Consolidation of Reward Memory during Sleep Does Not Require Dopaminergic Activation

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Abstract

■ Sleep enhances memories, especially if they are related to future rewards. Although dopamine has been shown to be a key determinant during reward learning, the role of dopaminergic neurotransmission for amplifying reward-related memories during sleep remains unclear. In this study, we scrutinize the idea that dopamine is needed for the preferential consolidation of rewarded information. We impaired dopaminergic neurotransmission, thereby aiming to wipe out preferential sleep-dependent consolidation of high- over low-rewarded memories during sleep. Following a double-blind, balanced, crossover design, 17 young healthy men received the dopamine d2-like receptor blocker sulpiride (800 mg) or placebo, after learning a motivated learning task. The task required participants to memorize 80 highly and 80 lowly rewarded pictures. Half of them were presented for a short (750 msec) and a long (1500 msec) duration, respectively, which permitted dissociation of the effects of reward on sleep-associated consolidation from those of mere encoding depth. Retrieval was tested after a retention interval of approximately 22 hr that included 8 hr of nocturnal sleep. As expected, at retrieval, highly rewarded memories were remembered better than lowly rewarded memories, under placebo. However, there was no evidence for an effect of reducing dopaminergic neurotransmission with sulpiride during sleep on this differential retention of rewarded information. This result indicates that dopaminergic activation likely is not required for the preferential consolidation of reward-associated memory. Rather, it appears that dopaminergic activation only tags such memories at encoding for intensified reprocessing during sleep. ■

INTRODUCTION

Every day, the brain encodes large quantities of new information, and sleep-related consolidation processes select the most relevant for long-term storage (Feld & Born, 2017; Wilhelm et al., 2011). During wakefulness, rewards play an important role to support this selection process, and functional connectivity between the hippocampus and reward-related areas at learning predicts memory retrieval a day later (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006). For this, the hippocampus, which is initially involved in all episodic memory storage, and the reward centers, that is, the ventral striatum and the ventral tegmental area (VTA), interact via a feedback loop (Lisman & Grace, 2005) that enables dopamine to exert its influence on the learned behavior (Schultz, 2007). However, although it seems clear that sleep plays an important role for the preferential consolidation of highly (over lowly) rewarded information (Studte, Bridger, & Mecklinger, 2017; Igloi, Gaggioni, Sterpenich, & Schwartz, 2015; Fischer & Born, 2009), it remains open whether this effect depends on enhanced dopaminergic activation during sleep.

Sleep has been shown to support the consolidation of newly formed memories through the repeated replay of neuronal memory traces (e.g., Diekelmann & Born, 2010; Ji & Wilson, 2007; Rasch, Büchel, Gais, & Born, 2007; Wilson & McNaughton, 1994). It has been proposed that this replay also involves dopaminergic pathways, thereby promoting better consolidation for the highly rewarded memories through enhanced neuroplasticity akin to processes acting during wakefulness (Feld, Besedovsky, Kaida, Münte, & Born, 2014). This view is supported by findings in rats that underwent reward learning, where hippocampal replay was tightly linked to ventral striatal replay (Lansink, Goltstein, Lankelma, McNaughton, & Pennartz, 2009; Pennartz et al., 2004). Replay during sleep was also found in the VTA (Valdés, McNaughton, & Fellous, 2015), thereby completing the hippocampal–ventral striatum–VTA loop implicated in this process. However, in another study, replay-associated VTA activation remained restricted to postencoding wakefulness and vanished during postencoding sleep (Gomperts, Kloosterman, & Wilson, 2015). Thus, an alternative view assumes that, rather than directly participating in sleep-dependent consolidation processes, dopamine activity

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elicited by rewards tags memory traces during encoding, leading to more intense replay and accompanied plasticity during subsequent sleep. This view is supported by the finding in mice that optogenetically stimulating dopamine release in the hippocampus during encoding increases replay and consolidation of respective memories during subsequent sleep periods (McNamara, Tejero-Cantero, Trouche, Campo-Urriza, & Dupret, 2014).

To collect causal evidence for or against a direct role of dopamine during sleep-dependent consolidation of reward-associated memories, we investigated, in humans, whether directly blocking dopamine interferes with the consolidation of such memories during sleep. In our Motivated Learning Task section, sleep has been confirmed to consolidate preferentially memory for high-rewarded pictures over low-rewarded pictures (Feld et al., 2014). On the basis of this evidence, we hypothesized that this difference would be wiped out, if dopaminergic transmission is blocked during sleep-dependent consolidation by administration of the dopamine d2-like receptor blocker sulpiride.

METHODS

Participants

Twenty healthy, native German-speaking men fulfilling the requirements to enter higher education, aged 25.30 years (18–30 years) on average and with an average body mass index of 23.38 kg/m^2 (20–25 kg/m^2), completed this study. Before entering the study, all participants underwent a routine medical examination to exclude any psychiatric, neurological, cardiovascular, endocrine, or gastrointestinal diseases. Participants with hypersensitivity to sulpiride or benzamide derivatives, with regular excessive alcohol consumption (regularly more than two bottles of beer per day), with nicotine consumption, or taking regular medication (i.e., including painkillers and sleeping pills) were excluded. The medical screening relied on a structured interview asking for current or past diagnosed conditions and a physical examination as well as a blood pressure and a routine blood screening test (including hemoglobin, sodium, potassium, calcium, chloride, glucose, bilirubin, glutamate pyruvate transaminase, alkaline phosphatase, gamma-glutamyl-transpeptidase, C-reactive protein, partial thromboplastin time), and only healthy participants were included. In addition, participants reported a normal sleep–wake cycle and no shift work, night work, or intercontinental flights (>4-hr time difference) for at least 6 weeks before the experiments. Participants were instructed to keep a regular sleep schedule in the week before the experiment (approximately sleeping from 23:00 to 7:00 each night), to go to bed at 23:00 the night before experiments, and to get up at 7:00 on experimental days as well as, during these days, not to take any naps, not to drink caffeine-containing drinks after 13:00, and also not to consume alcohol starting 1 day before the experimental nights. Adherence to these rules was assessed with a questionnaire at the very beginning on each experimental session.

Before the experimental nights, participants took part in an adaptation night under the same conditions as during the experiment, which included the placement of the electrodes for polysomnographic recordings and of the cannula for blood drawing. The ethics committee of the University of Tübingen approved the experiments. We obtained written informed consent from all participants before their participation.

Design and Procedures

The study followed a balanced, double-blind, placebo-controlled, within-participant crossover design (Figure 1A). Participants took part in two identical experimental sessions with the exception of administration of either sulpiride (four Dogmatil forte, sulpiride 200 mg, Sanofi Aventis) or placebo and parallel versions of the behavioral tasks where necessary, with at least 2 weeks of interval between the sessions. The dose of 800-mg sulpiride (oral administration, plasma maximum: 3–6 hr, plasma half-life for oral administration: average of 7–8 hr and ranges from 6 to 15 hr [Müller, Härtter, Köhler, & Hiemke, 2001; Bressolle, Brès, & Fauré-Jeantis, 1992; Wiesel, Alfredsson, Ehrnebo, & Sedvall, 1980]) was chosen, because at a lower dose, sulpiride is more likely to have an effect on presynaptic dopamine receptors and thus tends to increase dopamine release, whereas at 800 mg, postsynaptic effects predominate. A single dose of 800 mg resulted in a 65% blockade of striatal d2-like receptors without adverse events in healthy volunteers (Takano et al., 2006). Sulpiride was administered after the learning phase at 23:00, that is, 15 min before lights off. We chose this timing to maximize drug levels during the slow wave sleep (SWS)-rich first half of the night and thereby maximize the effects during occurrence of replay. The retrieval phase for the reward task was scheduled the next evening, that is, as late as possible (and more than two times the average drug half-life) to minimize the residual amount of drug circulating at retrieval testing and also to keep the study design comparable with Feld et al. (2014).

