Neurochemical mechanisms underlying sleep-dependent memory processing

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Marjan Alizadeh Asfestani
aus Teheran, Iran

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Dekan der Math.-Nat. Fakultät: Prof. Dr. W. Rosenstiel
Dekan der Medizinischen Fakultät: Prof. Dr. I. B. Autenrieth

1. Berichterstatter: Prof. Dr. / **PD Dr.** / Dr. Susanne Diekelmann

2. Berichterstatter: **Prof. Dr.** / PD Dr. / Dr. Birgit Derntl

Prüfungskommission: **Prof. Dr.** / PD Dr. / Dr. Jan Born

Prof. Dr. / **PD Dr.** / Dr. Susanne Diekelmann

Prof. Dr. / PD Dr. / Dr. Ingrid Ehrlich

Prof. Dr. / PD Dr. / Dr. Birgit Derntl

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SUMMARY

Sleep is beneficial for memory consolidation and enhances subsequent learning. It has been hypothesized that the reactivation of memories occurring during sleep, especially slow-wave sleep (SWS), would serve both of these memory processes. Although the benefit of sleep on learning and consolidation has repeatedly been demonstrated, the underlying neurochemical mechanisms supporting these functions of sleep are not yet fully understood. My thesis is centred on manipulating sleep-dependent memory consolidation by using pharmacological agents to unravel the neurochemical mechanisms that convert neural reactivation into plastic changes. My current work is focused on two major memory-related neurotransmitters, i.e., glutamate in the first study, and dopamine in the second study.

Glutamate is the main excitatory neurotransmitter in the human brain. This neurotransmitter is involved in different forms of plasticity. In the hippocampus, long-term potentiation (LTP), which is an important factor for synaptic consolidation is mediated, by NMDA receptors, one type of glutamate receptor, containing the NR2A subunits, and long-term depression (LTD) is mediated by NMDA receptors containing NR2B subunits. D-cycloserine (DCS) as NMDA-receptor co-agonist preferentially acts through NR2A containing receptors, which may favour LTP over LTD. Sleep-dependent declarative memory consolidation, has been shown to be facilitated by DCS administration. In the first study, we surveyed whether the administration of DCS during sleep impairs new declarative learning of a similar task after sleep due to the assumed enhanced potentiation of memory traces and corresponding increased proactive interference under DCS during sleep. This potentiation might reduce the capacity for new encoding in the hippocampus. Presumably, this reduction in subsequent new learning under DCS will be enhanced by learning new overlapping information (interference condition). Our results using DCS showed the predicted improvement in new learning after sleep compared to wakefulness. Unexpectedly, however, interference did not impair new learning but rather further improved it. This might be because rather than an interference effect processes of schema generation and knowledge abstraction may have

occurred. These effects seem to switch in a time-dependent manner. Furthermore, DCS did not impair, but rather improved new learning, and this was sleep-independent. Therefore, I speculate that forgetting, shown to rely on NMDAR-activation to erase old memories, boosts new learning through glutamatergic processes that occurs independent of sleep

Dopamine, as a major modulatory neurotransmitter, facilitates plasticity for reward-associated memories in the hippocampus and other reward-related midbrain structures during encoding. Sleep selectively benefits the strengthening and transformation of highly relevant memories like rewarded memories by selective replay. However, it is not completely clear whether or not these sleep-dependent consolidation processes also engage the dopaminergic circuitry, which facilitated their initial encoding. I conducted a neuropharmacological experiment in humans using sulpiride, a D2-like receptor antagonist, to block the effect of dopaminergic afferents in the hippocampus and thereby reduce plasticity. Our results showed that highly rewarded memories were remembered better than lowly rewarded ones under both sulpiride and placebo conditions. This means blocking dopaminergic neurotransmission did not impact the selectivity of sleep for consolidation. This finding indicates a less important role of dopaminergic pathways for the preferential consolidation of highly-rewarded memories during sleep compared to their role at encoding during wakefulness. We also found that better performance on highly rewarded items is linked to the time spent in sleep stage 4, which lends support to the idea that rewards increase replay activity during sleep to enhance relevant memories selectively.

