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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 (5CCPT) 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.

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 potently blocking or reversing the dopa-mine 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 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 ambulatory monitoring device (Vivometrics, Ventura, CA) worn around the torso to quantify motor activity. Participants then entered the BPM room, where they were asked to wait for 15 min without any instructions other than to wait as the experimenter prepares a separate task. Videos of the participants' activity in the room were sampled at 30 frames per second were stored on a computer in an adjacent room for analysis. Participants were notified during the informed consent process that they might be videotaped during a part of their examination, but were not specifically told when videotaping would occur.

To assess motor activity, mean acceleration in digital units was derived for each of the three 5-min time periods of the 15-min BPM session. Object interactions were quantified manually by trained raters blind to group condition. We quantified the total number of object interactions, defined as deliberate physical contact with a novel object with any part of the body, e.g., hand or foot.

To assess spatial patterns of behavior, digitized video images were subjected to frame-by-frame analysis with proprietary software (TopScan 1.0; Clever Systems Inc, Washington, DC) to generate x-y coordinates of participants within a 720 by 480-pixel grid. The x-y data were initially processed with a low-pass Butterworth filter to remove instrumental noise. Spatial d (i.e., dimensionality), measured between values of 1 and 2, indicates the extent to which a subject travels in a straight line (close to 1) or adopts a meandering path, such as very localized, circumscribed movements (close to 2). This measure is calculated by plotting successive x-y coordinates of the path traveled against varying lengths of measuring resolutions. Distance traveled is plotted against the number of movement counts using a double-logarithmic plot, with the slope of this line of fit being used to calculate spatial d (Geyer et al., 1986; Paulus and Geyer, 1991, 1993). Values at either end of this range may indicate perseverative behavior (Perry et al., 2009; Young et al., 2010). Activity counts, defined as the number of discrete instances of movement or the smallest measured change in x-y coordinates, were also derived.

Acceleration, object interaction, activity counts, and spatial d values greater than 3 standard deviations from the grand mean were considered outliers; these data were not included in the statistical analyses (4 subjects). Spatial d was not calculated for 2 subjects due to a software error. Group differences were tested using analyses of variance (ANOVA), with treatment (placebo, 200 mg modafinil, 400 mg modafinil) as the between-subjects measures. Effect sizes were calculated with partial eta-squared. Statistical analyses were conducted with SPSS version 22.0 (IBM Corporation 2013).

2.1.5.   Wisconsin card sorting task—Participants performed a computer version of the WCST-64 card version (Heaton, 1993). The WCST is a well-established measure of executive function, designed to assess deficits in rule attainment and cognitive set shifting linked to frontal cortex pathology (Goldberg and Miller, 1986; Perry and Braff, 1998). The WCST requires participants to sort cards based on three perceptual dimensions (color, shape, and number), and provides feedback to allow the subject to identify the correct matching rule. After a specific number of correct responses, the card sorting category changes. Failure to abandon the previous sorting rule when it has been explicitly changed is associated with prefrontal dysfunction and perseverative behavior, a tendency to engage in maladaptive repetitive responses (Perry and Braff, 1998). Dependent measures include: (1) total number of errors, (2) perseverative errors, and (3) number of categories completed. Error scores for the task are converted to *T* scores corrected for age and education, where a higher score indicates better performance on the measure. Results for two of the 62 volunteers were incorrectly recorded and subsequently excluded from the analysis.

2.2.   Mouse studies

2.2.1.   Behavioral pattern monitor (BPM)—Sixty-three C57BL/6J mice (31 female, 32 male) were obtained from Jackson Laboratories and tested at approximately 4 months of age. One month prior, these mice had previously been utilized for an unrelated study where they received a single intraperitoneal injection of either 0.56 mg/kg mecamylamine or saline immediately before a single 5-min session of the forced swim task. No other testing or experimental manipulation took place in the intervening period between these two

experiments. Throughout all procedures, these mice were housed 4 per cage in a reverse 12-h light-cycle (lights off at 8:00 a.m.) room in a UCSD-operated vivarium with food (Harlan 8604, Madison, WI, USA) and water available ad-libitum, except during the BPM test. Animals were transported to the testing room by 10:00 a.m. and allowed to acclimate for 1 h prior to testing, which took place between 11:00 a.m. and 5:00 p.m. over two consecutive days. Male mice were tested on day 1 and females on day 2. All testing procedures were approved by the UCSD Institutional Care and Use Committee, and all facilities met federal and state requirements for animal care as approved by the American Association for Accreditation of Laboratory Animal Care.

