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Psychostimulants may block long-term memory formation via degraded sleep in healthy adults

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ABSTRACT

Sleep is vital for biological function and long-term memory formation, with preferential enhancement of emotionally laden content. A growing trend in healthy young adults is the non-medical use of psychostimulants, or "smart drugs", to prevent sleep and, hopefully, enhance cognition. However, the effect of these drugs on sleep-dependent memory processes are unclear. Here, in a within-subject, double-blind, placebo-controlled design, we investigated the impact of morning administration of dextroamphetamine on memory retention of negative and neutral pictures after 1) 12 h of wake, and 2) 24 h with sleep. After 12-hrs of wake, stimulants increased hit rate for neutral, but not negative, pictures, compared to placebo. No differences in memory discrimination were found. In addition, stimulants impaired nighttime sleep and significantly reduced memory for neutral pictures at 24-hrs, compared to placebo. Again, no performance differences between drug conditions were found for negative pictures. Together, these findings suggest that stimulants impairment of nighttime sleep likely leads to next day memory costs.

1. Introduction

Sleep is a basic human need that supports many physiological processes and plays a critical role in the transformation of recent experiences into long-term memories (i.e., consolidation). A large corpus of studies has demonstrated that a period of sleep after encoding is necessary for the formation of long-term memories (Diekelmann & Born, 2010), with the amount of time in specific sleep stages contributing to this improvement (Stickgold, 2005). Slow wave sleep (SWS), in particular, correlates with post-sleep memory performance (Cairney, Durrant, Power, & Lewis, 2014; Cairney, Durrant, Hulleman, & Lewis, 2014), as well as with decreased hippocampal activation at retrieval (Cairney et al., 2014), suggesting a direct role for SWS in shifting explicit, hippocampal-dependent memories from recent to remote memory stores. In addition, selective obstruction of SWS impairs explicit memory (Casey, Solomons, & Steier, 2016). Recently, some studies have also focused on sleep's special role in the consolidation of emotionally-charged memories, with aspects of both SWS and REM playing important roles (Baran, Pace-Schott, Ericson, & Spencer, 2012; Hu, Stylos-Allan, & Walker, 2006; Nishida, Pearsall, Buckner, & Walker, 2009; Payne, Stickgold, Swanberg, & Kensinger, 2008; van der Helm & Walker, 2011; Wagner, Gais, & Born, 2001) (see Lipinska, Stuart, Thomas, Baldwin & Bolinger, 2019 for alternative interpretation). In light of the increasing trend in non-medical use of psychostimulants to stave off sleep among healthy students and young professionals (Schwartz, 2016; Smith & Farah, 2011), a critical question is how these drugs impact sleep-dependent memory in healthy adults.

Psychostimulants (e.g. methylphenidate and mixed-salt amphetamines), traditionally prescribed for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), are used by up to 35% of young adults as cognitive enhancers (Smith & Farah, 2011; Wilens, Adler, & Adams, 2008). Though some have highlighted their "cognitive enhancement" potential (Greely, Sahakian, & Harris, 2008), positive effects have been mostly reported in simple executive function tasks (i.e. vigilance, sustained attention, working memory; see Tselha, Whitehurst, Yetton, Vo, and Mednick (2019) for negative impact on working memory), whereas empirical studies of more complex cognitive processes have yet to show conclusive results (Ilieva, Boland, & Farah, 2013; Mommaerts, Beerens, & van den Block, 2013; Repantis, Schlattamann, Laisney, & Heuser, 2010; Smith & Farah, 2011; Volkow, Wang, & Fowler, 2004). On one hand, psychostimulants have been shown to enhance emotional memory in humans (Ballard, Gallo, & de Wit, 2013; Roozendaal & Hermans,

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2017), however, they have also shown null effects (Weafer, Gallo, & de Wit, 2014). Additionally, studies of non-emotional, neutral stimuli have shown positive (Ballard et al., 2013; Linssen, Vuurman, Sambeth, & Riedel, 2012; Soetens et al., 1993, 1995), null (de Wit, Enggasser, & Richards, 2002; Ilieva et al., 2013; Mommaerts et al., 2013) and negative effects (Elliot et al., 1997; Ilieva et al., 2013). Inconsistencies within and across studies are likely due to a range of factors, including cognitive task, study design, type of stimulant, timing of drug administration, human subject demographics, as well as indirect effects of these drugs on biological factors that have not been controlled.