Altogether, these two studies show that pharmacological manipulations can improve our current knowledge about the neurochemical mechanisms, which underlie sleep-dependent memory processes. Importantly, these direct manipulations in humans enabled us to investigate the complexity of human behaviour in response to neurochemical manipulation and allowed us to interpret these findings without translating them from animal models. This may allow developing new therapeutic applications for patients suffering from cognitive disorders with more confidence.

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Abbreviations

ACh	Acetylcholine
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic-acid
DCS	D-cycloserine
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
FTT	Finger tapping task
GABA	γ-amino-butyric acid
LC	Locus coeruleus
LTD	Long-term depression
LTP	Long-term potentiation
MLT	Motivated learning task
NMDA	N-methyl-D-aspartate
NonREM sleep	Non-rapid eye movement sleep
PI	Proactive interference
REM sleep	Rapid eye movement sleep
RI	Retroactive interference
SHY	Synaptic homeostasis theory
SOs	Slow oscillations
S/N	Signal to noise ratio
SN	Substantia nigra
SWA	Slow-wave activity
SWS	Slow wave sleep

TH+	Tyrosine-hydroxylase expressing
TMS	Transcranial magnetic stimulation
VTA	Ventral tegmental area

1. Synopsis

Sleep is universal among mammals and maybe among all animals. Even though during sleep activity is reduced, and organisms are less responsive to stimuli from the environment (Carskadon, 2011; Cirelli & Tononi, 2008), it should not be considered as a state, in which the brain and the body have shut down. Sleep has been shown to have several important functions, e.g., energy conservation (Roth et al., 2010), thermoregulation (Rechtschaffen & Bergmann, 1995), metabolic regulation, and detoxification of the brain from free radicals (Reimund, 1994).

In humans, sleep is crucial for normal cognitive function, as a lack of sleep critically affects several functions, including language, reasoning, attention, decision making, learning, and memory (Durmer & Dinges, 2005; Jackson et al., 2013; Killgore, 2010). Furthermore, an early study showed that the forgetting rate is lower during sleep comparing to wakefulness (Jenkins and Dallenbach, 1924). Historically, a reduction of forgetting due to interference was a core concept of why sleep benefits memory (Jenkins & Dallenbach, 1924; McGeoch, 1932; Ekstrand, 1967; Wixted, 2004; Ellenbogen et al., 2006), whereas in the recent decades, active memory consolidation during the retention interval between information uptake and retrieval has been attracting more attention (McGaugh, 2000; Feld & Diekelmann, 2015; Diekelmann & Born, 2010). Although there is already a broad body of evidence establishing a strong link between sleep and memory formation (Diekelmann & Born, 2010), the underlying neurochemical mechanisms remain poorly understood.

In the following sections, I will give a brief overview of sleep and memory and their interactions as well as the neurochemical agents involved in the regulation of memory processing during sleep. Subsequently, I will elaborate on how my current studies can add to our knowledge about sleep's role for memory consolidation and forgetting.

1.1. Introduction to sleep

Sleep in mammals is composed of two classical states: so-called rapid eye movement (REM) sleep – also known as 'paradoxical sleep' – and non-rapid eye movement (NonREM) sleep (Vorster & Born, 2015). In humans, periods of REM sleep were first identified by Aserinsky and Kleitman (1953), which ultimately led to the first manual of methods and criteria for scoring sleep (Rechtschaffen & Kales, 1968).