On the experimental nights (for an overview, see Figure 1A), participants arrived at 19:00 and filled in a general questionnaire, and then an intravenous cannula was placed for drawing blood. Afterward, electrodes were applied for polysomnographic recordings. Next, they filled in the questionnaires on mood and sleepiness. About 1 hr after cannula placement, the first blood sample was taken, and then the behavioral tasks were performed. First, they performed a vigilance task, and then the reward task was learned with immediate recall of half the items scheduled after a 15-min break. Then, after additional breaks of 5 min each, declarative and procedural contents were learned as control tasks.

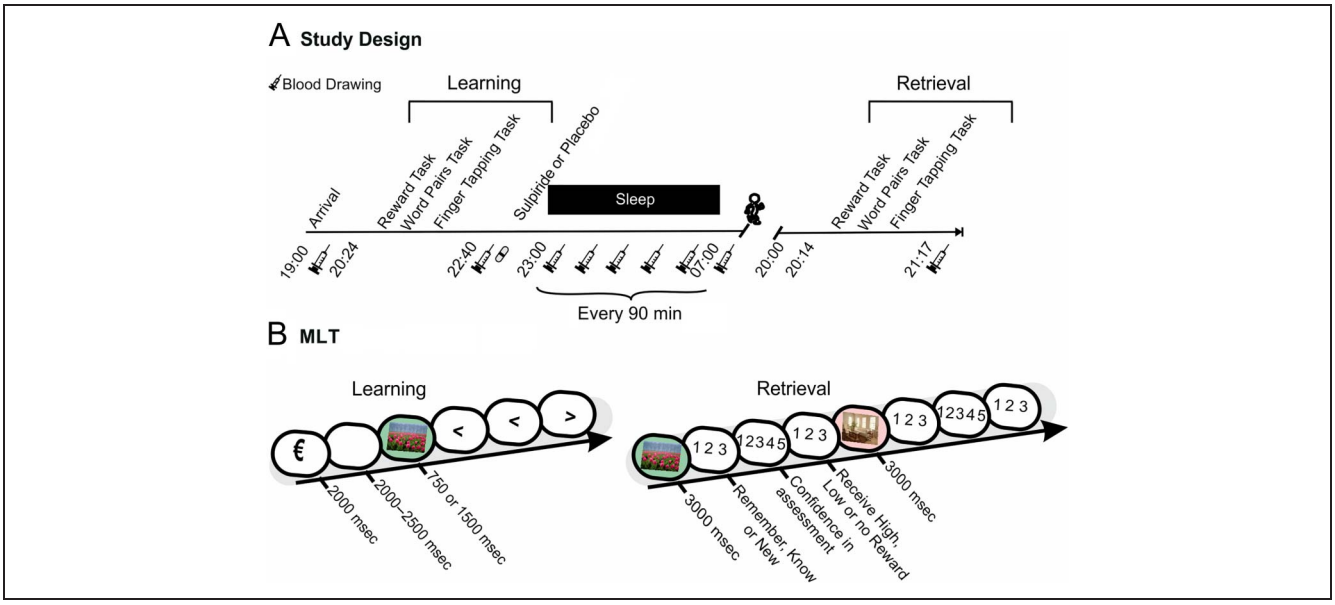

Figure 1. (A) Participants took part in two identical experimental sessions, except for the administration of placebo or sulpiride. They started the session at around 7:00; after preparing for blood sampling and sleep EEG, the learning phase started. Thereafter at 23:00, the capsules (sulpiride or placebo) were orally administered. Participants were awakened at 7:15 the next morning. The retention interval was approximately 22 hr, and retrieval was tested in the evening at approximately 20:00. 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) and Feld et al. (2014). 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 euro) or low (2 cents) reward for correctly identifying the picture at later recognition. After each picture, three items of a distractor task were presented, in which participants had to press the arrow key corresponding to the orientation of an arrow presented on the screen. At immediate (learning phase) and delayed (retrieval phase) recognition testing, participants were shown different sets of 80 new and 80 old pictures and had to identify them correctly, which led to them receiving the reward. For details on the retrieval procedure, please refer to the Methods section.

Afterward, they performed the vigilance task again and filled in the questionnaires on mood and sleepiness. At 22:50, blood was sampled again, and at 23:00, the participant orally received either sulpiride or placebo. Participants slept from 23:15 to 7:15, and a polysomnogram was recorded. During the night, blood was sampled every 1.5 hr starting at 0:30. A long thin tube connected to the cannula enabled blood collection during the night from an adjacent room without disturbing the participant's sleep. Participants were woken between 7:00 and 7:30 preferably from Sleep Stages 1 or 2. Next, they filled in mood questionnaires. Blood was sampled again approximately 15 min after waking up. Then, participants were allowed to shower and received a standardized breakfast (two slices of bread, butter, cheese, and water) before leaving the laboratory. In the evening of the same day, participants returned to the laboratory at 20:00 and filled in the mood and sleepiness questionnaires. Afterward, they performed the vigilance task and then the word fluency task. Next, they performed the finger sequence tapping task (first retrieval of the learned sequence was tested, and then a new control sequence was learned). After 5 min of break each, they were asked to retrieve the declarative word-pair task and to recognize the reward contents, respectively. Then, they performed the vigilance task and answered the mood and sleepiness questionnaires again. Blood was sampled once more at 21:30 before participants left the laboratory.

Motivated Learning Task

The motivated learning task was adapted from prior work of Feld et al. (2014) and required the participants to memorize 160 unique pictures of landscapes and living rooms in each of the two parallel versions (see Figure 1B). Presentation of 80 highly rewarded pictures was preceded (delay: 2000–2500 msec) by a 1-euro symbol, whereas the other 80 lowly rewarded pictures were preceded by a 2-cents symbol, and participants were informed that they would receive the respective reward for every hit during subsequent recognition. They were also informed that a correct rejection (identifying a novel picture as not being presented at learning) at recognition testing 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 yield high rewards as old. 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 lead to

differences in encoding depth, and we were interested whether the effect of sulpiride would be independent of this confound. 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. Participants 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 starting, participants were reminded of the reward contingencies (also by training on three pictures). During recognition testing, they were 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 (remember and know were equally treated as old judgments, and 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). Next, they judged their confidence in this answer by pressing a key on the keyboard (5 = *not very confident* to 1 = *very confident*). They also pressed a key (1, 2, or 3, respectively) according to whether they believed to receive a high reward, a low reward, or no 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 of how much they had earned after each recognition test (the message "You performed slightly above average and will receive X euros" was displayed with amounts varying between 47.5 and 52.5 euros). 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*-prime (d'), that is, the z value of the hit rate minus the z value of the false alarm rate, was calculated as the dependent variable, which is independent of response strategies. In the two reward conditions, the hit rates for the high- and low-reward pictures were calculated individually, and the corresponding subjective false alarm rates were used to calculate each d'. This was done, as we assumed that response bias, that is, the criterion to judge a specific picture as old defined as the negative mean of the z value of the hit rate and of the false alarm rate, would be affected by the participants' reward anticipation. 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