Methods and testing equipment for the mouse BPM have been described in detail previously (Geyer et al., 1986; Minassian et al., 2016; Perry et al., 2009; Risbrough et al., 2006; Young et al., 2010). Mice were tested in eight BPM chambers; each chamber consisting of a $30.5 \times 60 \times 38$-cm arena designed to detect horizontal and vertical activity, as well as nosepoking. Mice were placed in the upper left corner of the chamber at the beginning of a session which was immediately initiated.

Primary dependent measures were total activity counts, hole-pokes, rearing, and spatial d. Data were analyzed using ANOVA, with between-subjects factors of sex and treatment. Dependant variables were collapsed across sex where no main effect of sex was observed. Data were analyzed using Biomedical Data Programs software (Statistical Solutions Inc., Saugus, MA, USA) with an alpha level of 0.05.

2.2.2.   Drug preparation—Modafinil (Sigma Aldrich, St. Louis, MO, USA) was dissolved in warm (60°C) homogenized vehicle (1% methylcellulose and 5% Tween 80 in saline) and sonicated for 1 h at room temperature to produce the 32 mg/kg dose, from which 10.1 and 3.2 mg/kg doses were created. These doses were chosen for compatibility (in terms of mg/kg vs. human study) and with previous evidence of treatment-induced hyperarousal and increased wakefulness in mice (Willie et al., 2005). In the absence of a thorough and specific cross-species pharmacokinetic analysis of modafinil, we used dose conversion guidelines from Nair and Jacob (2016) to guide equivalent dosing in mice. Specifically, we divided the human dose (mg/kg, based on average bodyweight of participants) by a conversion factor of 0.081. The dose calculated came to roughly 33 mg/kg. Based on our own data, 32 mg/kg is sufficient to induce hyperactivity in the BPM (Young et al., 2011a) leading us to believe this estimated dose was higher than the dose required to improve 5C-CPT performance in our participants. Given that these guidelines were not specific to modafinil and based solely on human bodyweight in our studies resulted in doses of 3.2 mg/kg (for 200 mg), we therefore included two half-log doses lower starting from 32 mg/kg (10.1 and 3.2 mg/kg). Mice received one of three doses of modafinil or vehicle via intraperitoneal injection (10 ml/kg) immediately prior to the start of testing.

3.   Results

3.1.   Demographics and treatment randomization

Demographic information and treatment group sample sizes are reported in Table 2. Although a greater number of female participants participated in this study, the gender

difference did not reach statistical significance (Pearson $\chi^2_{(1,62)}$ = 1.61, p = 0.20). There were more females than males in the modafinil groups; this difference approached statistical significance (Fisher's Exact Test $_{(2,62)}$ = 4.43, p = 0.11). Participants did not differ significantly in terms of age ($F_{(2,61)}$ = 1.32, n.s.) or education ($F_{(2,61)}$<1, n.s.), although Body Mass Index (BMI) was higher in participants in the 200 mg modafinil group compared to placebo ($F_{(2,55)}$ = 4.89, p < 0.05).

3.2. Modafinil improved attention in healthy volunteers

Modafinil significantly improved attention as measured by d prime, ($F_{(2,58)}$ = 4.4, p < 0.05, partial η^2 = 0.18; Fig. 1A). *Post-hoc* analyses revealed that this enhancement was found with both doses of modafinil compared to placebo ($p < 0.05$). This improvement was driven by a strong trend towards increased hit rate, representing improved target detection ($F_{(2,58)}$ = 2.8, p = 0.07, partial η^2 = 0.019; Fig. 1B) in modafinil-compared to placebo-treated individuals ($p < 0.05$). Modafinil did not significantly alter false alarm rate, mean reaction time, or reaction time variability ($Fs_{(2,58)}$<1, n.s., Fig. 1C–F). No significant main effects or interactions with gender were evident for any of these variables.

3.3. Modafinil did not produce hyperactivity in healthy volunteers at pro-cognitive doses

Modafinil did not significantly alter any measure of activity in the human BPM as measured by activity counts, acceleration, specific object interactions, or spatial d ($Fs_{(2,57)}$<1, ns, Fig. 2A–D).

