Psychopharmacology (2010) 210:317–329
DOI 10.1007/s00213-010-1823-x

ORIGINAL INVESTIGATION

Effects of modafinil and methylphenidate on visual attention capacity: a TVA-based study

Kathrin Finke · Chris M. Dodds · Peter Bublak · Ralf Regenthal · Frank Baumann · Tom Manly · Ulrich Müller

Received: 20 October 2009 / Accepted: 1 March 2010 / Published online: 30 March 2010

Abstract
Introduction Theory of visual attention (TVA; Bundesen 1990) whole report tasks allow the independent measurement of visual perceptual processing speed and visual short-term memory (vSTM) storage capacity, unconfounded by motor speed. This study investigates how cognitive enhancing effects of psychostimulants depend on baseline performance and individual plasma levels.
Materials and methods Eighteen healthy volunteers (aged 20–35 years) received single oral doses of either 40 mg methylphenidate, 400 mg modafinil or placebo in a counterbalanced, double-blind crossover design. A whole report of visually presented letter arrays was performed 2.5–3.5 h after drug administration, and blood samples for plasma level analysis were taken.
Results Methylphenidate and modafinil both enhanced perceptual processing speed in participants with low baseline (placebo) performance. These improvements correlated with subjective alertness. Furthermore, we observed differential plasma level-dependent effects of methylphenidate in lower and higher performing participants: higher plasma levels led to a greater improvement in low-performing participants and to decreasing improvement in high-performing participants. Modafinil enhanced visual short-term memory storage capacity in low-performing participants.
Conclusions This is the first pharmacological investigation demonstrating the usefulness of a TVA task for high-resolution and repeated cognitive parameter estimation after cognitive-enhancing medication. Our results confirm previous findings of attentional capacity improvements in low

Finke and Dodds contributed equally as first authors and Manly and Müller as senior authors.

K. Finke
Department of Psychology, Experimental Psychology,
Ludwig Maximilian University,
Munich, Germany

C. M. Dodds · T. Manly
Medical Research Council Cognition and Brain Sciences Unit,
Cambridge, UK

C. M. Dodds · U. Müller
The Cambridge Institute of Behavioural and Clinical Neuroscience,
Department of Experimental Psychology, University of Cambridge,
Cambridge, UK

P. Bublak
Neuropsychology Unit, Neurology Clinic,
Friedrich Schiller University,
Jena, Germany

R. Regenthal · F. Baumann
Department of Clinical Pharmacology, University of Leipzig,
Leipzig, Germany

U. Müller
Department of Psychiatry, University of Cambridge,
Cambridge, UK

K. Finke (✉)
Department Psychology,
General and Experimental Psychology/Neuro-Cognitive Psychology,
Ludwig Maximilians University Munich,
Leopoldstr. 13,
80802 Munich, Germany
e-mail: finke@psy.uni-muenchen.de

performers and extend the baseline dependency model to methylphenidate. Plasma level-dependent effects of psychostimulants can be modelled on an inverted U-shaped dose–response relationship, which is highly relevant to predict cognitive enhancing and detrimental effects of psychostimulants in patients with cognitive deficits (e.g., attention deficit hyperactivity disorder) and healthy volunteers (e.g., self-medicating academics).

Keywords Dopamine · ADHD · Arousal · Attention · Behaviour · Cognitive · Human · Perception

Introduction

Psychostimulants have relatively small effects on cognitive functions in healthy volunteers without sleep deprivation (Koelega 1993; Müller et al. 2004; Randall et al. 2005b), and their measurement has to rely on sensitive and cognitively specific tasks. Previous studies investigating the effects of psychostimulants on cognitive performance in healthy volunteers have generally employed neuropsychological tests designed primarily for the assessment of cognitive deficits in brain-injured or psychiatric populations. Whilst these tests provide useful ways to categorise and measure debilitating cognitive deficits, they are not necessarily the optimum tools for teasing apart the more subtle effects of drugs on different component processes of cognition.

Methylphenidate and modafinil are two widely used psychostimulants that both exert their effects by enhancing the synaptic availability of the two catecholamines dopamine and noradrenaline (Berridge et al. 2006; Minzenberg and Carter 2008; Robbins and Arnsten 2009; Volkow et al. 2009). Thus, cognitive-enhancing effects on attentional and working memory performance can be expected even in healthy subjects.

Methylphenidate enhances dopamine levels by blocking the dopamine transporter and is an effective first-line treatment for attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults (NICE 2008). On the other hand, studies have reported mixed effects of methylphenidate on normal participants' attentional performance, with improvements in serial reaction time, vigilance, spatial working memory span or self-ordered spatial working memory tasks revealed in some studies (Camp-Bruno and Herting 1994; Clatworthy et al. 2009; Elliott et al. 1997; Halliday et al. 1986; Koelega 1993; Mehta et al. 2000; Strauss et al. 1984), but not in others (Turner et al. 2003b; Rogers et al. 1999). Likewise, modafinil, a non-amphetamine stimulant commonly prescribed for the treatment of narcolepsy and daytime sleepiness (Ballon and Feifel 2006; Becker et al. 2004; McClellan and Spencer 1998; Thorpy et al. 2003), has positive effects on ADHD symptoms (Rugino and Copley 2001; Taylor and Russo 2000; Turner et al. 2004) and can enhance attentional and working memory performance in healthy participants (Baranski et al. 2004; Dodds et al. 2009; Müller et al. 2004; Thomas and Kwong 2006; Turner et al. 2003a; Wesensten 2006; Winder-Rhodes et al. 2009; see Minzenberg and Carter 2008, for a review). Animal studies have also revealed improvement in depression-like attention deficits (Regenthal et al. 2009). However, several studies found no effects on sustained attention, spatial span and higher-order executive functions (Müller et al. 2004; Randall et al. 2003, 2005a; Turner et al. 2003b), whilst beneficial effects might be restricted to low-performing participants (Müller et al. 2004; Randall et al. 2005b). Both methylphenidate and modafinil are frequently mentioned in the context of cognitive or neuroenhancement (Larriviere et al. 2009).

Thus, specific patterns of attentional improvement evoked by methylphenidate and modafinil are difficult to classify (e.g., Randall et al. 2005b), and it remains unclear which neuro-cognitive processes are modulated by the two substances. For example, Naylor et al. (1986) demonstrated that speeding of response times after methylphenidate interacted with the complexity of required responses rather than with that of the stimulus material. Response time accelerations could thus be related to non-specific psychomotor arousal effects. Such results demonstrate the necessity of using more specifically tailored tasks in order to disentangle the influence of stimulants on (attentional) stimulus evaluation from that on (psychomotor) response selection processes.

Here, we use Bundesen's 'theory of visual attention' (TVA; Bundesen 1990, 1998; Bundesen et al. 2005) to address the effects of two widely used psychostimulants, methylphenidate and modafinil, on separate components of visual attention. TVA proposes two general capacity parameters of attention: visual perceptual processing speed C (number of elements processed/s) and visual short-term memory (vSTM) storage capacity K (number of elements maintained consciously in parallel). These represent 'latent' variables underlying observable performance and are estimated quantitatively by modelling performance in a psychophysical 'whole report' task with briefly presented letters.

These parameters have reasonable correlations with clinical measures of attentional response speed and vSTM storage capacity (Finke et al. 2005). However, unlike conventional neuropsychological tasks, TVA allows the exact quantification of these estimates, independently from each other and from motor side effects, within the same paradigm. Moreover, the method has been shown to be very sensitive even to small changes in attentional capacity (Habekost and Bundesen 2003). In an empirical confirmation of the independence of the parameters, visual perceptual processing speed, but not vSTM storage capacity, has been shown to temporarily increase after phasic-alerting

cues (Matthias et al. 2010). Therefore, this task seems especially suitable to investigate the mechanisms of attentional performance enhancement after psychostimulant medication in healthy volunteers.

