Original Articles

The impact of psychostimulants on sustained attention over a 24-h period

Lauren N. Whitehurst[a,*], Sara Agosta[b], Roberto Castaños[c], Lorella Battelli[b,d], Sara C. Mednick[e]

[a] *Department of Psychiatry, University of California, San Francisco, CA, USA*
[b] *Center for Neuroscience and Cognitive Systems@UniTn, Istituto Italiano di Tecnologia, Rovereto, Italy*
[c] *School of Medicine, University of California, Riverside, CA, USA*
[d] *Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA*
[e] *Department of Cognitive Science, University of California, Irvine, USA*

ABSTRACT

The off-label use of psychostimulants is a growing trend in healthy adults with many turning to these medications to increase alertness, attentional focus, and to help them study. However, the empirical literature on the efficacy of these medications for cognitive enhancement is controversial and the longer-term impact of these drugs on health and cognitive processing has not been thoroughly examined. Specifically, sleep supports daytime alertness, vigilance, and sustained attention, yet stimulants significantly disrupt sleep. Here, using a double-blind, placebo-controlled, crossover design, we tested the impact morning administration of psychostimulants (dextroamphetamine; DEX) had on: (1) tests of attention 75-min and 12-h after drug ingestion, (2) nighttime sleep and (3) post-sleep attention in healthy, young adults. First, we found that repeated testing led to significant decreases in performance from baseline in the placebo condition, and that DEX, compared to placebo, prevented deterioration at the 75-min test, and selectively for visual field at the 12 h and 24 h tests. We also found that stimulants, compared to placebo, benefitted attentional processing 75-min post-drug but this did not persist to the delayed test 12-h after drug administration. Additionally, morning stimulant administration resulted in robust nighttime sleep disruptions, yet post-sleep sustained attention was equivalent in the stimulant and placebo conditions, indicating that the initial boost to performance dissipated at 24 h, but the decrease was not significantly worse than placebo. Together, these results suggest that stimulant medications, commonly used off-label for cognitive enhancement may prevent deterioration of sustained attention brought on by repeated within-day testing. Additionally, these medications substantially disrupt nighttime sleep; which while coming at little cost to next-day attentional processing, may have steeper consequences for other cognitive domains.

1. Introduction

Amphetamine stimulants have been used effectively to treat neurobehavioral disorders (e.g. Attention Deficit Hyperactivity Disorder) and sleep/wake disruptions (e.g. excessive daytime sleepiness, narcolepsy) since the early twentieth century. However, more recently, these stimulant medications have been increasingly used off-label by healthy students and young professionals (Klein-Schwartz, 2002; Swanson, Wigal, & Volkow, 2011; Wilens et al., 2008) with the hope that these substances will enhance cognitive performance (Rabiner et al., 2009; Smith & Farah, 2011). While some academic commentaries have embraced a positive association between stimulants and cognition (Greely et al., 2008), empirical studies have yet to show conclusive findings, with differential effects both within and across cognitive domains (Ilieva, Boland, & Farah, 2013; Volkow et al., 2004; Mommaerts et al.,

2013; see Repantis, Schlattmann, Laisney, & Heuser, 2010; and Smith & Farah, 2011 for review).

One cognitive domain that has been the focus of several studies is attention— the sustained allocation of processing resources to relevant stimuli. Off-label users consistently endorse attentional-related benefits as a main reason for stimulant use (Rabiner et al., 2009; Teter, McCabe, LaGrange, Cranford, & Boyd, 2006), however the literature is inconclusive. For example, several studies have shown positive associations for both vigilance and attention (see Bagot and Kaminer, 2013 for review), whereas a *meta*-analysis of 10 cognitive enhancement studies examining an array of attentional tasks (e.g. simple and choice reaction time, selective and divided attention) found no benefit to attention from a single dose or repeated administration of amphetamine-based stimulants (vs. placebo; Repantis et al., 2010). Interestingly, most of the existing literature has used short-term experimental paradigms geared

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* Corresponding author.
  E-mail address: lauren.whitehurst@ucsf.edu (L.N. Whitehurst).

toward exploring the acute impact of prescription stimulants on cognitive performance, while little has focused on the longer-term consequences of off-label stimulant use. However, considering the growing trend in the use of prescription stimulant medications by healthy young adults (Swanson et al., 2011; Wilens et al., 2008), understanding subsequent health and cognitive consequences associated with non-medically necessary stimulant use is becoming more essential.

The obstruction of sleep (i.e. prolonged wakefulness) is a primary reason for off-label stimulant use in healthy adults [Sweeney, Sembower, Ertischek, Shiffman, & Schnoll, 2013; Teter et al., 2006; Wilens et al., 2008). Accordingly, one group of researchers reported that college students currently using or with a history of nonmedical psychostimulant use had decreased subjective sleep quality, increased sleep disturbance, and worse Pittsburg Sleep Quality Index scores when compared to non-users (Clegg-Kraynok, McBean, & Montgomery-Downs, 2011). Importantly, adequate nighttime sleep has been widely shown to support cognitive fitness, specifically daytime alertness, vigilance and sustained attention (Durmer & Dinges, 2005; van Dongen, Maislin, Mullington, & Dinges, 2003). Further, the daytime administration of psychostimulants (compared to placebo) has resulted in substantial nighttime sleep disruption (Barbanoj et al., 2008; Saletu et al., 1989). However, the impact of stimulant-induced sleep deterioration on subsequent cognitive processing has not been explored. This lack of research is surprising considering it has been established that psychostimulants may differentially impact cognitive performance depending on previous sleep quality (Bishop, Roehrs, Rosenthal, & Roth, 1997). In particular, one study showed that stimulants disproportionately benefit performance on a divided attention task when participants received less sleep (4 vs 8 h) the night before testing (Roehrs, Papineau, Rosenthal, & Roth, 1999). Still, the effect of stimulant's corrosion of nighttime sleep and the long-term impact on subsequent cognitive processes has not been carefully examined, which is the goal of the current study.

Here, we examined the acute and delayed (12 and 24 h) impact of stimulants on attentional processing and sleep. We used a within subjects, double-blind, placebo-controlled, crossover design, to examine the impact of morning administration of psychostimulants (dextroamphetamine; DEX) compared to placebo (PBO) on three testing conditions: (1) 75-min post-drug, (2) 12-h post-drug and (3) 24-h post-drug. We also measured brain activity during the night with electroencephalography (EEG) to examine the effect of stimulants on sleep architecture. We used a multiple object tracking (MOT) task; a well-validated task of sustained attention, whereby subjects are asked to track a subset of moving circles among moving distractors (Battelli, Alvarez, Carlson, & Pa-Leone, 2009; Pylyshyn & Storm, 1988). We examined both unilateral tracking performance, in which target objects were presented to either the left or right visual hemifield, and bilateral performance, where target objects were presented in both visual fields, simultaneously. Including a 24-h window in this methodological design allowed for a more careful examination of the interaction between the drug, attentional ability, and sleep physiology. Considering prior work showing acute cognitive-arousing properties of the stimulant that dissipate across the day (Asghar, Tanay, Baker, Greenshaw, & Silverstone, 2003), we hypothesized that, compared to placebo, stimulants would have an acute benefit on both unilateral and bilateral attentional tracking, but that these effects would not be present at a 12-h delay test. However, in terms of stimulant effects on sleep, prior studies have shown that physiological effects of stimulants on heart rate and blood pressure can outlast measurable performance change (Asghar et al., 2003; Barbanoj et al., 2008), suggesting that we should find significant sleep disruption even with morning drug administration. Furthermore, we predict reductions to post-sleep MOT performance as a result of the sleep impairment in the DEX group compared with PBO.