Because BMI was higher in the 200-mg modafinil group compared to placebo, the human BPM analyses were repeated with BMI as a covariate. There was no main effect of BMI nor did any of the activity measures reach or approach statistical significance.

3.4. Modafinil did not effect WCST performance

Modafinil did not significantly modify any measure of cognitive control or flexibility measured by the WCST ($Fs_{(2, 54)}$ 1.95, ns, Table 3). No significant sex by drug interactions were observed on any measure ($Fs_{(2, 54)}$ 1.88, ns).

3.5. Modafinil produced hyperactivity only at high doses in mice

Modafinil significantly increased activity (BPM transitions, $F_{(3,55)}$ = 10.2, p < 0.001, partial η^2 = 0.36; Fig. 3A). Post-hoc analyses revealed that only the 32 mg/kg modafinil significantly increased transitions compared with vehicle and all other groups ($p < 0.05$). Modafinil had no significant effect on holepoking ($F_{(3,55)}$<1, ns, Fig. 3B). Modafinil also significantly increased exploration (rearing, $F_{(3,55)}$ = 4.7, p < 0.01, partial η^2 = 0.20; Fig. 3C) and decreased spatial d ($F_{(3,55)}$ = 4.0, p < 0.05, partial η^2 = 0.18; Fig. 3D), again selectively at the 32 mg/kg dose. Main effects of sex were only observed on rearing ($F_{(3,55)}$ = 10.4, p < 0.01; partial η^2 = 0.16), with male mice exhibiting significantly more rearing than females. No significant sex by drug interactions were observed on any measure.

4. Discussion

Here, we report that modafinil improved 5C-CPT performance. Further, enhancement of attention/cognitive control was achieved at doses that did not induce hyperarousal in either healthy volunteers or mice. Therefore, it appears that the pro-cognitive effects of modafinil may be domain-specific, occurring independently from the levels of arousal induced by similar drugs, supporting its use as a pro-cognitive pharmacotherapy with a likely limited abuse potential.

Modafinil significantly improved attention in healthy volunteers as measured by d prime. This modafinil-induced improvement arose from a strong trend of modafinil increasing target detection (hit rate). Importantly, this increased target detection was accompanied by a reduced false alarm rate (though non-significant). Hence, modafinil-induced increased target detection was not driven by increased overall responsivity to stimuli, as supported by no change in reaction times. The human BPM and WCST data provide further evidence that the modafinil-induced improvement in attention (via target detection) was domain-specific, given that 5C-CPT improvement did not result from hyperarousal or preservative behavior in these volunteers. Cross-species testing in mice was able to replicate previously reported hyperactivity induced by high doses of modafinil (Young et al., 2011a), and demonstrate that this effect was observed irrespective of sex. Moreover, this modafinil-induced hyperactivity was not observed at lower doses, which may better represent the doses used in humans. Overall, these data indicate pro-cognitive properties of modafinil within the domain of attention and cognitive control at therapeutic doses that do not induce hyperactivity in healthy volunteers.

To our knowledge, these data represent the first evidence that modafinil can enhance baseline attention of healthy adults. Previously, improvements in cognitive function have been limited to studies involving tasks requiring exceptionally high cognitive demand (Muller et al., 2013), tasks unable to dissociate attention from other domains (Randall et al., 2005), or with participants experiencing sleep deprivation (Baranski et al., 2004; Muller et al., 2004), or psychiatric impairment (Minzenberg and Carter, 2008). Consistent with previous set-shifting-based tasks (Turner et al., 2003), modafinil did not affect WCST performance in healthy subjects. The 5C-CPT improvements highlighted in this investigation may therefore indicate highly domain-specific efficacy to improve attention and cognitive control of modafinil in improving baseline cognitive performance. The mechanism of action underlying this effect remains to be determined however. The pro-cognitive effects of modafinil may arise from its ability to facilitate middle frequency cortical oscillations (theta, alpha, beta) acutely (Minzenberg et al., 2014a, 2014b), or higher frequency cognitive-control related activity (gamma) with sustained treatment (Minzenberg et al., 2016). Further, McKenna and colleagues (McKenna et al., 2013) identified numerous regions underlying 5C-CPT performance using fMRI. They identified task-specific activation of premotor cortex, inferior parietal lobe, basal ganglia, and thalamus during target trials. In addition, activation in inferior frontal cortex, premotor cortex, presupplementary motor area, and inferior parietal lobe were observed during non-target trials. Given that this task is available for use in rodents (Barnes et al., 2012a, b; Young et al., 2009), future investigation will assess regional and/or neurochemical contributions to

distinct aspects of 5C-CPT task performance to determine where/how modafinil improves attention. Identification of these targets, which have remained elusive to date, could provide key insights leading to the development of more targeted pro-cognitive therapeutics.