The aim of this study was to investigate whether and to what degree single doses of methylphenidate and modafinil enhance the TVA visual speed (*C*) and vSTM storage capacity (*K*) parameters in young, healthy participants and whether objectively measured changes in visual perceptual speed are associated with changes in subjective alertness. Participants were classified as high or low performers based on prior evidence that the effectiveness of psychostimulants depends on baseline performance (Eagle et al. 2007; Müller et al. 2004; Randall et al. 2005b). We predicted that participants with lower baseline performance would show greater cognitive enhancement from single doses of methylphenidate and modafinil.

Materials and methods

Participants

Eighteen healthy participants, nine male and nine female, aged between 20 and 35 years, were recruited from the Cambridge local community and were included after medical screening. Participants had no history of psychiatric, neurological or cardiovascular illness, no history of drug addiction and no recreational use of psychostimulants in the last 3 months and had no major vision or motor impairments. They were asked to abstain from caffeine for at least 3 h before the testing sessions. Participants received financial compensation for their participation (£150 in total). The study protocol was given a favourable opinion by the Cambridge Research Ethics Committee (Ref:05/Q0108/482) and was exempted from EU Clinical Trial Directive regulations by the Medicines and Healthcare products Regulatory Agency (MHRA; London, UK). All participants gave written informed consent to participate in this study.

Experimental drugs

A double-blind, randomised and counterbalanced crossover design was used. Single oral doses of modafinil 400 mg or methylphenidate 40 mg or a placebo tablet, all hidden in identical opaque gelatine capsules, were administered on each testing day. Each participant was tested on 3 days separated by at least 1 week. The order of drug administration was completely balanced across participants, such that each of the six possible sequences was used in three participants. Cognitive testing was carried out between 150 min and 210 min after drug intake, i.e., around expected maximum plasma concentrations (c_{max}) of modafinil (McClellan and Spencer 1998; Wong et al. 1999) and methylphenidate, where c_{max} is reached ca. 60 min earlier (from 90 to 150 min in different studies) and has a higher inter-subject variability (e.g., Gualtieri et al. 1982; Midha et al. 2001; Müller et al. 2005; Wong et al. 1998). Nevertheless, in both drug conditions, it can be assumed that participants were tested near c_{max} and, thus, at biologically effective plasma levels. One blood sample per testing session was taken about 180 min after dosing. Plasma levels of methylphenidate or modafinil were analysed in order to control the randomisation, to measure representative drug concentrations around c_{max} and to assess the impact of individual plasma levels on changes of TVA parameters.

Plasma level analyses

Modafinil in all samples was analysed using a modified high performance liquid chromatographic method with diode array detection (Schwertner and Kong 2005). Separation of modafinil and difluoro-modafinil (internal standard) was performed on a Symmetry C18 reversed phase column after sample preparation by liquid/liquid extraction. Detection wavelength was 225 nm; the limit of quantitation was 0.05 mg/L.

Determination of methylphenidate in plasma samples was performed by liquid chromatography/electrospray ionisation mass spectrometry according to Doerge et al. (2000). After solid-phase extraction of plasma samples on Waters Oasis HLB cartridges, chromatographic separation was achieved by use of an Ultrasep RP18E column and deuterated methylphenidate as internal standard. The limit of quantitation was 2 μg/L.

Subjective alertness ratings

For each participant three subjective alertness ratings were obtained. A single visual analogue scale (VAS), measuring subjective alertness, was administered once at baseline ('t0'), once at 150 min after drug intake (directly before testing with whole report—'pre-testing'), and once at 210 min after drug intake (after testing—'post-testing').

Apparatus

Stimuli were presented on a 17-in. monitor with a black background colour, a refresh rate of 70 Hz and a resolution of 1024×768 pixel. The centre of the monitor was kept at eye height. The whole report was conducted in a dimly-lit room. The only luminance source was a small lamp positioned behind the monitor. The viewing distance was 50 cm.

Framework of the TVA approach

TVA (Bundesen 1990) is a mathematical model with strong relations to the biassed competition view of visual attention (e.g., Desimone and Duncan 1995). A detailed formal description and the equations of TVA can be found in Kyllingsbæk (2006). On this view, visual objects are processed in parallel and compete for selection. Competition for selection is decided according to a speed criterion, i.e., those objects processed the fastest are encoded first, until the vSTM store is filled. Objects receiving higher attentional weighting gain a speed advantage compared to other competitors and are therefore selected with a higher probability. In TVA, selection of an object is synonymous with its encoding into a vSTM store with limited capacity. Once encoded, an object is consciously represented and can be reported by the participant. But, only those objects are selected that are encoded before the sensory representation of the display vanishes and before the vSTM store is already filled. All other objects do not reach awareness. The selection probability of an object therefore is determined (a) by its processing rate v, and (b) by the capacity of the vSTM store of K objects.

The processing rate depends on the dynamics of the processing system. This is expressed as an exponentially rising probability for an object to be selected with increasing exposure duration. Mathematically, TVA models the dynamics of the processing systems by two parameters. The first is the processing capacity C, a speed parameter which refers to the participant's overall rate of information uptake in objects per second. It is defined as the summed processing rate v values across all objects in the field. The second and mathematically independent parameter is the vSTM storage capacity K, which is the number of objects a participant can maintain in parallel. Objects compete for complete processing according to their v values. The first K objects identified enter the vSTM store. The remaining objects are lost and are, thus, not available for report.

Within the computational framework of TVA the two basic attentional parameters can be derived from a participant's performance in a whole-report task. In this paradigm, participants are briefly presented with letter arrays, and their ability to report multiple letter stimuli is assessed as a function of the array exposure duration. The probability of identification is modelled by an exponential growth function, in which the growth parameter reflects the rate at which the stimuli can be processed (processing speed C), and the asymptote indicates the maximum number of objects that can be represented in parallel (storage capacity K). An extension as well as an interpretation of TVA at the level of neurons or neuronal assemblies, a 'Neural TVA' (NTVA) has been proposed (Bundesen et al. 2005).

TVA whole report task

The whole-report task, in which participants are required to report as many letters as possible from a briefly presented array, was applied as described in previous studies (Bublak et al. 2005; Duncan et al. 1999; Finke et al. 2005, 2006) (Fig. 1).

The letters could be named in any, arbitrary order. Participants were instructed to name only those letters they had recognised 'with certainty', in order to avoid guessing. There was no emphasis on reporting speed, i.e., the time window allowed for report was determined by the number of letters reported and by the participant's output speed. Note that, due to the non-speeded report and the fact that processing speed was measured as a function of accuracy at rising exposure durations (rather than as a function of report speed), no speed accuracy can occur in such a paradigm. The experimenter entered the letters into the keyboard and, then, started the next trial. In the first session, the whole-report experiment comprised two phases: In phase 1, three exposure durations were determined individually for each participant; in phase 2, the stimuli were presented to the participants for these exposure durations and the data were collected. In more detail, in phase 1 (consisting of 24 trials), it was tested whether a particular participant could report on average one letter correctly at an exposure duration of 43 ms. In our study, this was the case in each of the participants. Thus, 43 ms was then used in phase 2 as the 'intermediate' exposure duration, along with a shorter (22 ms) and longer (86 ms) exposure duration. In phase 2, letter displays were presented for the three exposure durations, in either masked or unmasked conditions. This resulted in six 'effective' exposure durations due to the fact