2. Experimental methods

2.1. Subjects

Forty-three, non-smoking participants between the ages of 18 and 35 (M_{age} = 20.60 ± 2.64 years, 22 Females) with no personal history of neurological, psychological, or other chronic illness provided informed consent, which was approved by the Western Institutional Review Board and the University of California, Riverside Human Research Review Board. Participants received monetary compensation. Individuals were excluded from participation if they self-reported: irregular sleep/wake cycles; a sleep disorder; personal or familial history of diagnosed psychopathology; personal history of high blood pressure, substance abuse/dependence; loss of consciousness greater than 2 min or a history of epilepsy; current use of psychotropic medications; non-correctable visual impairments and any cardiac or respiratory illness that may affect cerebral metabolism. This was determined during an in-person assessment in which research personnel conducted a modified version of the DSM-IV interview as well as reviewed a series of self-report health and wellness questions. Additionally, all participants underwent a medical history and physical appointment with a staff physician. All subjects were naïve to (or had limited contact) with either of the active medications in the study (< 2 lifetime use and no use in last year). No adverse events were reported by participants throughout the study.

2.2. Pharmacology

We used a single 20-mg dose of immediate release d-amphetamine (DEX) as it has been shown to produce modest but reliable behavioral effects in human volunteers in previous studies of stimulant cognitive enhancement (Brauer & de Wit, 1996; de Wit, Enggasser, & Richards, 2002). Immediate release DEX is a sympathomimetic amine with CNS stimulant activity (Federal Drug Administration, 2007) that reaches peak plasma concentrations by 3-h and has a mean elimination half-life between 4 and 6 h (Kolar et al., 2008). DEX and placebo capsules (PBO) were prepared by the MDMX Corona Research Pharmacy. DEX powders were encapsulated and visually indistinguishable from the placebo capsules, which were made of microcrystalline cellulose and contained no active medications.

2.3. Experimental design and protocol

2.3.1. Experimental design

This study employed a double-blind, placebo-controlled, within-subject, cross-over design. The order of drug conditions was randomized and counterbalanced. There was at least a one-week interval between each experimental visit to allow for drug clearance.

2.3.2. Procedure

All participants wore an actigraph and completed daily sleep diaries for one week prior to each in-lab visit to ensure participants were not sleep-deprived, received an average of 8 h of sleep per night, and spent at least 7 h in bed the night prior to each experimental visit. This was confirmed prior to each lab visit. Subjects reported to the laboratory at 8:00 AM. After compliance with sleep procedures was verified (5–10 min), subjects began the morning session where baseline speed thresholds for the MOT were calculated (see below). Shortly after, at 9:00 AM, either DEX or PBO was administered. Seventy-five minutes after drug ingestion (10:15 AM), when stimulant and placebo differences become maximally apparent (Asghar et al., 2003), participants were re-tested on the MOT task (Test I). After this testing period, subjects remained in the lab and were monitored by research assistants for four hours; after this monitoring period, subjects were permitted to leave the lab if study personnel confirmed that: (1) their systolic blood pressure was below 140 and their diastolic blood pressure was below

90, (2) resting heart rate below 100 bpm and (3) they did not report experiencing a racing heart, dizziness, headache, or nausea. During their time away, subjects were asked not to exercise, sleep, or consume drug substances. To ensure compliance, subjects wore their actigraph watch to monitor their sleep/wake activity and on their return to the lab they were asked to verbally confirm that they did not ingest any drug substances while they were away from the lab. At 9:00 PM, all subjects returned to the lab for another testing session, Test II. After task completion, subjects were prepared for nighttime sleep. A 32-channel electrode cap was attached to each participant followed by lights out at 11:00 PM. Participants were all provided private, sound-proofed rooms in the research sleep lab. Multiple participants could be tested in an individual night, however, much care was taken in the design of the sleep lab space so that minimal, if any, disruptions to sleep were a result of other participants in the study. Each night, participants were provided 10 h of time in bed and were awoken at 9:00 AM. This bedtime window was based on recommendations from the National Sleep Foundation (Hirshkowitz et al., 2015), however, subjects were not required to remain in bed for the entire window. Participants were encouraged to try to attain more sleep if they awoke prior to the 9:00 AM rise time, however they could begin morning procedures if they were not willing to remain in bed. Three subjects on the PBO night and seven subjects on the DEX night awoke before the scheduled Lights On time. Shortly after waking, subjects were provided a standardized breakfast and then retested on the MOT at 10:30AM (Test III) before they were permitted to leave the lab.

2.3.3. Multiple Object Tracking (MOT) task

Stimuli were presented using the psychophysical toolbox PsychoPy. As depicted in Fig. 1, all trials began with a white fixation point (a black circle, radius = 0.15°) on a gray background. At the start of the trial,

eight small, black circles (radius = 0.3°) were displayed on a computer screen, four on either side of a centered fixation. As the trial began, a subset of either 2 or 4 of the black circles began to flash at 2 Hz for 2 s, indicating them as targets. Once the target circles stopped flashing, they became indistinguishable from the other circles. Next, all circles moved on the screen in random, independent directions for 5 s, within a 6 × 6° region and centered 2° to the left and right of the fixation. During each trial, items did not cross the midline, moved at a constant speed, re-pelled each other to maintain center-to-center spacing of 1.5° and bounced off the invisible edges of the square region in which they moved. When the motion stopped, two of the circles were highlighted red and participants were asked if the circles were or were not initial targets. Subjects were prompted to respond using predetermined keys on the keyboard. There were two distinguishable trial types in each session, unilateral and bilateral. For the unilateral trials, two targets were flashed on one side (left or right) of the fixation, however for the bilateral trials, four targets were indicated, two targets on each side of the fixation cross. This resulted in 4 trial types: unilateral left (UniLeft), unilateral right (UniRight), bilateral left [(whereby the target will be tested in the left hemifield only, BiLeft) and bilateral right (BiRight; Fig. 1b) and subjects completed 16 trials per condition.

