Dopamine D2-like Receptor Activation Wipes Out Preferential Consolidation of High over Low Reward Memories during Human Sleep

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Abstract

■ Memory formation is a selective process in which reward contingencies determine which memory is maintained and which is forgotten. Sleep plays a pivotal role in maintaining information for the long term and has been shown to specifically benefit memories that are associated with reward. Key to memory consolidation during sleep is a neuronal reactivation of newly encoded representations. However, it is unclear whether preferential consolidation of memories associated with reward requires the reactivation of dopaminergic circuitry known to mediate reward effects at encoding. In a placebo-controlled, double-blind, balanced crossover experiment, we show that the dopamine D2-like receptor agonist pramipexole given during sleep wipes out reward contingencies. Before sleep, 16 men learned 160 pictures of landscapes and interiors that were associated with high or low rewards, if they were identified between new stimuli at retrieval 24 hr later. In the placebo condition, the participants retained significantly more pictures that promised a high reward. In the pramipexole condition, this difference was wiped out, and performance for the low reward pictures was as high as that for high reward pictures. Pramipexole did not generally enhance memory consolidation probably because of the fact that the dopaminergic agonist concurrently suppressed both SWS and REM sleep. These results are consistent with the concept that preferential consolidation of reward-associated memories relies on hippocampus-driven reactivation within the dopaminergic reward system during sleep, whereby during sleep reward contingencies are fed back to the hippocampus to strengthen specific memories, possibly, through dopaminergic facilitation of long-term potentiation. ■

INTRODUCTION

Memory formation is adaptive, and behavior that is associated with high reward increases in frequency while other behavior dwindles. This process has been linked to dopaminergic neuromodulation of learning processes (Shohamy & Adcock, 2010; Wise & Rompre, 1989). However, it remains unclear to what extent postencoding consolidation processes contribute to this effect, in addition to the immediate influence of reward at encoding. A large body of evidence has accumulated supporting sleep's beneficial role for memory consolidation. Sleep-dependent declarative memory consolidation is thought to rely mainly on the reactivation of traces that were encoded during prior wakefulness (Rasch & Born, 2013; Diekelmann & Born, 2010), and memories associated with high rewards benefit more from this process (Wilhelm et al., 2011; Fischer & Born, 2009). However, it remains unclear if sleep leads to the preferential consolidation of highly rewarded memories because reward present at learning tags these memories so that they are reactivated more frequently during subsequent sleep or rather the sleep-associated consolidation process itself involves reactivation of the dopaminergic reward circuitry associated with a specific memory. Here we probed the latter assumption by testing the effects of a dopaminergic agonist (pramipexole) on the sleep-associated consolidation of memories, which were associated with high or low rewards.

Correlated activity of neurons that encoded information during wake predicts their firing together during subsequent sleep in rodents (Wilson & McNaughton, 1994). This replay of neural representations during sleep occurs in the same sequence as during wakefulness and is coordinated between the hippocampus and the neocortex (Ji & Wilson, 2007; Skaggs & McNaughton, 1996). In humans, a causal role for these reactivations has been shown for declarative and skill memory (Antony, Gobel, O'Hare, Reber, & Paller, 2012; Rudoy, Voss, Westerberg, & Paller, 2009; Rasch, Buchel, Gais, & Born, 2007). During SWS, hippocampal reactivations lead striatal reactivations of place-reward information in rats, consistent with the view that striatal dopaminergic activation contributes to the consolidation of reward-related memory traces during sleep (Lansink, Goltstein, Lankelma, McNaughton, & Pennartz, 2009; Lansink et al., 2008).

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Journal of Cognitive Neuroscience 26:10, pp. 2310–2320
doi:10.1162/jocn_a_00629

Dopamine is a major neuromodulator and has been put forward as the main neurotransmitter mediating the preferential encoding of highly rewarding stimuli (Schultz, 2007; Wise, 2004; Wise & Rompre, 1989) by influencing plasticity in the hippocampus (e.g., Edelmann & Lessmann, 2013; Zhang, Lau, & Bi, 2009; Manahan-Vaughan & Kulla, 2003) and extrahippocampal reward-related structures like the ventral tegemental area (VTA) and the nucleus accumbens (NAcc; e.g., Schotanus & Chergui, 2008; Goto & Grace, 2005; Thomas, Malenka, & Bonci, 2000). These processes do not exclusively depend on immediate reward but are likewise triggered by the anticipation of reward in the future (Shohamy & Adcock, 2010). The preferential retention of high-reward items in anticipated reward paradigms such as the motivated learning (ML) task has been shown to rely on activity in the NAcc and VTA and the connectivity of these regions to the hippocampus during encoding (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006). Two major groups of dopamine receptor subtypes, the D1-like (D1/5) and D2-like receptors (D2/3/4), have been identified (Missale, Nash, Robinson, Jaber, & Caron, 1998). In the hippocampus, postsynaptic D1 and D2 receptors are most highly expressed, which corresponds to their agonists' ability to influence plasticity (Edelmann & Lessmann, 2013; Manahan-Vaughan & Kulla, 2003) and plasticity at hippocampal and prefrontal inputs to the NAcc is likewise modulated by D1 and D2 receptors (Goto & Grace, 2005), whereas D3 receptors have been shown to act as autoreceptors blunting reward signals (Sokoloff et al., 2006).

Pramipexole is an agonist of the D2-like dopamine receptors, that is, the D2 and D3 dopamine receptors (Antonini & Calandrella, 2011). It is widely used in the treatment of Parkinson's disease (Jankovic & Poewe, 2012) and of restless legs syndrome (Buchfuhrer, 2012), which are both related to pathological changes of midbrain dopaminergic neurons projecting to the BG (Connor et al., 2009; Dauer & Przedborski, 2003). Pramipexole has been shown to have reinforcing properties in conditioned place preference and self-administration paradigms in rodents (Engeln et al., 2012; Riddle, Rokosik, & Napier, 2012). Here, we administered the drug to increase dopaminergic activity during the sleep-associated consolidation of memories (pictures) associated with high or low reward. We expected that beyond generally enhancing consolidation of memories during sleep, the D2-like receptor agonist would nullify preferential consolidation of memories associated with high reward, inasmuch as reward circuitry would be equally active during reactivation of low reward memories.

