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Methylphenidate, modafinil, and caffeine for cognitive enhancement in chess: A double-blind, randomised controlled trial

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Abstract
Stimulants and caffeine have been proposed for cognitive enhancement by healthy subjects. This study investigated whether performance in chess – a competitive mind game requiring highly complex cognitive skills – can be enhanced by methylphenidate, modafinil or caffeine. In a phase IV, randomized, double-blind, placebo-controlled trial, 39 male chess players received 2×200 mg modafinil, 2×20 mg methylphenidate, and 2×200 mg caffeine or placebo in a 4×4 crossover design. They played twenty 15-minute games during two sessions against a chess

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program (Fritz 12; adapted to players' strength) and completed several neuropsychological tests. Marked substance effects were observed since all three substances significantly increased average reflection time per game compared to placebo resulting in a significantly increased number of games lost on time with all three treatments. Treatment effects on chess performance were not seen if all games ($n=3059$) were analysed. Only when controlling for game duration as well as when excluding those games lost on time, both modafinil and methylphenidate enhanced chess performance as demonstrated by significantly higher scores in the remaining 2876 games compared to placebo. In conjunction with results from neuropsychological testing we conclude that modifying effects of stimulants on complex cognitive tasks may in particular result from more reflective decision making processes. When not under time pressure, such effects may result in enhanced performance. Yet, under time constraints more reflective decision making may not improve or even have detrimental effects on complex task performance.

1. Introduction

Pharmacological cognitive enhancement (CE) is defined as the use of pharmacological substances with the purpose of enhancing cognitive abilities (Bostrom and Sandberg, 2009; Farah et al., 2004; Forlini et al., 2013; Greely et al., 2008; Hildt and Franke, 2013; Smith and Farah, 2011). Substances used with the intention of CE range from over-the-counter substances such as caffeine tablets, prescription drugs such as modafinil or methylphenidate to illegal substances like amphetamines if used for non-medical reasons such as "speed", ecstasy, methamphetamine (crystal meth) or others (de Jongh et al., 2008; Franke et al., 2014; Hildt and Franke, 2013; Mehlman, 2004). Whereas most people intend to avoid CE with stimulants due to safety and legal concerns, CE is practiced by a low, but significant proportion of healthy individuals including students and academics (Dietz et al., 2013; Franke et al., 2011, 2013; Maher, 2008; McCabe et al., 2014; Sahakian and Morein-Zamir, 2015; Sahakian et al., 2015; Wilens et al., 2008), especially in cognitively demanding situations (Burgard et al., 2013).

Methylphenidate is a catecholamine reuptake inhibitor that increases extracellular dopamine in fronto-striatal regions and norepinephrine particularly in frontal regions by binding to the respective transporter and thereby blocking it (Arnsten, 2006; Kuczenski and Segal, 1997; Volkow et al., 2009; Wood et al., 2013). Enhancing effects of methylphenidate have been shown on working memory, memory consolidation, speed of processing, and inhibitory control whereas effects of methylphenidate on attention and vigilance are rather mixed (cf. Caviola and Faber, 2015 for review).

Modafinil is a wakefulness-promoting agent whose precise mechanism of action is unclear up to date (de Jongh et al., 2008; Wood et al., 2013). Similar to methylphenidate, modafinil is assumed to primarily inhibit the reuptake of dopamine and norepinephrine thereby increasing extracellular levels particularly in fronto-striatal networks. In addition, modafinil is believed to exert secondary effects on several neurotransmitters including serotonin, glutamate,

GABA etc. (Mereu et al., 2013; Minzenberg and Carter, 2008; Repantis et al., 2010; Wood et al., 2013). Modafinil has been shown to improve attention, wakefulness and vigilance (Caviola and Faber, 2015; de Jongh et al., 2008; Minzenberg and Carter, 2008; Repantis et al., 2010). Mixed results have been reported with respect to effects on mnemonic functions (Caviola and Faber, 2015; de Jongh et al., 2008; Minzenberg and Carter, 2008; Sahakian et al., 2015).

Unlike methylphenidate and modafinil, caffeine does not exert its primary actions on the dopaminergic system, but rather acts as a nonselective antagonist by blocking adenosine receptors, i.e., the A_1 and A_{2A} receptor subtypes. It inhibits phosphodiesterase and thus the breakdown of the intracellular second messenger cAMP (Franke and Soyka, 2015; Wood et al., 2013). Assumedly, caffeine stimulates neural activity through higher noradrenaline emission (Caviola and Faber, 2015). Beneficial effects of caffeine have been reported on alertness and sustained attention particularly in simple tasks, encoding, and perceptual as well as response speed whereas findings regarding memnonic functions are rather heterogeneous (Caviola and Faber, 2015; Wood et al., 2013).

The relationship of catecholamine neurotransmitters, the arousal level of the neuronal network and the cognitive performance has repeatedly been suggested as being an inverted U-shape with optimal performance at intermediate catecholamine levels and impaired performance at lower or higher catecholamine levels (de Jongh et al., 2008; Schlosberg, 1954; Wood et al., 2013). Similarly, detrimental effects of high doses of caffeine have been shown whereas beneficial effects of low doses have been reported (Caviola and Faber, 2015). In addition, effects of stimulants on cognitive functions have been shown particularly in individuals with low baseline performance, i.e., individuals with rather poor scores in the assessed function under placebo, or individuals tested after sleep deprivation, which led to the hypothesis that the currently available neuroenhancers are only able to restore basic cognitive functioning to normal levels (de Jongh et al., 2008; Eagle et al., 2007; Hildt and Franke, 2013; Joos et al., 2013; Minzenberg and Carter, 2008; Rubia et al., 2009, 2011; Schmaal et al., 2013b; Zack and

Poulos, 2009). However, due to ceiling effects and/or the inverted U-shape model no performance-enhancing effect should in theory occur in cognitive high-performers (de Jongh et al., 2008; Minzenberg and Carter, 2008; Randall et al., 2005).