2.3.4. Baseline speed thresholds

To accurately assess each participant's attentional ability, we calculated individualized speed thresholds for the MOT task at the start of each experimental day. Thresholds were calculated for each task condition, UniLeft, UniRight, BiLeft, BiRight, as the speed at which participants could track the moving targets at 80% accuracy. Speed thresholds (cm/sec) were calculated separately and for each task condition (UniLeft UniRihgt, BiLeft, BiRight). Participants completed eight interleaved 3/1 staircases to assess their individual speed thresholds.
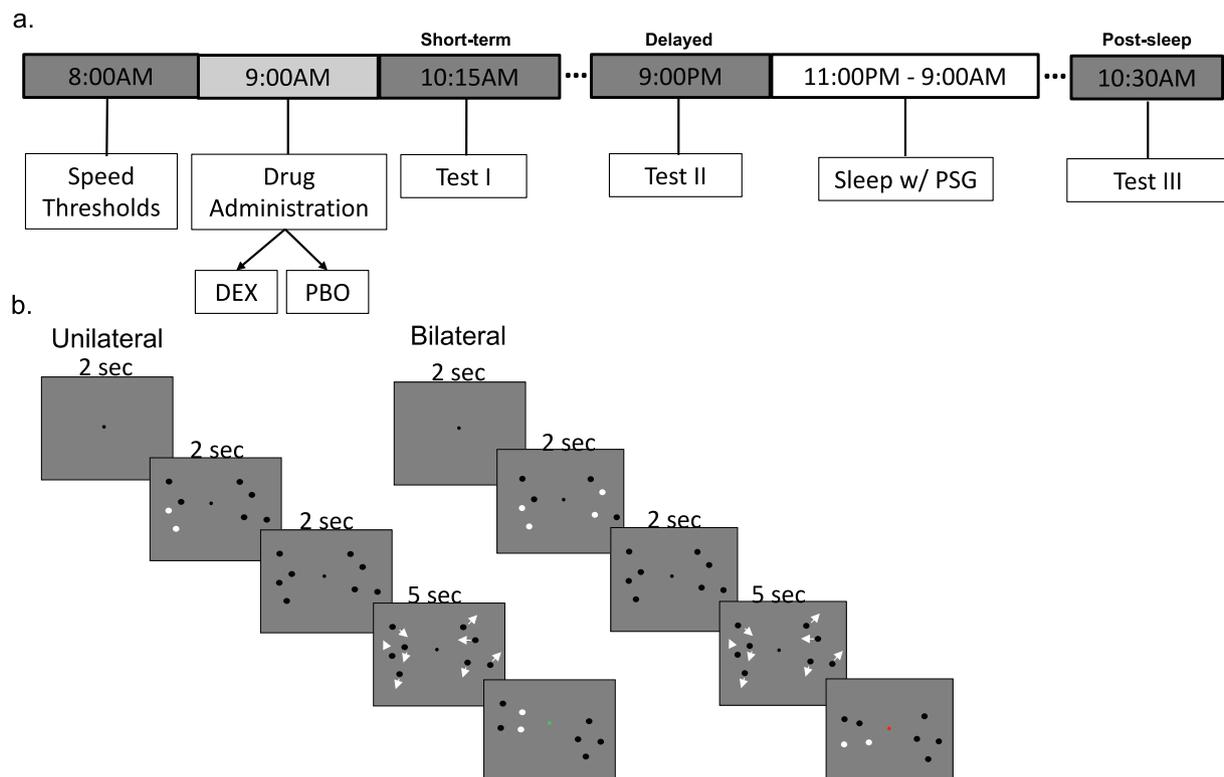

Fig. 1. Protocol & Multiple Object Tracking Task. (a) Study day protocol is depicted. (b) For the MOT task, all trials began with a black fixation on a gray background. At the start of the trial, eight small, black circles, were displayed on a computer screen, four on either side of a centered fixation cross. As the trial began, a subset of the black circles (either 2 or 4) began to flash, indicating them as targets. Once the objects stopped flashing, the targets became indistinguishable from the other objects. Next, all objects moved in random, independent directions (indicated by arrows) for 5 s. When motion ceased, two of the small, black circles were highlighted red (white here for display) and participants responded (using predetermined keys on a keyboard) if the circles were or were not two of the original flashing targets. Subjects were provided feedback via the center fixation, with a green circle indicating correct responses and a red circle indicating incorrect responses.

The staircases increased the speed after three correct trials and reduced it following a single incorrect response. Two staircases (one for the left visual field and one for the right visual field) started from a speed value of 2 cm/sec, the other two staircases started from a speed value of 5 cm/sec. The staircases terminated after a combined 16 reversals, with threshold parameters estimated from the last 3 reversals. Speed was adjusted to yield 80% accuracy in the target/distractor judgments. In order to prevent participants from inferring the appearance of the red circle from the speed at which the circles moved, (that could be different for the left and the right visual fields) we included two types of catch trials: (1) for 25% of the trials target circles moved at the same speed in the left and right visual fields; (2) to prevent the two left and right visual fields' staircase to end off phase (e.g. trials would be presented on one side only), the program continued to also present stimuli on the side where the threshold had been already estimated. Participants took, on average, 45 min to complete the baseline task. Subjects first completed a series of five practice trials in which the circles moved at 2 cm/sec.

2.3.5. Polysomnography (PSG)

EEG data were acquired using a 32-channel cap (EASYCAP GmbH) with Ag/AgCI electrodes placed according to an adapted 10–20 System (Jasper, 1958). 22 out of 32 electrodes were passive scalp recordings. The remaining electrodes were used for electrocardiogram (ECG), electromyogram (EMG), electrooculogram (EOG), ground, an online common reference channel (at FCz location, retained after re-referencing) and mastoid (A1 & A2) recordings. The EEG was recorded with a 1000 Hz sampling rate and was re-referenced to the contralateral mastoid (A1 & A2) post-recording. High pass filters were set at 0.3 Hz and low pass filters at 35 Hz for EEG and EOG. Only eight scalp electrodes (F3, F4, C3, C4, P3, P4, O1, O2), the EMG and EOG were used in the scoring of the nighttime sleep data. Raw data were visually scored by two trained sleep technicians. Prior to scoring these data, technicians were required to reach 85% reliability with each other and one other rater on two independent data sets. Data were scored in 30-sec epochs into Wake, Stage 1, Stage 2, Slow Wave Sleep (SWS; Stages 3 and 4) and rapid eye movement sleep (REM) and according to the Rechtschaffen and Kales (1968) manual. Minutes in each sleep stage were calculated. Additionally, wake after sleep onset (WASO) was calculated as total minutes awake after the initial epoch of sleep and sleep latencies were calculated as the time from lights out until the first epoch of sleep. Sleep efficiency (SE) was computed as total time spent asleep after lights out (11:00 PM) divided by the total time spent in bed (11:00 PM–9:00 AM).

2.3.6. Data reduction

Three subjects completed only one of the necessary visits due to scheduling conflicts and are excluded from both performance and sleep analyses. For two subjects, their morning behavioral performance was not properly recorded by the computer, so their data is not included in Test III's behavioral analyses. For six subjects, their nighttime sleep recording was corrupted and as such, they were not included in the sleep analyses. For two males and one female weight was not assessed during their initial interview. To maintain these subjects, the mean weight (by sex) was calculated and inserted as their values.