Given its limited affinity for DAT and NET (Volkow et al., 2009), the primary sites of action for classical stimulants that induce arousal states such as cocaine or amphetamine, it was necessary to determine whether these pro-cognitive effects were simply due to hyperarousal in the volunteers. At the pro-cognitive doses in healthy human volunteers, we found no evidence of hyperarousal in the BPM. Based on the weight of the human volunteers, the 200 and 400 mg doses equated to around 3.2–5.0 mg/kg. When assessed in mice, this dose (3.2 mg/kg) also did not affect activity in the BPM. Higher doses (32 mg/kg) were required to induce measurable arousal in both male and female mice, consistent with our earlier studies in males only (Young et al., 2011a). Ideally comparisons could be made at doses that achieve comparable peak plasma concentrations across species, although plasma concentrations and exact scaling parameters at doses <32 mg/kg have not been determined in C57Bl-6 mice to our knowledge. Given that modafinil is approved for treatment of narcolepsy, its therapeutic doses are thought to be comparable to wake-inducing (reducing non-REM sleep, increasing wakefulness) behavior in mice, observed in doses as low as 10 mg/kg (Willie et al., 2005). This dose resulted in modest but non-significant arousal effects in the BPM. While the current studies are not sensitive to rule out modest increases in arousal, these findings do support a lack of hyperarousal at these low doses in mice and in humans. Alternatively, calculations based on potential metabolism differences between mice and humans (Nair and Jacob, 2016) estimated the 400 mg dose (which improved 5C-CPT performance in humans), would be equivalent to 33 mg/kg in mice, the dose that induced hyperactivity in the mouse BPM here and in previous reports (Young et al., 2011a). It is therefore unlikely, that properties of modafinil conform to these general guidelines given the comparable wake-promoting effects described in mice at doses as low as 10 mg/kg (Willie et al., 2005). Similar scaling properties in the BPM have also been reported for amphetamine. When only accounting for cross-species differences in metabolism, doses of amphetamine producing hyperactivity in mice are insufficient to induce hyperactivity in humans (Minassian et al., 2016). Taken together, these data support the conclusion that the efficacy of modafinil as a cognitive enhancer is not attributable to a significant increase in overall arousal and, when tested in rodents, doses from 3 to 32 mg/kg should be investigated.

The potential pro-cognitive effects of modafinil are unlikely to be limited to one domain, (Minzenberg and Carter, 2008; Sahakian and Morein-Zamir, 2015), hence others remain to be tested. For example, although accurate performance in 5C-CPT was never explicitly rewarded, ongoing performance monitoring by the volunteer could imbue a degree of feedback-related reward, another behavior highly susceptible to reduction or inhibition of catecholamine reuptake (van Enkhuizen et al., 2013b; Young et al., 2011c; Zeeb et al., 2009). Hence, investigating feedback-related behavior would be beneficial. For example, the Iowa Gambling Task is another available cross-species task that measures feedback-related behavior during risky decision-making. Such tasks performed in humans and mice could be utilized to test whether the effects observed in the 5C-CPT were due to enhanced feedback-related processing of information in the task itself. In addition, using this cross-species task would further enable delineation of the mechanism(s) of action of modafinil (Young et al.,

2011a). If modafinil were found to increase reward-related feedback processing, concerns regarding abuse potential could increase and hamper the possible therapeutic use of modafinil as a cognitive enhancer. Additional known modafinil sites of action that could produce cognitive enhancement include effects on serotonin (Tanganelli et al., 1992), histamine (Scammell et al., 2000), orexin (Willie et al., 2005), GABA, or glutamate signaling (Ferraro et al., 1999). Studies assessing their potential role in these effects are required in the future, with the availability of the rodent 5C-CPT making such studies possible.

