was performed during a variable attentional control task. Although no behavioural differences were observed between modafinil and placebo groups, image analysis revealed decreased ACC activity following modafinil intake, taken by the authors to signify an *increase* in computational efficiency in this area, which is richly innervated by catecholaminergic neurons (Rasetti et al., 2010).

3.2.2. Working memory

No effect was associated with modafinil intake on many simple tests of verbal working memory (Baranski et al., 2004; Gilleen et al., 2014; Randall et al., 2005a, 2005b; Winder-Rhodes, 2010). Studies reported mixed results using the backwards digit-span task: three failed to show an effect (Müller et al., 2013 (a large between-subjects study; 200 mg dose); Pringle et al., 2013 (a medium-sized between-subjects study; 100 mg dose); Winder-Rhodes et al., 2010 (a small crossover study; 300 mg dose)), whereas two trials – with equivalent participant numbers and doses – reported an increased span after modafinil intake (Randall et al., 2005a, 2005b; Turner et al. 2003). Müller and colleagues (2004) found that despite no overall improvement in performance, on subtasks of the numeric working memory task that required more manipulation, poor baseline participants performed more accurately following modafinil ingestion. Finally, although Rasetti and colleagues found no difference in task performance on a 2-Back task, decreased activation was reported in right PFC during modafinil sessions. For non-verbal working memory, one large trial demonstrated fewer between-search errors in the modafinil group using the spatial working memory task (Müller et al., 2013), whereas two other large studies using similar doses did not (Randall et al., 2005a, 2005b; Turner et al. 2003).

3.2.3. Cognitive flexibility

Most studies assessing cognitive flexibility with simple tasks reported no benefit to modafinil intake (Randall et al., 2003, 2005a, 2005b; Turner et al. 2003), with one study even reporting a *decrease* in performance on the intra/extra dimensional set shift task (Randall et al., 2004).

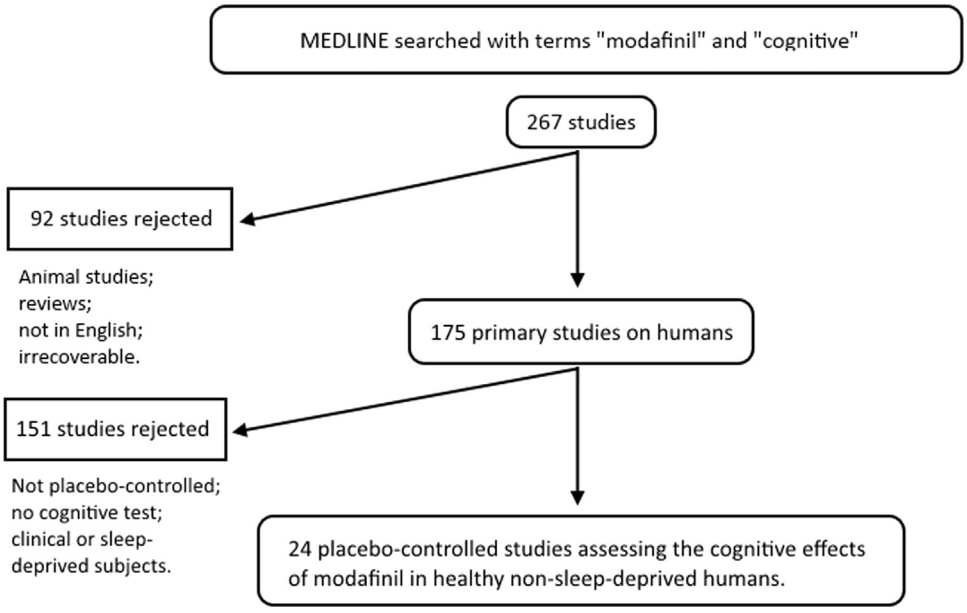

Figure 1 Flowchart of systematic search and selection protocol.