One of these uncontrolled factors that plays an important role in complex cognitive processing is also the primary goal of stimulant use, namely sleep loss (Barbanoj, Jordi Riba, Gimenez, Grasa, & Romero, 2008; Sweeney, Sembower, Ertischek, Shiffman, & Schnoll, 2013; Teter, McCabe, LaGrange, Cranford, & Boyd, 2006). Curiously, most studies examining the effect of these drugs on cognitive processes have ignored this important variable. Given the profound negative impact of psychostimulants on sleep, and the growing adoption of these drugs in mainstream culture, the current study used a, placebo-controlled, crossover design, to assess the impact of psychostimulants on sleep-dependent memory in healthy, well-rested adults (**see Protocol** Fig. 1). We hypothesized that stimulants, compared to PBO, would provide a short-term boost to memory across a day of wake for both neutral and emotional images. However, stimulants would also disrupt sleep, which would lead to reduced memory retention post-sleep.

Protocol: Subjects were administered either a 20 mg dose of dextroamphetamine (DEX) or placebo (PBO) at 9:00AM. Seventy-five minutes later, subjects encoded 20 negative and 20 neutral pictures in an emotional picture task. At 9:00PM, subjects' recognition memory was tested at Retrieval Test 1 (old: 10 negative, 10 neutral; new: 10 negative, 10 neutral). Subjects slept overnight in the sleep lab with 32-channel PSG recording. Subjects were woken at 9:00AM, ate a standardized breakfast, and were given Retrieval Test II at 10:30AM on the remainder of encoded images (10 negative, 10 neutral) and 20 new images (10 negative, 10 neutral).

2. Materials and methods

The aim of the current study was to determine the impact of morning administration of a commonly used off-label stimulant on memory. We examined the impact of the stimulant on recognition memory after 12 h of wake and 24 h including sleep in healthy, non-sleep-deprived adults. To this end, we used a double-blind, placebo-controlled, crossover design, in which subjects received the drug (dextroamphetamine; DEX vs. placebo; PBO) in the morning, 75 min (peak plasma for DEX) before memory encoding. Recognition memory was tested twice: 12 h after drug, and 24 h after drug, including overnight in the lab with polysomnography (PSG). We utilized an emotional picture task that included neutral and negative images (adapted from the International Affective Picture SystemLang, Bradley, & Cuthbert, 2008).

Subjects. Thirty-seven healthy, non-smoking participants between the ages of 18 to 30 (M_{age} = 21.00 ± 2.97 years, 19 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. All procedures were carried out in accordance with the relevant guidelines and regulations of the approved study. Participants received monetary compensation and/or course credit. Individuals were excluded from participation if they reported: irregular sleep/wake cycles; a sleep disorder; personal or familial history of diagnosed psychopathology; 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 self-reported responses to a series of health and wellness questions (e.g. demographics, first language, sleep behaviors, drug use, handedness, employment) that were approved by the study physician (see Supplementary Materials for full list). Additionally, all participants underwent a medical history and physical appointment with the study physician, which included a toxicology panel screening for Schedule I and II drug substances, including amphetamines. All subjects were naïve to or had limited contact with (<2 lifetime use and no use in last year) the active medication in the study. Even with this requirement, no adverse events were reported by participants throughout the study.

Drugs. We used a single 20-mg dose of immediate release DEX which was prepared by the MDMX Corona Research Pharmacy. Immediate release dextroamphetamine is a sympathomimetic amine with central nervous system stimulant activity (Food and Drug Administration,