Based on the criteria established by Rechtschaffen and Kales (1968), sleep researchers distinguish six vigilance stages (see Hypnogram in Figure 1). The first stage is known as quiet wakefulness (wake), characterized by high tonic muscular activity and, in the electroencephalogram (EEG), more than 50 % alpha rhythm (8-13 Hz) activity. Then there are four different stages (Stages 1-4), categorized together as NonREM sleep, roughly corresponding to sleep depth. Stage 1, occurs at the onset of sleep and in the transition between NonREM and REM sleep. It is defined by less than 50% alpha rhythm in the EEG. Stage 2, also called light sleep, which is distinguishable by the presence of sleep spindles (12-15 Hz, oscillation with the duration of more than 0.5 s) and K-complexes (sharp negative high-voltage deflexion of the EEG followed by a slower positive wave with a duration of more than 0.5 s). Stages 3 and 4 are known as slow-wave sleep (SWS, marked in blue in Figure 1) or as deep sleep. Here the delta waves (1-4 Hz) are prominent (stage 3 is defined by more than 20 % delta waves and stage 4 more than 50% delta waves). The sixth stage in this guideline is REM sleep (Marked in green in Figure 1), which is known for the hallmark rapid eye movements, EEG theta wave (4-8 Hz) prominence, and muscle atonia (Jones, 2005). While fast eye movements are common during REM sleep, in opposition, slow rolling eye movements are common during NonREM sleep, especially in sleep stage 1 (Brown et al., 2012).

As sleep proceeds, the humans brain shifts sequentially between NonREM and REM sleep (Born et al., 2006). There are, on average, four to six cycles during each night of

sleep, and each cycle regularly lasts 90-100 minutes (Duclos et al., 2015). SWS is more dominant in the cycles during early sleep (i.e., the first half of the night), whereas REM sleep is more frequent in cycles during late sleep (i.e., the second half of the night) (Plihal & Born, 1997, also see Figure 1).

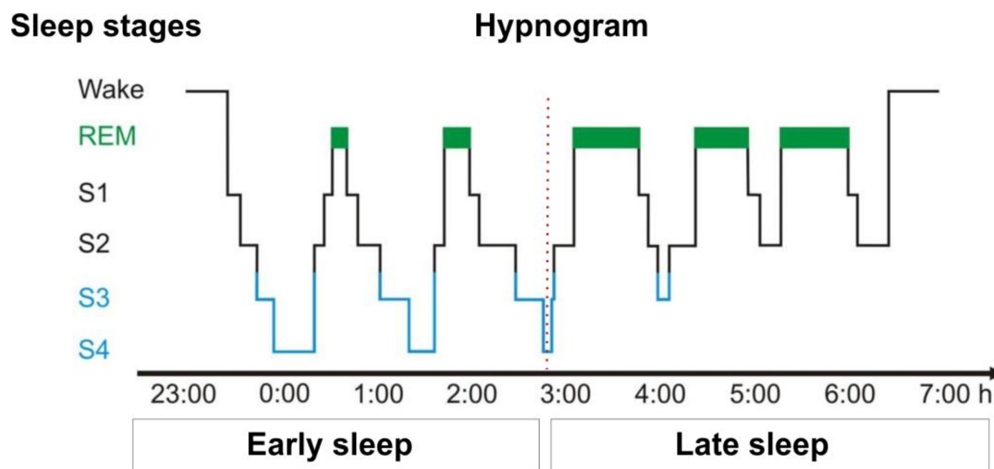

Figure 1. Schematic sleep hypnogram. During the first half of sleep (early sleep), NonREM sleep, especially SWS (S3+S4), dominates, whereas the second half (late sleep) is mainly dominated by REM sleep. Adapted from Feld and Diekelmann, 2015.

There exists a second major sleep scoring system, which is suggested by the American Academy of Sleep Medicine (AASM, Silber, et al., 2007), and that can be seen as an update of the former sleep manual. The scoring systems are largely similar since they are both based on polysomnography, which is the combination of EEG, electrooculography (EOG), and electromyography (EMG) recordings. Both systems also apply a classification for each 30-second epoch one of the sleep. The most prominent difference between the AASM manual and Rechtschaffen and Kales (1968) manual is that AASM lumps together sleep stages 3 and 4 into just stage 3 (N3). In this thesis, I followed the traditional Rechtschaffen and Kales manual (1968) for offline scoring, as this is still currently the most widespread manual used by sleep scientists and allows a more straightforward comparison to previous work.