3.2.4. Planning, decision-making, and fluid intelligence

Many studies also examined higher executive functionality, such as planning, decision making, and fluid intelligence, necessarily using more complicated tasks than those used for lower functions. In terms of planning and decision making, the Tower of London/One-Touch Stockings of Cambridge tasks were well represented, with two large studies reporting improved performance over all difficulties (Müller et al., 2013; Turner et al., 2003), and one small study reported improved performance on harder trials only (Winder-Rhodes et al., 2010). Interestingly, although Randall and colleagues observed an increase in speed on easier trials in keeping with the results above, they also found that the modafinil group exhibited *decreased* speed on harder trials (Randall et al., 2005a, 2005b). Finally, one small study reported no differences between modafinil and control group performance (Randall et al., 2003).

Fluid intelligence is the ability to cope with novelty, to think rapidly and flexibly, and to see relations amongst items independent of acquired knowledge, and is predictive of life outcomes such as income, performance at work, and health (Au et al., 2014; Sternberg et al., 2013). Using a logical reasoning task that probed fluid intelligence, Baranski and colleagues (2004) found that modafinil increased accuracy. Similarly, Esposito and colleagues reported that modafinil intake improved one measure of performance on Raven's Advanced Progressive Matrices, the best-known assessment of fluid intelligence. Although modafinil intake did not appear to affect overall performance between individuals' pre-drug and post-drug performance, individuals in the modafinil group exhibited greater improvement on medium difficulty trials than the control group (Esposito et al., 2013).

In summary, modafinil appears to exert a beneficial effect on executive functions, with some benefits seen in inhibitory control and working memory paradigms, and more marked effects in higher executive functions such as planning, decision making, and fluid intelligence.

3.3. Learning and memory

3.3.1. Non-verbal short-term memory

Makris and colleagues (2007) found that modafinil increased learning efficiency in a simple repeated acquisition of sequences task. Several studies used the delayed matching to sample task to evaluate modafinil's effects on visual short-term memory, with mixed results: two medium-sized between-subjects studies using 100 and 200 mg doses failed to demonstrate an effect (Randall et al., 2003, 2004), one smaller crossover study using 200 mg doses demonstrated a decrease in error rate after long delay conditions (Müller et al., 2004), and one large between-subjects study using 100 and 200 mg doses showed an *increase* in latency with similar accuracy (Turner et al., 2003). Interestingly, a large between-subjects study also showed a slowing of response times in the modafinil group on a similar visual short-term memory task: the pattern recognition memory task; this time with an *improvement* in performance (Randall et al., 2005a, 2005b). On the same task, another large between-subjects study using similar doses showed a decrease in incorrect choices with no effect on latency (Turner et al., 2003), and a third found improved performance on delayed but not immediate trials (Müller et al., 2013); by contrast, a fourth small crossover study failed to reveal any effect from 300 mg of modafinil (Winder-Rhodes et al., 2010). No effect was observed on several other tasks (Mohamed, 2014; Müller et al., 2013; Turner et al., 2003).

3.3.2. Verbal short-term memory

The results from studies assessing verbal short-term memory were broadly similar: Markis and colleagues again showed that modafinil intake improved performance, this time on a Sternberg number recognition task, with a concomitant decrease in reaction time at 4 and 5 h (Makris et al., 2007). Although several studies failed to show an effect on the forward component of the digit span (Mohamed,

2014; Müller et al., 2013; Pringle et al., 2013; Winder-Rhodes et al., 2010), two large trials did report a positive effect (Randall et al., 2005a, 2005b; Turner et al. 2003). No effect was seen on several other measures (Marchant et al., 2009; Randall et al., 2003, 2004, 2005a, 2005b).

In summary, some benefits were seen with modafinil on simple assessments on learning and memory, including both early and delayed performance. However, an equal number of studies failed to observe any effect.