METHODS

Participants

Sixteen young men aged 24.5 years (range = 19–30 years) participated in the study. Participants were nonsmoking, native German speaking. They underwent a routine health examination before participation to exclude any mental or physical disease, also excluding a history of psychiatric disorders by a structured interview. Participants did not take any medication at the time of the experiments and reported having a normal sleep–wake cycle for at least 6 weeks before the experiments. They were instructed to get up at 07:00 am on experimental days and, during these days, not to take any naps and not to ingest alcohol or, after 01:00 pm, caffeine-containing drinks. Before the experiment proper, participants took part in an adaption night under conditions of the experiment (i.e., including the placement of electrodes for polysomnographic recordings and insertion of an intravenous catheter). The experiments were approved by the local ethics committee. Written informed consent was obtained from all participants before the study.

Design and Procedure

The study followed a balanced, double-blind, placebo-controlled, within-subject, crossover design. Participants took part in two experimental sessions scheduled at least 14 days apart. Both sessions were identical but for the oral administration of placebo or pramipexole (Pramipexol Winthrop 0.35 mg—corresponding to 0.5 mg pramipexole dihydrochloride monohydrate, Fa. Winthrop Arzneimittel GmbH, Germany, plasma halftime: 8 hr, plasma maximum: 2 hr). To prevent periphery side effects of pramipexole, participants additionally received domperidone, a dopamine antagonist that does not cross the blood–brain barrier in both sessions (Motilium 20 mg, Nycomed GmbH, Germany, plasma halftime: 8 hr, plasma maximum: 1 hr), a procedure proved effective in several foregoing studies (e.g., Ye, Hammer, Camara, & Münte, 2011; Riba, Kramer, Heldmann, Richter, & Münte, 2008).

Figure 1A summarizes the experimental procedure. On experimental nights, participants arrived at the laboratory at 07:30 pm. Following insertion of an intravenous catheter and preparations for EEG and polysomnography, the participants learned the ML task between 08:30 and 09:30 pm. Afterwards, they learned control tasks (declarative word pair associates and procedural sequence finger tapping) with a 10-min break between each of the tasks; this order was chosen so that participants would be most attentive during encoding of the reward task. Fifteen minutes before lights were turned off (at 11:15 pm) to enable sleep, the participants were orally administered a capsule containing pramipexole or placebo, as well as the domperidone tablet. They were woken at 07:15 am and left the lab. During the following day, participants engaged in their usual activities. They were instructed to refrain from any stressful mental or physical activities and to keep a record of their activities during this day. In the evening, they returned to the lab at 08:00 pm, and retrieval of the memory tasks was tested—in reverse order of learning. (This was done as retrieval procedures for