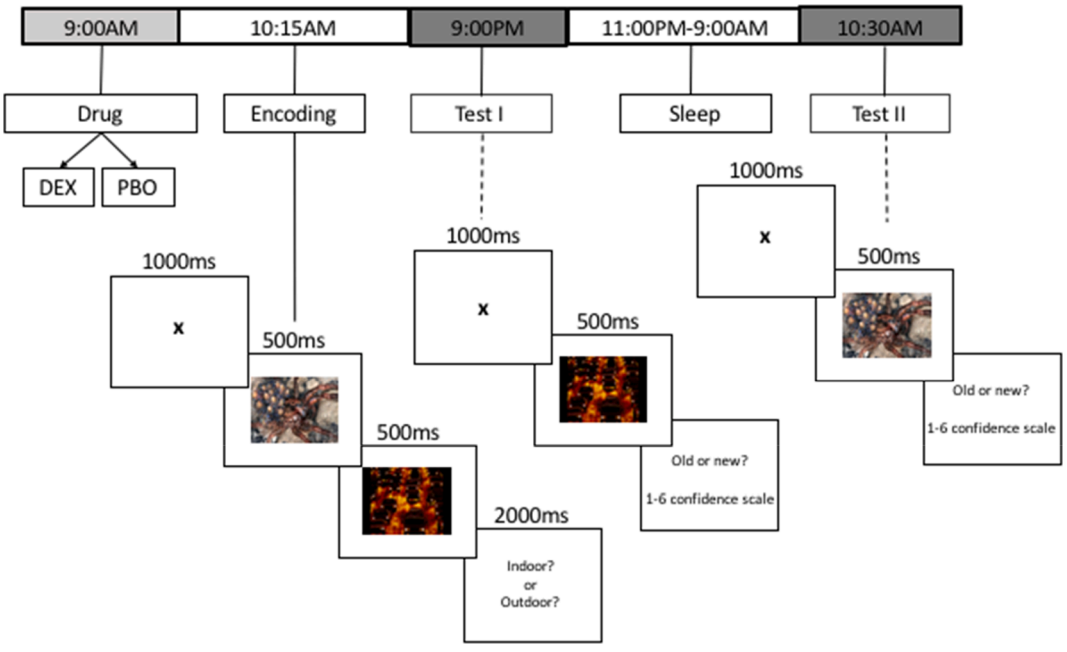

Fig. 1. Protocol & task figure.

2007) that has a mean elimination half-life between 4 and 6 h (Food and Drug Administration, 2007; Kolar et al., 2008). DEX powder was encapsulated and visually indistinguishable from the placebo capsule, which was made of microcrystalline cellulose and contained no active medications. Each of these visits were conducted at least 1 week apart to allow for drug washout.

Emotional Picture Task. All images were selected from the International Affective Picture System (IAPS) (Lang et al., 2008). The standardized arousal and valence ratings provided with the IAPS database were utilized to create stimuli. The rating system ranges from 1 to 9 with lower numbers representing more unpleasant, less arousing stimuli and higher numbers representing more pleasant, highly arousing stimuli. In the current study, neutral, low arousing (valence: $M = 5.13$; $SD = 1.44$; arousal: $M = 3.87$; $SD = 2.19$) and negative, highly arousing (valence: $M = 2.88$; $SD = 1.57$; arousal: $M = 5.52$; $SD = 2.09$) stimuli were chosen to maximize the difference between the images. During the encoding session, subjects viewed a fixation marker for 1000 ms before an image (20 negative and 28 neutral; 8 neutral images were used to control for primacy and recency effects) would appear on the center of the screen for 500 ms. Once the image disappeared, subjects were given 2000 ms to respond whether the image was taken indoors or outdoors. Images remained on the screen for 500 ms regardless of subject's response. No feedback was provided.

Retrieval Test: Each test included 20 of the pictures previously viewed at encoding (10 negative; highly-arousing; 10 neutral) and 20 novel images (10 negative; highly-arousing; 10 neutral), with Test 1 and Test 2 having a unique subset of the original 40 images. Subjects were shown a fixation for 1000 ms before an image would appear on the screen. The subjects were then prompted by the computer to respond if they remember seeing the image before on a 1 to 6 confidence scale with 1 = "very confident the image was present", 3 = "not sure, but think the image was present", 4 = "not sure, but think the image was not present", and 6 = "very confident the image was not present. Participants were required to provide a response for each image at retrieval without a response time limit. For the present analyses, confidence ratings were collapsed and subject's responses were interpreted as "present" vs "not present" regardless of scale rating. We assessed accuracy as the % of images correct at each Retrieval session and the discriminability index, *d'*, as the z transform of hit rate (% of images present at encoding *correctly* identified at test) – z transform false alarm rate (% of images *incorrectly* identified as present at encoding at test); zHitRate - zFalseAlarmRate. Additionally, we calculated difference scores between Retrieval Tests (Test 2 – Test 1) to examine performance change.

Task code was written in Matlab [Mathworks Inc, 2018] with Psychtoolbox (Kleiner et al., 2007), and is freely available online at [https://github.com/MednickLab/GenericMemoryTask].

2.1. Experimental design and protocol

Experimental Design. This study employed a double-blind, placebo-controlled, within-subject, cross-over design, in which every subject experienced each drug combination. The order of drug conditions was randomized and counterbalanced.