It is currently less known, however, whether the available substances are effective in enhancing cognitive functions in cognitively high-functioning subjects, i.e. whether they can lead to cognitive hyper-performance similar to physical enhancement in athletics (Hartgens and Kuipers, 2004; Healy et al., 2003). Yet, enhancing effects of stimulants on highly cognitively demanding tasks have been shown in healthy, non sleep-deprived individuals (Battleday and Brem, 2015; Müller et al., 2013; Winder-Rhodes et al., 2010). We thus aimed to assess whether administration of particularly commonly used cognitive enhancers such as methylphenidate and modafinil (e.g., Bisagno et al., 2016; Smith and Farah, 2011; Ragan et al., 2013; Sahakian et al., 2015; Wood et al., 2013) would affect chess performance. In addition, we intended to compare the impact of the above mentioned prescription drugs to one of the most common over-the-counter drug, i.e. caffeine (Ragan et al., 2013; Wood et al., 2013).

We hypothesized that the three substances are able to enhance chess performance in highly skilled tournament chess players if tested at their maximum performance. More specifically, by matching the skill level of the computer to the player's initially before the experiment according to the subject's Elo (Elo, 1978) or DWZ (German Evaluation Number) rating (both ratings are average estimates based on previous chess players' tournament performance), we expected an average score of 0.5 for every player in the placebo condition (the achievable scores ranged from 0 to 1: 0=loss, 0.5=draw, 1=win). After drug intake we expected higher average scores (>0.5) as compared to placebo.

2. Experimental procedure

2.1. Study design and participants

We conducted a phase IV, single-center, randomised, double-blind, placebo-controlled 4×4 crossover trial. All data were collected at the Department of Psychiatry and Psychotherapy, University Medical Center Mainz, Germany. Subjects were recruited with the help of the Hessian Chess Federation (Hessischer Schachbund) using announcements on the internet, in newspapers, and in mailings to members of the German Chess Federation. Announcements included the inclusion and exclusion criteria of the study for pre-selection of potential subjects by telephone interviews. Only those subjects who met the inclusion criteria were included in the study: male, healthy subjects, aged 18–60 years for whom an ELO/ DWZ (German Evaluation Number) rating exists which gives an estimate of the chess playing strength of the subject (Elo, 1978). Exclusion criteria were any current somatic medical condition (excluded by standard laboratory testing and a standard medical examination), a history of or any current mental disorder or psychoactive substance abuse (excluded by SCID-I and SCID-II assessments), being a smoker or former smoker less than five years ago, regular consumption of more than five cups of coffee per day or an irregular day and night rhythm (e.g. shift workers). Written informed consent was obtained from all participants. Compensation of €400 for the completion of the whole study was offered for participation.

2.2. Neuropsychological tests

All tests are well-established and validated to investigate different cognitive abilities (for detailed descriptions see the respective references). We used:

Psycho-Motor-Vigilance-Test (PVT; Dinges and Powell, 1985): Measures sustained attention by the help of reaction time measurements. Trail-Making-Test (TMT; Reitan and Wolfson, 1993): Measures visual attention, psycho-motor speed (TMT-A) and task switching capacity (TMT-B). Stroop-Test (Stroop, 1935): Measures selective attention, cognitive flexibility, and processing speed or interference resolution. Wisconsin-Card-Sorting-Test (WCST; Berg, 1948): Measures set-shifting, an executive ability to display flexibility in the face of changing schedules of reinforcement. A 64-card computerized version was used. Balloon Analogue Risk Task (BART; Lejuez et al., 2002): Assesses risk-taking behavior under conditions of uncertainty. Tower of Hanoi (ToH; Hofstadter, 1985): Measures problem solving capacity. The 6-ring version of the ToH was used.

2.3. Self-rating scales

All self-rating scales are well-established and validated to investigate different traits (for detailed descriptions see the respective references). We used: Profile of Mood Status (POMS; McNair et al., 1971): This questionnaire measures affective mood states by 65 self-report items. Achievement Motives Scale (AMS; Brunstein and Heckhausen, 2008): Assesses hope for success and fear of failure by a German short form (10 items). Evaluation of Risk Scale (EVAR; Killgore et al., 2006): Assesses five factors (energy, impulsiveness, self-control, danger seeking and invincibility) with the help of a scale consisting of 24 statements.

2.4. Sample size calculation

The sample size was determined by a two-sided significance level of 0.05. No data were available from previous experiments (an extensive search to identify relevant studies within PsycINFO and the ICTRP trials register up to August 2014 located only one study of chess problem solving after a series of blind caffeine or placebo (starch) applications with no beneficial effects of caffeine (Holck, 1933)). We assumed a difference of 1 point in 20 games of chess to be a relevant difference. Moreover, a standard deviation of 2 points was assumed. With a power of 80%, 40 patients were needed when using a paired t-test with a correlation of 0.4 between measurements. The calculations were performed using PROC POWER from SAS.

2.5. Study procedure

On each trial day, subjects arrived at 8.00 a.m. and received a standardised breakfast (8.00 to 8.15 a.m.) followed by the measurement of blood pressure, heart rate and temperature. After having completed the first set of neuropsychological tests and questionnaires (after having had breakfast) between 8.20 and 9.00 a.m., the first dose of caffeine, methylphenidate, modafinil or placebo was administered at 9.00 a.m. Immediately afterwards, 10 chess games had to be played using the chess program Fritz 12 which was adjusted exactly to the ELO/DWZ of each subject (see below). After completion of the first round of chess games approximately 2.5 h after the application of the first dose of the respective study medication, a second round of neuropsychological tests and questionnaires followed. Subsequently, adverse events (AE) were monitored. Following a standardised lunch, the subjects received the same drug as in the morning (caffeine, methylphenidate, modafinil or placebo). Immediately afterwards a second round of another 10 chess games followed at 1.00 p.m. Subsequently,

neuropsychological assessments were carried out about 2.5 h after the application of the second dose of the respective study medication, again followed by monitoring of AE. At 5.00 p.m. the study day ended. All trial days were at intervals of at least one week. Every trial day was followed by a telephone contact the next day including questions about any further AE. The study procedure was not changed after trial commencement.