Behavior

To control effects of the drug on declarative and procedural memory, we used a word-pair task and a finger sequence tapping task (Walker et al., 2003), respectively. In the declarative control task, participants learned a list of 40 associated word pairs (e.g., painter–pianist, presented for 4 sec each). After viewing the complete list of 40 pairs in a random order, participant's performance was tested using a cued recall procedure. After each response, the complete pair was displayed for 2 sec. This procedure was repeated until the participant reached 60% correct responses. The same cued recall procedure was used once more during the retrieval phase, except that no feedback of the correct answer was given. To measure the overnight retention, we calculated the absolute differences between word pairs recalled during the retrieval phase and word pairs recalled during the last run of the learning phase. For the procedural finger sequence tapping task, participants had to repeatedly input a five-element sequence (e.g., 4-1-3-2-4 or 4-2-3-1-4) with the fingers of their nondominant hand as fast and accurately as possible. This had to be done during twelve 30-sec trials interrupted by 30-sec breaks. We scored for speed (number of correctly completed sequences) and error rate (proportion of incorrectly tapped sequences). Learning performance was calculated by averaging performance for the last three of these trials. During the retrieval phase, participants performed another three trials, which were also averaged. The absolute differences between the retrieval phase and performance in the learning phase were calculated as a measure of overnight retention. As a control for effects of the drug during the retrieval phase, participants performed the trials of a novel unlearned control sequence.

During the retrieval phase, participants were also tested on a word generation task (Regensburger Wortflüssigkeitstest [Word Fluency Test]; Aschenbrenner, Lange, & Tucha, 2000) to control for effects of the drug on long-term memory retrieval function. Within 2 min each, participants had to generate as many words as possible first starting with a specified letter (p or m) and then from a specified category (jobs or hobbies). Further control measures were tested before and after the learning phase as well as the retrieval phase. We measured participants' vigilance with a 5-min version of the psychomotor vigilance task (PVT; Dinges et al., 1997), their mood with the Positive and Negative Affective Schedule (PANAS; Watson, Clark, & Tellegen, 1988), and their subjective sleepiness with the Stanford Sleepiness Scale (SSS; Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973). After finishing each session, participants

were asked if they believed to have received sulpiride or placebo.

Cortisol and Prolactin

Serum concentrations of cortisol and prolactin were measured with the ADVIA Centaur XPT chemiluminescent immunoassay system from Siemens Healthineers. The interassay coefficients of variation were 5% for cortisol and 2.5% for prolactin. The area under the curve (AUC) was calculated as the weighted mean of the interinterval approximation (time point n + time point $(n + 1)/2 \times$ interval duration) for five time points, which occurred between lights out and waking, that is, from 00:30 until 06:30.

Polysomnography, Sleep Scoring, and Spectral Analysis

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 (Brain Products GmbH). In addition, horizontal and vertical eye movements (horizontal and vertical EOG) 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, and 4; SWS, i.e., sum of Sleep Stages 3 and 4; rapid eye movement [REM] sleep) were calculated in minutes. In addition, average power spectra were calculated for non-REM sleep (Sleep Stages 2–4). Power spectra were calculated by fast Fourier transformation with a Hanning window applied to subsequent blocks of 2048 data points (~10.24 sec, three blocks per 30-sec epoch). The averaged spectra for each participant were filtered by a 5-point moving average to produce a smoothing of the fast Fourier transformation outcome. In the averaged spectra, mean power was determined for the 0.5- to 1-Hz slow oscillation, 1- to 4-Hz delta, and the 12- to 15-Hz sleep spindle frequency bands for non-REM sleep.

Data Reduction and Statistical Analysis

Three participants were excluded from the analysis; two of the participants spent too much time awake after sleep onset (wake during sleep, which is included in total sleep) and therefore did not receive enough sleep categorized as Sleep Stages 1–4 and REM sleep, and one of them had too long sleep latency, which resulted in very low total sleep time. This sample resulted in an achieved power of $1 - \beta = 0.63$, when assuming a false positive error rate of $\alpha = .05$, a correlation of $r = .65$ between the repeated measures, and a medium effect size of $f = 0.25$ (calculated in G*Power 3.1.9.4; Faul, Erdfelder, Lang, & Buchner, 2007). Under these assumptions, a power of $1 - \beta = 0.80$ would have been achieved with 24 participants. Regarding counterbalancing after exclusions, 9 of 17 participants received placebo in the first experimental session, and eight received sulpiride. During blood sampling, 73 draws (20.3% of the total) were missed because of blocked tubes (occurring typically when the participant bends his or her arm during sleep). Singular missing values were replaced by interpolating between the neighboring values. For two or more subsequent missing values, we calculated the average value of the rest of the participants at the same time point. Statistical analyses generally relied on ANOVAs (SPSS Version 21.0.0 for Windows) including repeated-measures factors Treatment (sulpiride vs. placebo), Reward (high vs. low), and Duration (long vs. short). Of note, applying our previous analysis approach (Feld et al., 2014), we did not include a repeated-measures factor for the learning and retrieval phases as different stimuli were used for immediate and delayed recognition in the motivated learning task. Moreover, this would have led to a four-factor ANOVA, which is hard to interpret. Significant interactions were followed up by post hoc t tests. Greenhouse–Geisser correction of degrees of freedom was used, if data violated the assumption of homoscedasticity.

RESULTS

Motivated Learning Task

During the learning phase, highly rewarded pictures were recognized better than lowly rewarded pictures (main effect of reward: $F(1, 16) = 25.03$, $p \leq .001$; Table 1 and Figure 2), and long-duration pictures were recognized better than short-duration pictures (main effect of Duration: $F(1, 16) = 6.75$, $p = .019$). There were no significant interaction effects and no main effect of Treatment in this analysis (all ps $> .511$).

During the retrieval phase, highly rewarded and longer duration pictures were recognized significantly better than lowly rewarded and short-duration pictures, respectively (main effect of Reward: $F(1, 16) = 8.94$, $p = .009$; main effect of Duration: $F(1, 16) = 20.54$, $p \leq .001$). However, there was no evidence of sulpiride affecting the recognition performance in general (main effect of Treatment: $F(1, 16) = 0.02$, $p = .892$) or recognition performance in the reward conditions differentially (Treatment × Reward: $F(1, 16) = 0.59$, $p = .454$). Of note, we also calculated d' by correcting the hit rates with