3.4. Creativity

In cognitive science, creativity is formally defined as the production of ideas and work that is both novel and appropriate (Dietrich, 2004), and has traditionally been thought to arise from cognitive and neural systems distinct from the domains involved with classical "intelligence" outlined above (although see Nusbaum and Silvia (2011)). Further, there is consensus that two broad creative sub-functions exist: *convergent* and *divergent* thinking. Convergent thinking underlies problem-solving abilities: arriving at a particular strategy and solution to link two disparate concepts (Mohamed, 2014). Modafinil intake did not affect convergent thinking in most studies (Mohamed and Lewis, 2014; Mohamed, 2014; Müller et al., 2013); however, when participants were separated into low- and high-creativity personalities in Mohamed's study – based on a pre-assessment personality questionnaire – participants with low creativity personalities were seen to score significantly higher than those with high baseline creativity in the modafinil group only (Mohamed, 2014). In contrast, divergent thinking relies on a person's ability to generate multiple associations or solutions to a subject or problem (Mohamed, 2014). Most studies did not report any effect of modafinil on simple divergent thinking paradigms (Mohamed, 2014; Müller et al., 2013; Randall et al., 2003, 2004, 2005a, 2005b). In a few studies, however, *impaired* performance was observed in the modafinil group: decreased fluency and elaboration on the abbreviated Torrance task (Mohamed, 2014); increased deliberation time on the Cambridge gambling task with no change in accuracy (Turner et al., 2003); and slower reaction times in the inhibition section of the Hayling sentence completion test (Mohamed and Lewis, 2014).

3.5. Complex tasks

Most of the tasks above are 'simple' in that they selectively assess one or two cognitive sub-functions. However, with testing of higher executive functions, which as noted are thought to rely on separately testable sub-functions, task procedures become more complicated, as do their results. Equally, their relevance is altered: tests assessing higher functions immediately appear more ecologically valid. The 'complex' tasks described below extend this framework, and use one or more advanced psychometric tasks to assess more global cognitive domains, typically also varying task difficulty. They are therefore also able to gather more information about different aspects of participants' performances: learning rates and value associations, in addition to reaction times and accuracies. However, these tests have mainly been used to test specific hypotheses about cognitive functioning, and consequently remain less well standardised. This means they are less suited to monitoring permutations of already well-described cognitive sub-functions, as their results are harder to generalise, and less evidence exists as to their modulation by different cognitive states.

Pringle and colleagues examined the effects of modafinil versus placebo in a compound learning task that also relied on attention and executive function. In this task, a set of two objects were briefly shown on a screen, followed by one or two dots in the position previously occupied by one of the objects, and participants were instructed to indicate the number of dots present as quickly as possible. In the first set of trials, dot location was predicted by particular object features, for example, the object coloured red. Then, representing an intra-dimensional switch, another colour became predictive in the second set of stimuli; in the third a different stimulus dimension – the shape of the object – became predictive (an extra-dimensional switch); and in the fourth, another shape became the salient indicator. Modafinil intake not only improved learning rates following the extra-dimensional shift, but also increased participants' accuracy across all blocks. The authors attribute this difference to better orientation of sustained attention in the modafinil group, driven by enhanced cognitive flexibility, decision making, and rule acquisition (Pringle et al., 2013).

In Marchant and colleagues' paradigm, stimuli were concurrently presented in visual and auditory streams, and participants had to identify non-targets and targets. In the constant condition, participants were informed that the target stimulus would be red objects in the first set of trials, and a low tone in the second. Thus, this section tested selective and sustained attention, and inhibitory control. In the alternating condition, participants were told that the salient stimulus dimension would alternate between red stimuli and the low tone; thus this section additionally probes short-term memory and cognitive flexibility. In the constant condition, all participants were more accurate at identifying non-targets rather than targets (this was unsurprising, as non-targets were presented at a higher frequency), with no differences observed between modafinil and placebo groups. In the alternating condition, however, subjects taking modafinil responded to non-targets and targets with similar accuracy (near-maximal), whereas those taking placebo did not detect targets with the same high accuracy as non-targets (Marchant et al., 2009); an effect suggestive of enhanced attentional and executive functions.

Geng and colleagues employed a decision-making task based on spatial probability, in which subjects were instructed to guess which of two boxes a stimulus would appear in. For the first 200 trials, the stimulus was presented at one location 70% of the time; in the second 200 trials, the stimulus was presented in either location 50% of the time. Modafinil intake was found to improve the rate at which subjects learnt the spatial probabilities underlying their choices, again attributed to an enhancement of executive functions with more accurate orientation of attention as a corollary (Geng et al., 2013).