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 visit. Subjects reported to the laboratory at 8:00AM. Upon arrival, all female-identifying participants were given a pregnancy test and a negative test result was verified. At 9:00AM, after compliance with sleep procedures was verified, subjects were administered either a 20 mg dose of dextroamphetamine (DEX) or placebo (PBO). Seventy-five minutes later (peak plasma concentration for DEX) subjects began the Encoding Session on the emotional picture task (EPT). After encoding, subjects remained in the lab and underwent monitoring (blood pressure, heart rate and subjective measurements every hour) until 2:00PM when they were permitted to leave, if cleared by study personnel. Clearance was given if study personnel verified that subjects: 1) systolic blood pressure was below 120 and their diastolic blood pressure was below 90 2) resting heart rate was below 100 bpm and 3) they passed gait testing and did not report experiencing a racing heart, dizziness, headache, or nausea. All subjects met these conditions and were able to leave the lab during their break. 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. All subjects returned to the lab at 9:00PM for Retrieval Test 1. After testing, subjects were prepared for nighttime sleep, which included a 32-channel electroencephalographic recording. Lights out was at 11:00PM. Subjects were woken up at 9:00AM the next morning and participants were provided a standardized breakfast. At 10:30AM, subjects completed Retrieval Test 2, and were permitted to leave the lab after being cleared by study personnel (Fig. 1).

Polysomnography (PSG). EEG data were acquired using a 32-channel cap (EASEYCAP GmbH) with Ag/AgCI electrodes placed according to the international 10–20 System (Jasper, 1958). 22 out of 32 electrodes were active 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. 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. High pass filters were set at 0.3 Hz and low pass filters at 35 Hz for EEG and EOG. Raw data were visually 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) (Rechtschaffen & Kales, 1968). Prior to sleep scoring, data were pre-processed using BrainVision Analyzer 2.0 (BrainProducts, Munich Germany) and all epochs with artifacts and arousals were identified by visual inspection and rejected. Minutes in each sleep stage were calculated and sleep latencies (SL) were calculated as the number of minutes from lights out until the initial epoch of sleep, Stage 2, SWS and REM. Additionally, wake after sleep onset (WASO) was calculated as total minutes awake after the initial epoch of sleep and sleep efficiency (SE) was computed as total time spent asleep after lights out (~11:00PM) divided by the total time spent in bed (~11:00PM-9:00AM) * 100.

Data Reduction. Eight subjects (6F) did not complete the study after their first visit due to scheduling conflicts. The weight measurements for one man and one woman were not assessed during their initial interview. To maintain these subjects, the mean weight, by sex ($Males_{weight} = 166.82$ lbs; $Female_{weight} = 135.17$ lbs), was calculated and inserted as their values.

2.2. Statistical analyses

Memory performance. To assess memory performance on the EPT, we used 2X2 repeated measures ANCOVA's (RM ANCOVA) with drug (DEX vs PBO) and valence (Neutral vs Negative) as within-subject factors and hit rate (proportion of pictures correct) and *d'* as the dependent variables for Test 1 and Test 2. To assess performance change, we calculated the Retrieval difference score (Test 2– Test 1) for hit rate and *d'* and conducted 2X2 RM ANCOVAs with DEX vs PBO and valence (Neutral vs Negative) as the within-subject factors. To account for differential drug absorption rates across our subjects due to weight (Markowitz & Patrick, 2017; Roberts et al., 2015) we entered weight (mean-centered) as a covariate in each of these analyses. If statistical conclusions differed based on the inclusion of this covariate, we also report statistics without the covariate for transparency (see Supplementary Table 1 for all statistical comparisons with and without weight as a covariate). For all behavioral comparisons, we report η^2_p for effect size.

Sleep. To examine the impact of stimulants on nighttime sleep we utilized RM ANCOVAs. Here, we examined the impact of DEX vs PBO on each nighttime sleep variable with TST, minutes in each stage (Stage 1, Stage 2, SWS, REM), WASO, sleep latencies (time from lights out to first epoch of Stage 2, SWS and REM) and SE as dependent variables and drug condition (DEX vs. PBO) as the within subject factor. In line with the performance analyses, we also included weight (mean centered) as a covariate and report η^2_p for effect size. For correlations between sleep features and performance indicators, Pearsons r was used. The descriptive sleep outcomes reported herein share a subset of data with sleep outcomes that have been reported in Tselha et al. (2019) (all but 9 subjects overlap) and (Whitehurst, Agosta, Castaños, Battelli, & Mednick, 2019) (all but 6 subjects overlap). Importantly, neither of these previous two studies examined long-term memory (Tselha et al., 2019): working memory capacity; (Whitehurst et al., 2019): attentional tracking) in our best effort to reduce interference effects across cognitive tasks.

Data Availability. The raw data that support the findings from this study can be found on the Mendeley Data Repository.