2.6. Stimulant medication

Due to the short half-life period of methylphenidate (2 h), the drugs were applied at two time points four hours apart during the day before each round of chess. According to previous studies showing cognitively enhancing effects of a single dose of the respective drugs as well as an impact on brain activation patterns in healthy participants and in different patient groups (Campbell-Meiklejohn et al., 2012; Gilleen et al., 2014; Killgore et al., 2008; Minzenberg et al., 2011; Moeller et al., 2014; Schmaal et al., 2013a, 2013b; Sugden et al., 2012; Wesensten et al., 2005; Zack and Poulos, 2009), the following drug doses were applied: 2×200 mg modafinil, 2×20 mg methylphenidate, and 2×200 mg caffeine. We were restricted to a maximum dose of 400 mg of caffeine which is the highest approved dose of caffeine containing drugs in Germany. Plasma levels of the three drugs were determined according to laboratory standards before, after 10 games, and finally after the afternoon chess session as an experimental control for effective drug resorption and plasma levels after drug administration.

2.7. Randomisation and masking

A randomisation list was prepared by the Interdisciplinary Centre for Clinical Trials (IZKS) of the University Medical Center Mainz to allocate the study participants to one of four treatment sequences (placebo-modafinil-caffeine-methylphenidate, caffeine-placebo-methylphenidate-modafinil, methylphenidate-caffeine-modafinil-placebo, modafinil-methylphenidate-placebo-caffeine) to adapt for potential learning effects. The block size was four. The pharmacy department prepared the study medication according to the randomisation list for double-blind application. Therefore, all substances were over-encapsulated by the pharmacy department to look entirely identical (2×2 identical capsules per visit). All subjects involved in conducting the study were blind until the trial was completely finished and the database was frozen.

2.8. Outcomes

The primary outcome was the score of each chess game (0=loss, 0.5=draw, 1=win). Secondary outcomes were the time use in each chess game, results of the above mentioned neuropsychological tests, AE and laboratory values.

   To determine the chess playing scores, subjects played against the chess playing program Fritz 12 (ChessBase GmbH, Hamburg). No "learning effect" for the machine was allowed. The human player's time limit was 15 min per game, with the allocation of this amount of time being entirely at the discretion of the player. The computer had 6 min for every game and was not allowed to move instantly in order to avoid the psychological pressure on a human player facing an opponent whose moves are quasi instantaneous. This modification of the chess playing program had no influence on its choice of move.

   The strength of the chess program was adjusted to the player's strength according to his chess rating performance. This was done only once for each subject before the games began and was kept constant throughout the experiment. Additionally, the software of the program was adjusted in a way that it changed the colour of the pieces automatically after each game. This is important as the

player who moves the white pieces always begins the game and is supposed to have a slight advantage. Time use was recorded. Unless the time limit was overstepped (losing the game), a game ended through checkmate, resignation or when a draw was reached (stalemate, threefold repetition or the computer accepting a draw offer).

   AE were monitored by asking the participants for free recall at the end of each trial day and one day later as part of a follow-up phone contact. Additionally, the following laboratory parameters were assessed prior to the first drug application: electrolytes, proteins, red and white blood cell counts and thyroid parameters. Prior to the first drug application, before the second drug application and at the end of the trial day cortisone and plasma levels were assessed.

2.9. Statistical analysis of the chess games

The study was conducted as a 4×4 crossover study with a Williams design. The variables analysed were the result (0=loss, 0.5=draw, 1=win) and the time used [seconds] for each chess game. For the primary outcome analysis on substance effects on chess performance, a linear (ordinary least squares) model with repeated measurements was used (Generalized Estimating Equations, GEE). Within the model, caffeine, methylphenidate and modafinil served as fixed effects. The two-sided level of significance was set to 5%. The analysis was based on all observed chess games. No missing values were replaced. Time to event data were displayed by Kaplan-Meier plots including 95%-confidence intervals (CI) adjusted for repeated measurements. The primary analysis included all games (n=3059) and was conducted to assess the effect of drug administration on chess performance and reflection time. Secondary analyses were conducted to assess whether performance changes are present when controlling for match duration (n=3059) or only in those games not lost on time (n=2876).

2.10. Statistical analysis of neuropsychological tests and self-rating scales

The results of the neuropsychological assessment were analysed by repeated measures ANOVA for subjects and fixed factors for treatment, sequence and period. Compound symmetry was assumed and the degrees of freedom were adjusted according to the method of Kenward and Rogers. The analysis population consisted of all patients randomised (Intent to Treat Population, ITT Population).

   We were specifically interested in three domains: (i) alertness and psychomotor speed as assessed by the PVT and TMT (A and B) from the neuropsychological task battery and subscales of the POMS (fatigue and vigor); (ii) risk taking as assessed by BART from the neuropsychological test battery and the self-rating scales AMS (hope for success/fear of failure) and EVAR; (iii) behavioral and cognitive control as assessed by Wisconsin card sorting test (set shifting), the ToH (planning), and the Stroop test (interference resolution) from the neuropsychological task battery. To correct for multiple testing per domain and prevent false positive results because of alpha-error accumulation, we applied a Bonferroni correction for the number of tests per domain (psychomotor speed: $p < 0.05/5 = 0.010$; risk-taking: $p < 0.05/4 = 0.013$; cognitive control: $p < 0.05/5 = 0.010$). Only significant overall treatment effects were explored further using post-hoc tests of the active substances versus placebo. Again, Bonferroni correction was applied ($p < 0.05/3 = 0.017$). No interactions were investigated.