2.3.7. Statistical analyses

To assess differences in MOT performance between DEX and PBO at each of the three tests, we used 2X2X2 repeated measures ANOVA's (RM ANOVA) with accuracy (proportion of trials correct at set 80% speed threshold) as the dependent variable and drug condition (DEX vs PBO), Visual Field (Left vs Right) and Trial Type (Uni vs Bi) as within subject factors. We included weight (mean centered) as a covariate in each of these analyses to control for differential drug absorption rates across our participants and include drug order (first visit PBO vs DEX) to control for superficial order effects in cognitive performance. We

report partial eta squared (η_p^2) for effect size. Additionally, we assessed performance change from baseline using one-sample t-tests. Here, we compared performance at each test within trial type (Uni vs Bi) and Visual Field (Left vs Right) for each drug condition (DEX vs PBO) to the 80% baseline accuracy threshold. We used a Bonferroni corrected p-value of 0.002 (p = 0.05/24) to determine significance. To examine the impact of stimulants on nighttime sleep we again utilized RM ANOVAs. Here, we entered each nighttime sleep variable (total sleep time (TST), minutes in each stage (Stage 1, Stage 2, SWS, REM), wake after sleep onset (WASO), sleep latency (time from lights out to first epoch of sleep) and sleep efficiency (SE; total sleep time/time in bed (lights out − lights on * 100) as dependent variables and drug condition (DEX vs. PBO) as the within subject factor. In line with the performance models, we also included weight (mean centered) as a covariate and report partial eta squared for effect size. Lastly, we used Pearsons R to examine the relationship between MOT performance at Test III and the difference score (Test III – 0.80 baseline threshold accuracy) and each nighttime sleep feature.

2.3.8. Data statement

Raw data that support the analyses herein has been made available with the manuscript.

3. Results

Baseline MOT Thresholds: MOT baseline speed averages were as follows: PBO: UniLeft M = 12.31, SD = 3.07; UniRight M = 11.83, SD = 3.56; BiLeft M = 8.01, SD = 2.42; BiRight M = 8.08, SD = 2.52; DEX: UniLeft M = 12.50, SD = 3.37; UniRight M = 12.24, SD = 3.80; BiLeft M = 8.08, SD = 2.52; BiRight M = 7.57, SD = 2.59. No differences between PBO and DEX visits within visual field were present: UniLeft (t = 0.37, p = 0.71), UniRight (t = 0.83, p = 0.41), Bileft (t = 0.19, p = 0.85), BiRight (t = 0.87, p = 0.39)

3.1. What is the immediate impact of stimulants on sustained attention?

First, we examined if individuals performed better in the DEX or PBO condition compared to baseline. Using one-sample t-tests, we compared performance accuracy at Test 1, 75-min after drug ingestion to the 80% accuracy threshold at baseline. For Uni trials, performance did not change from baseline for either DEX or PBO (all p's > 0.08) For Bi trials, individuals performed significantly worse compared to baseline in the PBO condition for both BiLeft (t = −3.85, p < 0.001) and BiRight trials (t = −3.30, p = 0.002). No significant differences were found in the DEX condition compared to baseline after Bonferroni correction (BiLeft: p = 0.15; BiRight: p = 0.01). To examine the impact of DEX compared to PBO 75-min after drug ingestion, we utilized 2X2X2 RM ANOVA's with Drug (PBO vs DEX), Trial type (Uni vs Bi) and Visual Field (Left vs Right) as within-subject factors. Here, a significant main effect of Drug ($F_{(1,33)}$ = 6.33, p = 0.03, η_p^2 = 0.13) emerged with individuals performing 4% better after DEX compared to PBO and a significant effect of Trial Type ($F_{(1,33)}$ = 9.94, p = 0.003, η_p^2 = 0.23) with individuals performing 6.3% better on Uni compared to Bi Trials. No interactions between within subject factors emerged (all p's > 0.15; Fig. 2). Together, these results suggest (1) that similar to orientation discrimination (Censor, Harris, & Sagi, 2016; Censor & Sagi, 2008; Censor, Karni, & Sagi, 2006; Mednick et al., 2002, 2013; Mednick, Drummond, Arman, & Boynton, 2008) repeated, within-day testing in a MOT task leads to performance deterioration and (2) that DEX, compared to PBO, may somewhat protect both unilateral and bilateral attentional processing abilities, as the magnitude of deterioration was greater in the PBO than DEX condition.

3.2. Is there a delayed impact of stimulants on sustained attention?

Our next goal was to unpack any delayed effects that DEX may have
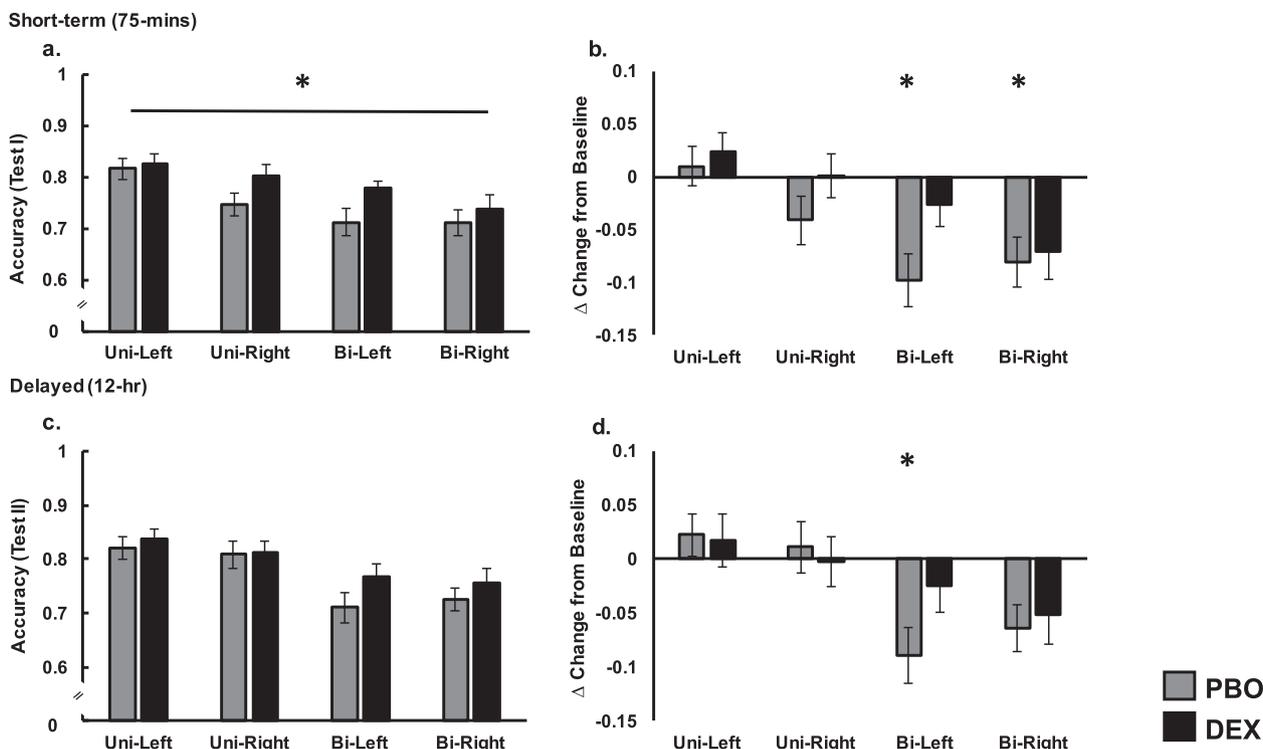
Fig. 2. Stimulants enhance immediate attentional processing. Performance on a multiple object tracking task at short-term (a, b; 75 min post drug), and delayed (c, d; 12 h post drug) testing intervals for both unilateral (Uni-Left, Uni-Right) and bilateral (Bi-Left, Bi-Right) task performance. (a) After stimulant ingestion (black bars), performance was enhanced at the short-term delay compared to placebo (gray bars). Asterisk indicates p < 0.05. (b) Significant deterioration from baseline was detected for both bi-lateral testing conditions in the placebo condition, however, these performance decrements were mitigated after stimulant ingestion. Asterisks indicate p < 0.002. (c) No difference in performance between stimulant and placebo was detected at the 12-h delay. (d) Deterioration from baseline was present at the 12-h delay for the Bi-Left condition. Again, stimulants attenuated performance decline. Asterisks indicate p < 0.002.