Neurotransmitters, hormones, and sleep

The neurochemical environment, including neurotransmitters and hormones, in the brain, can differ depending on wake and sleep states and even across different sleep stages (Holst & Landolt, 2018). For example, during SWS, cortisol, acetylcholine (ACh), and noradrenaline have very low levels (Born et al., 1997; Aston-Jones & Bloom, 1981; Weitzman et al., 1971; Marrosu et al., 1995). Inversely gonadotropin, growth hormone, and prolactin levels, are increased during this stage (Born & Fehm, 1998; Gore, 1998). On the other hand, serotonergic and noradrenergic activity reaches an intermediate level during SWS and drops to a minimum during REM sleep (Rasch & Born, 2013).

Glutamate is an amino acid that also acts as the main excitatory neurotransmitter in the brain (Meldrum, 2000). Levels of glutamate are increased during REM sleep as well as during wakefulness, while they are decreased during Non-REM (Dash et al., 2009). Recently, it has been proposed that glutamate is the main regulator of arousal and, together with γ-amino-butyric acid (GABA) are playing an important role in promoting waking and sleep states (Saper & Fuller, 2017). In addition, it has been strongly suggested that the switch from SWS to REM sleep is because of the interaction of multiple populations of glutamatergic and GABAergic neurons in the posterior hypothalamus and the brainstem (Luppi & Fort, 2019).

Dopamine serves as a hormone, neurotransmitter, and neuromodulator (Beaulieu & Gainetdinov, 2011; Palacios-Filardo & Mellor, 2019; Yeragani et al., 2010). Likewise, levels of dopamine seem to be reduced during sleep (Feenstra et al., 2000; Sowers & Vlachakis, 1984). Lena et al. (2005) have shown that dopamine has higher activity during wake and REM sleep compared to its reduction during SWS (Lena et al., 2005). Changes in central dopaminergic synaptic transmission has been shown in different disorders, such as Parkinson's disease (due to dopamine depletion) and schizophrenia (due to hyperdopaminergia) (Carlsson, 1987; Mazei-Robison et al., 2005; Greenwood et al., 2006). Patients with these diseases demonstrate considerable disturbance in sleep, like REM sleep behaviour disorder

(Abbott, 2005; Gagnon et al., 2002), excessive daytime sleepiness (Adler, 2005), and decreased REM sleep latency (Maggini et al., 1986). This evidence suggests that dopamine might play a role in regulating the sleep-wake cycle (Dzirasa et al., 2006).

1.2. Overview of memory

Memory is the ability to encode, consolidate, and retrieve information, which can influence future action (Squire & Wixted, 2011). While learning and retrieval are supposed to be most effectively accomplished during wakefulness, consolidation is assumed to benefit most from sleep (Diekelmann & Born, 2010; Rasch & Born, 2013). Human memory is divided into short term memory (STM), which lasts for a few seconds, and long term memory (LTM), which might last from minutes to years. Long term memory is comprised of declarative or explicit memory, as well as non-declarative or implicit memories (Figure 2). Pioneering research by Scoville and Milner (1957), on the patient Henry Gustav Molaison (H.M.), whose medial temporal lobes (MTL) were resected bilaterally, provided strong support for the crucial role of this structure for long-term declarative memory (Corkin, 2002).

A few years later, studying H.M. yielded first evidence showing the independence of skill learning from declarative memory. During the learning of a sensorimotor task (Milner, 1962). His performance improved on the task across and during days of training even though he was not able to remember explicitly that he had practiced the task before.

Declarative memories, including episodic and semantic memory, are available to conscious recollection and are hippocampus-dependent (Squire et al., 1993), Episodic memory refers to the autobiographical memories like memory for events that have a specific spatial and temporal context (Tulving, 2005). They can be learned fast, but also tend to be forgotten quickly (Wixted, 2004). Repeated encoding or activation of overlapping episodic memories results in semantic memory formation (Winocur et al., 2010). Semantic memory

refers to general knowledge about the world, and it is independent of contextual features (Squire & Dede, 2015).