2.11. Statistical analysis of plasma levels

To compare plasma levels before (T_0), after the morning chess session (T_1), and after the afternoon chess session (T_2), we

conducted separate repeated measures ANOVAS for each of the three drugs (i.e., caffeine, methylphenidate, and modafinil) and across treatments. Degrees of freedom of the overall F-Test were adjusted according to Brunner, Domhof, and Langer. Post-hoc t-tests comparing the three plasma levels were Bonferroni corrected.

2.12. Ethics statement

The clinical trial was registered according to www.clinicaltrials.gov (No. NCT01834547) and it was approved by the local ethics committee (Mainz: No. 837.351.10(7360)). All experiments have been conducted according to the principles expressed in the Declaration of Helsinki. All subjects were informed extensively about the study procedure prior to participation and gave written informed consent prior to participation.

3. Results

3.1. Randomised participants

Between 14 July 2011 and 27 January 2013, 39 of 40 randomised subjects received all trial medications (methylphenidate, modafinil, caffeine, and placebo) in a randomised order on four different trial days and were all included in the statistical analyses. One subject dropped out before the first trial day due to a car accident after the screening procedure. Baseline demographic and clinical characteristics of the 40 participants who entered the ITT analysis as well as of the 39 participants who received all trial medications are given in Table 1.

3.2. Primary and secondary outcomes

Results on chess performance are given in Table 2. By matching the skill level of the computer to the player's skill level according to the ELO or DWZ rating, we expected an average score of 0.5 for every player in the placebo condition (note that scores are: 0=loss, 0.5=draw, 1=win). We found an average score of 0.510 for chess performance under placebo which is close to the expected score.

In our primary analysis, we first examined whether the three substances were able to enhance chess playing performance in all games (a total of $n=3059$). We found

higher average scores for all three substances (0.542–0.552) implying that the players performed 3–4 percentage points (or 6–8 percent) above placebo performance. However, the respective regression estimates did not exceed trend level when compared to placebo. Controlling for visit and sequence did not affect the results.

Even if treatment had no significant effect on the chess score (i.e., ratio of matches won), it had a significant effect on subjects' behavior. Their average reflection time per game increased, from 436.8 s during placebo, to 552.8 s during modafinil ($p<.001$), to 547.3 s during methylphenidate ($p<.001$), and to 530.1 during caffeine ($p<.001$). Fig. 1 illustrates the average reflection time per game over all moves and shows that the average reflection time per game during all treatments is considerably higher compared to placebo between moves 11 and 25, i.e. the most complex phase of a chess game. Towards the end of the games, average reflection time decreased again, indicating that subjects came under time pressure. Fig. 2 illustrates the risk of losing a game over time and shows that the probability of losing a game increased as the game approached the time limit (i.e. 900 s.). As a consequence of the increased average reflection time per game in the treatment conditions (Fig. 1), the number of games lost on time or due to time trouble was significantly higher under modafinil ($n=88$, $p<0.001$), methylphenidate ($n=104$, $p<0.001$), and caffeine ($n=70$, $p<0.023$) as compared to placebo ($n=30$).

To gain further insight in possible treatment effects, we performed secondary, exploratory analyses. First, to control for reflection time, we included game duration as a covariate ($n=3059$). This revealed significant treatment effects for modafinil, methylphenidate and caffeine (Table 2B).

Next, we assessed whether drug administration had an effect on chess performance in those games not lost on time. Therefore, the primary analysis was repeated, however including only those games that were not lost on time ($n=2876$). In these games, both methylphenidate and modafinil had a significantly enhancing effect on chess performance, whereas the enhancing effect of caffeine did not exceed trend level (Table 2B).

To gain further insight in cognitive processes we assessed treatment effects on the above mentioned neuropsychological tests (Table 3) and self-rating scales (Table 4). We first asked whether treatments increased alertness and basic psychomotor speed which were tested by the PVT and TMT from the neuropsychological task battery and subscales of the POMS (fatigue and vigor). Although the neuropsychological tests did not show any differences between treatment conditions, subjects treated with methylphenidate or caffeine felt significantly less fatigued and had more vigor compared to the placebo condition (POMS).

Secondly, since especially modafinil has been shown to modulate a variety of executive functions including behavioral and cognitive control as well as risk taking behavior (Campbell-Meiklejohn, 2012; Killgore et al., 2008; Minzenberg and Carter, 2008) we asked whether treatment might have influenced the degree of control and risk-taking behavior. To assess treatment effects on risk taking, we considered BART from the neuropsychological
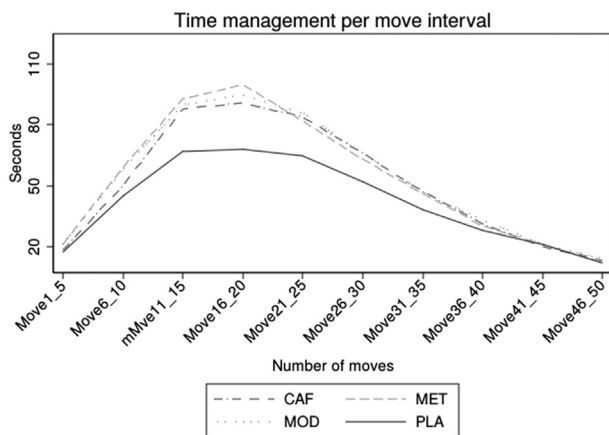
Table 1	Baseline demographic and clinical characteristics.

	$N=40$ entering the ITT analysis	$N=39$ who received all study medications
Age [years]	37.0 (12.5)	37.3 (12.5)
Weight [kg]	80.8 (13.8)	81.0 (13.9)
Height [cm]	179.7 (6.8)	179.7 (6.9)
BMI	25.0 (3.7)	25.0 (3.7)
ELO	1677.4 (338.4)	1670.4 (340.0)
IQ (according to HAWIE)	127.7 (11.2)	127.7 (11.3)

BMI=Body Mass Index; HAWIE=Hamburg Wechsler Intelligence Test; ()=standard deviation (SD), ELO=Elo rating, not available for all subjects; in those cases replaced by the equivalent to the similarly scaled Deutsche Wertungszahl (DWZ).