These findings are limited by significant differences in the gender makeup of the treatment groups. Overall, a greater number of females participated in the human studies and treatment randomization resulted in fewer males in the two modafinil groups compared to placebo. As a result, this study was likely underpowered to detect drug by gender interactions, increasing the probability of type II error in the BPM experiment if a sexually dimorphic response to modafinil exists. If this were the case, any heightened response to modafinil in males in the BPM could have been statistically blunted overall by the low participation of this group. Given a review of the literature, there is little evidence currently to suggest a sexually dimorphic response to modafinil. Further, no sexually dimorphic response was observed in mice where statistical power was not an issue. Thus, while further study will be required to fully rule out this possibility, we do not find convincing evidence to suspect prominent gender differences in the present study.

5. Conclusions

In summary, it is clear that modafinil effectively enhances cognitive ability within the domain of attention and cognitive control in healthy adult volunteers. Further, this pro-cognitive effect is domain-specific insofar as it is achieved at doses that did not result in hyperactivity. Although the precise mechanism underlying this effect remains to be determined, the availability of rat and mouse 5C-CPTs (Barnes et al., 2012a, b; Young et al., 2015; Young et al., 2011b) enables the use of neuroscience techniques to determine underlying mechanisms. Furthermore, given that patients with schizophrenia exhibit deficient 5C-CPT performance (Young et al., 2013), the present findings support the suggestion that modafinil may remediate such a deficit.