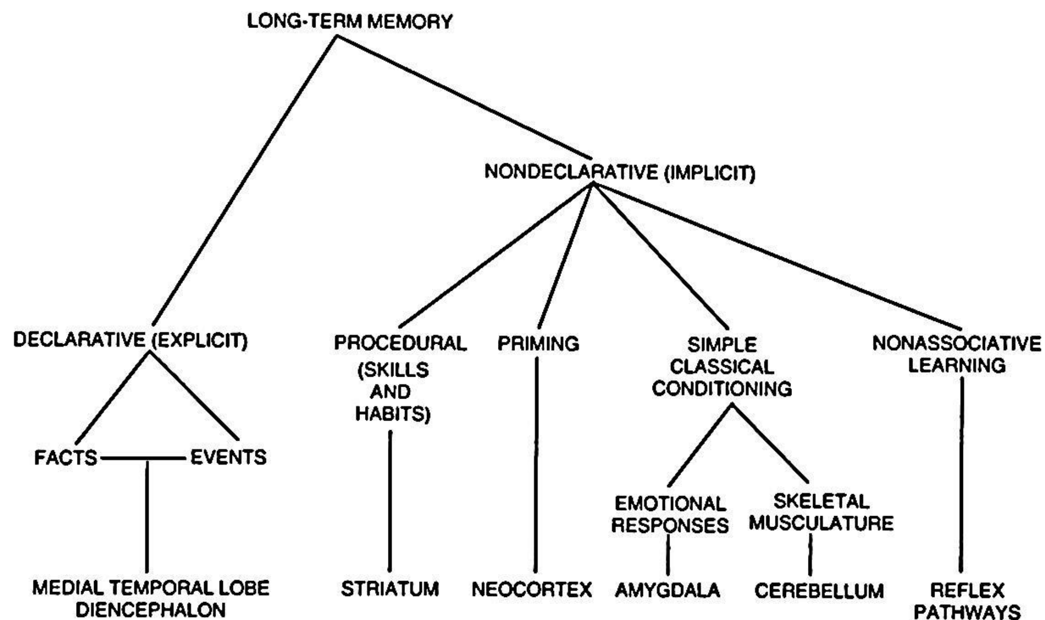

Figure 2. A taxonomy of long-term memory systems. Considering the specific brain structures involved in each system. Adapted from Squire & Zola, 1996.

Non-declarative memories, as opposed to the declarative memories, do not engage MTL structures, and it is an umbrella term, which includes different memory systems that are dependent on several brain regions (Squire & Zola, 1996; Rasch & Born, 2013, see Figure 2). Non-declarative memory includes procedural memories for motor skills, perceptual skills, priming, conditioning, and non-associative learning (Squire and Zola, 1996). Notably, non-declarative memories are slow at learning (Squire et al., 1993) and can be implicitly learned and recalled without awareness. There are different tasks for assessing procedural memories, for example, finger tapping sequences are commonly used to assess explicit motor skill (Walker et al., 2002; Rasch et al., 2009) or the visual texture discrimination task for measuring perceptual skills (Gais et al., 2000).

Memory formation stages

A core question in the field of memory research is how the brain acquires new information without overwriting and deleting the older memories, which is known as the "stability-plasticity dilemma" (Abraham & Robins, 2005). The two-stage memory formation mechanism, which is proposed by Marr (1971), offers a solution to this dilemma. Based on this mechanism, memories are initially encoded in a fast learning store and are then gradually transferred to a slow learning store for long-term storage. In the case of the declarative memory system, this process will be supported by a collaboration of the hippocampus as a fast learner and neocortex as a slow learner (Marr, 1971; McClelland et a., 1995)