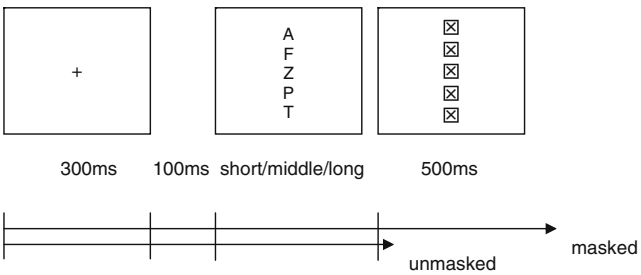

Fig. 1 Schematic representation of the whole report procedure and the possible display conditions. First, a *cross* is presented centrally that has to be fixated by the participant. After a short ISI, the letter display is briefly presented with one of three different exposure durations (22, 43 or 86 ms). In masked trials, *square masks* are presented immediately at each previous letter position, constraining letter processing to their presentation time. In unmasked trials, due to visual persistence, letter processing is prolonged beyond their presentation time, by several hundred milliseconds. In this way, by using three exposure durations in either masked or unmasked trials, six effective exposure durations result. The participant's task is to report as many letters as possible

that masks terminate iconic stimulus representation which adds to presentation time in conditions without masking. (see Sperling 1960). Therefore, it was possible to sample the time-accuracy-function across a broad performance spectrum including near-threshold as well as near-ceiling performance. Overall, there were six different trial conditions (3 exposure durations×2 masking conditions), with 16 trials for each of the six conditions, presented in randomised order. From the whole-report functions, the TVA parameters for visual vSTM storage capacity and processing speed were then derived individually for each participant (see Kyllingsbæk 2006).

Analysis of TVA whole report parameters

Each participant's qualitative performance was quantitatively described by TVA model fitting, which produced estimates for processing speed C and vSTM storage capacity K, separately for the different drug conditions. In addition, two parameters were estimated: t_0, the minimal effective exposure duration or perception threshold and μ, the estimated duration of iconic memory buffering in unmasked displays. These serve the estimation of the relevant parameters C and K. However, they are of no further relevance for our study. Parameter C was estimated as the summed v values for the objects presented and reflects the total rate of information uptake (number of elements per second). Parameter K reflects, in effect, the maximum number of letters reported on any single trial.

Definition of low- and high-performing participants

Feola et al. (2000) and Eagle et al. (2007) divided groups of relatively fast and relatively slow responders according to their baseline stop signal reaction time performance. The TVA attentional processing capacity parameters visual perceptual processing speed C and working vSTM storage capacity K are assumed to be independent from each other and therefore we used two different baselines for speed and storage capacity. These were defined by individual parameter estimates in the placebo condition.

Results

Plasma level analysis

Plasma analyses confirmed randomisation. No study drug concentrations were found in the placebo condition samples, and typical plasma levels were detected in all samples from modafinil and methylphenidate days. Single dose administrations of modafinil resulted in t1 plasma concentrations of mean, 8.16 µg/L (SD, 1.97) and median, 7.62 µg/L (range, 4.95–13.37). These values are in good agreement with published c_{max} data (Burnat et al. 1998; Müller et al. 2004) and reflect the known linear dose–concentration relationship (Robertson and Hellriegel 2003). Measured methylphenidate plasma concentrations ranged between 3.9 and 34.1 µg/L (mean, 14.8; SD, 8.66; median, 12.55 µg/L) and matched the therapeutic relevant drug concentration range (5–60 µg/L), with one exception.

Subjective alertness ratings

The deviation in millimetres of the bisection mark on the visual analogue scale from the extreme left end of the scale (alert) was measured, converted to a proportion of the overall length of the line (1 = very drowsy, 100 = alert), and arcsine transformed (Fig. 2). The first ratings at t0 were performed before dosing to measure baseline alertness at the start of a testing session. The ratings at pre- and post-testing are used as indicators for the actual, drug-modulated alertness state during the TVA task.

First, we tested whether any difference occurred between the two psychostimulant drug conditions. Arcsine transformed values of the visual analogue scale were subjected to a 3×2 repeated measures ANOVA with the factors Time (t0, pre-testing and post-testing) and condition (methylphenidate, modafinil). The main effect of time was nonsignificant [$F(2,32)=1.68$; $p>0.20$], as, more importantly, was that of condition [$F(1,16)=0.0$; $p>0.95$] and the interaction [$F(2,32)=0.81$; $p>0.45$]. Thus, we used the average alertness across the two psychostimulant conditions at each time point as indicators of the general effect of stimulant medication on subjective alertness.

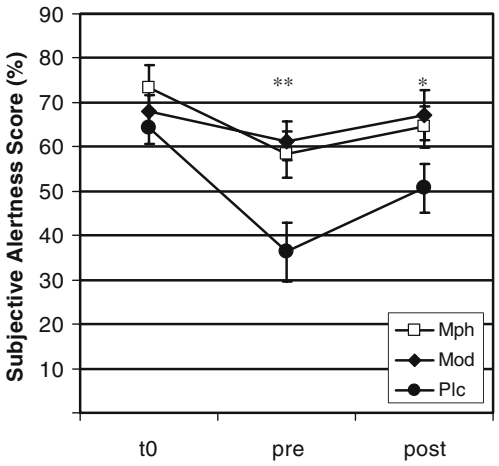

Fig. 2 Subjective alertness scores as a percentage of the length of the VAS line (1 = drowsy, 100 = alert) in the psychostimulant (drug: mean of both stimulant conditions) and the placebo (Plc) conditions, at time-points t0 (before dosing), pre (before whole report application), and post (after end of testing). Asterisks indicate significant differences between alertness ratings under drug and placebo (*: $p<0.05$; **: $p<0.01$)

In order to test whether the drugs induced differences in the subjective alertness compared to the placebo condition, a 3×2 repeated measures ANOVA was conducted, again with the factors time and condition (stimulant drug, placebo). The main effects of time [$F(2,16)=11.45$; $p<0.01$] and condition [$F(1,17)=14.30$; $p<0.01$] were significant, as was the time× condition interaction [$F(2,16)=3.75$; $p<0.05$].

Separate ANOVAs for the factor time revealed a significant decrease of subjective alertness only in the placebo [$F(2,16)=12.54$; $p<0.01$] and not in the stimulant drug condition [$F(2,16)=2.81$; $p=0.10$]. Post-hoc t tests revealed that, as expected, baseline participants' alertness ratings did not differ at t0 before dosing [$t(17)=1.46$, $p>0.15$], whereas later, significantly lower ratings were obtained after placebo compared to psychostimulant drug intake [pre-testing: $t(17)=4.11$, $p<0.01$; post-testing: $t(17)=2.60$, $p<0.05$].

In order to test whether higher intracerebral drug availability was related to higher alertness, we correlated individual plasma levels with subjective alertness ratings at pre-testing. Significant correlations were found for both modafinil ($r=0.54$; $p<0.05$) and methylphenidate concentrations ($r=0.52$; $p<0.05$). Participants with higher plasma levels around t_{max} felt more alert than participants with lower concentrations of the same medication.

TVA whole report parameters

For each dataset, the best fits to the data based on TVA parameter estimates were derived using the maximum likelihood method (e.g., Ross 2000). There was a high correspondence between the observed values and those predicted by the TVA. Across all participants, in the methylphenidate condition, best fits accounted for 61–95% of the variance of the mean scores across the different exposure duration and masking conditions (mean, 85%), in the modafinil condition for 55–97% (mean, 84%) and in the placebo condition for 62–97% (mean, 84%).