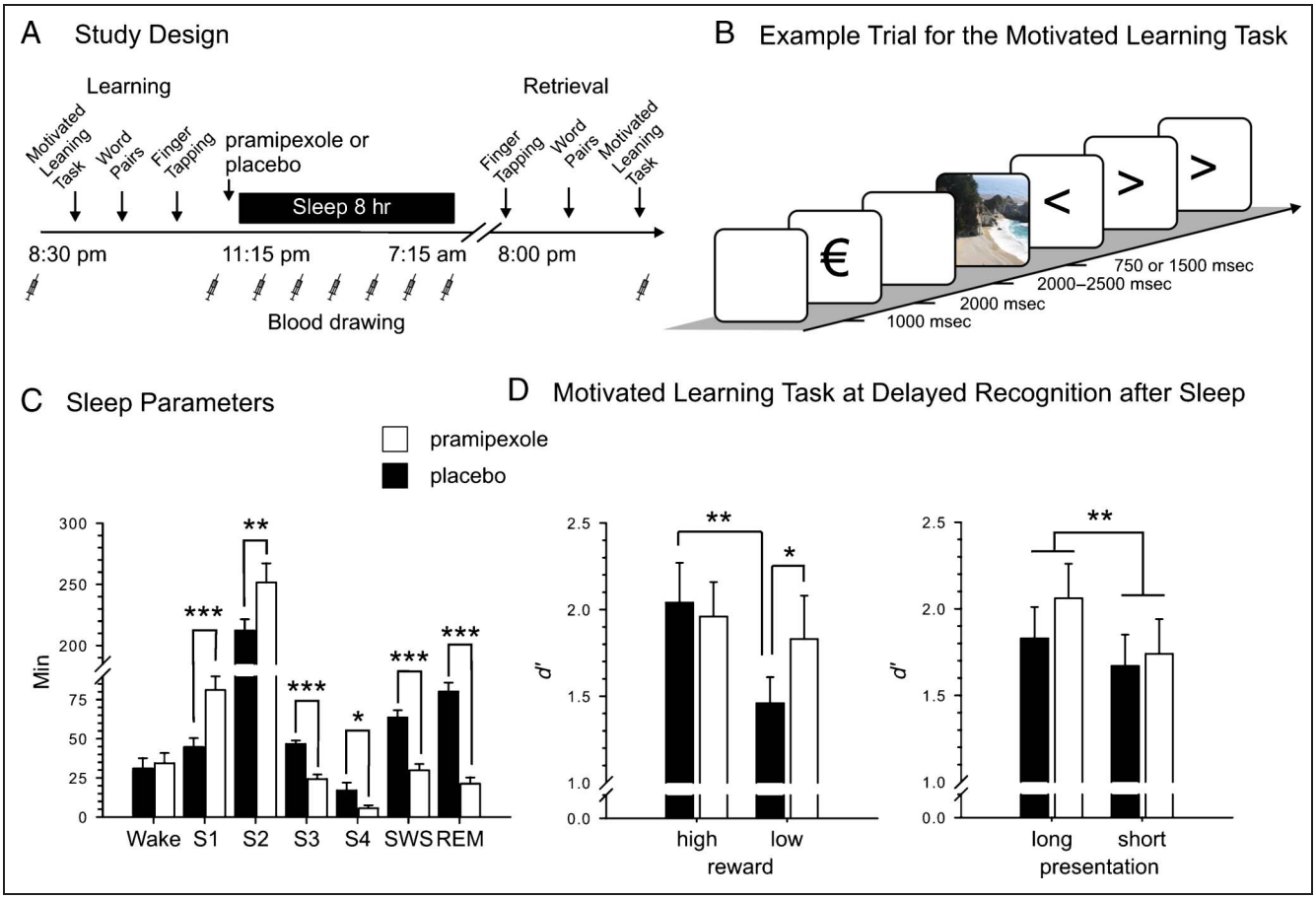

Figure 1. (A) Study design: Participants took part in two identical experimental sessions, but for the administration of placebo or pramipexole. Following preparation for blood sampling, the learning phase started at 8:30 pm. Thereafter and 15 min before the participant went to bed (at 11:15 pm), the capsules were orally administered. Participants were awakened at 7:15 am in the next morning. The retention interval was approximately 24 hr, and retrieval was tested at 8:00 pm. Blood was drawn before and after learning, after retrieval, and in 1.5-hr intervals during the night. (B) The motivated learning task was adapted from Adcock et al. (2006). At learning participants were presented 160 pictures for 750 msec (short presentation) or 1500 msec (long presentation). Each picture was preceded by a slide indicating a high (1 €) or a low (2 cents) reward for correctly identifying the picture at later recognition. After each picture, participants performed on three items of a distractor task, which afforded pressing the arrow key corresponding to the orientation of an arrow presented on the screen. At immediate and delayed recognition testing, participants were shown different groups of 80 new and 80 old pictures and had to identify them correctly, which earned them their reward (see Methods for details). (C) Mean (±*SEM*) time (in min) spent in non-REM Sleep Stages S1, S2, S3, and S4; in SWS (i.e., the sum of S3 and S4); and in REM sleep is provided for the pramipexole (empty bars) and placebo condition (black bars). (D) Performance on the ML task for the delayed recognition test during the retrieval phase after sleep. Mean (±*SEM*) performance is indicated as *d*, that is, the *z* value of the hit rate minus the *z* value of the false alarm rate. $n = 14$ ($n = 13$ for ML task). ***$p \leq .001$, **$p \leq .01$, *$p \leq .05$.

the word pairs and the sequence finger tapping were short [i.e., <8 min] compared with the longer picture recognition test taking about 30 min.) At learning and retrieval, control tests of vigilance, mood, and subjective sleepiness were also performed. Blood was sampled before and after learning, after retrieval, and at 1.5-hr intervals during the night. For this purpose, the intravenous catheter was connected to a long thin tube to enable blood collection from an adjacent room without disturbing the participant's sleep.

The EEG was recorded continuously from electrodes (Ag-AgCl) placed according to the 10–20 System, referenced to two linked electrodes attached to the mastoids. EEG signals were filtered between 0.16 and 35 Hz and sampled at a rate of 250 Hz using a BrainAmp DC (BrainProducts GmbH, Munich, Germany). Additionally, horizontal and vertical eye movements (HEOG, VEOG) and the EMG (via electrodes attached to the chin) were recorded for standard polysomnography. Sleep architecture was determined according to standard polysomnographic criteria using EEG recordings from C3 and C4 (Rechtschaffen & Kales, 1968). Scoring was carried out independently by two experienced technicians who were blind to the assigned treatment. Differences in scoring between the scorers were resolved by consulting a third experienced technician. For each night, total sleep time and time spent in the different sleep stages (wake; Sleep Stages 1, 2, 3, 4; SWS, that is, sum

of Sleep Stages 3 and 4; REM sleep) was calculated in minutes.

ML Task—Reward Memory

The ML task was adapted from the reward learning paradigm reported by Adcock et al. (2006) and required the participants to memorize 160 pictures of landscapes and living rooms (Figure 1B). Presentation of 80 of these pictures was preceded (delay 2000–2500 msec) by a €1 symbol whereas the other 80 were preceded by a 2 cents symbol, and participants were informed they would receive the respective reward for every hit during subsequent recognition. They were also informed that a correct rejection would earn them 51 cents and that for a miss or a false alarm they would lose 51 cents. This was done to exclude potential strategy effects, for example, only choosing items that would, with high certainty, yield high rewards. Forty pictures each of the two reward conditions were presented for 750 and 1500 msec, respectively, to control for effects of encoding depth. Encoding depth was manipulated as the reward manipulations may also have influenced encoding depth, and we were interested if the effect of pramipexole would be independent of this. Each picture was followed by three items of a distraction task where participants had to press one of two buttons according to the orientation of an arrow presented on the screen, and 1 sec later, the next trial started. Participants were allowed to train the task for three items including the recognition procedure before learning the pictures, and the first two and last two pictures that were added in addition to the 160 pictures were excluded from later recognition testing to buffer recency and primacy effects. They were also informed that recognition would be tested twice, immediately after learning and in the evening of the next day. Immediate recognition started 15 min after learning had finished and before participants were reminded of the reward contingencies (also by training on three pictures). They were then shown 80 of the original pictures together with 80 new pictures in a pseudorandom order and asked to indicate for each picture if they remembered or knew the picture (correct answers were summed and used to calculate individual hit rates) or if it was new by pressing a key on the keyboard (1, 2, or 3, respectively). They also pressed a key (1 or 2, respectively) according to whether they believed to receive a high or a low reward for the answer (thus, incorrect remember and know judgments allowed us to calculate individual false alarm rates for high and low reward categories). All participants received mock feedback ("You performed slightly above average and will receive € xx" with amounts varying between 47.5 and 52.5 euros) of how much they had earned after each recognition test. This was done to keep participants motivated while controlling effects of high or low performance. Delayed recognition that was performed the next evening was identical, but the other 80 learned pictures were used and 80 completely new pictures were shown in comparison. *d*, that is, the *z* value of the hit rate minus the *z* value of the false alarm rate, was calculated as dependent variable, which is independent of response strategies. We also calculated the accuracy of participants reward knowledge, that is, the proportion of correctly categorized high and low reward hits.