Finke and colleagues analysed participants' performance on a whole report task, according to the "theory of visual attention" model. In this task, participants viewed a column

of five simultaneously presented letters for a brief period of time, followed by either blank space (the "unmasked" condition) or an identically positioned column of five crosses (the "masked" condition). Stimuli were presented for a variable amount of time, and, after a variable pause (masked or unmasked), participants were instructed to recall as many of the letters as possible. According to the theory of attention model, visual objects are processed in parallel, and compete for space in a visual short-term memory store according to the attentional weighting they receive. Modafinil was found to increase the uptake of information (in other words, processing speed) in low baseline performers, as well as the storage capacity in this group. The authors again posit that these benefits were probably due to modafinil's upregulation of PFC-based processes involved in executive function, manifesting in improved attentional functions (Finke et al., 2010).

Gilleen and colleagues combined cognitive training on a language learning paradigm with twelve days of either modafinil or placebo intake. In their task, auditory neologisms were presented with a visual object within a rapidly presented series. 50 word-picture combinations were target pairings – these were presented twice as frequently – whereas all other combinations were unpaired. After each pairing was presented, participants had to identify whether it was a target or not, with the only indicator being the increased incidence of target pairings, and experience in previous days. This task relies on multiple memory domains, as well as attentional components, and those taking modafinil exhibited enhanced learning rates early in the training period, and maintained superior performance overall, and at follow up two weeks later. Notably, those with high baseline intelligence scores – measured using the Wechsler Abbreviated Scale of Intelligence – progressed more quickly in the modafinil group than those with low baseline intelligence scores on all days of training (1–10), an effect not seen in the placebo group (Gilleen et al., 2014).

When these results are considered together, it appears that modafinil exerts a complex effect on cognitive domains, in general driving benefits in attention and memory through enhancement of higher executive functions. Positive results are observed in all of these studies, suggesting increased testing times and more complicated paradigms might be necessary to consistently reveal the cognitive benefits of modafinil intake.

3.6. Alteration of mood and side effects

70% of studies assessed the influence of modafinil intake on mood, and although a small number of studies reported a clustering of positive effects centred on the ability of modafinil to promote alertness/energy and ameliorate feelings of tiredness, the majority reported no changes. Notably, very few studies reported potentially negative effects, such as increased anxiety (Randall et al., 2003) and decreased contentedness (Marchant et al., 2009). Nine out of 24 (37.5%) of the studies in our review reported side effects: of these, 78% reported no side effects, and the remaining two reported that a small minority of participants had experienced insomnia, headache, stomach ache or nausea, and dry mouth (Gilleen et al., 2014; Müller et al., 2013). Further, modafinil did not appear to affect motor excitability (Liepert et al., 2004). Encouragingly, the only study to assess modafinil's abuse potential corroborates consensus that it is low (Makris et al., 2007).

4. Discussion

4.1. Summary

When simple psychometric assessments are considered, modafinil intake appears to enhance executive function, variably benefit attention and learning and memory, and have little effect on creativity and motor excitability. When more complex tasks are considered, modafinil appears to enhance attention, higher executive functions, and learning and memory. *Negative* cognitive consequences of modafinil intake were reported in a small minority of tasks, and never consistently on any one: decreased performance on a cognitive flexibility task (the intra/extra-dimensional set shift task in Randall et al. (2004)), increased deliberation time during harder trials on a planning task (the One-Touch Stockings of Cambridge task in Randall et al. (2005a, 2005b)), increased deliberation time on one divergent thinking task (the Cambridge Gambling Task in Turner et al. (2003)), and decreased performance on another (the abbreviated Torrance in Mohamed (2014)). It appears that modafinil exerts minimal effects on mood – if anything improving it – and only rarely causes minor adverse effects.