Visual perceptual processing speed

Drug effects on speed in participants with low and high baseline speed

Low-performing participants with respect to speed were defined as those whose placebo baseline visual perceptual processing speed was below the group's median of 45.6 objects/s ($n=9$). These participants were able to process significantly more objects/s in the methylphenidate [$M=46.83$, SD=8.42; $t(8)=4.18$, $p<0.01$] as well as in the modafinil condition [$M=42.91$, SD=12.98; $t(8)=2.60$, $p<0.05$] compared to the placebo condition ($M=34.29$, SD=9.62) (Fig. 3). No significant speed difference was found between the methylphenidate and the modafinil condition [$t(8)$ 1.37, $p>0.20$]. In contrast, in the group with relatively high baseline speed ($n=9$), there were no significant differences in speed between the different treatment conditions (all $p>0.60$).

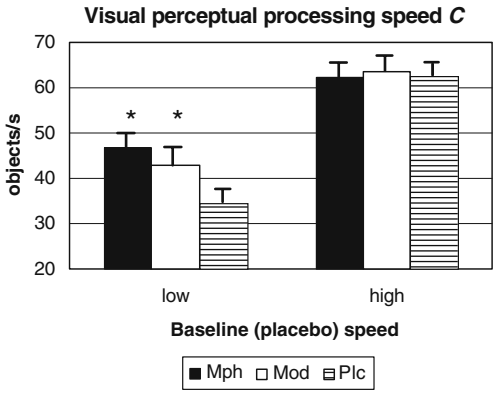

Fig. 3 Visual perceptual processing speed C in the methylphenidate, modafinil and placebo condition. Mean TVA parameter estimates, separately for participants with slow (*left*) and high (*right*) baseline speed (under placebo). The error bars indicate the standard errors. Abbreviations: Mph, methylphenidate;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

In order to consider the possibility of regression to the mean effects, correlations were calculated between the placebo baseline measures of processing speed and the change between the placebo and the drug conditions. A significant correlation of $r=-0.59$ ($p<0.01$) was revealed for methylphenidate, while the correlation for modafinil was not significant ($r=-0.40$; $p>0.10$). Regression to the mean effects can only occur when change and initial status are significantly correlated (Barnett et al. 2004; Rocconi and Ethington 2009); this means it may have affected the difference between the placebo and methylphenidate condition but does not explain baseline performance-dependent effects of modafinil. In order to reduce a possible bias induced by regression to the mean, we made an adjustment to the baseline score according to the procedure introduced by Roberts (1980). The adjustment is equal to the initial score plus the product of one minus the test–retest reliability by the mean for the total sample minus initial score. After applying this adjustment, we obtained the following results: In the low-baseline group, we replicated a significantly higher speed in the methylphenidate [$t(8)=3.74$, $p<0.01$, one-tailed] as well as in the modafinil [$t(8)=1.94$, $p<0.05$, one-tailed] treatment compared to the placebo condition. Again, no significant differences between treatment conditions were found in high baseline speed subjects (all $p>0.30$). Thus, the results cannot be simply explained by a tendency for participants who scored below average to do better on another occasion and for those who performed above average to do worse.

To assess whether the same participants gained from methylphenidate and modafinil, we correlated the differ-

ences in processing speed (i.e., the speed increases). A significant correlation of both drug conditions of $r=0.78$ ($p<0.01$) was observed. Participants who benefited relatively more from a single dose of modafinil also benefited more from the stimulating effect of methylphenidate.

Relationship between processing speed acceleration and plasma level

In order to examine whether the individual plasma level concentration influenced the effect of the drug on perceptual processing speed *C*, correlations were computed between the relative gain in the methylphenidate and the modafinil conditions compared to the placebo condition (in %) and the plasma levels of methylphenidate and modafinil (Fig. 4).

For methylphenidate, we found distinct results for low and high baseline-performing participants. Low baseline performers showed higher processing speed improvements with higher plasma level concentration ($r=0.62$, $p<0.05$, one-sided), although it has to be taken into account that the correlation was driven by an outlier value. In contrast, participants with high baseline performance showed a trend for the opposite effect, i.e., higher processing speed improvements with lower plasma levels ($r=-0.51$; $p<0.08$, one-sided). For modafinil, no significant correlations were found in any of the two participant groups (both $p>0.15$).

Relationship between processing speed and subjective alertness

To test for an association between visual perceptual processing speed *C* and subjective alertness in faster and slower performing participants, correlations were computed between the TVA parameter *C* estimates, and the VAS values averaged across the pre-testing (150 min after drug intake and before whole report administering) and the post-testing (210 min after substance intake and after whole report administering) assessment. This was done to obtain the relationship between attentional performance and subjective alertness at these two time points which were closest to the attention performance task. Absolute alertness ratings (not difference scores) were used for this analysis. Separate analyses were computed for the processing speed estimates in the three treatment (drugs or placebo) conditions and the respective alertness ratings. In slower participants (i.e., those participants who gained from psychostimulant medication) subjective alertness scores and the visual perceptual processing speed estimates correlated significantly ($r=0.73$; $p<0.05$) in the methylphenidate condition. There was a similar correlation on trend level ($r=0.55$; $p<0.07$) in the modafinil condition. Such positive correlations indicate that those participants who felt relatively alert following psychostimulants also showed relatively fast processing speed in these conditions (Fig. 5). No comparable correlations were found for participants with fast baseline speed (both $p>0.80$). No significant correlations between speed and alertness were observed in the placebo condition (both subgroups $r>0.70$).

Visual short-term memory storage capacity

Drug effects on short-term memory storage capacity

Low-performing participants with respect to vSTM storage capacity were defined as those whose vSTM storage capacity values were below the group's median of $K=3.90$ ($n=8$). Within this subgroup there was a significant vSTM storage capacity increase after modafinil ($M=4.0$, SD=0.8) as compared to placebo [$M=3.5$, SD=0.2; $t(7)=1.91$; $p<0.05$; one-tailed] (Fig. 6). However, within the same group, there was no effect of methylphenidate ($M=3.7$, SD=0.7) compared to placebo [$t(7)=0.58$; $p>0.25$; one-tailed]. Furthermore, within the group with high baseline performance, there

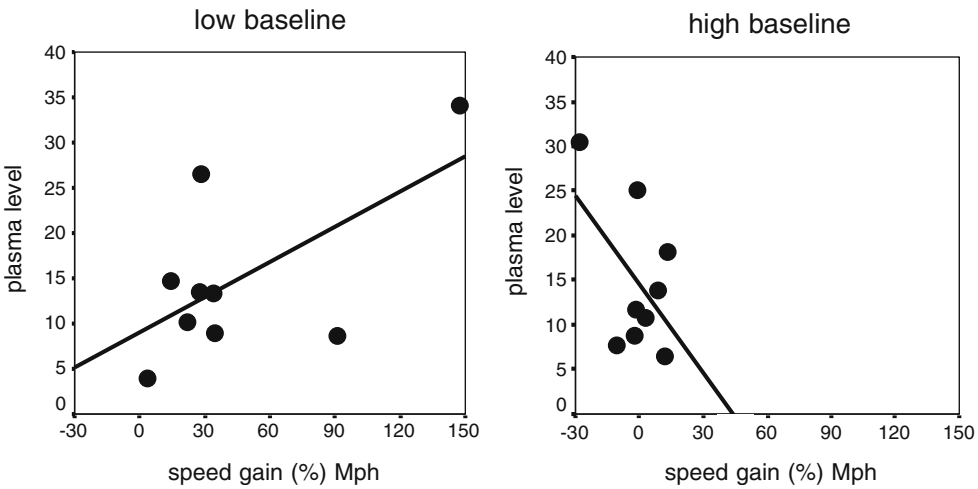

Fig. 4 Relationship between visual perceptual processing speed and plasma level. Scatter plots relating the difference in the TVA parameter processing speed after methylphenidate compared to the placebo condition to the plasma level of methylphenidate, separately for participants with low baseline (*left*) and high baseline performance (*right*). Abbreviation: Mph, methylphenidate