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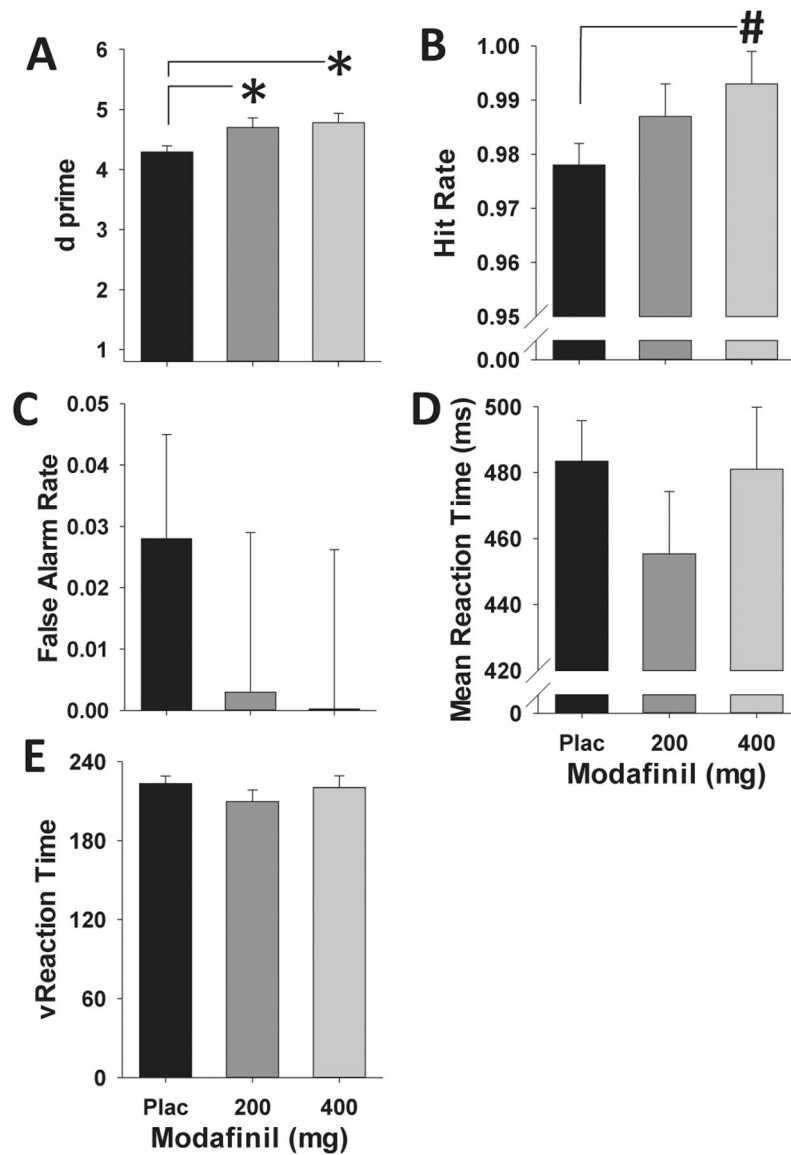
**Fig. 1. Modafinil Improves Attention as Measured by the 5C-CPT.**
D prime is significantly increased compared to placebo (Plac) by the 200 and 400 mg doses of modafinil (A). This modafinil-induced enhancement of signal detection was driven by a strong trend toward improved hit rate (target detection) in these groups (B). No significant effects of modafinil were observed in terms of false alarm rate (C), mean reaction time (D), or reaction time variability (E), at the doses tested. Data presented as mean + SEM, * denotes $p < 0.05$ vs. Plac. # denotes $p < 0.1$ vs. Plac.
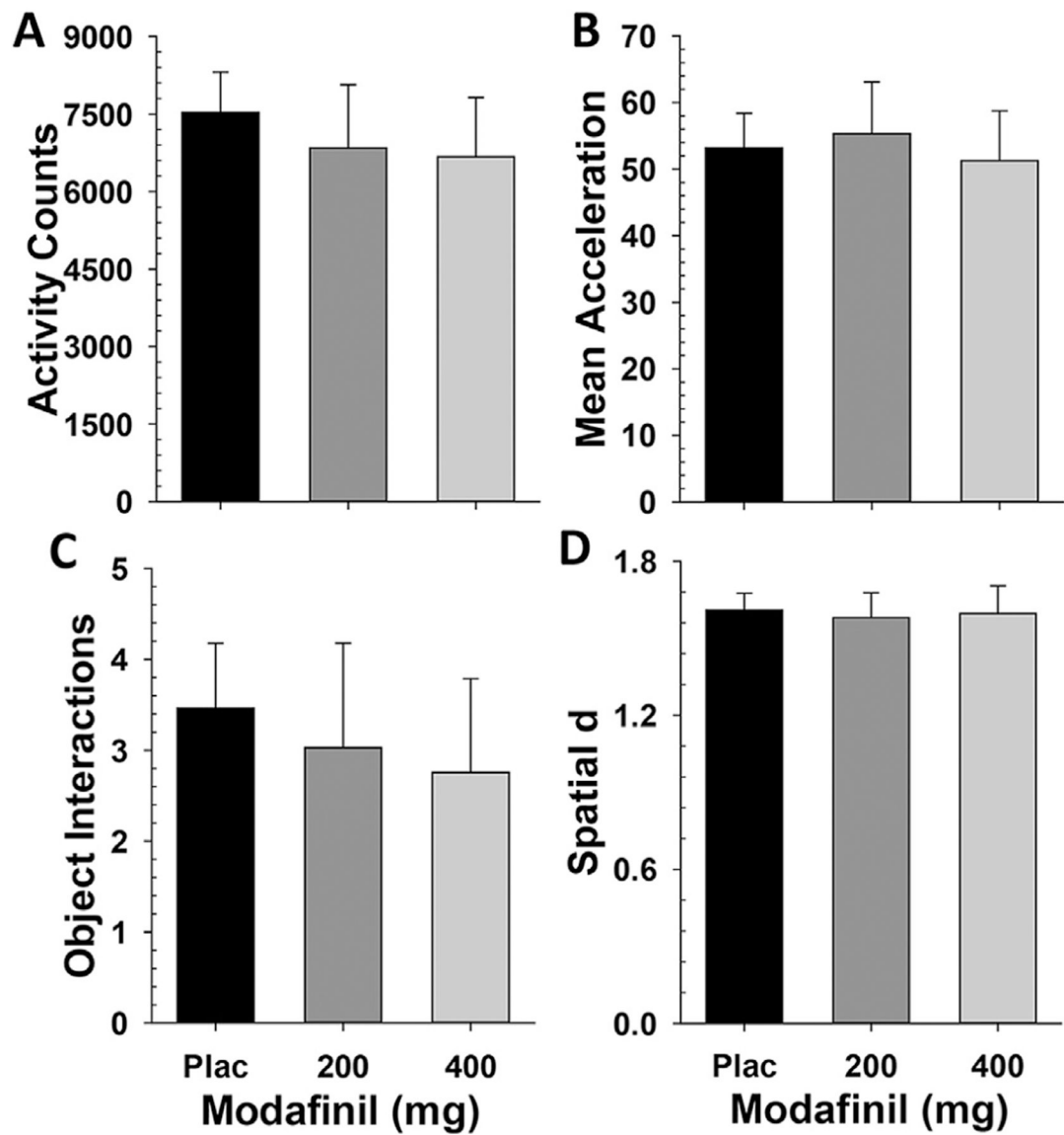
Fig. 2. Modafinil does not induce hyperactivity in the human BPM at doses efficacious to improve attention.

