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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