Table 2 Descriptive statistics and regression estimates for treatments.

	Modafinil	Methylphenidate	Caffeine	Placebo
A. Descriptive statistics				
Number of games	763	757	760	779
Wins (1 point)	388	375	383	356
Losses (0 point)	309	312	317	340
Draws/ties (1/2 point)	66	70	60	83
Sum of scored points	421	410	413	397.5
Average score	0.552	0.542	0.543	0.510
Average score*20 games	11.04	10.84	10.86	10.20
Sum of scored points	421	410	413	397.5
B. Regression estimates				
Score in all games ($n=3059$)	0.551 (0.024) $p=0.094$	0.541 (0.023) $p=0.188$	0.543 (0.023) $p=0.164$	0.510 (0.028)
Score with control for time use ($n=3059$)	0.563 (0.025) $p=0.004$	0.551 (0.027) $p=0.021$	0.548 (0.025) $p=0.018$	0.486 (0.051)
Score excluding games lost on time ($n=2876$)	0.599 (0.025) $p=0.005$	0.589 (0.026) $p=0.014$	0.567 (0.025) $p=0.080$	0.522 (0.030)

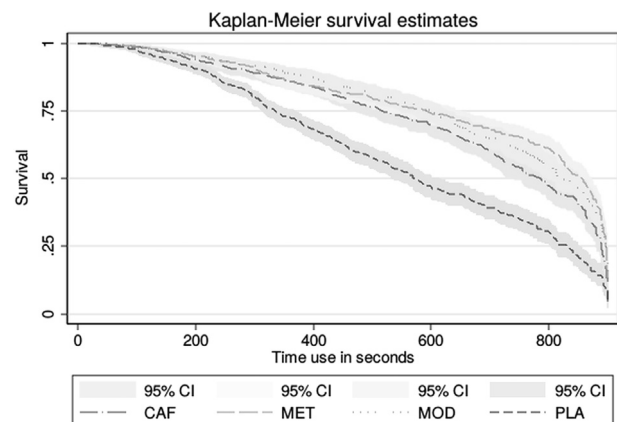Standard error of regression estimates is given in parenthesis.

Fig. 1 Reflection time per move interval, descriptive plot. CAF=caffeine; MET=methylphenidate; MOD=modafinil; PLA=placebo.

Fig. 2 Probability of not losing the game, survival rate estimation (Kaplan–Meier). CAF=caffeine; MET=methylphenidate; MOD=modafinil; PLA=placebo; CI=confidence interval.

test battery and the self-rating scales AMS and EVAR. After applying Bonferroni correction all results just failed to reach significance.

To assess treatment effects on behavioral and cognitive control, we considered Wisconsin card sorting test (set shifting), the ToH (problem solving), and the Stroop test (interference resolution) from the neuropsychological task battery. Significant treatment effects on executive task performance were only present in Stroop RT, i.e. faster interference resolution when treated with methylphenidate compared to placebo. Including POMS fatigue or vigor as covariates to control for effects of fatigue or motivation did not affect the results (data not shown).

3.2.1. Plasma levels

Descriptive statistics are summarized in Table 5. Plasma levels differed significantly for each treatment and overall

(caffeine: $F_{(2, 72)}=154.44$, $p<0.001$; methylphenidate: $F_{(2, 68)}=206.03$, $p<0.001$; modafinil: $F_{(2, 72)}=499.35$, $p<0.001$; overall $F_{(2, 74)}=469.78$, $p<0.001$).

Post-hoc pair wise comparisons between measurements revealed that for each drug and overall, plasma level at T_1 was significantly enhanced as compared to T_0, and plasma level at T_2 was significantly enhanced as compared to both T_0 and T_1 (all $p<0.001$).

3.2.2. Adverse events

A total number of 66 short term AE were reported by 29 subjects, of which 56 events in 22 subjects were substance related. Substance related AE were observed in 15 subjects (22 events) treated with modafinil, 11 subjects treated with methylphenidate (20 events), and 6 subjects (8 events) treated with caffeine compared to 2 subjects (6 events)

Table 3 Neuropsychological test performance.

	Modafinil	Methylpheni- date	Caffeine	Placebo	*Treatment effect F-value*	*Treatment effect p-value*
PVT (s)	334.70 (82.70)	332.64 (72.69)	334.96 (110.91)	342.46 (74.54)	0.12	0.949
TMT-A	14.13 (4.21)	14.58 (4.53)	14.83 (4.98)	15.09 (4.45)	2.24	0.088
TMT-B	27.13 (13.82)	25.09 (10.17)	24.82 (11.44)	25.90 (10.02)	0.98	0.405
Stroop (s)	55.34 (10.82)	54.07 (11.55)**	54.91 (13.43)[#]	56.96 (13.96)	**4.16**	**0.008**
Stroop (errors)	0.25 (0.36)	0.28 (0.48)	0.16 (0.29)	0.23 (0.38)	0.77	0.513
WCST	0.23 (0.17)	0.24 (0.18)	0.27 (0.18)	0.23 (0.17)	1.50	0.219
BART (max. score)	810.41 (176.53)	795.08 (172.71)	784.38 (170.33)	731.76 (159.87)	2.80	0.043
TOH (s)	235.01 (239.23)	243.49 (218.58)	224.55 (177.82)	189.19 (148.01)	1.18	0.320
TOH (moves)	79.32 (27.37)	79.33 (22.09)	85.88 (35.65)	75.64 (16.32)	2.41	0.071

Values shown are mean and standard deviation (in parenthesis) in neuropsychological tests for each treatment condition. The reported *F*- and *p*-values are derived from within-subjects repeated measures ANOVAs with four treatment factors (modafinil, methylphenidate (MPH), caffeine, and placebo). Significant Bonferroni corrected post-hoc tests are indexed by: *$p<0.05$; **$p<0.01$; ***$p<0.001$; trend: [#] $p<0.1$.

