



Modafinil improves attentional performance in healthy, non-sleep deprived humans at doses not inducing hyperarousal across species

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ABSTRACT

The wake-promoting drug modafinil is frequently used off-label to improve cognition in psychiatric and academic populations alike. The domain-specific attentional benefits of modafinil have yet to be quantified objectively in healthy human volunteers using tasks validated for comparison across species. Further, given that modafinil is a low-affinity inhibitor for the dopamine and norepinephrine transporters (DAT/NET respectively) it is unclear if any effects are attributable to a non-specific increase in arousal, a feature of many catecholamine reuptake inhibitors (e.g., cocaine, amphetamine). These experiments were designed to test for domain-specific enhancement of attention and cognitive control by modafinil (200 and 400 mg) in healthy volunteers using the 5-choice continuous performance task (5C-CPT) and Wisconsin Card Sort Task (WCST). An additional cross-species assessment of arousal and hyperactivity was performed in this group and in mice (3.2, 10, or 32 mg/kg) using species-specific versions of the behavioral pattern monitor (BPM). Modafinil significantly enhanced attention (d prime) in humans performing the 5C-CPT at doses that did not affect WCST performance or induce hyperactivity in the BPM. In mice, only the highest dose elicited increased activity in the BPM. These results indicate that modafinil produces domain-specific enhancement of attention in humans not driven by hyperarousal, unlike other drugs in this class, and higher equivalent doses were required for hyperarousal in mice. Further, these data support the utility of using the 5C-CPT across species to more precisely determine the mechanism(s) underlying the pro-cognitive effects of modafinil and potentially other pharmacological treatments.

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1. Introduction

Cognitive deficits, particularly in the domains of attention and cognitive control, are key features of multiple psychiatric illnesses, e.g., schizophrenia (SCZ), bipolar disorder (BD), and attention deficit hyperactivity disorder (ADHD). Traditional treatments such as methylphenidate have been considered as therapeutic agents in the treatment of impaired attention and cognitive control. There has been longstanding reticence to use these drugs for individuals with SCZ and BD however, since they can exacerbate many of their

symptoms (Chiarello and Cole, 1987). Further, given the mechanism of action of stimulants in potentially blocking or reversing the dopamine transporter (DAT), these drugs carry a high potential for abuse (Volkow and Swanson, 2003). The lack of pro-cognitive pharmacotherapies with low abuse potential stands as a critical treatment gap for individuals suffering from these illnesses (Fusar-Poli et al., 2015; Geddes and Miklowitz, 2013; Lindenmayer et al., 2013).

Modafinil, a low potency inhibitor of the DAT and norepinephrine transporter (NET), is a Federal Drug Administration-approved compound that was developed to increase wakefulness in the treatment of narcolepsy (Madras et al., 2006; Volkow et al., 2009). This drug however, is increasingly used off-label to remediate deficient attention and cognitive control in psychiatric patients (Minzenberg and Carter, 2008), as well as a cognition-enhancing

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aid in academic institutions (Sahakian and Morein-Zamir, 2015). Certainly, there are myriad findings reporting modafinil-induced improved working memory, cognitive control, and sustained attention in healthy sleep-deprived volunteers, psychiatric populations, and rodents (Sahakian and Morein-Zamir, 2015). Improved cognition in non-sleep deprived healthy adults has been rarely observed however (Baranski et al., 2004; Battleday and Brem, 2015; Muller et al., 2004), except at the highest levels of difficulty in working memory, or in higher order planning and decision-making tasks (Battleday and Brem, 2015; Muller et al., 2013; Turner et al., 2003). Modafinil-induced improvements in the attentional domain have yet to be observed in healthy adults, which contrasts with what has been seen with high-potency DAT inhibitors such as amphetamine (Linssen et al., 2014; Smith and Farah, 2011).

In addition to improving attention, high-potency DAT inhibitors such as amphetamine also increase arousal (Bensadoun et al., 2004; Berridge, 2006; Kalivas and Volkow, 2005), an effect linked to its abuse potential (Sahakian and Morein-Zamir, 2015). In both healthy human volunteers and mice, D-amphetamine increases activity in the behavioral pattern monitor (BPM) at clinically relevant doses (Minassian et al., 2016). Similarly, modafinil increases activity in the mouse BPM (Young et al., 2011a) and increases motivation in mice as measured by progressive ratio breakpoint (Young and Geyer, 2010) at similar doses (32 mg/kg). It would therefore be important to separate the potential effect of modafinil on attention from its effects on arousal. In terms of feedback-related decision-making, amphetamine increased safe lever choice preference (preference for low risk, low reward option), while the more selective DAT inhibitor GBR12909 worsened performance, and modafinil had no effect in a mouse consolidation-dependent Gambling Task (van Enkhuizen et al., 2013b). This suggests a separation of the effect of modafinil from other DAT inhibitors in a risk-based decision-making task. The effect of modafinil on various psychiatric-related behaviors, however, remains unclear. The use of cross-species tasks would enable future studies to investigate mechanism-related effects of modafinil in rodents using neuroscience tools not available for testing in humans.