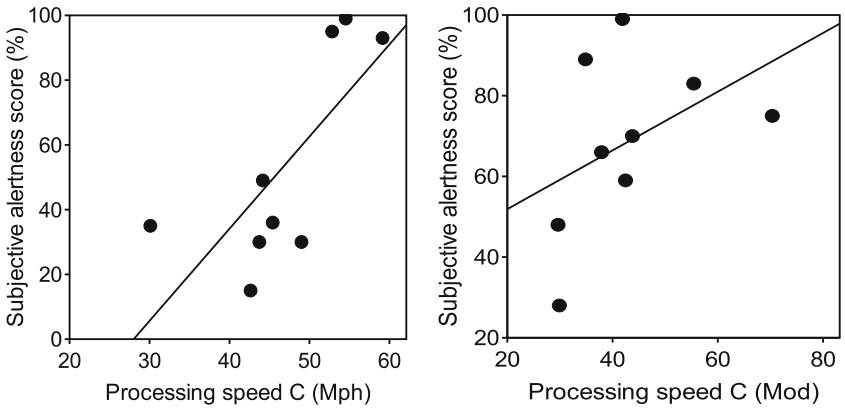

Fig. 5 Relationship between visual perceptual processing speed and alertness in participants with low baseline (placebo condition) speed. Scatter plots relating the TVA parameter processing speed in the methylphenidate (*left*) and in the modafinil (*right*) condition to the subjectively experienced level of alertness (average score across pre- and post-testing ratings). Abbreviations: Mph, methylphenidate; Mod, modafinil

were no significant differences between the different drug conditions (all $p>0.2$).

Analogous to the procedure for processing speed, we correlated the baseline (placebo) estimation of vSTM storage capacity to the change in this TVA parameter, to test for possible influences of regression to the mean in our results. Far-from-significant correlations were obtained for both methylphenidate ($r=-0.25$; $p>0.30$) and for modafinil ($r=-0.12$; $p>0.60$). Therefore, it appears quite unlikely, that our results can be explained by regression to the mean effects.

Discussion

Enhancing effects as a function of baseline performance

In low baseline performers, both substances had significant cognitive-enhancing effects, whereas in high performers, no effects were observed. These effects persisted after correction for potential biases induced by regression to the mean effects (Roberts 1980). Both methylphenidate and modafinil exert their effects by enhancing the availability of dopamine and noradrenaline. Methylphenidate has been shown to increase both dopamine and noradrenaline in the prefrontal cortex in rats (Berridge et al. 2006; Robbins and Arnsten 2009). For modafinil (Volkow et al. 2009), but not for methylphenidate (Volkow et al. 2001), it has been shown that plasma level concentration correlates positively with [11C]raclopride displacement, an indirect measure of dopamine release. Furthermore, modafinil enhances task-related phasic activity in the locus coeruleus noradrenaline system (Minzenberg et al. 2008). Comparable single doses of methylphenidate and modafinil may have differential effects on dopamine versus noradrenaline release, however, there are no studies with head-to-head comparisons of the two drugs using microdialysis in animals or PET tracer displacement in humans so that neurotransmitter-specific interpretations of differential cognitive enhancing effects would be speculative.

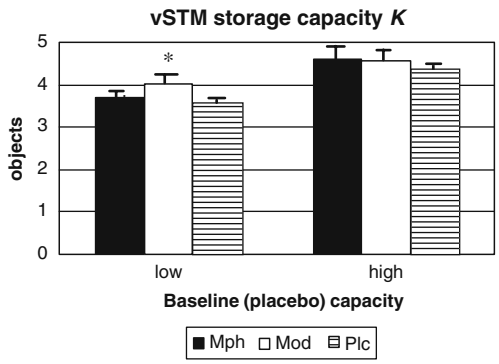

Fig. 6 Visual short-term memory storage capacity *K* in the methylphenidate, modafinil and placebo condition. Mean TVA parameter estimates, separately for participants with relatively low (*left*) and relatively high (*right*) baseline storage capacity (under placebo). Error bars indicate standard error.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

It has been repeatedly suggested that the relationship between performance and psychostimulant medication is complex and follows an inverted U-shaped curve (Arnsten and Goldman-Rakic 1998; Barch 2004; Castner et al. 2000), whereby an optimal level of performance is reached at a medium dopamine and noradrenaline level and hypo- as well as hyperdopaminergic states can lead to a decrease in attentional performance. Thus, baseline levels of dopamine might play an important role in determining whether a psychostimulant drug enhances performance. Specifically, participants with low dopamine levels may benefit more from psychostimulant treatment than those with medium or higher dopamine levels. Thus, our data seem to confirm an inverted U-shaped relationship between cognitive baseline performance, i.e., in this case processing speed and vSTM

capacity, and the subsequent response to a drug (see, e.g., Farah et al. 2009; Kimberg et al. 1997; Robbins and Sahakian 1979, for a similar discussion).

Drug effects on visual perceptual processing speed

With respect to visual perceptual processing speed we found cognitive enhancing effects of both psychostimulants, which the parameter-based approach allowed us to quantify: Low-performing participants were able to process approximately 12 more objects per second in the methylphenidate condition and approximately eight more objects per second in the modafinil condition compared to the placebo condition. Thus, methylphenidate accelerated processing speed by about 37% and modafinil by about 23% in this group, whereas high performers showed no such improvement. Effects of drug plasma levels also showed differential effects on drug-induced enhancements in processing speed in the two groups. In low performing participants, higher methylphenidate plasma levels led to a greater improvement in speed, whilst in high performing participants, higher methylphenidate plasma levels led to a smaller improvement in speed. These correlations have to be interpreted cautiously due to the fact that the number of participants was rather small and, in the case of low performing participants, was also influenced by an outlier. Nevertheless, there seems to be at least a tendency for an inverted U-shaped function in plasma-level effects. Future studies should aim at confirming this effect with greater reliability as well as unbound free drug fraction. These plasma level-dependent effects were specific to the methylphenidate condition. As previously reported (Müller et al. 2005; Schlösser et al. 2009), interindividual variation in plasma levels of methylphenidate was considerably high 1.5 h after identical dosing. The variation in plasma levels of modafinil was smaller than that of methylphenidate plasma levels and the lack of plasma-dependent effects of modafinil can be explained by its relative homogeneous concentration across subjects.

Since assessment was not dependent on response-times, psychostimulant effects on processing speed reflect ‘pure’ attentional rather than non-specific global psychomotor or arousal responses to the drugs. In contrast to those of Naylor et al. (1985), these results indicate that early stimulus-related processing is affected and that the effect of the drugs is not limited to response-selection.

In the neuro-computational model of the NTVA (Bundesen et al. 2005), perceptual categorizations of objects are assumed to be based on activations (v values) in the set of neurons that represent an object. The speed at which a visual object x is categorised is determined by the number of cortical neurons representing object x on the one hand and by the level of activation of the individual neurons representing object x on the other. In these terms, an NTVA-based interpretation of our finding of acceleration of processing speed after both psychostimulants would be that both methylphenidate and modafinil influence the processing system by a mechanism that either results in a larger set of neurons to be allocated to the five target letters presented and/or that stimulates the activation of these neurons to a higher level. Participants whose processing speed improved as a result of substance intake in our study showed a positive correlation between subjective alertness and visual perceptual processing speed. Persistent, tonic changes of alertness are assumed to be mediated by noradrenergic activation of a thalamo-cortical network, involving frontal and parietal regions predominantly of the right hemisphere (Coull et al. 1998; Sturm and Willmes 2001). Matthias et al. (2010) have demonstrated an enhancement of visual perceptual processing speed under both tonic and phasic alertness conditions. Therefore, it can be assumed that speed effects of methylphenidate and modafinil result from the impact of these drugs on the (tonic) alertness system of the brain (Posner and Petersen 1990).