4.2. Mechanistic speculations

These findings are in keeping with the effects reported in clinical and sleep-deprived populations (Minzenberg and Carter, 2008; Mohamed and Lewis, 2014), and are supported by the molecular, imaging, and electrophysiological literature, allowing speculation as to the *cognitive* mechanisms by which modafinil might engender neuroenhancement. Modafinil is known to amplify endogenous arousal systems, seen in pupillography (Hou et al., 2005), hormone and enzyme levels (Samuels and Hou, 2006; Winder-Rhodes et al., 2010), imaging (Minzenberg et al., 2008), and electrophysiology (Della Marca et al., 2004). As arousal subserves all other attentional capacities, which in turn underlie many aspects of higher cognition, it is conceivable that this 'bottom-up' effect is responsible for the benefits observed on simple measures of attention, executive function, learning and memory following modafinil intake. Certainly, an increase in arousal could explain observations that modafinil amplifies task-induced deactivation of the "default mode network" – which is active in the absence of salient stimuli or attention-demanding tasks (Minzenberg et al., 2011), or the brainstem-based potentiation of somatosensory-driven high frequency oscillations (Della Marca et al., 2004). However, on most direct measures of arousal itself, no benefit to modafinil intake was seen. Instead, a more compelling theory is that modafinil stimulates improved performance in the range of tasks reported herein mainly as a downstream effect of enhancement of 'top-down' cognitive control processes. Behaviour support for this second theory comes from the consistently improved performance in executive function paradigms, and positive

results from complex trials primarily involving these functions. Further, the task-related changes in ACC and PFC activity during executive control tasks (Minzenberg et al., 2008; Rasetti et al., 2010), as well as in EEG alpha, beta, and theta activity (Minzenberg et al., 2014), are also consistent with amplification of activity in executive-control-related brain regions (which are richly innervated by catecholaminergic neurons (Rasetti et al., 2010)).

Such a theory is undoubtedly a simplification of the intricate effect of modafinil on the networks underlying cognition. The more marked improvements on tasks assessing multiple cognitive domains and sub-domains – as well as the permutation of many major neurotransmitter systems – indicate that there is much more to be discovered about this interaction. As our theories of intelligence increasingly follow a neural network philosophy (Jung and Haier, 2007), perhaps the neuronal causality of modafinil's cognitive effects will be more faithfully explicated. Indeed, the value of this approach can be seen in the imaging studies above, where modafinil intake increases blood flow to diverse network and specific regions, including the hippocampus, (Joo et al., 2008), and activates multi-areal brain *networks* subserving attention and executive functions (Esposito et al., 2013) and multiple cortical areas during associative learning (Ghahremani et al., 2011).

Finally, discrepancies in the relationship between modafinil intake and speed of cognitive processing reported above merit further discussion. In attention- and executive function-based paradigms, modafinil on average improved immediate reaction times, with or without enhanced accuracy. However, in short-term memory studies, the benefits of modafinil were most marked in delayed recognition conditions, and in some tests of planning and creativity, increased deliberation time was seen in the modafinil group, without improved performance. These findings on one hand imply that modafinil intake assists with focussing cognitive resources on attention-based tasks, endowing benefits on rapid and delayed singular responses, but also hint that these improvements have the unwanted corollary of impairing functions that benefit from more protracted contemplation. It is essential that future work analyses these effects more rigorously.

4.3. Methodological points

The discrepancy between the mainly null results from simple tests, with the exception of those assessing executive functions, and the mainly positive results from more complex testing paradigms highlighted by this review warrants further discussion and investigation. In terms of complex tasks, a systematic bias towards positive results could have been introduced through study design or study execution (a universal bias from task design is less likely because of the varied nature of these tasks). One source of study-design-based error could be the equal weighting we have accorded to results from crossover and between-subject trials. In the former, a participant's performance on a test under one condition (for example, modafinil intake) is compared to their own performance under another condition (for example, placebo), and in the latter one group's performance under one condition on a test is compared to a control group's performance on the same test. It has been argued that repeating psychometric tests in crossover tests introduces practice effects that vary unpredictably between individuals and cognitive tasks, and could bias results (Hartley et al., 2003; Lowe and Rabbitt, 1998; Randall et al., 2004; Rose and Lin, 1984). Fortunately, however, the preponderance for each study design is roughly equal within simple and complex task groups, and repeated dose studies use complex tasks with adaptive assessment platforms that should obviate these practice effects. Equally, the prolonged testing experience associated with complex tasks may have allowed more opportunities for experimenters to influence participants. Against this argument is the fact that in the two studies that did assess participant blinding, participants were able to guess they had taken modafinil 55% of the time in a *complex* crossover trial (Gilleen et al., 2014), but 75% in a *simple* between-subjects study (Turner et al., 2003).