For constructing task stimuli, 32 similar groups of 20 pictures each were generated with regard to mean valence and arousal ratings as assessed in a pilot study ($n = 5$). The presentation of the groups was then balanced across the old/new, immediate/delayed recognition, short/long presentation, and high/low reward conditions for the different participants.

Control Measures—Declarative and Procedural Memory Tasks

The declarative verbal paired associates task required learning a list of 40 pairs of semantically related words (e.g., clock–church). Different wordlists were used on the participants' two experimental nights. During the learning phase, the word pairs were presented sequentially on a computer screen, each for 4 sec, separated by ISIs of 1 sec. After presentation of the entire list, performance was tested using a cued recall procedure, that is, the first word (cue) of each pair was presented and the participant had to name the associated second word (response). The correct response word was then displayed for 2 sec, regardless of whether the response was correct or not, to allow reencoding of the correct word pair. The cued recall procedure was repeated until the participant reached a criterion of 60% correct responses. Retrieval in the evening after sleep was tested using the same cued recall procedure as during the learning phase, except that no feedback of the correct response word was given. Absolute differences between word pairs recalled at retrieval testing and on the criterion trial during learning served as a measure of overnight retention. Several studies showed that consolidation of word pairs profits particularly from SWS (e.g., Plihal & Born, 1997; Ekstrand, Barrett, West, & Maier, 1977; Table 1).

The finger sequence tapping task was adopted from earlier studies, indicating very robust sleep-dependent improvements in this task (Walker et al., 2003). It requires the participant to repeatedly press one of two 5-element sequences (e.g., 4-1-3-2-4 or 4-2-3-1-4) with the fingers of the nondominant hand on a keyboard as fast and as accurately as possible for 30-sec epochs interrupted by 30-sec breaks. The numeric sequence was displayed on the screen at all times to keep working memory demands at a minimum. A key press resulted in a white asterisk appearing underneath the current element of the sequence. Each 30-sec trial was scored for speed (number of correctly completed sequences) and errors. After each 30-sec trial, feedback was given about the number of correctly completed sequences and error rate. At learning, participants trained on twelve 30-sec trials. The

Table 1. Memory Tasks

	Placebo		*Pramipexole*		
ML Task Immediate Recognition					
High reward	2.52	(0.24)	2.42	(0.23)	*ns*
Low reward	2.10	(0.23)	2.33	(0.25)	*ns*
Long duration	2.41	(0.21)	2.47	(0.23)	*ns*
Short duration	2.21	(0.20)	2.28	(0.23)	*ns*
Paired Associates Learning Task					
Blocks to criterion	1.64	(0.31)	1.86	(0.33)	*ns*
Learning	28.86	(1.16)	29.07	(1.10)	*ns*
Retrieval	28.21	(0.93)	28.43	(0.61)	*ns*
Absolute difference	−0.64	(0.93)	−0.64	(0.61)	*ns*
% of learning	98.10	(3.58)	97.78	(2.21)	*ns*
Finger Tapping Task - Correct Sequences					
Learning	17.52	(1.20)	18.30	(1.38)	*ns*
Retrieval	20.67	(1.30)	21.40	(1.66)	*ns*
Absolute difference	3.14	(0.96)	3.10	(0.58)	*ns*
% of learning	120.39	(6.49)	117.03	(3.51)	*ns*
Finger Tapping Task - Error Rates					
Learning	9.34	(2.40)	7.78	(1.54)	*ns*
Retrieval	6.50	(1.08)	6.92	(1.64)	*ns*
Absolute difference	2.84	(2.53)	0.86	(1.35)	*ns*
Finger Tapping Task - Control Sequence					
Correct sequences	15.10	(1.25)	15.45	(1.51)	*ns*
Error rate in percent	9.16	(2.07)	8.71	(1.60)	*ns*

Mean (±*SEM*) values are given for the pramipexole and placebo conditions. ML Task (reward learning): *d* is provided for performance during the learning phase. Paired Associates Learning Task (word pairs): Total amount of recalled words is given for criterion trials at learning and at retrieval. Additionally, percent values of retrieved words are provided relative to learning performance at the criterion trial (set to 100%). Finger Tapping Task: Average number of correctly tapped sequences per 30-sec trial and error rates (in percent) for finger sequence tapping during the last three 30-sec trials at learning, the three trials at retrieval, and for the untrained control sequence at retrieval. Additionally, percent values of correctly tapped sequences at retrieval are provided relative to learning performance (set to 100%). *ns*: $p > .10$

average score for the last three of these trials was used to indicate learning performance. At retrieval in the evening after sleep, participants were tested on another three trials. Overnight changes in performance were calculated as absolute differences in speed and error rate between the three trials at retrieval and the last three trials at learning. Effects unspecific to the actually learned sequence, that is, general increases in RT, were measured during the retrieval phase after sleep by assessing performance on three blocks of a new sequence after recall of the trained sequence.