Drug effects on vSTM storage capacity

Differential effects of the two drugs on vSTM storage capacity were observed in this study. Only modafinil enhanced vSTM storage capacity, and this effect was again limited to participants with relatively low baseline storage capacity. These participants were able to maintain, on average, 4 instead of 3.5 objects consciously in the short-term memory; i.e., an enhancement of storage capacity of 14%. Methylphenidate, on the other hand, did not significantly enhance vSTM storage capacity, even in the subgroup of participants with relatively low capacity values after placebo.

The baseline-dependent benefit of modafinil found in our study in participants performing relatively poorly closely resembles the prior finding of Müller et al. (2004) who found an enhancing effect of modafinil on working memory performance especially in lower performing young healthy participants. Comparably, in a study of Randall et al. (2005b), modafinil-induced improvements in vigilance and speed of performance have been found only in participants with lower IQ. And even effects on task-dependent activation of the locus coeruleus system after modafinil were mainly seen in lower performing participants (Minzenberg et al. 2008).

The lack of methylphenidate effects on vSTM storage capacity contrasts with some previous studies showing cognitive enhancing effects of methylphenidate on self-ordered spatial working memory (Clatworthy et al. 2009; Elliott et al. 1997; Evans et al. 2001; Mehta et al. 2000) and dose-dependent effects on accuracy and speed of performance in a one-back task (Cooper et al. 2005). In all those

studies, target items were accompanied by visual distractors. Mehta et al. (2000) argued that the mechanisms by which methylphenidate improves performance in this task might be improved signal-to-noise ratio in the neuronal working memory network due to more effective processes of target selection and distractor inhibition. Such an effect is indeed known for catecholamines (Foote and Morrison 1975) and is in accordance with the activation alterations in prefrontal areas that are involved in executive short-term maintenance functions (e.g., Goldman-Rakic 1995).

While methylphenidate, via top-down controlled executive functions, may improve working memory performance in a task that requires planning, updating and manipulation of actively maintained short-term store information in the presence of distracting information, it may, however, not affect the more basic storage capacity component of vSTM, i.e., the number of objects that can be maintained in parallel.

We used a single-dose 40 mg of methylphenidate, which was comparable or below those in more recent studies showing cognitive effects (Clatworthy et al. 2009; Elliott et al. 1997; Mehta et al. 2000; Turner et al. 2003b; Rogers et al. 1999), whereas we used a relatively high 400 mg dose of modafinil which was above those in most other studies (Randall et al. 2003, 2004, 2005a, b; Turner et al. 2003a; Müller et al. 2005; Minzenberg et al. 2008; Winder-Rhodes et al. 2009;). Thus, an alternative explanation for the differences in the effects on working memory storage capacity would be a dose difference, i.e., a relatively low and inefficient dose of methylphenidate as compared to a sufficiently high dose of modafinil.

In NTVA, it is postulated that when an object enters vSTM, the activation of those neurons representing the object's features in different high-level visual processing streams (Milner and Goodale 1995; Ungerleider and Mishkin 1982) is sustained by incorporating the object into a feedback loop gated by the vSTM system (Hebb 1949). A central role in the conscious maintenance of objects in vSTM is attributed to the thalamus. More precisely, it is assumed that the vSTM map of objects might be located in the thalamic reticular nucleus (TRN). The TRN has a topographical visual representation so that it might be able to focus on a specific area of the visual field. Furthermore, all fibres connecting the thalamus with the cortex pass through TRN. Therefore, the TRN might gate thalamocortical feedback loops sustaining the activity in high-level visual areas representing the objects in vSTM. Interestingly, Urbano et al. (2007) have found that modafinil might play a decisive role in the enhancement of thalamocortical activity in that it increases the neuronal electrotonic coupling.

Based on the evidence of the role of the prefrontal cortex in short-term memory performance (Courtney et al. 1998), Bundesen et al. (2005) additionally suggest that the prefrontal cortex might play a decisive role in vSTM storage capacity. In accordance with this view, Minzenberg et al. (2008) found that modafinil enhances task-related phasic activity in the locus coeruleus and the prefrontal cortex and increases functional connectivity between these structures, while inhibiting tonic non-task related activity in the locus coeruleus. The modulatory role of the locus coeruleus on prefrontal cortex activity is assumed to consist of a flexible "gating" mechanism that ensures the maintenance of goal representations (e.g., Miller and Cohen 2001; Robbins and Roberts 2007). Thus, an enhancement of the number of objects that can be maintained in vSTM in parallel after administration of modafinil might be related to an optimised signal-to-noise ratio in active, task-related vSTM ensembles.

Limitations of this study are the relatively small sample size and the fact that only one plasma sample was taken. Most of the observed drug effects in the overall sample and subgroups were, however, significant and not confounded by order or practice. More time points for plasma samples would have allowed the calculation of more sophisticated pharmacokinetic and/or pharmacodynamic (PK/PD) parameters; this was, however, not the aim of our study. The number of plasma samples was minimised so that participation was not compromised or biased by a too invasive protocol.

Conclusions

Psychostimulant effects on processing speed as observed here are consistent with methylphenidate and modafinil operating along an inverted U-shaped function. Both drugs improve processing speed, but only in low-performing participants, presumably due to relatively lower baseline levels of dopamine and noradrenaline in this group. Furthermore, the effects of methylphenidate plasma levels depend on baseline performance; in low-performing participants, higher methylphenidate plasma levels were associated with *greater* improvements in performance, while in high-performing participants, higher levels of methylphenidate plasma were associated with relatively *smaller* improvements in performance. This, to our knowledge, is the first demonstration of a differential plasma level-dependent effect of a psychostimulant on behavioural performance in low- and high-performing participants and suggests a complex relationship between baseline performance, active methylphenidate dose and cognitive effects. The clinical implication is that higher doses of methylphenidate may be more effective in relatively low-performing individuals (e.g., patients with attentional deficits), while lower doses of methylphenidate may be more effective in relatively high-performing individuals.

Acknowledgments We would like to thank Hermann J. Müller, Werner X. Schneider and Trevor W. Robbins for their support of this research. This study was funded by grants of the Medical Research Council (MRC) to TM and of the Deutsche Forschungsgemeinschaft (DFG; project MU 773/6-1). UM was supported by an MRC pathfinder grant.

Disclosure/Conflict of interest U. Müller has received research grant support from Janssen-Cilag and honoraria or travel expenses from Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Pharmacia-Upjohn, and UCB Pharma. R. Regenthal has received research grant support from Pfizer.