on attentional processing during the extended post-drug administration period. To achieve this, we tested the impact of DEX vs PBO at Test II, 12 h after drug ingestion (2–3 DEX half-lives). Again, we first examined the difference in performance in the PBO and DEX conditions from baseline. For Uni trials, we did not find a difference from baseline for any trial type for PBO or DEX conditions (all p's > 0.27). For BiLeft trials, individuals performed significantly worse in the PBO condition compared to baseline (t = −3.37, p = 0.002). No other differences at Test II survived Bonferroni correction (all p's > 0.005). Here, $2 \times 2 \times 2$ RM ANOVA's revealed a significant main effect of Trial ($F_{(1,33)} = 10.95$, p = 0.002, $\eta_p^2 = 0.25$) with Uni trials outperforming Bi trials (($\Delta = 8.0\%$). However, stimulants no longer provided significant enhancement compared to placebo ($\Delta = 2.7\%$; $F_{(1,33)} = 3.23$, p = 0.08, $\eta_p^2 = 0.09$). No differences between Left and Right visual fields ($F_{(1,33)} = 0.33$, p = 0.57, $\eta_p^2 = 0.01$) were present at Test II. No interactions between the within subject factors were present (all p's > 0.07). This suggests that the more resource demanding attentional task continued to deteriorate across the day with PBO, specifically in the left visual field, and that stimulants helped subjects resist this deterioration and hold attentional ability at baseline levels across an extended 12-h testing period (see Fig. 2).

3.3. What is the impact of stimulants on nighttime sleep?

Nighttime sleep results are displayed in Table 1. After DEX, subjects showed significant reductions in total sleep time (TST) (p > 0.001; $\eta_p^2 = 0.43$), SWS (p = 0.013; $\eta_p^2 = 0.19$) and REM (p > 0.001; $\eta_p^2 = 0.42$), along with marginal reductions in Stage 2 sleep (p = 0.06; $\eta_p^2 = 0.11$) compared to PBO. Additionally, subjects had increased Stage 1 sleep (p = 0.003; $\eta_p^2 = 0.26$) WASO (p = 0.001; $\eta_p^2 = 0.30$), longer sleep latencies (p = 0.006; $\eta_p^2 = 0.23$), and decreased sleep efficiency (p > 0.001; $\eta_p^2 = 0.52$) after a day with DEX compared to PBO. These

Table 1
Nighttime sleep descriptive statistics.

	Placebo	Stimulant	Significance
TST	537.22 (45.38)	486.59 (70.21)	< 0.001
Stage 1	13.89 (8.39)	20.17 (10.32)	0.003
Stage 2	284.72 (50.10)	267.41 (54.18)	0.06
SWS	109.37 (35.96)	98.20 (33.66)	0.013
REM	129.22 (32.17)	100.81 (35.97)	< 0.001
WASO	31.44 (27.12)	52.89 (35.15)	0.001
SL	6.73 (5.85)	16.00 (18.65)	0.006
SE %	92.44 (5.44)	84.44 (9.69)	< 0.001

Note: Table represents mean and the standard deviation, in parentheses, of each sleep parameter; TST = Total Sleep Time; SWS = Slow Wave Sleep; REM = Rapid Eye Movement sleep; WASO = Wake After Sleep Onset (calculated as the minutes of wake after first epoch of sleep); SL = Sleep Latency (calculated as the time to first epoch of sleep); SE = Sleep Efficiency. All stats are represented in minutes besides SE which is in percentage.

results suggest that, in line with predictions, morning administration of DEX substantially decreases nighttime sleep, reducing total time spent asleep as well as minutes spent in Stage 2, SWS and REM.

3.4. Does the erosion of nighttime sleep by DEX impact post-sleep attentional processing?

To understand the impact morning administration of stimulants may have on attentional processing after 24 h, we examined performance at Test III post-sleep. For Uni trials, no differences between Test III performance and baseline emerged (all p's > 0.06). For BiRight trials, performance at Test III was significantly worse compared to baseline in the PBO condition (t = −4.12, p < 0.001). No differences between Test III and baseline emerged for Bi trials in the DEX condition
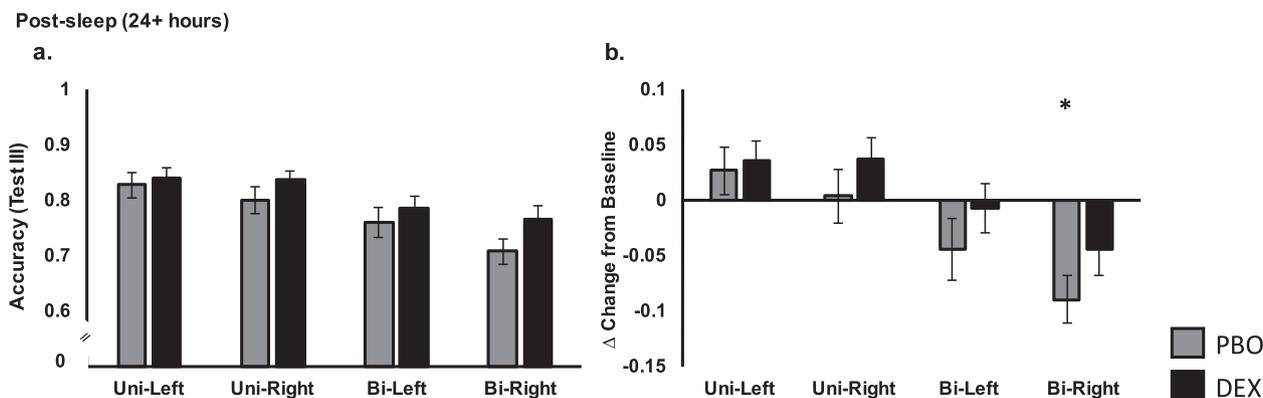
Post-sleep (24+ hours)

Fig. 3. Post-sleep attentional processing (24 + hour Test). (a) No differences emerged between drug conditions post-sleep. (b) Significant performance deterioration in the Bi-Right condition emerged between PBO and baseline; stimulant administration attenuated this decline. Asterisks indicate p < 0.002.