Conversely, the simple psychometric tasks used by the majority of studies could have lacked sufficient sensitivity to detect cognitive effects in the healthy and mostly student-based populations tested. With this in mind, it is a notable *non sequitur* that tests that reliably report cognitive *dysfunction* are equally qualified to detect improved cognitive performance in healthy adults. A key example of the inadequacy of some testing paradigms is the use of the "clock test" in some of these studies, which involves drawing hands onto a clock at specific times (for example, in Randall et al. (2005a, 2005b)). Whilst in ill populations this test offers a valuable screening tool of poor cognitive function (Shulman, 2000), it is clearly a poor differentiator of normal or high-performing healthy individuals. Indeed, ceiling performances were consistently observed within simple tasks, for example on the pattern recognition memory task (Müller et al., 2013; Randall et al., 2005a, 2005b; Turner et al., 2003; Winder-Rhodes et al., 2010), the delayed matching to sample task (Randall et al., 2003, 2004; Turner et al., 2003), the rapid visual information processing task (Randall et al., 2005a, 2005b), the spatial working memory task (Turner et al., 2003; Winder-Rhodes et al., 2010), the preparing-to-overcome-prepotency tasks (Minzenberg et al., 2008, 2014), and the Sternberg number recognition task (Makris et al., 2007). When these ceiling effects were lessened by only analysing data from low baseline performers, many studies actually did detect significant differences between modafinil and placebo groups (Minzenberg et al., 2014; Mohamed, 2014; Müller et al., 2004; Randall et al., 2005b). Several groups have commented this issue, noting, for example, that it may explain why robust effects on these same tasks are seen with sleep deprivation (Müller et al., 2004), when all participants effectively become low baseline performers. They also suggest that these tasks are in their current state inappropriate for detailed assessment of healthy individuals (Müller et al., 2004), and must be revised or abandoned in favour of more complex testing paradigms (Finke et al., 2010; Müller et al., 2013; Pringle et al., 2013). Recognition of the limitations of simple psychometric tests is also seen in the temporal succession of simple with complex ones over the last decade. Thus, it appears that within research on modafinil, any consensus about cognitive benefits has to this point been limited by the use of simplistic testing

paradigms. These ceiling effects must be addressed in future work; certainly before discourse on the ability of low and high baseline participants to benefit from modafinil can offer real value.

4.4. Recommendations for future studies of neuroenhancement techniques and agents

If the literature surrounding modafinil—one of the most promising and highly-investigated neuroenhancers to date—presents this many barriers to comparison and interpretation, it stands to reason that cognitive assessment of neuroenhancement *in general* may benefit from the development of novel or improved methodological approaches. As the first stage in this process, and in order to guide future neuroenhancement studies, we propose the following framework, centred on the principles of, on one hand, sensitivity and reproducibility, and, on the other, ecological validity (see Table 3).

The 'simple' task designs described above are extremely useful tools for dissecting the influence of a substance or process on higher cognitive functions. Equally important, their internal validity is high, at least within clinical populations (Levaux et al., 2007; Sweeney et al., 2000). Hence, if the ceiling effects encountered in these studies could be ameliorated, they would still add much valuable information to any assessment of supra-normal cognition. One solution to this problem is to integrate them into more advanced software platforms, which would still be standardised, but could be set to increase task difficulty via more complex task demands and shorter response windows. More complex tasks could then be integrated into the basic software package as additional modules, meaning more nebulous domains and cognitive processes could be investigated with reference to changes in basic systems, and a high internal consistency in the literature could be established.

Table 3 Methodological recommendations for neuroenhancement studies.