References

Arnsten AFT, Goldman-Rakic PS (1998) Noise stress impairs prefrontal cortical function in monkeys: evidence for a hyperdopaminergic mechanism. Arch Gen Psychiatry 55:362–368

Ballon JS, Feifel D (2006) A systematic review of modafinil: potential clinical uses and mechanisms of action. J Clin Psychiatry 67:554–566

Baranski JV, Pigeau R, Dinich P, Jacobs I (2004) Effects of modafinil on cognitive and meta-cognitive performance. Hum Psychopharmacol 19:323–332

Barch DM (2004) Pharmacological manipulation of human working memory. Psychopharmacology 174:126–135

Barnett AG, van der Pols JC, Dobson AJ (2004) Regression to the mean: what it is and how to deal with it. Int J Epidemiol 34:215–220

Becker PM, Schwartz JR, Feldman NT, Hughes RJ (2004) Effect of modafinil on fatigue, mood, and health-related quality of life in patients with narcolepsy. Pycholpharmacol 171:133–139

Berridge CW, Devilbiss DM, Andrzejewski ME, Arnsten AFT, Kelley AE, Schmeichel B, Hamilton C, Spencer RC (2006) Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognition. Biol Psychiatry 60:1111–1120

Bublak P, Finke K, Krummenacher J, Preger R, Kyllingsbæk S, Müller HJ, Schneider WX (2005) Usability of a theory of visual attention (TVA) for parameter-based measurement of attention II: evidence from two patients with frontal or parietal damage. J Int Neuropsychol Soc 11:843–854

Bundesen C (1990) A theory of visual attention. Psychol Rev 97:523–547

Bundesen C (1998) A computational theory of visual attention. Phil Trans R B 353:1271–1281

Bundesen C, Habekost T, Kyllingsbæk S (2005) A neural theory of visual attention: bridging cognition and neurophysiology. Psychol Rev 112:291–328

Burnat P, Robles F, Do B (1998) High-performance liquid chromatographic determination of modafinil and its two metabolites in human plasma using solid-phase extraction. J Chromatogr B 706:295–304

Camp-Bruno JA, Herting RL (1994) Cognitive effects of milacemide and methylphenidate in healthy young adults. Psychopharmacology 115:46–52

Castner SA, Williams GV, Goldman-Rakic PS (2000) Reversal of antipsychotic-induced working memory deficits by short term dopamine D_1 receptor stimulation. Science 287:2020–2022

Clatworthy PL, Lewis SJG, Birchard L, Hong YT, Izquierdo D, Clark L, Cools R, Aigbirhio FI, Baron J-C, Fryer TD, Robbins TW (2009) Dopamine release in dissociable striatal subregions predicts the different effects of oral methylphenidate on reversal learning and spatial working memory. J Neurosci 29:4690–4696

Cooper NJ, Keage H, Hermens D, Williams LM, Debrota D, Clark CR (2005) The dose-dependent effect of methylphenidate on performance, cognition and psychophysiology. J Integr Neurosci 4:123–144

Coull JT, Frackowiak RS, Frith CD (1998) Monitoring for target objects: activation of right frontal and parietal cortices with increasing time on task. Neuropsychologia 36:1325–1334

Courtney SM, Petit L, Maisog JM, Ungerleider LG, Haxby JV (1998) An area specialized for spatial working memory in human frontal cortex. Science 279:1347–1351

Desimone R, Duncan J (1995) Neural mechanisms of selective visual attention. Ann Rev Psychol 18:193–222

Dodds CM, Müller U, Manly T (2009) Effects of psychostimulants on alertness and spatial bias in healthy participants. J Cogn Neurosci 21:529–537

Doerge DR, Fogle M, Paule MG, McCullagh M, Bajic S (2000) Analysis of methylphenidate and its metabolites ritalinic acid in monkey plasma by liquid chromatography/electrospray ionisation mass spectrometry. Rapid Comm Mass Spectrom 14:619–623

Duncan J, Bundesen C, Olson A, Humphreys G, Chavda S, Shibuya H (1999) Systematic analysis of deficits in visual attention. J Exp Psychol: Gen 128:450–478

Eagle DM, Tufft MRA, Goodchild HL, Robbins TW (2007) Differential effects of modafinil and methylphenidate on stop-signal reaction time task performance in the rat, and interactions with the dopamine receptor antagonist *cis*-flupenthixol. Psychopharmacology 192:193–206

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

Evans SW, Pelham WE, Smith BH, Bukstein O, Gnagy EM, Greiner AR, Altenderfer L, Baron-Myak C (2001) Dose-response effects of methylphenidate on ecologically valid measures of academic performance and classroom behavior in adolescents with ADHD. Exp Clin Psychopharmacol 9:163–175

Farah MJ, Haimm C, Sankoorikal G, Chatterjee A (2009) When we enhance cognition with Adderall, do we sacrifice creativity? A preliminary study. Psychopharmacology 202:541–547

Feola TW, de Wit H, Richards JB (2000) Effects of d-amphetamine and alcohol on a measure of behavioral inhibition in rats. Behav Neurosci 114:838–848

Finke K, Bublak P, Krummenacher J, Kyllingsbæk S, Müller HJ, Schneider WX (2005) Usability of a theory of visual attention (TVA) for parameter-based measurement of attention I: evidence from normal subjects. J Int Neuropsychol Soc 11:832–842

Finke K, Bublak P, Dose M, Müller HJ, Schneider WX (2006) Parameter-based assessment of spatial and non-spatial attentional deficits in Huntington's disease. Brain 129:1137–1151

Foote SL, Morrison JH (1975) Effects of putative neurotransmitters on neuronal activity in monkey auditory cortex. Brain Res 86:229–242

Goldman-Rakic PS (1995) Architecture of the prefrontal cortex and the central executive. Ann NY Acad Sci 769:71–84

Gualtieri CT, Wargin W, Kanoy R, Patrick K, Shen CD, Youngblood W, Mueller R, Breese G (1982) Clinical studies of methylphenidate serum levels in children and adults. J Am Acad Child Psychiatry 21:19–26

Habekost T, Bundesen C (2003) Patient assessment based on a theory of visual attention (TVA). Subtle deficits after a right frontal lesion. Neuropsychologia 41:1171–1188

Halliday R, Callawy E, Naylor H, Gratzinger P, Prael R (1986) The effect of stimulant drugs on information processing in elderly adults. J Gerontol 41:748–757

Hebb DO (1949) Organization of behavior. Wiley, New York

Kimberg DY, D'Esposito M, Farah MJ (1997) Effects of bromocriptine on human subjects depends on working memory capacity. Neuroreport 8:3581–3585

Koelega HS (1993) Stimulant drugs and vigilance performance: a review. Psychopharmacology 111:1–16

Kyllingsbæk S (2006) Modeling visual attention. Behav Res Methods 38:123–133

Larriviere D, Williams MA, Rizzo M, Bonnie RJ, AAN Ethics, Law and Humanities Committee (2009) Responding to requests from adult patients for neuroenhancements: guidance of the Ethics, Law and Humanities Committee. Neurology 73:1406–1412

Matthias E, Bublak P, Müller HJ, Schneider WX, Krummenacher J, Finke K (2010) The influence of phasic alertness on spatial and non-spatial components of visual attention. J Exp Psychol: Hum Percept Perform 33:38–56

McClellan KJ, Spencer CM (1998) Modafinil: a review of its pharmacology and clinical efficacy in the management of narcolepsy. CNS Drugs 9:311–324

Mehta MA, Owen AM, Sahakian BJ, Mavaddat N, Pickard JD, Robbins TW (2000) Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. J Neurosci: 20: RC65: 1–6

Midha KK, McKay G, Rawson MJ, Korchinski ED, Hubbard JW (2001) Effects of food on the pharmacokinetics of methylphenidate. Pharm Res 18:1185–1189

Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. Ann Rev Neurosci 28:167–202

Milner AD, Goodale MA (1995) The visual brain in action. Oxford University Press, Oxford

Minzenberg MJ, Carter CS (2008) Modafinil: a review of neurochemical actions and effects on cognition. Neuropsychopharmacology 33:1477–1502

Minzenberg MJ, Watrous AJ, Yoon JH, Ursu S, Carter CS (2008) Modafinil shifts human locus coeruleus to low-tonic, high-phasic activity during functional MRI. Science 322:1700–1703