3. Results

3.1. Stimulants increase short-term retrieval of neutral memories.

We first assessed memory for negative and neutral images at Test 1, after 12 h of wake with either 20 mg of dextroamphetamine or placebo (PBO; Fig. 2**a**). Repeated Measures (RM) ANOVA's, with weight included as a covariate, revealed a significant Drug X Valence interaction for hit rate ($F_{(1,27)} = 4.52$; $p = .04$; $\eta^2_p = 0.14$). In the PBO condition, participants demonstrated higher hit rates for negative images compared to neutral images (p = .03). Additionally, stimulants provided a 6% boost to hit rates for neutral images compared to PBO (p = .01), however, had no impact on emotional pictures (p = .90). RM ANOVA's without weight revealed a similar trend, however, there was a reduction in effect size ($F_{(1,28)} = 4.03$; p = .055; $\eta^2_p = 0.12$). No statistically significant main effects or interactions emerged for *d'* (p > 0.16)a.

3.2. Morning administration of stimulants disrupt nighttime sleep.

As expected, morning stimulant administration resulted in vast disruptions to nighttime sleep architecture (Table 1**)** as measured with polysomnography, including decreased total sleep time ($F_{(1,26)} = 17.64$; $p < .001$; $\eta^2_p = 0.40$) and sleep efficiency (total time in bed/total time asleep * 100; $F_{(1,26)} = 23.63$; $p < .001$; $\eta^2_p = 0.48$), increased wake after sleep onset ($F_{(1,26)} = 10.37$; $p = .003$; $\eta^2_p = 0.28$) and longer latency to sleep onset ($F_{(1,26)} = 8.62$; $p = .007$; $\eta^2_p = 0.25$), Stage 2 ($F_{(1,26)} = 12.15$, $p = .002$; $\eta^2_p = 0.32$), SWS ($F_{(1,26)} = 15.97$, $p < .001$; $\eta^2_p = 0.38$) and rapid eye movement sleep (REM; $F_{(1,26)} = 15.96$, $p < .001$; $\eta^2_p = 0.38$). Additionally, stimulants increased time in Stage 1 sleep ($F_{(1,26)} = 12.85$; $p = .001$; $\eta^2_p = 0.33$), and reduced SWS ($F_{(1,26)} = 6.48$; p = .02; $\eta^2_p = 0.20$) and REM sleep ($F_{(1,26)} = 14.86$; p = .001; $\eta^2_p = 0.36$). No statistically significant reductions in Stage 2 sleep were detected (p = .20; $\eta^2_p = 0.06$; Table 1).

3.3. Stimulants impair memory retrieval post-sleep.

Next, we examined the differential impact of DEX and PBO on next-day memory performance at Test 2 and the Forgetting difference score (Test 2-Test 1) using a 2x2 RM ANCOVA with hit rate and *d'* as the dependent variables and drug condition (PBO vs DEX) and valence (Negative vs Neutral) as the within-subject factors. No effects emerged at Test 2 for hit rate or *d'* (all p's > 0.09). In contrast with prior findings we found no specific enhancement of negative over neutral memories in the PBO condition (Fig. 2**b;** Table 2). For the Forgetting difference score, a significant Drug X Valence interaction emerged for hit rate ($F_{(1,27)} = 8.23$, p = .008; $\eta^2_p = 0.23$; Fig. 2**c;** Table 2) and *d'* ($F_{(1,27)} = 5.19$, p = .03; $\eta^2_p = 0.16$; Fig. 2**d;** Table 2), with impaired recognition of neutral memories in the DEX condition compared to placebo (hit accuracy: p = .021; *d'*: p = .01), and impaired recognition of negative compared to neutral memories in the PBO condition (*d'*: p = .029). After sleep, subjects experienced significant memory loss indicated by reductions in hit rate and in d', compared to placebo.

As a follow-up, we examined if overnight sleep was correlated with performance post-sleep. Here, we correlated performance for both neutral and negative pictures in our PBO and DEX conditions (hit rate and *d'* at Test 2 and the difference scores) with 8 sleep variables that showed significant nighttime sleep disruptions: TST, SE, SWS mins, REM mins, sleep latency and latency to Stage 2, SWS and REM. For the PBO condition, no correlations between any of the sleep features and memory for neutral or negative images reached significance thresholds (all p's > 0.07). However, for the DEX condition, negative correlations between memory performance for neutral images and latency to sleep (Test 2 d': r = 0.41, p = .02; *d'* difference score: r = -0.44, p = .014), latency to Stage 2 (Test 2 *d'*: r = -0.38, p = .03; *d'* difference score: r = -0.37, p = .04), latency to SWS (Test 2 Hit Accuracy: r = -0.43, p = .017) and latency to REM sleep (Hit Accuracy difference score: r = -0.38, p = .03; *d'* difference score: r = -0.47, p = .008). No relations were found between sleep and negative images in the DEX condition. Together, these correlations paint a consistent picture that stimulants' widespread impairments to sleep can lead to significant reductions in next day memory performance.