(all p's > 0.06; Fig. 3b). While there was still a nominal increase in accuracy in the DEX vs PBO condition post-sleep (Δ = 3.3%), this did not reach significance ($F_{(1,33)} = 3.34$, p = 0.08, $\eta_p^2 = 0.09$). Additionally, no effect of Visual Field was found ($F_{(1,33)} = 3.10$, p = 0.054, $\eta_p^2 = 0.11$). However, like previous sessions, a main effect of Trial type ($F_{(1,34)} = 9.98$, p = 0.003, $\eta_p^2 = 0.23$) was present, with individuals performing 8% better after Uni compared to Bi trials. No interactions between the within subject factors emerged (all p's > 0.14; Fig. 3a). Thus, though morning administration of stimulants resulted in significant nighttime sleep disruption, we did not see a significant cost to next day sustained attention.

Lastly, we conducted correlations between polysomnographic sleep features and post-sleep MOT performance at Test III and the difference score (Test III – 80% baseline threshold). For Test III performance, no significant relationships emerged (all p's > 0.05). For the difference score, we did detect significant correlations in the PBO condition between UniLeft performance and minutes in REM sleep (r = 0.38, p = 0.03, wake after sleep onset (r = −0.43, p = 0.01, and sleep efficiency (r = 0.35, p = 0.04), however, none of these correlations survived Bonferroni correction, alpha = 0.05/28 or 0.0018. Similarly, for the DEX condition, a significant correlation between minutes in SWS (r = −0.37, p = 0.02) and post-sleep performance emerged for the Bi-Left condition, but again this analysis did not survive a multiple testing correction.

4. Discussion

The goal of the current study was to understand the impact of psychostimulants on sustained attention and sleep in healthy, young adults. We obtained baseline measures on the multiple object tracking task in the morning before drug administration, and three times after drug administration: 75-min, 12-h, and 24-h. First, we report a novel finding with MOT performance that repeated testing led to decreases in performance from baseline across the day. Second, after PBO, we found deterioration in performance at the 75-min test, and at the 12 h and 24 h tests, yet no such deterioration occurred after DEX. Additionally, morning stimulant administration came at a substantial cost to nighttime sleep, however, at the 24-h test, no differences emerged between baseline performance and post-sleep performance in the DEX condition, whereas performance remained significantly worse in the placebo condition (though non-significant differences between DEX and PBO at the 24-h test were found). Together, these results indicate (1) that selective attention is vulnerable to performance deterioration with repeated within-day testing and (2) that psychostimulants may provide a significant and sustained respite from this downward trajectory, despite the damaging impact they may have on nighttime sleep. Furthermore, the extended impact of stimulants on cognitive performance and nighttime sleep suggests that amphetamine metabolites may influence

physiological systems well past their known half-life (4–6 h; Kolar et al., 2008).

This is one of the first studies that we know of to investigate the impact of repeated MOT testing and report deterioration across testing sessions. Prior work has demonstrated a similar effect of repeated testing on a perceptual orientation discrimination task (i.e., the texture discrimination task; Mednick et al., 2002). This body of work demonstrated that repeated testing across a day of wake resulted in a linear increase in thresholds that was binocular and specific to the orientation of the target elements (Mednick, Arman, & Boynton, 2005), implicating early stages of the visual stream rather than general fatigue. Furthermore, Censor and colleagues demonstrated that such adaptation-like performance decrements can be modulated with fewer trials (Censor & Sagi, 2008) and with post-training sleep (Mednick et al., 2002, 2003; Censor & Sagi, 2008). They hypothesize that short practice sessions with a stimulus may increase efficiency and prevent saturation of the network processing the visual trace. A more efficient network would be able to process longer sessions with lower signal-to-noise ratio and prevent performance decrements, as compared to long sessions that saturate the network, reduce efficiency, and cause elevated thresholds. Taken together with the current findings of attentional deterioration with repeated testing, we hypothesize that adaptation and saturation of the network may also occur at higher level processing areas of visual cortex that serve sustained attention. More research is needed, however, to determine whether attentional adaptation is governed by similar psychophysical properties, such as time-on-task and task feature specificity. Further, stimulants had the surprising effect of preventing performance deterioration across a day of testing and providing carry-over benefits to next-day performance, compared to baseline, despite their marked degradation to sleep. However, in the present study, we did not assess deterioration curves across the testing periods (75-min, 12 h, 24 h) due to low statistical power. Future investigations should examine the linear relationship between repeated testing sessions and attentional performance to more carefully characterize this phenomenon. Additionally, more research is needed to understand the mechanisms underlying psychostimulant's long-term support of sustained attentional processes.

Why didn't the degradation to sleep by stimulants negatively impact MOT performance? Studies have shown that partial sleep deprivation can lead to notable lapses in attention (Durmer & Dinges, 2005; Lo et al., 2012) and that a midday nap, paired with training, can improve selective attention in an attentional blink task (Cellini et al., 2015). Studies have also shown that short, 15-min daytime naps can result in boosts to attentional abilities (se Milner & Cote, 2009 for review), suggesting that small bouts of sleep may be adequate to recover basic attentional skills. Remarkably, in the current study, stimulant-induced sleep disruption did not manifest as a substantial attentional deficit the next day, with moderate boosts to sustained attention 24 + hours later.