Table 1. Memory Tasks

	Placebo		*Sulpiride*		*p Value*	*Effect Size*
MLT learning phase						
High reward	2.58	(0.22)	2.65	(0.20)	.682	0.101
Low reward	1.66	(0.20)	1.75	(0.24)	.582	0.136
Long duration	2.10	(0.21)	2.15	(0.22)	.774	0.071
Short duration	1.90	(0.18)	1.98	(0.21)	.643	0.115
MLT retrieval phase						
High reward	1.87	(0.19)	1.77	(0.18)	.493	0.170
Low reward	0.99	(0.20)	1.09	(0.25)	.613	0.125
Long duration	1.52	(0.16)	1.33	(0.19)	.191	0.331
Short duration	1.05	(0.15)	1.20	(0.14)	.225	0.306
Finger tapping						
Correctly tapped sequences						
Learning phase	22.63	(1.40)	21.01	(1.51)	.167	0.351
Retrieval phase	26.00	(1.71)	23.41	(1.72)	.069	0.474
Absolute difference	3.37	(0.83)	2.40	(0.68)	.416	0.203
% of learning	115.47%	(3.72%)	112.18%	(3.63%)	.584	0.136
Error rates						
Learning phase	0.07	(0.02)	0.13	(0.03)	.089	0.439
Retrieval phase	0.09	(0.02)	0.07	(0.01)	.483	0.174
Absolute difference	1.71	(2.08)	−5.71	(2.61)	.059	0.493
Control sequence						
Correct sequences	18.65	(1.70)	18.69	(1.46)	.982	0.006
Error rate in percent	9.85%	(1.68)	9.31%	(1.76)	.809	0.059
Word pairs						
Blocks to criterion	1.59	(0.17)	1.76	(0.16)	.188	0.334
Learning phase	29.59	(0.96)	31.47	(0.88)	.052	0.510
Retrieval phase	28.06	(1.59)	29.47	(1.22)	.380	0.219
Absolute difference	−1.53	(0.98)	−2.00	(0.78)	.729	0.086
% of learning	94.09%	(3.57%)	93.57%	(2.61%)	.915	0.026

Mean (±*SEM*) values are provided for the sulpiride and placebo conditions. Motivated learning task (MLT): d' is provided for performance during the learning phase and the retrieval phase. Finger tapping task: the average number of correctly tapped sequences per 30-sec trial and error rates (in percentage of total tapped sequences) for finger sequence tapping during the last three 30-sec trials of the learning phase, the three trials during the retrieval phase, and for the untrained control sequence. In addition, the absolute difference (retrieval–learning) and percentage of learning (Retrieval/Learning × 100) are provided. Word-pair task: The total amount of recalled words is given for the criterion trial during the learning phase and the recall trial during the retrieval phase. In addition, the absolute difference (retrieval–learning) and percentage of learning (Retrieval/Learning × 100) are provided**.** Cohen's *d* is provided as an effect size statistic.

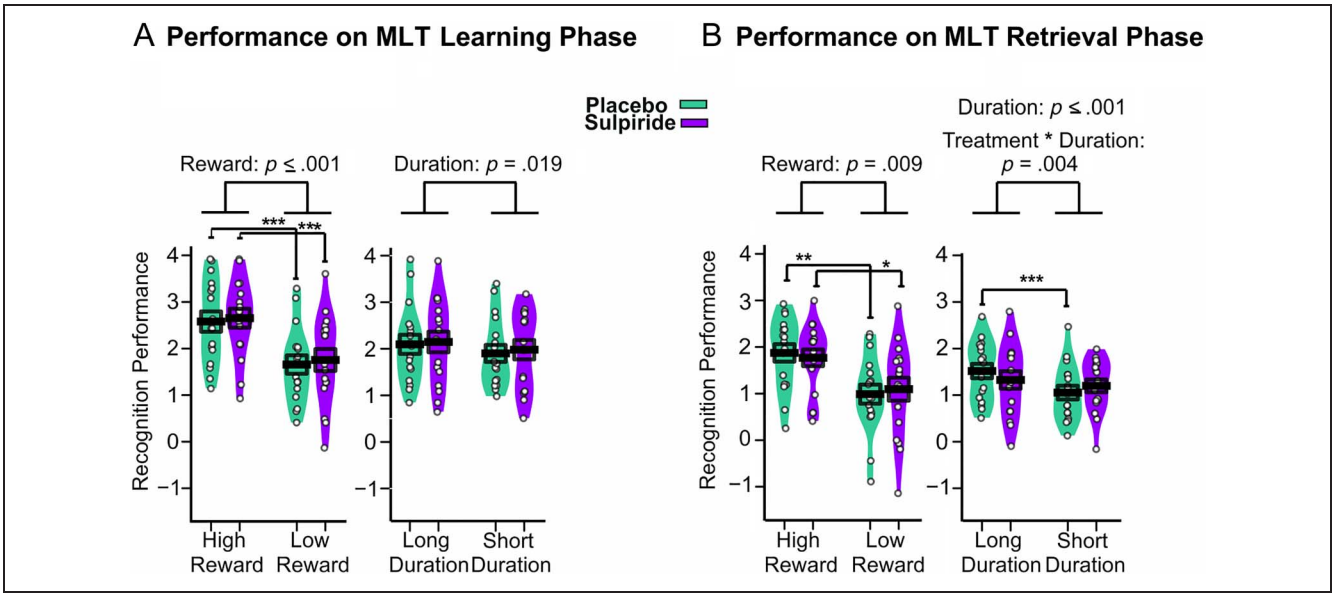

Figure 2. (A) Performance on the motivated learning task for the immediate recognition test during the learning phase before sleep and (B) delayed recognition test during the retrieval phase after sleep for the sulpiride (purple) and placebo (green) conditions. Mean (±*SEM*) performance is indicated as d', that is, the z value of the hit rate minus the z value of the false alarm rate. $n = 17$. *$p \leq .05$, **$p \leq .01$, and ***$p \leq .001$.

false alarm rates per session, and there is also no Treatment × Reward interaction during the retrieval phase, $F(1, 16) = 1.94$, $p = .18$. In addition, we performed two one-sided test analyses in jamovi (Version 1.2) for large effects (Cohen's $d = 0.8$) for this contrast, which can reasonably be ruled out (upper bound: $t(16) = -2.54$, $p = .01$; lower bound: $t(16) = 4.06$, $p \leq .001$). To test the robustness of this null effect, an exploratory overall analysis including learning phase and retrieval phase data was conducted, which also did not yield an effect of sulpiride regarding high or low rewards (Treatment × Reward: $F(1, 32) = 0.57$, $p = .460$). Rather than an effect on rewards, we found that sulpiride diminished the performance difference between long- and short-duration pictures during the retrieval phase (Treatment × Duration: $F(1, 16) = 11.06$, $p = .004$). In the placebo condition, long-duration items were recognized better than short-duration items (long duration: mean = 1.52, $SD = 0.64$; short duration: mean = 1.05, $SD = 0.61$), $t(16) = 6.23$, $p \leq .001$, which was not true for the sulpiride condition (long duration: mean = 1.33, $SD = 0.77$; short duration: mean = 1.20, $SD = 0.57$), $t(16) = 1.44$, $p = .170$ (Figure 2).

To determine response strategies, we calculated the response bias, that is, the negative mean of the z value of the hit rate and of the false alarm rate. In both recognition phases, participants' reactions were more conservative for the high-reward pictures (learning phase: $F(1, 16) = 18.18$, $p \leq .001$; placebo: high reward mean = 0.37, $SD = 0.32$, and low reward mean = 0.02, $SD = 0.45$ [$t(16) = 5.01$, $p \leq .001$]; sulpiride: high reward mean = 0.29, $SD = 0.37$, and low reward mean = −0.02, $SD = 0.44$ [$t(16) = 3.19$, $p = .006$]; retrieval phase: $F(1, 16) = 6.39$, $p = .022$, placebo: high reward mean = 0.36, $SD = 0.53$, and low reward mean = 0.09, $SD = 0.54$ [$t(16) = 2.14$, $p = .048$]; sulpiride: high reward mean = 0.50, $SD = 0.44$, and low reward mean = 0.15, $SD = 0.47$ [$t(16) = 2.52$, $p = .023$]; Table 2). None of the other contrasts was significant (all ps > .189).