Balloon Analog Risk Task = BART; Psycho-Motor-Vigilance Test = PVT; sec = seconds; TMT = Trail-Making-Test; TOH = Tower of Hanoi; Wisconsin-Card-Sorting-Test = WCST.

Table 4 Self-rating scores.

	Modafinil	Methylphenidate	Caffeine	Placebo	*F*-value	*p*-value
EVAR (total score)	1236.22 (215.15)	1220.99 (217.13)	1232.07 (210.70)	1203.86 (246.95)	1.76	0.159
AMS success	16.47 (2.43)	16.57 (2.44)	16.49 (2.62)	16.09 (2.87)	0.70	0.551
AMS failure	7.09 (2.57)*	7.22 (2.58)[#]	7.51 (2.72)	7.64 (2.64)	**3.38**	**0.021**
POMS Fatigue	6.33 (4.90)	5.61 (4.82)*	5.39 (4.01)**	7.37 (5.63)	**4.26**	**0.007**
POMS Vigor	14.22 (5.44)	15.82 (6.36)**	15.78 (5.67)**	13.26 (5.99)	**4.85**	**0.003**

Values shown are mean scores and standard deviation (in parenthesis) from standardized questionnaires for each treatment condition. The reported *F*- and *p*-values are derived from within-subjects repeated measures ANOVAs with four treatment factors (modafinil, methylphenidate (MPH), caffeine, and placebo). Significant Bonferroni corrected post-hoc tests are indexed by: *$p<0.05$; **$p<0.01$; ***$p<0.001$; trend: [#] $p<0.1$.

Table 5 Plasma levels of experimental substances.

	Modafinil	Methylphenidate	Caffeine
T_0	0.10 mg/l (0.00)	1.00 μg/l (0.00)	1.41 mg/l (0.94)
T_1	3.56 mg/l (0.92)	6.94 μg/l (2.05)	4.07 mg/l (1.36)
T_2	6.11 mg/l (1.40)	9.10 μg/l (3.06)	6.08 mg/l (2.02)

Mean plasma levels and standard deviations (in parenthesis) of modafinil, methylphenidate, and caffeine were determined as an experimental control before drug administration (T_0), after completion of chess morning session at 1 p.m. (T_1) and after completion of chess afternoon session at 5 p.m. (T_2). Limit of detection: Modafinil: 0.10 mg/l; Methylphenidate: 1.00 μg/l; Caffeine: 1.00 mg/l.

who reported AE during the placebo treatment. The most common side effects were headaches (modafinil $n=7$ (7 subjects), methylphenidate $n=6$ (5 subjects), caffeine $n=3$ (3 subjects), placebo $n=1$ (1 subject)), difficulties falling asleep (modafinil $n=9$ (9 subjects), methylphenidate $n=3$ (3 subjects), caffeine $n=1$, placebo $n=1$ (1 subject each)), and agitation (modafinil $n=0$, methylphenidate $n=3$ (2 subjects), caffeine $n=0$, placebo $n=0$). Laboratory analyses showed no abnormalities.

4. Discussion

This is, at least to our knowledge, the first study showing that modafinil, methylphenidate and caffeine modify complex cognitive performance in a highly demanding task such as playing chess in highly skilled tournament chess players. All three substances significantly increased average reflection time per game as compared to placebo. Consequently more games were lost on time. Only when controlling for game duration or when excluding chess games lost due to time constraints we observed enhancement effects of those substances on chess performance. It is quite likely that two effects are at work that offset each other.

Two possible mechanisms could lead to such increased reflection times: First, information processing might be

slowed down in the sense that participants under stimulants need more time to maintain the same quality of their moves. Chess results should then remain unchanged apart from the fact that they lose on time more often. Second, individuals are reflecting longer in the sense of accumulating more information, i.e., investigating more lines and making better moves on average. Chess results should then improve, but the effect might be offset by more losses on time. Our analysis provides evidence for the second mechanism since increased reflection times under stimulants led to a much better quality of play in the middle game. However, this comes at the price of losing more games on time or due to time trouble. This suggests that neuroenhancers do not enhance the quality of thinking and decision-making per time unit but improve the players' ability or willingness to spend more time on a decision and hence to perform more thorough calculations. This is in line with earlier findings demonstrating increased response latencies in different tasks and cognitive functions. Turner et al. (2003) demonstrated increased response latencies in a spatial planning task as well as in a delayed matched to sample task upon modafinil administration. Increased response latencies were accompanied by improved performance in the spatial planning task. Moeller et al. (2014) showed increased post-error slowing and a tendency for increased accuracy in a Stroop task upon methylphenidate administration. Taken together, these findings indicate that stimulants may influence the speed-accuracy trade-off during cognitive tasks (but see Winder-Rhodes et al., 2010 for opposing results). In other words, these substances may be able to convert fast and shallow thinkers into deeper but somewhat slower thinkers (see Kahneman system 1 and 2 individuals for chess player examples (Kahnemann, 2003)). This process of deeper thinking that has been shown to be specifically beneficial for chess players (Moxley et al., 2012; van Harreveld et al., 2007) may lead to a more advantageous decision-making process given that sufficient reflection time is provided. Importantly, tournament chess players at all levels differ greatly in their likelihood of getting into time trouble. For those who typically do not, the offsetting effect of neuroenhancers does not play a role, and they improve performance even if games lost on time are included in the analysis. In sum, these results suggest that most players will benefit from CE, in particular from modafinil and methylphenidate, while those who tend to be rather slow thinkers may even perform worse in time-restricted games.