One potential explanation for the non-significant increase in post-sleep attentional performance after a day with stimulants may be due to stimulant-driven task-specific, procedural learning of the MOT task at Test I and Test II. This protective learning benefit against deterioration may have had 24 h carry over effects to Test III. In other words, stimulants may have assisted learning after repeated testing, but the disruption to sleep, by the stimulant, decreased the magnitude of overnight benefit. Notably, although significant sleep disruption after stimulants was observed, all subjects were allotted 10 h in bed, and with DEX they received ~8 h of sleep, compared to ~9+ hours after PBO. The 10 h of time in bed permitted was in line with recommendations from the National Sleep Foundation with young adult (18–25 years old) sleep recommendations ranging from 7 to 9 h, with some individuals requiring up to 11 h of sleep per night (Hirshkowitz et al., 2015). Considering subjects attained 9 h of sleep in the placebo condition, which was counterbalanced with the stimulant visit, does suggest a necessary sleep need, which was degraded after stimulant administration. In more naturalistic settings, where people do not have extended time in bed, this hour of sleep reduction would likely have much larger consequences. One potential interpretation of these findings is that while a complete lack of sleep will decrease attentional functioning, sustained attentional processing may be resilient to small variations in sleep. This stands in contrast with other cognitive domains, like memory, that require sleep for performance improvement (Mednick, Nakayama, & Stickgold, 2003; Stickgold, James, & Hobson, 2000). However, most cognitive neuroscience studies examining sleep restriction use experimental designs with either full sleep or partial sleep deprivation (4–5 h of sleep), thus studies do not typically examine the impact of 1 h or less on cognition. It is important to note that a wide range of sleep and health studies have shown that reducing sleep by just one hour at night can come at significant costs to cardiovascular and metabolic health (St Onge et al., 2016; Watson et al., 2017). Therefore, future studies investigating long-term effects of psychostimulant usage should investigate a wider range of cognitive and health domains and examine the impact of shorter bouts of sleep loss on cognitive function. It is also important to note that the small 3–4% increases in performance after dextroamphetamine, both after acute and delayed administration and a night of sleep, were not significantly different from performance at baseline. Considering the nature of these substances and the potential costs of use, as noted herein as substantial sleep disruption, and the prominent risk for abuse of these addictive amphetamine-based medications, repeated use of amphetamines may result in compounding effects on sleep that could ultimately lead to worse cognitive performance over time. Also, increased drug tolerance with repeated administration may mitigate long-term stimulant-related benefits.

To truly understand the implication of these results, it is important to contrast how individuals may use these substances in practice and the application provided in the current study. Specifically, we utilized one morning administration of the stimulant and tested the impact across 24+ hours. However, in practice, students may take these medications at varying times across the circadian day. Additionally, we utilized one 20-mg dose of DEX, which because of individual differences in metabolic rate, this approach may not have had optimal cognitive or behavioral effects for all participants. Though this approach is ecologically-valid, and in line with how students and young adults use stimulant medications off-label (DuPont, Coleman, Bucher, & Wilford, 2010; Rabiner et al., 2009), it is important for future investigations to vary both drug dose, drug type, as well as administration times to understand the range of potential effects on and interactions with circadian rhythms, sleep and cognition. Considering different stimulant compounds, like caffeine and modafinil, have different mechanisms of action (Fredholm, 1995; Lin, Hou, & Jouvet, 1996), it is also important to understand how results from amphetamine-based drug substances generalize to other stimulant medications. Also, to understand heterogeneity in drug responses, future studies should measure biomarkers (e.g. blood, saliva) to determine metabolic breakdown of the drug over

time. Importantly, in the current study, to increase ecological-validity, we allowed subjects to leave the lab if vital signs and gait testing permitted. Though we engaged a within-subject design to help control for within-subject variability in study outcomes, activities outside of the lab may have impacted in-lab behaviors. Future studies should take this into consideration.

In summary, stimulant medications, commonly used off-label for cognitive enhancement, prevented deterioration of sustained attention brought on by repeated within-day testing. Additionally, these medications substantially disrupt nighttime sleep; which while coming at little cost to next-day attentional processing, may have steeper consequences for other cognitive domains. Additionally, long-term stimulant usage should be examined.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

References

Asghar, S. J., Tanay, V., Baker, G. B., Greenshaw, A., & Silverstone, P. H. (2003). Relationship of plasma amphetamine levels to physiological, subjective cognitive and biochemical measures in healthy volunteers. *Human Psychopharmacology, 18,* 291–299.

Bagot, K. S., & Kaminer, Y. (2013). Efficacy of stimulants for cognitive enhancement in non-attention deficit hyperactivity disorder youth: A systematic review. *Addiction, 109,* 547–557.

Barbanoj, M. J., Riba, J., Clos, S., Giménez, S., Grasa, E., & Romero, S. (2008). Daytime Ayahuasca administration modulates REM and slow-wave sleep in healthy volunteers. *Psychopharmacology (Berl), 196,* 315–326.

Battelli, L., Alvarez, G. A., Carlson, T., & Pa-Leone, A. (2009). The role of the parietal lobe in visual extinction studies with transcranial magnetic stimulation. *Journal of Cognitive Neuroscience, 21,* 1946–1955.

Bishop, C., Roehrs, T., Rosenthal, L., & Roth, T. (1997). Alerting effects of methylphenidate under basal and sleep-deprived conditions. *Experimental and Clinical Psychopharmacology, 5,* 344–352.

Brauer, L. H., & de Wit, H. (1996). Subjective responses to d-amphetamine alone and after pimozide pretreatment in normal, healthy volunteers. *Biological psychiatry, 39*(1), 26–32.

Cellini, N., Goodbourn, P. T., McDevitt, E. A., Martini, P., Holcombe, A. O., & Mednick, S. C. (2015). Sleep after practice reduces the attentional blink. *Attention, Perception, & Psychophysics, 77,* 1945–1954.

Censor, N., Harris, H., & Sagi, D. (2016). A dissociation between consolidated perceptual learning and sensory adaptation in vision. *Scientific Reports, 6*(1), https://doi.org/10.1038/srep38819.

Censor, N., Karni, A., & Sagi, D. (2006). A link between perceptual learning, adaptation and sleep. *Vision Research, 46*(23), 4071–4074. https://doi.org/10.1016/j.visres.2006.07.022.

Censor, N., & Sagi, D. (2008). Benefits of efficient consolidation: Short training enables long-term resistance to perceptual adaptation induced by intensive testing. *Vision Research, 48*(7), 970–977. https://doi.org/10.1016/j.visres.2008.01.016.

Clegg-Kraynok, M. M., McBean, A. L., & Montgomery-Downs, H. E. (2011). Sleep quality and characteristics of college students who use prescription psychostimulants non-medically. *Sleep Medicine, 12,* 598–602.

de Wit, H., Enggasser, J. L., & Richards, J. B. (2002). Acute administration of d-amphetamine decreases impulsivity in healthy volunteers. *Neuropsychopharmacology, 27*(5), 813–825.

DuPont, R. L., Coleman, J. J., Bucher, R. H., & Wilford, B. B. (2010). Characteristics and motives of college students who engage in nonmedical use of methylphenidate. *American Journal on Addictions, 17,* 167–171.

Durmer, J. S., & Dinges, D. F. (2005). Neurocognitive consequences of sleep deprivation. *Seminars in Neurology, 25,* 117–129.

Food and Drug Administration (2007). Adderall CII. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/011522s040lbl.pdf.

Fredholm, B. B. (1995). Adenosine, adenosine receptors and the actions of caffeine. *Pharmacology & Toxicology, 76,* 93–101.

Greely, H., Sahakian, B., Harris, J., Kessler, R. C., Gazzaniga, M., Campbell, P., & Farah, M. J. (2008). Towards responsible use of cognitive-enhancing drugs by the healthy.

Nature, 456, 702–705.

Hirshkowitz, M., Whiton, K., Albert, S. M., Alessi, C., Bruni, O., DonCarlos, L., ... Hillard, P. J. A. (2015). National Sleep Foundation's sleep time duration recommendations: Methodology and results summary. *Sleep Health, 1*, 40–43. https://doi.org/10.1016/j.sleh.2014.12.010.