In humans, modafinil did not produce significant increases in locomotor activity measured by total activity counts (A), acceleration (B), or specific object interactions (C), nor did it affect spatial d (D). Data presented as mean + SEM.
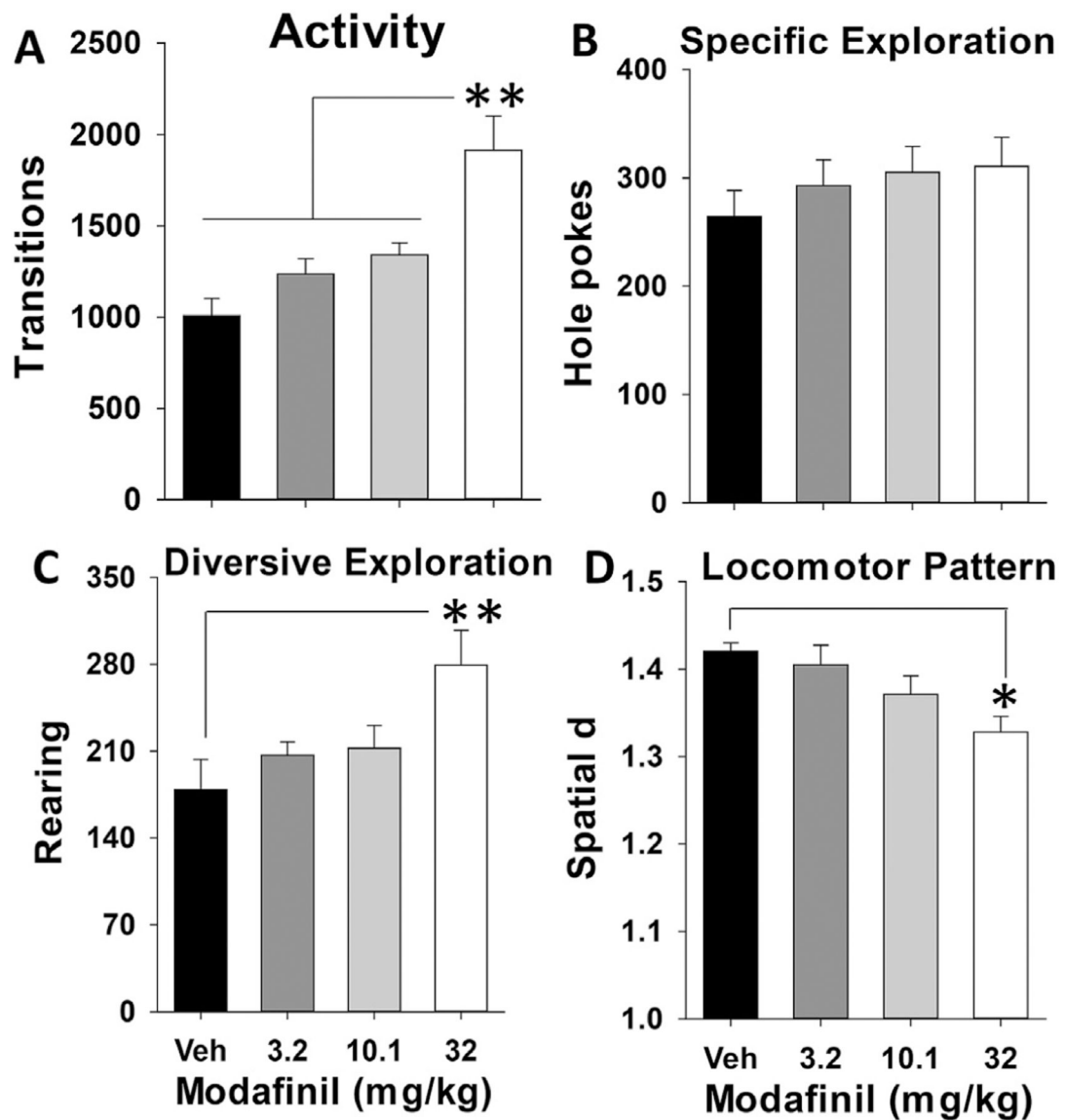
Fig. 3. Modafinil induces hyperactivity in mice at high doses.
Modafinil dose dependently increased horizontal activity (A) at 32 mg/kg compared to all other doses. No significant changes in specific exploration (hole poking) (B) were seen at any dose of modafinil. Diversive exploration (rearing) (C) was significantly increased compared to control at the highest dose. The 32 mg/kg dose also significantly decreased circumscribed, meandering locomotor patterns as measured by spatial d (D). Data presented as mean + SEM, * denotes $p < 0.05$ vs. vehicle (Veh), ** denotes $p < 0.01$ vs. Veh.
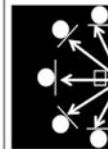
Table 1