It is very likely that treatment effects on chess performance are mediated by treatment effects on executive functions underlying chess. Indeed, reaction times in the Stroop task, an executive task testing interference resolution (Stahl et al., 2014), were significantly shorter with methylphenidate as compared to placebo. The same effect was present after caffeine intake but did not exceed trend level. Interference resolution as measured by the Stroop task depends on a subject's ability to ignore irrelevant distractors (stimulus interference) (Stahl et al., 2014). Interference resolution has been shown to be specifically relevant for novices and intermediate chess players, whereas parallel processing may allow expert players to avoid interference inhibition while performing rapid and efficient processing (Postal, 2012). In addition, it has been shown that expert players immediately and exclusively focus on the relevant aspects in a chess task whereas novices perform visual search by also examining irrelevant aspects (Bilalić et al., 2010). Despite the enhancing effects of stimulants on reaction times in the Stroop task these insights suggest that modification of decision making in highly skilled chess players may rely more strongly on other aspects than interference inhibition whereas improved interference inhibition might play an important role in novices and intermediate players. Since more deliberative thinking has been shown to be beneficial for expert as well as non-expert chess players regardless of the level of complexity of a problem (Moxley et al., 2012) which is reflected in slower but more accurate responses, in the given sample deeper, more deliberative thinking may thus have contributed more strongly to the effects on chess playing behavior. Taken together, our data suggest that the modification of the decision making process is mediated by at least two cognitive components of decision making, interference resolution and more importantly information accumulation favoring longer reflection times when playing chess as seen in the present study.

How could stimulants applied in the current study have affected activity of neural networks underlying these cognitive functions? Two neuroimaging studies using a Stroop paradigm revealed methylphenidate induced changes in activity of the anterior cingulate cortex (ACC). Moeller et al. (2014) showed that methylphenidate not only increased post-error slowing but modulated prefrontal areas involved in error-related processing (i.e., dorsal ACC and dorsolateral prefrontal cortex, DLPFC). Similarly, methylphenidate enhanced ACC activity in substance dependent patients (Goldstein and Volkow, 2011). Moreover, ACC signal increase was associated with improvement of task accuracy in that study. Interestingly, both ACC and DLPFC have been associated with decision making processes, particularly with the amount and the rate of information accumulation (Mulder et al., 2014; van Maanen et al., 2015). Increased reflection times after drug administration in the present study may thus be mediated by activation changes in particularly these dopaminergically innervated PFC areas.

Effects of stimulants have not only been shown on specific brain areas, but also on intrinsic large-scale functional networks and changes in between-network functional connectivity (Schmaal et al., 2013a). More specifically, Modafinil significantly increased the negative coupling between executive function networks (task-positive networks) and the default mode network (task-negative network) during resting state functional imaging. Furthermore, these changes in between-network coupling were associated with a modafinil-induced improvement in cognitive control (Schmaal et al., 2013a). This finding supports the notion that modafinil may enhance the efficacy of prefrontal cognitive information processing (Rassetti et al., 2010). A similar mechanism has also been discussed for methylphenidate which increases signal-to-noise ratio in target neurons and may enhance the saliency of the task at hand (Volkow et al., 2001).

Effects of caffeine on brain activation as assessed in neuroimaging studies are similar to those of methylphenidate and modafinil, although the substances differ in their

pharmacological profiles. The effects of caffeine are mediated through its non-selective antagonistic effects on A_1 and A_{2A} adenosine receptors, whereas methylphenidate and modafinil exert their actions mainly via dopaminergic and noradrenergic effects (Wood et al., 2013). Recent studies consistently report caffeine-induced task-related changes mainly in medial and lateral prefrontal areas including ACC and DLPFC (Klaassen et al., 2013; Diukova et al., 2012; Haller et al., 2013; Koppelstaetter et al., 2008). Since the concentration of A_1 adenosine receptors in contrast to A_{2A} adenosine receptors is differentially distributed and specifically high in the prefrontal cortex (besides basal ganglia and neocortical regions), this may indicate that such activation changes are mainly modulated by the neuroexcitatory action of caffeine on the specific brain areas being involved in executive functions (for review see Koppelstaetter et al., 2010). The prefrontal cortex which is critically involved in higher cognitive functions receives ascending input of various neuromodulatory systems including the dopaminergic system. The neuroexcitatory effect of caffeine on cognition may thus be exerted by its secondary effects on neurotransmitter systems such as dopaminergic transmission (Koppelstaetter et al., 2010). Moreover, besides the direct effects, caffeine may exert indirect effects on cognitive functions via arousal modulation, e.g. by modulating the prefrontal cortico-thalamic loop involved in the interaction between arousal and top-down control (Klaassen et al., 2013).

Apart from interference resolution other functions implied in chess cognition might have been influenced by stimulant intake, such as attention, spatial planning, problem solving and various memory functions including working and recognition memory (Atherton et al., 2003; Bilalić et al., 2009, 2010; Campitelli et al., 2007; Chase and Simon, 1973; Gobet, 1998; Guida et al., 2012; Postal, 2012; Wright et al., 2013). Assessing all of these functions was beyond the scope of the current study. Instead, we focused on some selected fundamental functions. We investigated whether treatments increased alertness and basic psychomotor speed which might have contributed to enhancement effects as suggested by earlier studies (Kelley et al., 2012; Repantis et al., 2010; Wesensten et al., 2005; Borota et al., 2014). Although the psycho-motor-vigilance (PVT) test and the trail making test part A and B did not show any differences between treatment conditions, subjects treated with methylphenidate and caffeine felt significantly less fatigued and had more vigor compared to the placebo condition (POMS). We hypothesized that this reported increase in endurance might have contributed to playing more successfully while using substances. However, when analysing the game results across the total time span, we found no particular performance enhancement during the later games where tiredness naturally might have occurred. We suggest in line with others (Battleday and Brem, 2015; Müller et al., 2013) that stimulants may particularly in complex rather than in simple tasks enhance attention as well as higher cognitive functions in healthy participants. Hence, in a highly complex task such as chess this reported increase in endurance contributed to playing more successfully while using substances whereas no effects on simple

psychomotor test were present. A previous study has shown effects of stimulants on task enjoyment (Müller et al., 2013). Treatment effects may thus also have been mediated by increased task enjoyment. Since we did not directly assess task enjoyment this needs to be systematically assessed in future studies.