4. Discussion

Sleep is essential for long-term memory formation, and poor sleep can have deleterious consequences. In the current study, we examined the potential cost of non-medical psychostimulant use on sleep-dependent memory processes in healthy, well-rested adults. We found that stimulants increased hits for neutral pictures but had no impact on d' after 12 h. Additionally, morning stimulant administration resulted in significant nighttime sleep disruptions and decreased neutral picture memory the next day. Together, these results suggest that psychostimulants may impair long-term memory formation by disrupting sleep-dependent consolidation processes.

Prolonged wakefulness is one of the main reasons individuals turn to stimulants, in the hopes that evading sleep will increase time on task and enhance performance (Clegg-Kraynok, McBean, & Montgomery-Downs, 2011; Sweeney et al., 2013; Teter et al., 2006). Indeed, stimulants have been shown to increase attention and focus (Bagot & Kaminer, 2013), declarative memory encoding for emotional and neutral stimuli (Roozendaal & Hermans, 2017), and long-term memory retrieval (Soetens et al., 1993, 1995). Specifically, results from both animal and human studies report that administering noradrenergic agonists during, or directly after, a learning event leads to better memory (McGaugh, 2013; Roozendaal & Hermans, 2017; Soetens et al., 1993, 1995). However, prolonged wakefulness has also repeatedly been shown to reduce cognitive function (Durmer & Dinges, 2005; van Dongen, Maislin, Mullington, & Dinges, 2003). Our current findings suggest that the missing piece between these two seemingly contradictory outcomes is the role of sleep. Here, stimulants had little impact on memory

[a] *Due to the lack effects in d' at Test 1, we wanted to ensure that effects reported for hit rate were not primarily due to a shift in biased responding across drug conditions. To assess this, we utilized repeated measures ANOVAs to calculate differences in criterion c (-0.50*(z(H)+z(FA)) for both Test 1 and Test 2. For Test 1, we did not find any significant differences; Emotion: $F_{(1,27)}$=3.635; p=.067; η^2_p=0.119, Drug: $F_{(1,27)}$=1.08; p=0.308; η^2_p=0.038, Interaction: $F_{(1,27)}$=0.811; p=.376; η^2_p=0.029. For Test 2 we did find a significant main effect for emotion, Emotion: $F_{(1,27)}$=4.72; p=.04; η^2_p=0.14, where subjects were biased toward Hit responses for negative* vs. *neutral pictures. No effects emerged for Drug: $F_{(1,27)}$=0.151; p=.701; η^2_p=0.005 and there was no Interaction: $F_{(1,27)}$=0.78; p=.38; η^2_p=0.02.*

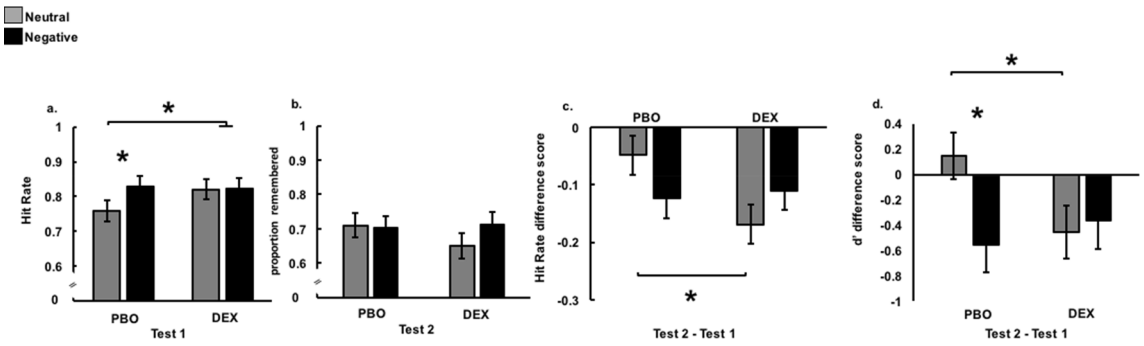

Fig. 2. a-d. a. Morning administration of stimulants (DEX) increased hit accuracy for neutral images (gray bars) at Test 1, after 12-hrs of wake, resulting in similar performance as negative images (black bars). **b**. No difference between drug conditions was found for performance at Test 2. **c and d.** Forgetting difference scores (*Test 2-Test 1 accuracy and d'*) show significantly worse memory for neutral, but not negative, pictures in the DEX condition compared with PBO. For *d'*, participants also performed worse on negative pictures, compared to neutral, in the PBO condition. Error bars represent standard error of the mean, asterisks represent significance at the $p < .05$ level.

Table 1
Nighttime sleep parameters by drug condition.