We also separately analyzed hit rates and false alarm rates, which largely paralleled data for the sensitivity index. Of note, we did not find a significant interaction effect of treatment and reward in the retrieval phase, $F(1, 16) = 1.30$, $p = .27$, corroborating our null finding of no treatment effect on reward memory using the d' measure, thereby indicating that our main finding does not rely on a specific analysis strategy. Hit rates were higher for longer duration pictures (learning phase: $F(1, 16) = 7.39$, $p = .015$; retrieval phase: $F(1, 16) = 21.69$, $p \leq .001$) and highly rewarded pictures (learning phase: $F(1, 16) = 7.10$, $p = .017$), and at learning and retrieval, false alarm rates were reduced for highly rewarded pictures (learning phase: $F(1, 16) = 12.59$, $p = .003$; retrieval phase: $F(1, 16) = 6.34$, $p = .023$). For the hit rate, we also found that sulpiride differentially affected performance for long- and short-duration items, during the retrieval phase (Treatment × Duration: $F(1, 16) = 12.02$, $p = .003$; see Table 2).

We additionally analyzed subjective hit rates for high- and low-rewarded items (see Table 3 for descriptive statistics), that is, items that were old and that were judged by the participants to earn high or low rewards, and we did not find any main effect of Treatment or Reward or their interactions in both learning and retrieval phases (all ps ≥ .122). In addition, we analyzed hit rates for items that were correctly categorized as high- or low-reward items, and no significant main effect or interaction was

Table 2. Motivated Learning Task Additional Response Information

	Placebo		*Sulpiride*		*p Value*	*Effect Size*
Hits						
Learning phase						
High reward	0.79	(0.04)	0.82	(0.03)	.198	0.325
Low reward	0.76	(0.04)	0.79	(0.03)	.391	0.214
Long duration	0.80	(0.03)	0.82	(0.03)	.296	0.262
Short duration	0.75	(0.04)	0.78	(0.03)	.286	0.268
Retrieval phase						
High reward	0.69	(0.05)	0.63	(0.04)	.173	0.346
Low reward	0.64	(0.04)	0.64	(0.04)	.915	0.026
Long duration	0.73	(0.04)	0.65	(0.05)	.028	0.588
Short duration	0.59	(0.05)	0.62	(0.04)	.441	0.192
False alarms						
Learning phase						
High reward	0.07	(0.02)	0.09	(0.03)	.435	0.194
Low reward	0.23	(0.05)	0.25	(0.05)	.597	0.131
Retrieval phase						
High reward	0.14	(0.03)	0.12	(0.03)	.439	0.192
Low reward	0.31	(0.06)	0.29	(0.06)	.617	0.124
Response bias						
Learning phase						
High reward	0.37	(0.08)	0.29	(0.09)	.276	0.274
Low reward	0.02	(0.11)	−0.01	(0.11)	.588	0.134
Retrieval phase						
High reward	0.36	(0.13)	0.50	(0.11)	.178	0.342
Low reward	0.09	(0.13)	0.15	(0.11)	.432	0.195

Mean (±*SEM*) values are given for the sulpiride and placebo conditions for hits, false alarms, and response bias during the learning phase and the retrieval phase. Cohen's *d* is provided as an effect size statistic.

found either (all *p*s ≥ .207). We also analyzed confidence ratings for high- and low-reward hits as well as subjective high- and low-reward hits (see Table 3 for descriptive statistics). For both types of hits during the learning phase, confidence was higher for highly rewarded memories (learning phase, reward: $F(1, 16) = 7.02$, $p = .017$; retrieval phase, reward: $F(1, 16) = 5.69$, $p = .030$), and the same pattern was found for the retrieval phase (learning phase, reward: $F(1, 16) = 46.95$, $p \leq .001$; retrieval phase, reward: $F(1, 16) = 21.58$, $p \leq .001$). Furthermore, in the retrieval phase, both analyses provided evidence of a main effect of Treatment, indicating that the drug enhanced confidence in general (hits, treatment: $F(1, 16) = 4.14$, $p = .059$; subjective hits, treatment: $F(1, 16) = 5.25$, $p = .036$). Finally, we analyzed source memory for high- and low-reward hits, which did not show any significant differences (learning phase: all *p*s ≥ .333; retrieval phase: all *p*s ≥ .341).

Table 3. Motivated Learning Task Additional Response Information

	Placebo		*Sulpiride*		*p Value*	*Effect Size*
Subjective hits						
Learning phase						
High reward	0.71	(0.07)	0.75	(0.07)	.511	0.163
Low reward	0.79	(0.06)	0.83	(0.07)	.495	0.169
Retrieval phase						
High reward	0.59	(0.08)	0.58	(0.07)	.823	0.551
Low reward	0.70	(0.08)	0.66	(0.06)	.498	0.168
Correctly categorized hits						
Learning phase						
High reward	0.39	(0.03)	0.43	(0.04)	.299	0.260
Low reward	0.42	(0.04)	0.45	(0.04)	.383	0.218
Retrieval phase						
High reward	0.30	(0.04)	0.29	(0.03)	.705	0.094
Low reward	0.34	(0.05)	0.33	(0.03)	.971	0.009
Confidence ratings						
Learning phase						
High reward	1.76	(0.11)	1.74	(0.11)	.825	0.055
Low reward	1.93	(0.17)	1.81	(0.10)	.486	0.173
High reward (subjective hits)	1.43	(0.10)	1.36	(0.08)	.515	0.161
Low reward (subjective hits)	2.06	(0.14)	2.11	(0.14)	.757	0.076
Retrieval phase						
High reward	2.34	(0.15)	2.15	(0.16)	.038	0.548
Low reward	2.48	(0.18)	2.27	(0.17)	.136	0.381
High reward (subjective hits)	1.98	(0.16)	1.62	(0.11)	.053	0.507
Low reward (subjective hits)	2.65	(0.16)	2.51	(0.16)	.357	0.230
Reward source memory Judgments						
Learning phase						
High reward	0.49	(0.03)	0.52	(0.04)	.444	0.190
Low reward	0.55	(0.05)	0.57	(0.04)	.714	0.090
Retrieval phase						
High reward	0.43	(0.05)	0.46	(0.04)	.503	0.166
Low reward	0.51	(0.05)	0.54	(0.05)	.604	0.128

Mean (±*SEM*) values are given for the sulpiride and placebo conditions for subjective hits (i.e., hits that were categorized as high or low reward by the participant), correctly categorized hits, confidence ratings (note low values equal high confidence), and reward source memory.