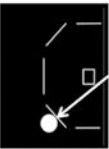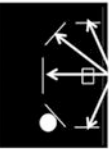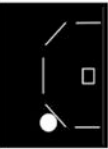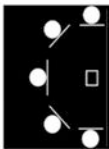**A description of behavior, calculations, and interpretation used to quantify effects in the 5C-CPT.**

White arrows in diagrams indicate possible joystick movements for the behavior being demonstrated.

Behavior/Calculation	Measure	Description
	Hit	Response to target stimulus in correct location
	Incorrect	Response to target stimulus, but in the wrong location
	Miss	Nonresponse (failure to respond) to target stimulus
	Correct Rejection (CR)	Appropriate withholding of prepotent response to nontarget stimulus
	False Alarm (FA)	Innappropriate non-withholding of prepotent response to nontarget stimulus
	Premature	Response during intertrial interval when no stimulus has yet been presented
Total elapsed time to respective action	Cumulative Latencies	Cumulative latencies to responses, including correct, incorrect, false alarms, and premature responses
$\dfrac{\text{Hits}}{(\text{Hits + Misses})}$	Hit Rate (pHR)	Proportion of correct responses vs. misses to target stimuli
$\dfrac{\text{False Alarms}}{(\text{False Alarms + Correct Rejections})}$	False Alarm Rate (pFA)	Proportion of false alarm responses vs. correct withdrawal to non-target stimuli
z(pHR)-z(pFA)	d Prime	Parametric measure for the difference between p[Hit Rate] and p[False Alarm Rate] to determine *differentiation of stimuli*

Table 2

Demographic information for subjects given placebo (n=33), modafinil 200 mg (n=14) and modafinil 400 mg (n=15).

Groups differed only in Body Mass Index (placebo < 200 mg modafinil, * = main effect of group). No other significant differences were found for any other variable analyzed.

Variable	Placebo	200 mg Modafinil	400 mg Modafinil
Sex			
Male	18	4	4
Female	15	10	11
Mean (SD) age in years	23.4 (4.2)	24.6 (4.0)	25.5 (5.3)
Mean (SD) years of Education	14.8 (1.8)	14.9 (2.1)	14.7 (1.4)
Mean (SD) Body Mass Index * (kg/m^2)	22.7 (3.0)	26.7 (5.2)	24.8 (4.2)

Table 3

Modafinil does not significantly alter performance of the WCST.

Measure	Mean (SEM)	F	p-value
Total Correct		0.73	0.49
Placebo	48.3 (1.8)		
200 mg Modafinil	45.4 (3.1)		
400 mg Modafinil	46.6 (3.3)		
Total Errors		0.75	0.48
Placebo	15.6 (1.8)		
200 mg Modafinil	18.6 (3.1)		
400 mg Modafinil	17.4 (3.3)		
% Perseverative Responses		0.91	0.41
Placebo	37.4 (1.8)		
200 mg Modafinil	28.3 (8.8)		
400 mg Modafinil	44.6 (3.6)		
% Perseverative Errors		1.04	0.36
Placebo	35.2 (4.6)		
200 mg Modafinil	27.9 (7.8)		
400 mg Modafinil	45.1 (8.4)		
% Nonperseverative Errors		0.09	0.91
Placebo	50.6 (5.2)		
200 mg Modafinil	50.4 (8.8)		
400 mg Modafinil	54.3 (9.4)		
Categories Completed		0.24	0.79
Placebo	3.5 (0.3)		
200 mg Modafinil	3.3 (0.4)		
400 mg Modafinil	3.6 (0.5)		
Trials to Complete 1st Category		1.95	0.15
Placebo	14.2 (2.3)		
200 mg Modafinil	19.5 (3.8)		
400 mg Modafinil	21.3(4.1)		