	Placebo	Dextroamphetamine
TST*	534.93 (9.05)	491.93 (11.85)
Stage1 min*	13.93 (1.64)	21.62 (1.92)
Stage2 min	283.04 (10.37)	270.68 (9.66)
SWS min*	109.25 (7.3)	96.62 (6.64)
REM min*	128.7 (6.17)	103 (6.73)
WASO*	31.77 (5.16)	53.77 (6.95)
SE (%)*	92.21 (1.07)	84.85 (1.81)
Sleep Onset*	6.82 (1.14)	13.79 (2.09)
Stage2 Onset*	10.45 (1.61)	20 (2.58)
SWS Onset*	20.3 (1.92)	32.25 (3.37)
REM Onset	114.32 (9.24)	177.09 (12.23)

Note: Table represents mean and the standard error of the mean (SE) of each sleep parameter for each drug condition. 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); SO = Sleep Onset (calculated as the time from lights out to first epoch of sleep); SE = Sleep Efficiency. Each stage onset variable was calculated as the time from lights out to each sleep stage (i.e. Stage 2, SWS and REM). All stats are represented in minutes besides SE which is in percentage. Asterisks represent significance at $p < 0.05$.

performance after 12 h of wake as only modest increases to hit rate and no changes to d' were present at Test 1. Instead, stimulant-induced losses of sleep resulted in worse memory performance the next day. This suggests that using psychostimulants may come at a substantial cost to next-day memory retention, an outcome likely at odds with one of the primary non-medical reasons people, and especially students, are turning to these medications.

Psychostimulants likely disrupt memory processes by preventing new memories from undergoing critical sleep-dependent consolidation, which stabilizes and integrates new learning into long-term memory stores. Previous studies suggest that both SWS and REM interact to ensure lasting memory traces. Following encoding, episodic memories are thought to get repetitively re-activated during SWS in both the hippocampus (where memories are stored quickly and for a short time period), and in the cortex (where they are stored at a slower rate in an overlapping and distributed manner across several memory networks) (O'Reilly, Bhattacharyya, Howard, & Ketz, 2014). Through a constant hippocampo-cortical dialogue, SWS reactivations mediate the redistribution of information in cortical long-term memory stores, a process known as "systems consolidation." (Born & Wilhelm, 2012; Diekelmann & Born, 2010; Genzel, Kroes, Dresler, & Battaglia, 2014; Mednick, Cai, Shuman, Anagnostaras, & Wixted, 2011; Tononi and Cirelli, 2003, 2014) Although REM sleep has been implicated in the processing of the affective components of memories (Lipinska et al., 2019; Payne & Kensinger, 2010), there is less support for its role in non-emotional episodic memory consolidation. In the current study, we found that dextroamphetamine indiscriminately reduced nighttime sleep, which lead to reductions in post-sleep memory performance. Specifically, increased latencies to fall asleep, Stage 2, SWS and REM were associated with poorer memory performance the next day. This suggests that psychostimulants' broad blockade of both SWS and REM likely reduced sleep-dependent reactivation and integration of recent memories and increased overnight forgetting rates. On the other hand, we found that in the placebo condition, subjects had higher *d'* for neutral compared to negative material after sleep, which is at odds with traditional hypotheses of sleep-dependent emotional memory enhancement. This effect was due to greater false alarms, but not accuracy, to negative vs neutral pictures after sleep. These and other similar results suggest that people may be more prone to falsely remember negatively-valenced information (Dougal & Rotello, 2004; Xie & Zhang, 2017) and that sleep may exacerbate this effect (Darsaud et al., 2011; Pardilla-Delgado & Payne, 2017). It is also important to note that those who did not have considerable latencies to sleep after the stimulant showed improvements in memory accuracy the next day. This suggests that, for some users, stimulant benefits to memory at encoding may persist if there is little harm to nighttime sleep.

Several neurotransmitters may be responsible for the prevention of systems consolidation by psychostimulants. Stimulants primarily increase levels of norepinephrine and dopamine, both of which stave off sleep, promote arousal (Mitchell & Weinshenker, 2010; Monti & Monti,

Table 2
Behavioral Performance at Retrieval Tests 1 and 2.

	Test I				Test II			
	Placebo		d-amphetamine		Placebo		d-amphetamine	
	Neutral	Negative	Neutral	Negative	Neutral	Negative	Neutral	Negative
Hit Rate	0.76 (0.03)	0.83 (0.03)	0.82 (0.28)	0.82 (0.03)	0.71 (0.04)	0.70 (0.03)	0.65 (0.04)	0.71 (0.04)
False Alarm Rate	0.16 (0.03)	0.17 (0.03)	0.17 (0.02)	0.20 (0.03)	0.10 (0.02)	0.17 (0.03)	0.13 (0.02)	0.17 (0.03)
d'	2.10 (0.22)	2.40 (0.19)	2.26 (0.16)	2.23 (0.16)	2.24 (0.14)	1.80 (0.18)	1.85 (0.17)	1.87 (0.19)

Note: Table represents mean and the standard error of the mean (SE) of each performance parameter for each drug and valence condition.