Control Measures—General Retrieval Performance, Vigilance, Sleepiness, and Mood

At retrieval, to exclude effects of the drug on general retrieval performance, participants were tested on a word generation task (Regensburger Wortflüssigkeitstest [WFT]; Table 2 for means and *SEM*s of the control measures). They were asked to generate as many words as possible

Table 2. Control Measures

	Placebo		*Pramipexole*		
SSS					
Before learning	2.71	(0.24)	2.71	(0.24)	*ns*
After learning	3.57	(0.43)	4.00	(0.26)	*ns*
Before retrieval	2.43	(0.20)	2.71	(0.28)	*t*
After retrieval	2.64	(0.23)	3.00	(0.26)	*t*
Positive Affect (PANAS)					
Before learning	26.71	(1.80)	25.21	(1.30)	*ns*
After learning	21.79	(1.68)	19.93	(1.53)	*ns*
Before retrieval	25.43	(1.77)	25.36	(1.61)	*ns*
After retrieval	24.21	(1.83)	24.64	(1.66)	*ns*
Negative Affect (PANAS)					
Before learning	11.14	(0.39)	10.71	(0.29)	*ns*
After learning	11.36	(0.55)	11.21	(0.43)	*ns*
Before retrieval	10.64	(0.17)	11.36	(0.62)	*ns*
After retrieval	10.50	(0.17)	11.00	(0.55)	*ns*
PVT					
Before learning	3.40	(0.07)	3.35	(0.09)	*ns*
After learning	3.22	(0.10)	3.20	(0.10)	*ns*
Before retrieval	3.48	(0.09)	3.49	(0.10)	*ns*
After retrieval	3.36	(0.10)	3.35	(0.11)	*ns*
WFT					
Category	19.36	(1.18)	18.71	(0.87)	*ns*
Letter	16.50	(1.37)	15.64	(1.59)	*ns*

Mean (±*SEM*) values are given for the pramipexole and placebo conditions. SSS = Stanford Sleepiness Scale (subjective sleepiness); PANAS = Positive and Negative Affective Scale (mood); PVT = Psychomotor Vigilance Task (reaction speed = 1/[RT in msec]); WFT = Word Fluency Test (Regensburger Wortfluessigkeitstest) measuring general retrieval capabilities. *t* (trend): $0.05 \leq p \leq .10$ and *ns*: $p > .10$.

within a 2-min interval after being cued with either a letter (p or m) or a category (professions or hobbies).

The following control measures were assessed once before and once after each learning and retrieval phase. Mean RTs were assessed as a measure of vigilance in a 5-min version of the Psychomotor Vigilance Task (PVT; Dinges et al., 1997) that required pressing a button as fast as possible whenever a bright millisecond clock presented on a dark computer screen started counting upward. After the button press, this clock displayed the RT. The median reaction speed (i.e., 1/[RT in msec]) was calculated for each participant. Mood was measured using the 10 positive and 10 negative items of the Positive and Negative Affective Schedule (PANAS; Watson, Clark, & Tellegen, 1988), where participants respond to items (e.g., "Do you momentarily feel scared?") on a 5-point Likert scale ranging from 1 = *not at all* to 5 = *very much*. Subjective sleepiness was assessed with the one-item Stanford Sleepiness Scale (SSS; Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973), ranging from 1 = *Feeling active, vital, alert, or wide awake* to 8 = *Asleep*. At the end of the experiment, participants were asked if they believed to have received an active agent or placebo.

Control Measures—Blood Samples

Samples for measuring hormone concentrations were kept frozen at −80°C until assay. Cortisol, growth hormone, and prolactin levels were determined in serum using commercial assays (Immulite, Siemens Medical Solutions Diagnostics, Los Angeles, CA). Intra- and interassay coefficients of variation were <10%.

Data Reduction and Statistical Analysis

Data from two participants were completely discarded because of poor sleep during the placebo night. Data from one participant were not included in the analysis of the ML task, as he remembered an unusual amount more of the low reward items than of the high reward items in the placebo condition (i.e., the difference between high and low reward was more than 2 *SD*s from the group mean, probably reflecting a misunderstanding of the rather complex task instruction or an unusual encoding strategy). For two participants, hormonal data sets were incomplete because of problems with blood sampling during sleep. Statistical analyses generally relied on ANOVAs (SPSS version 21.0.0 for Windows) including a repeated-measures factor Treatment (substance vs. placebo) and, where appropriate, the factor Phase (learning vs. retrieval). As analyses revealed a strong suppressive influence of pramipexole on both SWS and REM sleep, main analyses of memory performance included the individual difference in wake time between treatment conditions as covariate to account for this sleep disruption. Wake time (i.e., the amount of time spent awake between sleep onset and lights on) was used for these analyses because it did not differ significantly between treatment conditions. As awakenings are usually transient in healthy young men, this measure reflects the amount and length of awakenings during sleep and, thus, the severity of sleep fragmentation. For analysis of pictures, additional Reward and Duration factors were introduced, representing recognition of high versus low reward pictures and long versus short stimulus presentation, respectively. The analyses of the pictures did not include a factor Phase as immediate and delayed recognition were performed on different sets of stimuli. Significant ANOVA interactions were specified by post hoc *t* tests. Degrees of freedom were corrected according to Greenhouse–Geisser where appropriate.

RESULTS

Sleep Parameters

Total sleep time was 441.71 min and 435 min for placebo and pramipexole, respectively, and mean (*SEM*) time in minutes spent in the different sleep stages are provided in Figure 1C. Time spent in Sleep Stages 3 and 4, SWS and REM sleep, was significantly reduced by pramipexole ($t(13) = 6.91, p \leq .001$; $t(13) = 2.38, p \leq .05$; $t(13) = 6.11$, $p \leq .001$; $t(13) = 11.04, p \leq .001$, respectively), whereas time in Sleep Stages 1 and 2 was increased ($t(13) = -6.76$, $p \leq .001$; $t(13) = -3.29, p \leq .01$).

Memory Tasks

Pramipexole significantly increased the retrieval of low reward pictures after sleep, $F(1, 11) = 5.91, p \leq .05$ (see Figure 1D for means and *SEM*). The analysis of retrieval performance after sleep revealed that longer duration pictures and high reward pictures were retained better ($F(1, 11) = 18.99, p \leq .01$; $F(1, 11) = 5.41, p \leq .05$). There was also an interaction between treatment and reward, $F(1, 11) = 5.20, p \leq .05$. The lower-order ANOVAs revealed a superiority of high reward over low reward for the placebo condition, $F(1, 11) = 8.19, p \leq .01$, but not for the pramipexole condition ($p = .80$).