Table 4. Power Spectral Analysis

	Placebo		*Sulpiride*		*p Value*	*Effect Size*
Delta (1–2 Hz)						
F3 (n = 15)	271.29	(37.66)	271.49	(32.68)	.992	0.003
F4 (n = 15)	262.76	(44.84)	276.45	(33.58)	.533	0.165
Fz (n = 16)	312.71	(39.60)	325.00	(36.08)	.435	0.201
C3 (n = 15)	169.33	(21.12)	162.24	(20.07)	.603	0.137
C4 (n = 16)	167.00	(21.52)	172.26	(20.04)	.672	0.108
Cz (n = 15)	222.93	(31.10)	219.48	(26.77)	.791	0.070
P3 (n = 16)	134.22	(19.12)	139.76	(20.47)	.697	0.099
P4 (n = 16)	154.93	(24.80)	135.89	(16.23)	.240	0.306
Pz (n = 12)	190.89	(29.53)	209.29	(31.19)	.291	0.320
Slow oscillation (0.5–1 Hz)						
F3 (n = 15)	588.26	(73.99)	539.43	(53.53)	.482	0.187
F4 (n = 15)	572.89	(79.71)	606.45	(96.34)	.683	0.108
Fz (n = 16)	657.82	(74.26)	669.75	(58.61)	.865	0.043
C3 (n = 15)	426.38	(65.06)	385.85	(46.80)	.544	0.161
C4 (n = 16)	432.33	(59.08)	412.03	(40.75)	.724	0.090
Cz (n = 15)	546.68	(74.60)	509.50	(58.68)	.590	0.142
P3 (n = 16)	371.34	(54.51)	388.85	(61.60)	.821	0.057
P4 (n = 16)	419.63	(59.88)	353.95	(39.29)	.252	0.298
Pz (n = 12)	452.82	(65.48)	535.47	(84.64)	.315	0.304
Spindle (12–15 Hz)						
F3 (n = 15)	2.53	(0.24)	2.34	(0.26)	.256	0.306
F4 (n = 15)	2.49	(0.29)	2.39	(0.24)	.722	0.094
Fz (n = 16)	2.96	(0.26)	2.86	(0.28)	.550	0.153
C3 (n = 15)	2.52	(0.26)	2.41	(0.30)	.410	0.219
C4 (n = 16)	2.58	(0.23)	2.73	(0.33)	.486	0.178
Cz (n = 15)	3.96	(0.39)	3.80	(0.40)	.367	0.241
P3 (n = 16)	2.68	(0.30)	2.67	(0.34)	.948	0.016
P4 (n = 16)	2.88	(0.27)	2.72	(0.30)	.443	0.197
Pz (n = 12)	4.37	(0.51)	4.11	(0.49)	.340	0.288

Mean (±*SEM*) values are given for the sulpiride and placebo conditions for power of delta, slow oscillation, and spindle bands during non-REM sleep. Because of missing data, sample size differs for each channel.

Control Measures

Declarative and Procedural Memory Tasks

In the declarative word-pair task, we found no effect of sulpiride on retention, $t(1, 16) = 0.35, p = .729$. Under sulpiride, participants recalled significantly fewer word pairs during the retrieval phase than during the learning phase, $t(16) = 2.56$, $p = .021$. However, this difference was already apparent during the learning phase, $t(16) = -2.10$, $p = .052$ (Table 1). There was no difference between the treatments regarding the amount of runs needed to reach the learning criterion, $t(16) = -1.38$, $p = .188$.

In the finger tapping task, there was a trendwise effect for error rates decreasing more in the sulpiride condition across the retention interval, $t(16) = 2.03$, $p = .059$. However, this was from a trendwise higher baseline in the learning phase, $t(16) = -1.81$, $p = .089$. For the correctly tapped sequences, we found a trendwise effect for participants tapping less correct sequences in the sulpiride condition during the retrieval phase, $t(16) = 1.95$, $p = .069$. There was no effect of sulpiride on the control sequence only performed during the retrieval phase (correct sequences: $t(16) = -0.02$, $p = .982$; error rates: $t(16) = 0.25$, $p = .809$).

Word Fluency, Vigilance, Mood, and Subjective Sleepiness

Descriptive data can be found in Table 5. We did not find any significant differences in long-term memory retrieval performance (as measured by the word fluency task, all ps $\geq .868$). In the vigilance task (PVT), we found significantly higher reaction speed (i.e., RT-1) in the placebo condition after the retrieval phase, $t(16) = 3.13$, $p = .006$, all other ps $\geq .637$. In the placebo condition compared with the sulpiride condition, the mood questionnaire (PANAS) showed significantly higher positive mood before the retrieval phase, $t(16) = 2.25$, $p =$

Table 5. Control Measures

	Placebo		*Sulpiride*		*p Value*	*Effect Size*
SSS						
Before learning	2.94	(0.16)	2.94	(0.26)	1.000	0.00
After learning	3.71	(0.27)	4.47	(0.26)	.014	0.667
Before retrieval	2.29	(0.22)	3.00	(0.32)	.090	0.438
After retrieval	2.71	(0.19)	3.00	(0.33)	.206	0.320
Positive affect (PANAS)						
Before learning	2.42	(0.09)	2.48	(0.13)	.567	0.142
After learning	1.91	(0.15)	1.77	(0.13)	.273	0.276
Before retrieval	2.58	(0.16)	2.18	(0.15)	.039	0.547
After retrieval	2.32	(0.12)	2.15	(0.14)	.115	0.404
Negative affect (PANAS)						
Before learning	1.08	(0.03)	1.06	(0.04)	.563	0.143
After learning	1.04	(0.01)	1.01	(0.01)	.056	0.500
Before retrieval	1.02	(0.01)	1.01	(0.01)	.579	0.137
After retrieval	1.02	(0.03)	1.01	(0.01)	.668	0.106
PVT						
Before learning	3.56	(0.09)	3.59	(0.07)	.637	0.022
After learning	3.45	(0.10)	3.45	(0.09)	.977	0.007
Before retrieval	3.54	(0.10)	3.55	(0.08)	.853	0.201
After retrieval	3.53	(0.10)	3.33	(0.07)	.006	0.759
WFT						
Category	20.18	(0.91)	20.24	(1.26)	.964	0.011
Letter	19.94	(1.01)	20.12	(1.39)	.868	0.041

Mean (±*SEM*) values are provided for the sulpiride and placebo conditions. For the psychomotor vigilance task, reaction speed = 1/(RT in msec). 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) long-term retrieval capabilities.