Task design
In order to attain the sensitivity to detect supra-normal improvements in cognition, studies should use computer-based assessment paradigms that:
1. Are designed for use in healthy rather than clinical or animal populations;
2. Focus on one or more cognitive domains and their sub-domains;
3. Integrate adaptive training and testing components;
4. Include testing on other un-trained cognitive domains.
Trial design
In order to emulate real-world conditions surrounding ideal use of neuroenhancement, studies should:
1. Test over multiple days;
2. Include follow-up testing;
3. Use a design that includes between-subjects and within-subjects testing;
4. Include analysis of high and low baseline performers;
5. Be required to report side effects using a standardized and rigorous system.

The additional advantages of such an approach are myriad: integration of adaptive training and testing regimes, so that learning in each cognitive-subdomain could also be measured; more comprehensive analysis of participant performance, with the ability to compare every aspect of their actions; and game-based incentive structures, obviating the decline in performance that follows prolonged testing (Kennedy and Scholey, 2004). Using the same system, testing could be conducted on untrained tasks and their cognitive sub-domains, to identify any transfer of cognitive ability (see Gilleen et al. (2014), or be used for re-testing at later dates, to identify lasting effects.

The output of neuroenhancement-related research is aimed at a fundamentally different population from most prior work on cognitive modulation – those seeking elective self-improvement of their own cognitive abilities, rather than those hoping to treat cognitive deficits. Consequently, methodologies of research in this area need to be considered anew, in order to probe supra-normal cognitive enhancement in ecologically valid settings whilst retaining rigorous testing conditions. Most tasks and projects in life necessitate learning and operating within a system for multiple days, and individual users are interested primarily in how their own performance will change, rather than the average of a group. Thus, testing regimes should be based over multiple days, and allow analysis within and between single participants' performances. Baseline testing is also essential; as an absolute measure of individual performance, to ensure that ceiling and floor performances are not limiting the usefulness of results, and to allow speculation on whether and why some groups benefit more from particular agents or techniques. Makris and colleagues' (2007) finding of improved reaction times four and five hours after modafinil ingestion serves as a reminder that under real-life conditions, performance is likely to be affected by fatigue even within a single working day. In this case, modafinil's eugeroic properties are evidently beneficial; however, more generally studies should make more effort to examine the length of performance benefits offered by an agent or technique for neuroenhancement.

Finally, in the set of studies we examined, reporting of side effects was egregiously low and inconsistent. Given the potentially far-reaching consequences of neuroenhancement research, future studies must be required to report side effects, using a rigorous and standardized system.

5. Conclusion

In this review, we have highlighted that modafinil provides some benefit to cognition, in particular executive functions, speculated on the mechanisms by which it may do so, and offered critical analysis on the methodology that has been employed to date in healthy, non-sleep-deprived individuals. As this is a retrospective analysis, we must emphasise that these conclusions and explanations remain necessarily weaker than if integrated into prospective study questions; indeed, this is a secondary and explicit aim of the text.

A full discussion of the rationale for, possibility of, and ethical issues surrounding neuroenhancement is beyond the scope of this review (for attempts at such, see Maslen et al. (2014) and Persson and Savulescu (2008)). However, it is

noteworthy that with more protracted and complex testing, more benefits are being associated with modafinil use rather than less, which suggests that modafinil may well deserve the title of the first well-validated pharmaceutical 'nootropic' agent. This observation is also true of non-invasive brain stimulation techniques, in which more integrative cognitive assessments and physiological recordings are yielding increasingly valuable insights into the mechanisms by which they may engender cognitive enhancement (see, for example, Battleday et al. (2014) and Santarnecchi et al. (2015)). In this vein, we hope our recommendations for future study will assist in advancing and consolidating the cognitive investigation of neuroenhancement agents, and, in doing so, contribute valuable information to wider discourse on the achievability and role of neuroenhancement within wider society.

Conflict of interests

The authors declare no conflict of interests.

Contributors

R.M. Battleday conducted the literature review and wrote the article. A-K. Brem assisted with critical analysis and writing the article.

Funding source

This work was conducted without any input from funding sources.

Acknowledgements

None.

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