Note that in these analyses we used differences in wakefulness during the sleep interval as covariate to account for the sleep disruption observed after pramipexole. However, analyses without the covariate showed a similar picture, with statistical trends for increased retention of low reward pictures, $t(12) = -2.12, p = .056$, in the pramipexole condition as compared with placebo, as well as for the Reward main effect and the Treatment × Reward interaction ($F(1, 12) = 4.19, p = .063$ and $F(1, 12) = 3.63$, $p = .081$, respectively). Also, the difference between high and low reward conditions was only prominent for the placebo condition, $t(12) = 3.00, p \leq .01$, but not for the pramipexole condition ($p = .60$). During immediate recognition before sleep, there was a main effect of Duration, $F(1, 12) = 11.65, p \leq .01$ (see Table 1 for means and *SEM*s) but, interestingly, no main or interaction effects

for Reward ($p > .14$). An analysis including immediate and delayed recognition in the placebo condition revealed main effects of Phase, Reward, and Duration ($F(1, 12) = 39.32$, $p \leq .001$; $F(1, 12) = 9.04$, $p \leq .01$; $F(1, 12) = 5.51$, $p \leq .05$) but no interaction effects ($p > .58$).

Response bias calculated as the negative mean of the z value of the hit rate and the z value of the false alarm rate were comparable between the treatment conditions at delayed recognition ($p > .19$; see Table 3 for a summary of means and *SEM*s of hits, false alarms, and response bias). Analysis of response bias during immediate recognition, however, revealed that participants were more conservative for high reward pictures, $F(1, 12) = 4.88$, $p \leq .05$; there also was an interaction between Treatment and Reward, $F(1, 12) = 6.55$, $p \leq .05$, which was reflected by a more conservative strategy for high reward pictures in the placebo condition, $t(12) = 2.68$, $p \leq .05$. This argues toward concentrating the analyses on the d measures reported above, as they are independent of response bias. At delayed recognition and immediate recognition, hit rates were higher for longer duration pictures ($F(1, 12) = 14.11$, $p \leq .01$ and $F(1, 12) = 9.82$, $p \leq .01$, respectively). There were statistical trends for false alarm rates being reduced for high reward pictures during delayed, $F(1, 12) = 3.00$, $p \leq .10$, and immediate recognition, $F(1, 12) = 4.48$, $p \leq .10$. No main or interaction effects for participants' accurate categorization of hits to reward category were found at immediate (pramipexole: high 0.48 ± 0.06, low 0.49 ± 0.07; placebo: high 0.57 ± 0.05, low 0.47 ± 0.06, $p > .46$) or delayed recognition (pramipexole: high 0.50 ± 0.09, low 0.46 ± 0.07; placebo: high 0.52 ± 0.07, low 0.49 ± 0.08, $p > .46$) and Accuracy did not differ from chance ($p > .20$, tested against .5 chance level).

Table 3. ML Task: Additional Response Information

	Placebo		*Pramipexole*		
Hits					
Immediate recognition					
High reward	0.72	(0.05)	0.74	(0.05)	*ns*
Low reward	0.73	(0.05)	0.76	(0.04)	*ns*
Long duration	0.75	(0.05)	0.78	(0.04)	*ns*
Short duration	0.69	(0.05)	0.73	(0.05)	*ns*
Delayed recognition					
High reward	0.61	(0.07)	0.62	(0.06)	*ns*
Low reward	0.57	(0.07)	0.64	(0.06)	*ns*
Long duration	0.61	(0.07)	0.67	(0.06)	*ns*
Short duration	0.57	(0.07)	0.58	(0.06)	*ns*
False Alarms					
Immediate recognition					
High reward	0.04	(0.01)	0.06	(0.01)	*ns*
Low reward	0.11	(0.03)	0.10	(0.03)	*ns*
Delayed recognition					
High reward	0.06	(0.02)	0.08	(0.02)	*ns*
Low reward	0.13	(0.02)	0.11	(0.03)	*ns*
Response Bias					
Immediate recognition					
High reward	0.59	(0.08)	0.44	(0.10)	*
Low reward	0.34	(0.12)	0.35	(0.11)	*ns*
Delayed recognition					
High reward	0.67	(0.15)	0.63	(0.13)	*ns*
Low reward	0.51	(0.16)	0.49	(0.13)	*ns*

Mean (±*SEM*) values are given for the pramipexole and placebo conditions. *ns*: $p > .10$.

*$p \leq .05$.

The declarative and procedural memory tasks did not yield differences between placebo and pramipexole (see Table 1 for means and *SEM*s). Neither the difference between word pairs recalled at learning and retrieval ($p > .99$) nor performance at learning, blocks needed to reach criterion or performance at retrieval in the word pair associates task ($p > .34$) differed between placebo and pramipexole conditions. An analysis comparing learning and retrieval for individual treatment conditions revealed no significant differences ($p > .31$). Likewise, in the finger sequence tapping task, the differences between correctly tapped sequences as well as error rate at learning and retrieval ($p > .46$) were not significantly affected by treatment, and performance at learning before treatment, at retrieval after treatment, and on the control sequence at retrieval was comparable between treatments ($p > .28$). However, at retrieval, participants tapped more correct sequences than during learning, $F(1, 13) = 22.03$, $p \leq .001$, and this was also true in an individual analysis for both of the treatment conditions (pramipexole: $t(13) = 5.30$, $p \leq .001$ and placebo: $t(13) = 3.28$, $p \leq .01$). No such effect was evident for error rates ($p > .26$).