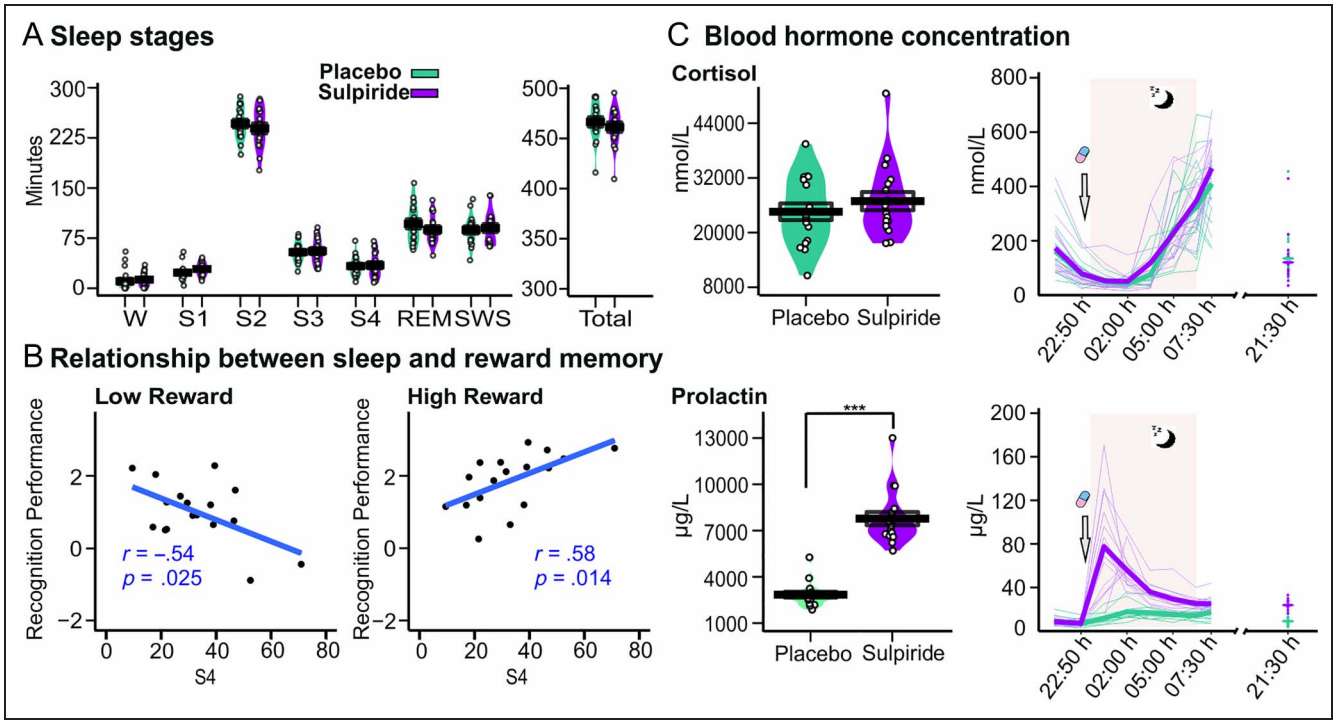

Figure 3. (A) Sleep stages. Mean (±*SEM*) time (in minutes) spent in Non-REM Sleep Stages S1, S2, S3, and S4; in REM sleep; and in SWS (i.e., the sum of S3 and S4) and total sleep time are provided for the sulpiride (purple) and placebo (green) conditions. (B) Correlation across placebo condition between Sleep Stage 4 and low- as well as high-rewarded memories, respectively. (C) Blood hormone concentration. Values for cortisol and prolactin are shown at the top and bottom, respectively. Mean (±*SEM*) AUC (from 00:30 until 06:30) is shown on the left, and mean (thick lines) and individual data (thin lines) per time point are shown on the right. The sulpiride condition is shown in purple, and placebo is shown in green. ***$p \leq .001$.

.039, and a trend toward more negative mood after the learning phase, $t(16) = 2.06$, $p = .056$. In the sulpiride condition compared to the placebo condition, there was some evidence for increased subjective sleepiness (SSS) after the learning phase, $t(16) = -2.75$, $p = .014$, and a trend toward increased sleepiness before the retrieval phase, $t(16) = -1.81$, $p = .090$. Participants were not able to discriminate between sulpiride and placebo (McNemar's exact test: $p \geq .791$).

Cortisol and Prolactin

We found no evidence of sulpiride affecting cortisol levels in general (treatment: $F = 1.65, p = .22$) or at specific time points (Treatment × Time Point: $F(1, 16) = 0.92, p = .45$). However, prolactin levels were increased in the sulpiride condition at some time points (Treatment: $F(1, 16) = 227.00$, $p \leq .001$; Time Point: $F(1, 16) = 40.49$, $p \leq 0.001$; Treatment × Time Point: $F(1, 16) = 37.32$, $p \leq .001$). This was true for all samples from 00:30 until 21:30 (post hoc t test, all ps $\leq .001$) as well as in an analysis of the AUC from 00:30 until 06:30, $t(16) = -16.81, p \leq .001$ (see Figure 3C). This effect can be explained by dopamine having a strong inhibitory effect on prolactin secretion (Fitzgerald & Dinan, 2008). Because prolactin was still elevated during the retrieval phase in the sulpiride condition, it is likely that an active level of the drug remained. This may explain lowered reaction speed and positive mood in the sulpiride group at this time point. Because our timing of the retrieval phase was already maximally postponed after intake, this residual amount of drug cannot be prevented in our paradigm.

Sleep Parameters

Total sleep time and time spent in the different sleep stages did not significantly differ between the treatment conditions (all ps $\geq .199$; see Figure 3A). In post hoc analyses, we explored correlations between sleep parameters and performance on the reward memory task in the placebo condition (Figure 3B). We found a significant positive correlation between the time spent in Sleep Stage 4 and retrieval phase recognition performance for highly rewarded pictures ($r = .58, p = .014$), whereas this relationship was negative for lowly rewarded pictures ($r = -.54, p = .025$). Meaning that participants generally performed better on highly rewarded picture recognition and worse on lowly rewarded picture recognition the more Sleep Stage 4 they had. This relationship remained largely consistent but was slightly weaker, when data for both conditions were pooled with similar correlations between the time spent in Sleep Stage 4 and retrieval phase performance (highly rewarded pictures: $r = .50$, $p = .041$; lowly rewarded pictures: $r = -.48$, $p = .053$). To explore this relationship further, we correlated the delta (1–2 Hz at Fz), slow oscillation (0.5–1 Hz at Fz), and fast

spindle (12–15 Hz at Cz) frequency bands during non-REM sleep with the retention of reward-associated memories. None of the relationships was significant (all ps ≥ .074). None of the investigated frequency bands differed between the placebo and sulpiride conditions (see Table 4). Of note, because of loose electrodes, the number of participants differs between channels, and this information is provided in Table 4.

DISCUSSION

We investigated whether activation of the dopaminergic reward network during sleep is necessary for selective consolidation of highly over lowly rewarded memories. To this end, we blocked around 65% of dopamine d2-like receptors—using the selective antagonist sulpiride—during sleep after participants learned a set of highly or lowly rewarded pictures. We found that, generally, highly rewarded pictures were retained better than lowly rewarded pictures across sleep, which is in line with a role of sleep in preferentially consolidating rewarded memories and concurs with earlier reports (Feld et al., 2014; Adcock et al., 2006) as well as with reports of sleep preferentially enhancing the retention of highly over lowly rewarded information (e.g., Igloi et al., 2015). Contrary to our hypothesis, sulpiride did not affect these reward-related differences in retention. Rather, we found that sulpiride diminished the preferential retention of deeply over shallowly encoded pictures. Importantly, the dopaminergic receptor antagonist did not significantly alter sleep architecture. Together, these findings might hint toward a less crucial contribution of dopaminergic activation during sleep to the preferential consolidation of reward-associated memory.

Both in the sulpiride and placebo conditions, participants recognized highly rewarded pictures better than lowly rewarded pictures at retrieval testing after sleep. With respect to previous studies, this finding reflects the successful involvement of midbrain dopaminergic structures during the encoding of reward-related information in the hippocampus by our motivated learning task (Geddes, Mattfeld, de los Angeles, Keshavan, & Gabrieli, 2018; Spaniol, Schain, & Bowen, 2014; Wolosin, Zeithamova, & Preston, 2012), which is eventually necessary for sleep to selectively enhance highly rewarded information (Studte et al., 2017; Igloi et al., 2015; Fischer & Born, 2009). There is overwhelming evidence that this sleep-dependent consolidation relies on the replay of neuronal memory traces during SWS (e.g., Bendor & Wilson, 2012; Rudoy, Voss, Westerberg, & Paller, 2009; Rasch et al., 2007; Wilson & McNaughton, 1994). In addition, some studies suggested that the reward circuitry of the brain, that is, the hippocampus–ventral striatum–VTA–hippocampus loop, participates in this replay (Valdés et al., 2015; Lansink et al., 2008, 2009; Pennartz et al., 2004). However, as our data revealed, a potent reduction of dopaminergic neurotransmission using sulpiride does not block the enhanced consolidation of highly over lowly rewarded information, and thus, the dopaminergic reward circuits seem not to engage in this consolidation process. This finding agrees with a recent study of single-unit recordings in the hippocampus and VTA of rats, which learned reward locations in a maze (Gomperts et al., 2015). Here, replay during quiet wakefulness directly after task performance showed a co-involvement of hippocampus and VTA, whereas this relation was not evident for replay during subsequent SWS. Another study in rats showed that dopaminergic activation during learning can enhance replay during sleep even in the absence of a behavioral effect at learning (McNamara et al., 2014). Those findings, in combination with the present data, support the idea that augmented neuronal replay, rather than coactivation of dopaminergic neurotransmission, is the major player enhancing memory consolidation for highly rewarded information during sleep.