Müller U, Steffenhagen N, Regenthal R, Bublak P (2004) Effects of modafinil on working memory processes in humans. Psychopharmacology 177:161–169

Müller U, Suckling J, Zelaya F, Honey G, Faessel H, Williams SCR, Routledge C, Brown J, Robbins TW, Bullmore ET (2005) Plasma level-dependent effects of methylphenidate on task-related functional magnetic resonance imaging signal changes. Psychopharmacology 180:624–633

National Institute for Health and Clinical Excellence (NICE) (2008) Attention deficit hyperactivity disorder. Diagnosis and management of ADHD in children, young people and adults. NICE clinical guideline 72. London: NICE

Naylor HN, Halliday R, Callawy E (1985) The effect of methylphenidate on information processing. Psychopharmacology 86:90–95

Posner MI, Petersen SE (1990) The attention system of the human brain. Ann Rev Neurosci 13:25–42

Randall DC, Shneerson JM, Plaha KK, File SE (2003) Modafinil affects mood, but not cognitive function, in healthy young volunteers. Hum Psychopharmacol Clin Exp 18:163–173

Randall DC, Fleck NL, Shneerson JM, File SE (2004) The cognitive-enhancing properties of modafinil are limited in non-sleep-deprived middle-aged adolescents. Pharmacol Biochem Behav 77:547–555

Randall DC, Shneerson JM, File SE (2005a) Cognitive effects of modafinil in student volunteers may depend on IQ. Pharmacol Biochem Behav 82:133–139

Randall DC, Viswanath A, Bharania P, Esabagh SM, Harley DE, Shneerson JM, File SE (2005b) Does modafinil enhance cognitive performance in young volunteers who are not sleep-deprived? J Clin Psychopharmacol 25:175–179

Regenthal R, Koch H, Köhler C, Preiss R, Krügel U (2009) Depression-like deficits in rats improved by subchronic modafinil. Psychopharmacology 204:627–639

Robbins TW, Sahakian BJ (1979) 'Paradoxical' effects of psychomotor stimulant drugs in hyperactive children from the standpoint of behavioural pharmacology. Neuropharmacology 18:931–950

Robbins TW, Roberts AC (2007) Differential regulation of fronto-executive function by the monoamines and acetylcholine. Cereb Cortex 17(Suppl 1):i151–i160

Robbins TW, Arnsten AFT (2009) The neuropsychopharmacology of fronto-executive function: monoaminergic modulation. Ann Rev Neurosci 32:267–287

Roberts AOH (1980) Regression toward the mean and the regression-effect bias. In: Echternacht G (ed) New directions for testing and measurement, vol 8. Jossey-Bass, San Francisco, pp 59–82

Robertson P, Hellriegel ET (2003) Clinical pharmacokinetic profile of modafinil. Clin Pharmacokinet 42:123–137

Rocconi LM, Ethington CA (2009) Assessing longitudinal change: adjustment for regression to the mean effects. Res High Educ 50:368–376

Rogers RD, Blackshaw AJ, Middleton HC, Matthews K, Hawtin K, Crowley C, Hopwood A, Wallace C, Deakin JFW, Sahakian BJ, Robbins TW (1999) Tryptophan depletion impairs stimulus-reward learning while methylphenidate disrupts attentional control in healthy young adults: implications for the monoaminergic basis of impulsive behaviour. Psychopharmacology 146:482–491

Ross SM (2000) Introduction to probability and statistics for engineers and scientists. Academic Press, San Diego

Rugino TA, Copley TC (2001) Effects of modafinil in children with attention-deficit/hyperactivity disorder: an open-label study. J Am Acad Child Adolesc Psychiatry 40:230–235

Schlösser RGM, Nenadic I, Wagner G, Zysset S, Koch K, Sauer H (2009) Dopaminergic modulation of brain systems subserving decision making under uncertainty: a study with fMRI and methylphenidate challenge. Synapse 63:429–442

Schwertner HA, Kong SB (2005) Determination of modafinil in plasma and urine by reversed phase high-performance liquid-chromatography. J Pharm Biomed 37:475–479

Sperling G (1960) The information available in brief visual presentations. Psychological Monogr 74:1–29

Strauss J, Lewis JL, Korman R, Peloquin L, Perlmutter RA, Salman LF (1984) Effects of methylphenidate on young adults' performance and event-related potentials in a vigilance and a paired-associates learning test. Psychophysiology 21:609–621

Sturm W, Willmes K (2001) On the functional neuroanatomy of intrinsic and phasic alertness. Neuroimage 14:76–84

Taylor FB, Russo J (2000) Efficacy of modafinil compared to dextroamphetamine for the treatment of attention deficits hyperactivity disorder in adults. J Child Adolesc Psychopharmacol 10:311–320

Thomas RJ, Kwong KK (2006) Modafinil activates cortical and subcortical sites in the sleep-deprived state. Sleep 29:1471–1481

Thorpy MJ, Schwartz JR, Kovacevic-Ristanovic R, Hayduk R (2003) Initiating treatment with modafinil for control of excessive daytime sleepiness in patients switching from methylphenidate: an open-label safety study assessing three strategies. Psychopharmacology 167:380–385

Turner DC, Robbins TW, Clark K, Aron AR, Dowson J, Sahakian BJ (2003a) Cognitive enhancing effects of modafinil in healthy volunteers. Psychopharmacology 165:260–269

Turner DC, Robbins TW, Clark K, Aron AR, Dowson J, Sahakian BJ (2003b) Relative lack of cognitive effects of methylphenidate in elderly male volunteers. Psychopharmacology 168:455–464

Turner DC, Clark K, Dowson J, Robbins TW, Sahakian B (2004) Modafinil improves cognition and response inhibition in adult attention-deficits/hyperactivity disorder. Biol Psychiatry 55:1031–1040

Ungerleider LG, Mishkin M (1982) Two cortical visual systems. In: Ingle DJ, Goodale MA, Mansfield RJW (eds) Analysis of visual behavior. MIT Press, Cambridge, pp 549–586

Urbano FJ, Leznik E, Llinás RR (2007) Modafinil enhances thalamocortical activity by increasing neuronal electrotonic coupling. Proc Nat Am Soc 104:12554–12559

Volkow ND, Wang G, Fowler JS, Logan J, Gerasimov M, Maynard L, Ding Y, Gatley SJ, Gifford A, Franceschi D (2001) Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. J Neurosci 21:121

Volkow ND, Fowler JS, Logan J, Alexoff D, Zhu W, Telang F, Wang G-J, Jayne M, Hooker JM, Wong C, Hubbard B, Carter P, Warner D, King P, Shea C, Xu Y, Muench L, Apelskog-Torres K (2009) Effects of modafinil on dopamine and dopamine transporters in the male human brain. J Am Med Assoc 301:1148–1154

Wesensten N (2006) Effects of modafinil on cognitive performance and alertness during sleep deprivation. Curr Pharmaceutical Design 12:2457–2471

Winder-Rhodes SE, Chamberlain SR, Idris MI, Robbins TW, Sahakian BJ, Müller U (2009) Effects of modafinil and prazosin on cognitive and physiological functions in healthy volunteers. J Psychopharmacol [Epub ehead of publication]

Wong YN, King SP, Laughton WB, McCormick GC, Grebow PE (1998) Single-dose pharmacokinetics of modafinil and methylphenidate given alone or in combination in healthy male volunteers. J Clin Pharmacol 38:276–282

Wong YN, King SP, Simcoe D, Gorman S, Laughton W, McCormick GC, Grebow P (1999) Open-label, single-dose pharmacokinetic study of modafinil tablets: influence of age and gender in normal subjects. J Clin Pharmacol 39:281–288