General Retrieval Performance, Vigilance, Mood, and Subjective Sleepiness

There were no significant differences in general retrieval performance (as measured by the word fluency task), in RTs on the PVT, and mood (as assessed by the PANAS) between pramipexole and placebo conditions at learning or retrieval ($p > .25$; Table 1 for means and *SEM*s). At retrieval, there was a trend toward increased subjective sleepiness in the pramipexole condition (before retrieval: $t(13) = -1.75$, $p \leq .10$; after retrieval: $t(13) = -2.11$, $p \leq .06$). Participants could not differentiate if they had received placebo or an active substance ($\chi^2_{(1)} = .14$, $p = .70$).

Blood Hormone Concentrations

For cortisol and growth hormone levels, there was a trend for main effect of Treatment ($F(1, 11) = 4.68$, $p = .054$ and $F(1, 11) = 3.89$, $p = .074$, respectively). This was because of increased cortisol (pramipexole: 7.09 ± 0.90 μg/dl, placebo: 3.67 ± 0.97 μg/dl at 03:30 am) and growth hormone (pramipexole: 3.01 ± 1.04 ng/ml, placebo: 0.36 ± 0.11 ng/ml at 05:00 am) concentrations at night following pramipexole intake ($t(11) = 3.30$, $p \leq .01$; $t(11) = 2.44$, $p \leq .05$). Serum prolactin levels were not significantly different between pramipexole and placebo conditions ($p = .45$).

DISCUSSION

In this study, we aimed to clarify whether the preferential consolidation of memories associated with reward involves the reactivation of dopaminergic reward circuitry during sleep. For this purpose, we enhanced dopaminergic activity during a period of retention sleep by administration of the D2-like receptor agonist pramipexole, which, if reactivation of dopaminergic circuitry is of relevance, should enhance memory consolidation during sleep, in particular for memories associated with low rather than high reward. Our data of the placebo condition replicate findings by Adcock et al. (2006) in showing a robust reward effect on memory 24 hr after learning. Importantly, as we expected, rather than enhancing memories that were associated with a high reward, pramipexole wiped out differences in retention performance between low and high reward memories. Unexpectedly, overall memory consolidation in the reward task, as well as in the procedural and declarative control tasks, was not increased by pramipexole, which may be because of the fact that the D2-like receptor agonist distinctly impaired SWS and REM sleep (Dzirasa et al., 2006). This direct effect of pramipexole on sleep limits the explanatory power of this study.

The finding, in the placebo condition, that reward only differentially affected recognition performance of pictures at delayed recognition after sleep, but not at immediate recognition testing right after learning before sleep, lends to the idea that sleep substantially contributes to forming memories specifically associated to reward, beyond supporting the preferential maintenance of memories associated with high reward, which corresponds to findings that monetary reward effects are stronger after retention intervals of several days (Murayama & Kuhbandner, 2011). However, the lack of clear differential effects of low versus high reward at immediate recognition could also be because of ceiling effects as here all recognition scores were rather high; additionally, the treatment conditions differed regarding bias at immediate recognition. In an analysis of the placebo condition, the respective Phase × Reward interaction term failed to reach significance; however, this analysis is limited by the fact that different recognition stimuli were tested at immediate and delayed recognition. All in all, the issue of sleep being critical for the formation of representations distinctly differing in strength depending on the associated reward remains to be further explored.

Whatever the cause for the absence of differences in immediate recognition of memories associated with low and high reward, at the delayed recognition after sleep high reward memories were clearly better recognized than low reward memories in the placebo condition, and this difference was wiped out by pramipexole. In rats during sleep reactivation of cell assemblies that were active together during prior wake has been shown in the hippocampus (Ji & Wilson, 2007; Skaggs & McNaughton, 1996) and ventral striatum (Lansink et al., 2008; Pennartz et al., 2004). Therefore, the preferential consolidation of high reward memories might be mediated by reactivation within the hippocampus that initiates the reactivation of the striatal reward centers (Lansink et al., 2009), leading to a feedback of reward signals from the striatum to the hippocampus during sleep, via a feedback loop that may also include the VTA (Lisman & Grace, 2005). Another possibility is that reward-associated memories that are deemed important for future behavior are already tagged before sleep by prefrontal processes for preferential reactivation during sleep (Wilhelm et al., 2011). Indeed, it has been shown that the reactivation frequency of cells within the hippocampus during sleep can be preferentially enhanced by exogenous cues (Bendor & Wilson, 2012) and that such reactivations induced by exogenous cues in particular benefit low-value representations (Oudiette, Antony, Creery, & Paller, 2013). However, differential effects of reward on consolidation during sleep being solely conveyed by a tagging that takes place before sleep would not explain that enhancing D2-like receptor activation during sleep nullifies any difference in recognition between memories associated with low and high reward.

It is probable that the reward promised for later retrieval increased encoding strength, and we, therefore, additionally manipulated this factor by presenting pictures for a short or a long duration. Consequently, the longer duration led to a robust increase in recognized pictures. However, our finding that the reward-related effect of pramipexole did not depend on or interact with the duration of stimulus presentation precludes that effects of D2-like receptor activation were conveyed via encoding strength per se as a mechanism that might mediate sleep's influence on memory (Drosopoulos, Schulze, Fischer, & Born, 2007). Interestingly, duration also did not interact with reward to influence retention performance in the placebo condition, indicating that reward information and encoding depth are independent mediators of sleep-dependent memory consolidation.