At a first glance, the present results are at odds with our study where the dopamine d2-like receptor agonist pramipexole selectively enhanced sleep-dependent consolidation of lowly rewarded pictures in the same task (Feld et al., 2014). However, unlike sulpiride, pramipexole administration caused severe disturbances of sleep. In fact, in mice, optogenetically activating dopaminergic neurons of the VTA were found to promote wakefulness, whereas inhibition of the same cells suppressed wakefulness, even in the presence of highly appetitive or threatening stimuli (Eban-Rothschild, Rothschild, Giardino, Jones, & de Lecea, 2016). Against this backdrop, it seems prudent to interpret the effects of pramipexole in that study as nonphysiological, that is, assuming that the enhancing effect the drug had on low-reward items was secondary to its arousing effects.

Our additional post hoc correlation analyses of the placebo condition revealed further hints consistent with a role of replay in specifically enhancing highly rewarded information. Here, time spent in deepest SWS (i.e., Sleep Stage 4) positively correlated with recognition performance of highly rewarded pictures but negatively correlated with performance on low-reward pictures. Replay has been especially connected to consolidation during SWS, and Sleep Stage 4 has the most slow oscillations (of all sleep stages). These are thought to drive spindles top–down and, eventually, memory replay activity together with ripples in hippocampal networks (Staresina et al., 2015; Diekelmann & Born, 2010; Clemens et al., 2007). Ripples together with spindles are likely the oscillations, which promote the neuroplasticity that strengthens memory traces in this process (Khodagholy, Gelinas, & Buzsáki, 2017; Sadowski, Jones, & Mellor, 2016; van de Ven, Trouche, McNamara, Allen, & Dupret, 2016; Girardeau, Cei, & Zugaro, 2014). Importantly, hippocampal ripples appear to be simultaneously involved in processes of synaptic downscaling and forgetting (Norimoto et al., 2018; Feld & Born, 2017; Tononi & Cirelli, 2014) and, thus, represent a putative mechanism explaining

our observation that time in Stage 4 sleep was also negatively correlated with recognition of low-reward items. However, the exploratory nature of this analysis limits this finding's generalizability to new data sets and therefore should be replicated.

Our finding that the enhanced recognition of highly rewarded pictures was already strongly evident at immediate recall, during the learning phase, points toward the dopaminergic system exerting its enhancing role on rewarded information already during learning (Miendlarzewska, Bavelier, & Schwartz, 2016; Wolosin et al., 2012). Although some studies suggest that rewards mainly enhance memory performance after a delay rather than directly after learning (Patil, Murty, Dunsmoor, Phelps, & Davachi, 2017; Feld et al., 2014; Murayama & Kuhbandner, 2011; Wittmann et al., 2005). What is important here is that this reward effect during the learning phase cannot be taken as evidence that preferential consolidation of highly rewarded information occurs in relation to encoding strength alone, as our task also included pictures that were shown for a short or long duration. This also led to a recognition advantage for long-duration pictures during the retrieval phase that, however, was wiped out by sulpiride during sleep. This finding opens the possibility that dopamine plays a non-reward-related role during sleep, possibly in relation to recently discovered postencoding memory enhancement of novel stimuli by release of dopamine in the hippocampus that is mediated by the locus ceruleus (Takeuchi et al., 2016), a brain region with activity regulated by the sleep slow oscillation (Eschenko, Magri, Panzeri, & Sara, 2012). Of note, this finding was not predicted before conducting our study, and Takeuchi and colleagues tested blocking d1-like rather than d2-like receptors in the hippocampus, so future research will have to scrutinize these effects.

A conceptually interesting and unresolved issue arises from the use of lures in the recognition phase of the motivated learning task that are not objectively associated with a reward category, unlike affective versions of the task, where the lure stimuli carry the same category information as the targets. Our version of the task used here and in work published earlier (Feld et al., 2014) is an adaptation of the paradigm used by Adcock et al. (2006). The original task used hit rates as main dependent variables that cannot differentiate shifts in criterion from differences in memory strength (Macmillan & Creelman, 2005) and did not penalize misses. Therefore, higher hit rates for high-reward items may occur because participants are using a more lenient criterion when they expect a high reward rather than because of a stronger memory for high-reward items. Because that research relied on brain imaging, its main message is unaffected by this, but research focusing on the behavioral outcome, in our view, needs to deal with this issue. Our version of the task aims to resolve it with two strategies: first, by asking the participants to indicate for each recognition trial whether it was a high- or low- reward trial, which allowed us to calculate the bias-free d' measure we report in the Results section and, second, by penalizing false alarms and misses, which disincentivized switching to a lenient criterion on high-reward trials. Although d' was our a priori data reduction choice, it is important to realize that this procedure induces another potential confound; that is, participants may judge false alarms as low reward because of low confidence in their memory, thereby inflating the high versus low reward memory difference measured using d'. Our data provide some evidence that this may be the case (i.e., absence of source memory for reward category and low confidence for false alarms) but do not allow a final verdict. Importantly, the main findings in the current article are not affected by this, as our analyses hold even when using hit rate rather than d' (no Treatment × Reward interaction: $F(1, 16) = 1.30$, $p = .27$; see Results for details). However, the conceptual importance of this issue calls for future studies to construct a task that experiences neither of the abovementioned issues. In fact, we are currently developing a version of the task that has been inspired by these considerations and that provides objective reward cues also during the recognition phase.

One limitation of our study is that we blocked d2-like dopamine receptors, and therefore finding no interaction between treatment and reward consolidation does not rule out that d1-like receptors play a more important role during sleep. Considering evidence that both d2-like and d1-like receptors are implicated in hippocampus-dependent tasks and reward learning (Hopf, Cascini, Gordon, Diamond, & Bonci, 2003; Manahan-Vaughan & Kulla, 2003; Wilkerson & Levin, 1999; Ikemoto, Glazier, Murphy, & McBride, 1997), future studies should focus on d1-like receptor-related effects using drugs like L-dopa or dietary dopamine depletion (Montgomery, McTavish, Cowen, & Grasby, 2003) during sleep-dependent consolidation. In addition, the complexity of the study somewhat limited the achievable sample size, which needs to be considered when interpreting the results, especially regarding correlation analyses. Furthermore, the current work did not make use of a sleep deprivation control, which somewhat limits the interpretation regarding an overall effect of sleep on reward memory.

In conclusion, our data might challenge the idea that replay during sleep engages dopaminergic inputs to the hippocampus via a feedback loop consisting of the brain's reward centers to selectively enhance information related to high rewards. Rather, it seems likely that a form of dopamine-related tagging occurs at encoding that enhances replay activity for relevant memories during sleep, thereby strengthening them.

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