Selective and sustained attention were assessed using the Stroop task and the PVT, respectively. Whereas interference inhibition and the closely related aspect of selective attention in the Stroop task (Melara and Algom, 2003) improved after methylphenidate and caffeine administration, no effect of stimulants on sustained attention was found.

To assess planning and problem solving capacity, ToH or Tower of London (ToL) tasks are often utilized. Using the ToL task, Unterrainer et al. (2006) demonstrated better planning performance along with longer planning duration in chess players as compared to non-chess players; however, these effects could not be replicated in a later study (Unterrainer et al., 2011). We included the 6-ring version of the ToH to assess complex problem solving abilities rather than planning performance which is rather assessed using the 3-ring version of the ToH (please cf. Shallice, 1982). We did not observe enhancing effects of any of the stimulants on problem solving capacity. Yet, an enhancing effect may be observed when the problem solving task is chess specific as it has often been shown that superiority of chess experts is limited to chess-specific tasks and specifically present in the respective area of expertise (Bilalić et al., 2009, 2010; Gong et al., 2015). This holds true for problem solving as well as for memory functions (Bilalić et al., 2009; Gong et al., 2015). Neither chess specific problem solving nor spatial planning or memory function were assessed in the current study. Previous studies have shown enhancing effects of stimulants on memory functions as well as planning capability (e.g., Caviola and Faber, 2015; Killgore et al., 2009; Koppelstaetter et al., 2008; Linssen et al., 2014; Mehta et al., 2000; Müller et al., 2013; Winder-Rhodes et al., 2010). Treatment effects on working memory capacity and spatial planning performance may thus have additionally contributed to performance enhancement after drug administration.

While all three substances significantly modified the subjects' behavior, i.e. reflection time and performance when controlling for game duration, the effects on neuropsychological measures and self-rating scales differed. Methylphenidate and caffeine both had significant effects on Stroop interference resolution and on several self-rating scores. Yet, a significant effect of modafinil was only present for the 'fear of failure' subscale of the AMS. The relationship of catecholamine neurotransmitters and the cognitive performance has been suggested as being an inverted U-shape with optimal performance at intermediate catecholamine levels (de Jongh et al., 2008; Schlosberg, 1954; Wood et al., 2013) and has been shown to depend on task difficulty (Müller et al., 2013). Therefore, the dose of modafinil in the present study may have been appropriate for modifying the behavior and specifically reflection time during a very complex task such as playing chess, whereas it may not have been optimal for improving performance in comparatively less complex tasks such as the

neuropsychological tests in the given study. Previous studies have shown effects of lower doses of modafinil, i.e., a single dose of 100 mg (e.g., Esposito et al., 2013; Pringle et al., 2013) whereas most studies used a single dose of 200 mg (e.g. Gilleen et al., 2014; Minzenberg et al., 2011; Müller et al., 2013; Schmaal et al., 2013a, 2013b). Moreover, Randall et al. (2005) have suggested that high-IQ may limit detection of modafinil's positive effects. Thus, more optimal levels of arousal in highly intelligent and highly skilled individuals may have been produced at lower doses.

We believe that our results are of relevance to chess competitions. First, although the number of games per day (20) is higher than in typical rapid chess events, the total time subjects spent at the chessboard is comparable to high-level tournament chess. Hence our findings regarding methylphenidate and modafinil should have a high external validity. Second, the enhancement effects of methylphenidate and modafinil as seen in our study are large and relevant: An effect magnitude of a coefficient of 0.05 as found for methylphenidate and modafinil when the five slowest players were excluded would bring a player from world rank 5000 to 3500 ($+35$ Elo points). In a single game, the effect size corresponds to the first-mover advantage of having the white pieces (which increases the winning probability by 5 percentage points in our sample).

Apart from risks for the individual (Franke et al., 2012; Gahr et al., 2014; Iversen, 2009; Wilens et al., 2008), doping (which is possible as shown in our study) is threatening "fair play" in chess. Our data should therefore stimulate the doping debate in chess and should encourage the regular use of doping controls in competitive chess games. The World Chess Federation (FIDE position towards the World Anti Doping Agency Policy, 2014) has adopted the list of prohibited substances of the World Anti Doping Agency (WADA) and especially names amphetamines, ephedrine, modafinil and methylphenidate as well as pseudoephedrine as most relevant banned substances. However, the fact that both WADA and FIDE do not see any problems with caffeine, which is not part of the list of prohibited substances and only monitored, is questioned by our data (FIDE).

In spite of the thorough examination of psychiatric disorders prior to including subjects, we did not formally assess study subjects for ADHD symptoms such as inattention, hyperactivity or impulsivity during the study which should be mentioned as limiting factor of the present study.

We conclude that in sum, the present study shows that pharmacological modification of complex cognitive performance in a highly demanding task is possible most likely by modifying decision making processes. More reflective decision making may enhance performance when no time limit for the task at hand is present but may have disadvantageous effects under time constraints especially in individuals who tend to be rather slow thinkers.

Contributors

K.L., A.G.F. and H.E.B. designed the clinical trial. A.G.F., K.S., A.A., S.G., K.R., T.R., H.E.B. were responsible for data acquisition. C.R., B.F., C.G. and P.G. analysed the data of the study. K.L., O.T., A.S., P.G., C.R., B.F. and A.G.F. interpreted the results and wrote the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest statement

All authors declare to have no competing interests.

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