In an attempt to parse these potential domains of effect, we assessed the effects of clinically relevant doses of modafinil in healthy, non-sleep deprived human volunteers in the five-choice continuous performance task (5C-CPT), Wisconsin Card Sort Task (WCST), and the human BPM. These tests are validated for the assessment of attention and cognitive control (Cope et al., 2016; Lustig et al., 2013), and arousal and exploration (Minassian et al., 2011; Perry et al., 2009; van Enkhuizen et al., 2013a), respectively. We also determined the effects of modafinil on the arousal and exploratory behavior of male and female mice at doses that are directly comparable to those used in human testing. Given the separation of effects for more selective DAT inhibitors, we hypothesized that modafinil would improve attention without inducing hyperarousal.

2. Material and methods

2.1. Healthy volunteer studies

2.1.1. Volunteer recruitment

Procedures were approved by The University of California San Diego (UCSD) School of Medicine's institutional review board. Using online advertisements and flyers posted throughout the community, 61 male and female participants were recruited according to the following inclusion criteria: 1) Ages 18–35; 2) In good general health; 3) No lifetime history of an axis I or axis II disorder; 4) No first-degree relative with a history of psychotic or mood disorder; and 5) No specific contraindications or previous adverse

reactions to amphetamine. Exclusion criteria included the following: 1) Clinically significant electrocardiogram or physical exam determined by the study physician; 2) Women with a positive serum HCG pregnancy test or who are lactating; 3) History of alcohol or substance (e.g., sedative-hypnotics, cannabis, stimulants, opioids, cocaine, hallucinogens) abuse or dependence within the last 30 days, or a positive urine toxicology screen for illegal substances completed on study entrance. Nicotine abuse or dependence was not an exclusion criterion; 4) Current severe, systemic medical illness that may compromise cognitive functioning or serious cardiac disease; and 5) Current or history of neurological disorder such as seizures or stroke, Parkinson's disease, dementia, or a history of head injury with loss of consciousness for at least 15 min. Data from a subset of the placebo group has been published previously (Minassian et al., 2016), but recruitment and consenting procedures were identical and overlapping for participants in the placebo group.

2.1.2. Randomization and drug treatment

Participants meeting all inclusion/exclusion criteria were randomized, double blind, into one of three groups: placebo, 200, or 400 mg modafinil. During the consenting process, volunteers were told they could receive either amphetamine, caffeine, modafinil or placebo to limit expectations of drug effects, as this investigation was part of a larger study designed to assess the effects of stimulants on cognition and behavior.

2.1.3. 5 Choice continuous performance task

Procedures for the human version of the 5C-CPT have been described in detail (McKenna et al., 2013; van Enkhuizen et al., 2014; Young et al., 2013). In brief, participants were positioned 60 cm away from a 56 cm computer monitor. A spring-mounted analog joystick was provided to the participant to record responses using their dominant hand. This joystick automatically returned to center when released following a response. Participants were forewarned that 5 white lines (3 cm) in an arc would appear on the black background. If a single white dot (2 cm diameter) appeared behind any of the lines, they were instructed to move the joystick in the corresponding direction (target). If dots appeared behind all lines, they were instructed to avoid responding on the joystick (non-target). See Table 1 for descriptions of each trial type and explanation of outcome variables. Before performing 5C-CPT, participants were allowed one 12-trial practice session (10 target and 2 non-target trials, randomly presented). The full task consisted of 270 trials, 225 target and 45 non-target, presented pseudo-randomly to ensure no more than three consecutive presentations of the same trial type. This high ratio of target:non-target trial types engendered prepotent responses relevant to the cognitive control aspect of 5C-CPT performance (Young et al., 2016). To reduce temporal predictability of stimulus presentation, 5C-CPT trials were separated by a variable intertrial interval (ITI; 0.5, 1, or 1.5 s) following presentation of the stimulus on the previous trial. ITI length was chosen pseudo-randomly to ensure that no more than three of one specific ITI occurred consecutively. Response outcomes were recorded according to criteria in Table 1, including hits, misses, false alarms (FA), and correct rejections (CR) that were used to calculate hit rate (HR), false alarm rate (FAR), and signal detection variables of d-prime (d' , signal detection).

2.1.4. Behavioral pattern monitor

The procedures and testing room for the human behavioral pattern monitor (BPM) have been described in detail previously (Henry et al., 2010, 2011, 2013a, 2013b, Minassian et al., 2010; Minassian et al., 2016; Perry et al., 2009; Young et al., 2007). Before entering the BPM room, patients were fitted with an

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