Ilieva, I., Boland, J., & Farah, M. J. (2013). Objective and subjective cognitive enhancing effects of mixed amphetamine salts in healthy people. *Neuropharmacology, 64*, 496–505.

Jasper, H. H. (1958). Report of committee on methods of chemical examination in electroencephalography. *Electroencephalography and Clinical Neurophysiology, 10*, 370–375.

Klein-Schwartz, W. (2002). Abuse and toxicity of methylphenidate. *Current Opinion in Pediatrics, 14*, 219–223.

Kolar, D., Keller, A., Golfinopoulos, M., Cumyn, L., Syer, C., & Hechtman, L. (2008). Treatment of adults with attention-deficit/hyperactivity disorder. *Neuropsychiatric Disease and Treatment, 4*, 107–121.

Lin, J., Hou, Y., & Jouvet, M. (1996). Potential brain neuronal targets for amphetamine-, methylphenidate-, and modafinil-induced wakefulness, evidenced by c-fos immunocytochemistry in the cat. *Proceedings of the National academy of Sciences of the United States of America, 93*, 14128–14133.

Lo, J. C., Groeger, J. A., Santhi, N., Arbon, E. L., Lazar, A. S., Hasan, S., et al. (2012). Effects of partial and acute total sleep deprivation on performance across cognitive domains, individuals and circadian phase. *PLoS ONE, 7*, e45987.

Mednick, S. C., Arman, A. C., & Boynton, G. M. (2005). The time course and specificity of perceptual deterioration. *Proceedings of the National Academy of Sciences, 102*(10), 3881–3885.

Mednick, S. C., Drummond, S. P. A., Arman, A Cyrus, & Boynton, Geoffrey M (2008). Perceptual deterioration is reflected in the neural response: fMRI study of nappers and non-nappers. *Perception, 37*(7), 1086–1097.

Mednick, S. C., McDevitt, E. A., Walsh, J. K., Wamsley, E., Paulus, M., Kanady, J. C., & Drummond, S. P. A. (2013). The critical role of sleep spindles in hippocampal-dependent memory: A pharmacology study. *Journal of Neuroscience, 33*, 4494–4504.

Mednick, S. C., Nakayama, K., Cantero, J. L., Atienza, M., Levin, A. A., Pathak, N., & Stickgold, R. (2002). The restorative effect of naps on perceptual deterioration. *Nature Neuroscience, 5*(7), 677–681.

Mednick, S., Nakayama, K., & Stickgold, R. (2003). Sleep-dependent learning: A nap is as good as a night. *Nature Neuroscience, 6*, 697–698.

Milner, C. E., & Cote, K. A. (2009). Benefits of napping in healthy adults: Impact of nap length, time of day, age and experience with napping. *Journal of Sleep Research, 18*, 272–281.

Mommaerts, J. L., Beerens, G., van den Block, L., Soetens, E., Schol, S., van de Vijver, E., & Devroey, D. (2013). Influence of methylphenidate treatment assumptions on cognitive function in healthy young adults in a double-blind, placebo-controlled trial. *Psychology Research and Behavior Management, 6*, 65–74.

Pylyshyn, Z. W., & Storm, R. W. (1988). Tracking multiple independent targets: Evidence for a parallel tracking mechanism. *Spatial Vision, 3*, 179–197.

Rabiner, D. L., Anastopoulos, A. D., Costello, E. J., Hoyle, R. H., McCabe, S. E., & Swartzwelder, H. S. (2009). Motives and perceived consequences of nonmedical ADHD medication use by college students: Are students treating themselves for attention problems. *Journal of Attention Disorders, 13*, 259–270.

Rechtschaffen, A. & Kales, A. (1968). A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects.

Repantis, D., Schlattmann, P., Laisney, O., & Heuser, I. (2010). Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review. *Pharmacological Research: The Official Journal of the Italian Pharmacological Society, 62*, 187–206.

Roehrs, T., Papineau, K., Rosenthal, L., & Roth, T. (1999). Sleepiness and the reinforcing and subjective effects of methylphenidate. *Experimental and Clinical Psychopharmacology, 7*, 145–150.

Saletu, B., Frey, R., Krupka, M., Anderer, P., Grünberger, J., & Barbanoj, M. J. (1989). Differential effects of a new central adrenergic agonist—modafinil—and d-amphetamine on sleep and early morning behavior in young healthy volunteers. *International Journal of Clinical Pharmacy, 9*, 183–195.

Smith, M. E., & Farah, M. J. (2011). Are prescription stimulants "smart pills"? The epidemiology and cognitive neuroscience of prescription stimulant use by normal healthy individuals. *Psychological Bulletin, 137*, 717–741.

St Onge, M.-P., Grandner, M. A., Brown, D., Conroy, M. B., Jean-Louis, G., Coons, M., & Bhatt, D. L. (2016). Sleep duration and quality: Impact on lifestyle behaviors and cardiometabolic health. *Circulation, 134*. https://doi.org/10.1161/CIR.0000000000000444.

Stickgold, R., James, L., & Hobson, J. A. (2000). Visual discrimination learning requires sleep after training. *Nature Neuroscience, 3*, 1237–1238.

Swanson, J. M., Wigal, T. L., & Volkow, N. D. (2011). Contrast of medical and nonmedical use of stimulant drugs, basis for the distinction, and risk of addiction: Comment on Smith and Farah (2011). *Psychological Bulletin, 137*, 742–748.

Sweeney, C. T., Sembower, M. A., Ertischek, M. D., Shiffman, S., & Schnoll, S. H. (2013). Nonmedical use of prescription ADHD stimulants and preexisting patterns of drug abuse. *Journal of Addictive Diseases, 32*, 1–10.

Teter, C. J., McCabe, S. E., LaGrange, K., Cranford, J. A., & Boyd, C. J. (2006). Illicit use of specific prescription stimulants among college students: Prevalence, motives, and routes of administration. *Pharmacotherapy, 26*, 1501–1510.

van Dongen, H. P. A., Maislin, G., Mullington, J. M., & Dinges, D. F. (2003). The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep, 26*, 117–126.

Volkow, N. D., Wang, G., Fowler, J. S., Telang, F., Maynard, L., Logan, J., et al. (2004). Evidence that methylphenidate enhances the saliency of a mathematical task by increasing dopamine in the human brain. *The American Journal of Psychiatry, 161*, 1173–1180.

Watson, N. F., Buchwald, D., Delrow, J. J., Altemeier, W. A., Vitiello, M. V., Pack, A., ... Gharib, S. A. (2017). Transcriptional signatures of sleep duration discordance in monzygotic twins. *Sleep, 40*. https://doi.org/10.1093/sleep/zsw019.

Wilens, T. E., Adler, L. A., Adams, J., Sgambati, S., Rotrosen, J., Sawtelle, R., et al. (2008). Misuse and diversion of stimulants prescribed for ADHD: A systematic review of the literature. *Journal of the American Academy of Child and Adolescent Psychiatry, 47*, 21–31.