2007; Robbins, 1997), and are critical during memory encoding. Interestingly, Berry and colleagues identified a forgetting mechanism that is regulated by dopamine and dependent on arousal level, with dopamine-dependent forgetting suppressed under conditions of low arousal, such as during sleep, and enhanced by activation of sensory pathways (Berry, Cervantes-Sandoval, Chakraborty, & Davis, 2015). This model fits with earlier models of memory that proposed sleep plays a passive role in memory consolidation by suppression of plasticity and the retroactive interference that causes forgetting (Jenkins & Dallenback, 1924; Wixted, 2004). A more recent model, the Opportunistic Consolidation model, combines aspects of both active and passive models, suggesting that sleep is a low interference condition providing the optimal state for the initiation of active systems consolidation, with low plasticity during SWS as a prerequisite for sleep-facilitated consolidation (Mednick et al., 2011). Additionally, stimulants also indirectly promote acetylcholine, another neurotransmitter implicated in sleep-dependent memory consolidation. Specifically, cholinergic transmission is high during wake and is thought to contribute to attention, focus and memory encoding (Hasselmo, 1999), whereas during SWS sleep, acetylcholine plummets to its lowest levels, before peaking during REM (Tyree & de Lecea, 2017). This decrease in acetylcholine during SWS is understood to facilitate hippocampal-cortical feedback (Hasselmo, 1999), whereas the increases during REM have been associated with emotional plasticity (Walker & van Der Helm, 2009). Indeed, studies have found that increasing cholinergic transmission during SWS, with cholinesterase inhibitors, blocks hippocampal-dependent memory consolidation (Gais & Born, 2004). To our knowledge, no studies have investigated how cholinergic agonists or antagonists during REM sleep impact emotional memory retention. In the current study, stimulant's artificial and prolonged boosts of dopamine, norepinephrine, and acetylcholine may have interrupted natural cycling between SWS and REM, exhibited by increased sleep latencies and awakenings, which likely decreased SWS-dependent consolidation mechanisms and interfered with REM-based cholinergic processing. This is a notable drawback of using psychostimulant medications for cognitive enhancement, as stimulants enhancement of normal fluctuations in these key neurotransmitters prioritizes encoding capabilities, but undermines consolidation. Yet, both are critical for long-term cognitive success.

In contrast with several findings implicating noradrenergic activity in boosting memory for emotionally arousing experiences (McGaugh, 2013; Roozendaal & Hermans, 2017), we did not find preferential enhancement of negative memories with stimulants. One alternative view of stimulant cognitive enhancement that may help explain these discrepant results focuses on dopaminergic salience enhancement, which can make boring tasks more interesting (Volkow et al., 2004). In one study, researchers discovered that a single dose of stimulant (20 mg methylphenidate) before a math task led to increased reports of the task as interesting, exciting, and motivating, yet overall performance was not changed. In the current study, stimulants may have increased the salience of neutral pictures at encoding, indicated by increased hits, and similarly tagging them for further consolidation as if they were naturally salient negative images. Additionally, morning (9AM) drug administration occurred when endogenous levels of both norepinephrine and dopamine (the main neurochemical targets of amphetamines) are typically at ceiling (Tyree & de Lecea, 2017), which may have impacted our ability to further boost subject's memory for the emotional images. To further tease apart stimulants' effect on cognition, future studies should administer stimulants at various times across the circadian day, coinciding with peaks and dips in endogenous dopaminergic and noradrenergic cycles, allowing for a more systematic investigation of these two neurotransmitters actions on stimulant cognitive enhancement. Furthermore, administering the drug before vs after encoding will further dissociate the drug effects on different stages of memory, something we were not able to examine within the current design.

In conclusion, we found that performance benefits from stimulants are short-lived, as stimulant-induced sleep impairments lead to post-sleep memory degradation. This suggests that using stimulant medications as cognitive enhancers have negative consequences for sleep-dependent cognitive outcomes.

CRediT authorship contribution statement

Lauren N. Whitehurst: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Visualization. **Sara C. Mednick:** Conceptualization, Methodology, Validation, Writing - review & editing, Supervision, Funding acquisition.

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None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nlm.2020.107342.

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