Whereas reinforcing effects of pramipexole have been consistently demonstrated in rats (Engeln et al., 2012; Riddle et al., 2012), in human fMRI studies, reward-related effects of pramipexole expressed themselves in reduced

activation of reward networks probably reflecting the inhibition of endogenous dopamine release via presynaptic autoreceptors (McCabe, Harwood, Brouwer, Harmer, & Cowen, 2013; Riba et al., 2008). Moreover, performance on the same task as was used here was shown to rely on NAcc and VTA activity during the encoding session and the connectivity of these brain areas to the hippocampus as measured by blood oxygen-dependent activity (Adcock et al., 2006), and reactivation of brain areas involved in prior encoding has been proposed to be causal to sleep-dependent memory consolidation (Rudoy et al., 2009; Rasch et al., 2007). Combining these pieces of evidence, we suppose that in the placebo condition of our experiment, when pictures were reactivated, inputs from the reward circuits modulated memory according to the reward contingencies learned during encoding. Under pramipexole, however, with inhibition of the reward centers via presynaptic D2-like receptor activity and globally enhanced activation of postsynaptic D2-like receptors in the NAcc and the hippocampus, reactivation efficacy is balanced out for memories with high and low rewards (see Figure 2, for an overview of the proposed mechanisms). Specifically, the drug seems to substitute globally (i.e., for high and low reward traces) for dopamine's local plastic effects (i.e., on high reward traces only) that have been inhibited by autoreceptor activation, thereby matching retention performance of low reward and high reward pictures under pramipexole to high reward performance under placebo. In line with this assertion, pramipexole during encoding blocked the discrimination between high reward stimuli and low reward stimuli in a reward learning task (Santesso et al., 2009; Pizzagalli et al., 2008). This interpretation also fits well with reports of increases in compulsive behavior in patients with restless leg syndrome and Parkinson disease treated with pramipexole (Pourcher, Remillard, & Cohen, 2010; Weintraub et al., 2010; Aiken, 2007). It is quite possible that these patients feel the urge to perform certain maladaptive behavior because pramipexole leads to a blunting of reward contingent consolidation of adaptive behavior during sleep.

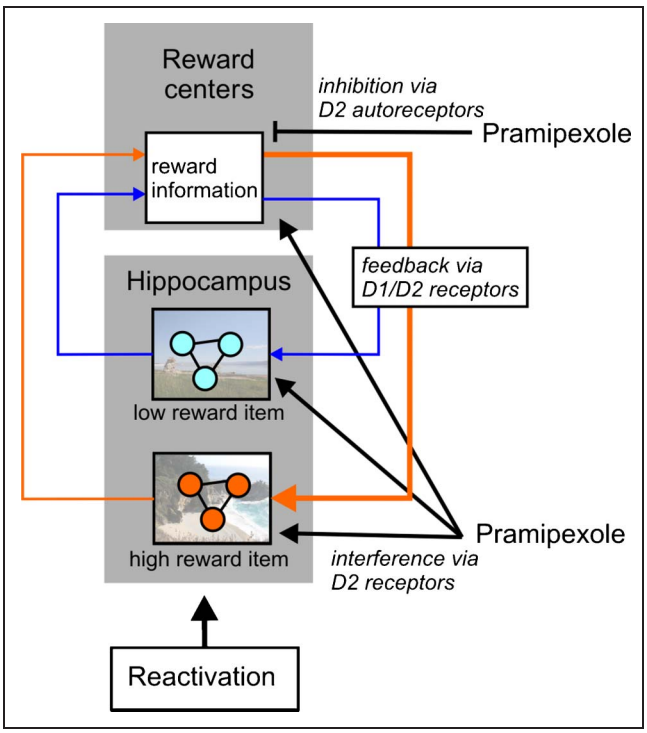

Figure 2. Proposed mechanisms of the effects of pramipexole on memory consolidation during sleep. During consolidation, the reactivation of memory traces in the hippocampus engages reward centers (like the ventral tegmental area or the ventral striatum including the NAcc) that were also active during their encoding in the prior wake state, which leads to a relay of reward information to the hippocampus via a feedback loop. The reported effects can be explained by pramipexole inhibiting the reward centers via dopaminergic autoreceptors. Concurrently, pramipexole may interfere with reward information at postsynaptic dopamine receptors in the hippocampus or in the reward centers. Ultimately, it may turn out that both mechanisms contribute to the reported effect.

Unexpectedly, pramipexole did not increase the overall amount of pictures that were retained or improve performance on any of the other memory tasks, which may be because of the disrupting effects of the drug on sleep, suppressing both SWS and REM sleep. Alternatively, this may also indicate that the effect of pramipexole is conveyed mostly by inhibiting the reward centers via autoreceptors, thus leaving unrewarded memories unchanged.

The causal role of SWS for hippocampus-dependent memory has been repeatedly shown (e.g., Marshall, Kirov, Brade, Molle, & Born, 2011; Marshall, Helgadottir, Molle, & Born, 2006). To the best of our knowledge, this study is the first to examine effects of pramipexole on sleep in healthy volunteers. However, the present findings fit well to observations in restless leg patients exhibiting massive changes in sleep architecture after acute administration of the D2-like receptor agonist, which likewise comprised marked reductions in SWS and REM sleep in favor of Sleep Stages 1 and 2 (Saletu, Anderer, Saletu-Zyhlarz, Hauer, & Saletu, 2002).

Ultimately, our data in combination with foregoing animal studies suggest that sleep-dependent consolidation adapts behavior to future rewards through the hippocampus-driven feedback of reward contingencies from the reward system to the hippocampus, thereby selectively strengthening those memories during reactivation that promise high rewards. This strengthening might be achieved by the modulatory effect of dopamine on plasticity in the hippocampus (e.g., Edelmann & Lessmann, 2013; Zhang et al., 2009; Manahan-Vaughan & Kulla, 2003) but could also occur in extrahippocampal structures (Schotanus & Chergui, 2008; Goto & Grace, 2005; Thomas et al., 2000). The action of pramipexole obliterating this adaptation process by wiping out reward contingencies during consolidation sleep opens the possibility of manipulating maladaptive but highly rewarding behavior after its encoding, for example, to buffer effects of relapse in drug addicts.

Acknowledgments

The authors would like to thank Barbara Linz for helpful comments regarding the study design, Seza Bolat for medical supervision of the study, Timo Baum for assisting data collection, and Martina Grohs and Heidi Ruf for performing blood analyses. This research was supported by grants from the Deutsche Forschungsgemeinschaft SFB 654 "Plasticity and Sleep" and from the German Federal Ministry of Education and Research (BMBF) to the German Center for Diabetes Research (DZD e.V.; 01GI0925).

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