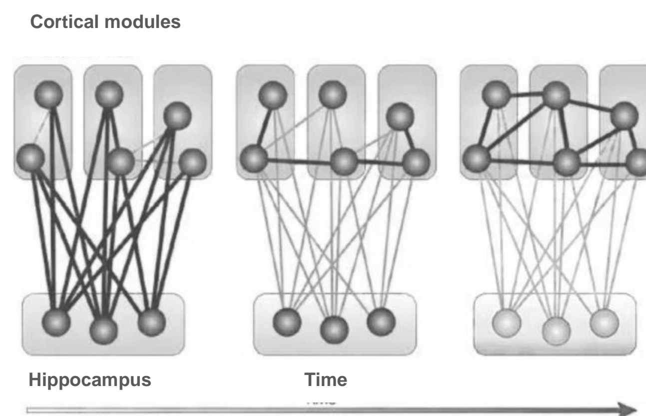

Figure 3. Standard consolidation model. According to this early model, the hippocampus initially serves as a hub, which binds new memory traces and disengages as soon as cortical traces can represent the memory without its support. Adapted from Frankland & Bontempi 2005.

According to the standard consolidation model (Frankland & Bontempi, 2005), during wakefulness, information is encoded into the hippocampus (temporary store) and in parallel into distributed cortical areas (long-term store). Consecutive reactivation of the information in the hippocampal-cortical network is assumed to result in an accelerated strengthening of cortico-cortical connections. This increase in the strength of the cortico-cortical connections ultimately allows new memory representations to become independent of the hippocampus and to be gradually integrated with pre-existing cortical memories (see Figure 3). Initially, the

hippocampus acts as a hub that can bind the memory elements in the cortex (Winocur et al., 2010; Battaglia et al., 2011) since it takes longer time for the cortex to form direct connections between these memory representations. The overlapping reactivation of memories, which have shared information, would lead to the formation of overarching schemata (Lewis & Durrant, 2011) and will make the integration of new memories easier.

Müller and Pilzecker (1900) were the first to coin the term consolidation for the process of stabilizing newly encoded memories (Müller & Pilzecker 1900; Lechner et al., 1999). Consolidation not only involves in the reorganization at the system level but also at the synaptic level, which is known as synaptic consolidation (Dudai, 2004). During synaptic consolidation, memories are strengthened, and this strengthening involves those particular synapses that were involved in encoding of the memory trace. This process can be disturbed through the administration of protein synthesis blockers within a short time interval after learning (Bourtchouladze et al., 1998; Xia et al., 1998).

Different forms of synaptic plasticity

Synaptic transmission can be modified by neuronal activity; it can be enhanced or depressed. These activity-dependent changes in the efficiency of the pre-existing synapses are known as synaptic plasticity. Ramón y Cajal (1984), has suggested that new memories are generated when the synaptic strength shows long-lasting changes (Citri & Malenka, 2008), which was later advanced by Donald Hebb in 1949, who proposed that formation of associative memories in the brain rely on the correlation of the presynaptic neuron firing and postsynaptic neuron also firing.

Long-term potentiation (LTP) and long-term depression (LTD)

In the mammalian brain, the two major forms of long-lasting synaptic plasticity are known as long-term potentiation (LTP) and long-term depression (LTD). LTP and LTD are characterized by a long-lasting increase or decrease in synaptic strength, respectively (Bear & Malenka, 1994). The initial experiments performed by applying current using an extracellular

electrode showed that a few seconds of high-frequency electrical stimulation can cause LTP for days or even weeks (Bliss & Lomo, 1973), whereas low-frequency stimulation causes an opposite process so-called LTD (Bear & Malenka, 1994; see Figure 4). Of note, LTD has several forms and functions, including homosynaptic (induced in the conditioned input), heterosynaptic (induced in a non-conditioned input), induced de novo, or following LTP (depotentiation; Collingridge et al., 2010).

According to the revised synaptic tagging and capture hypothesis (Redondo & Morris, 2011) for LTP induction, four steps need to be considered: (1) in the early phase of LTP (E-LTP) synapses receive a tag, (2) during the late phase of LTP (L-LTP), plasticity-related proteins (PrPs) are synthesized and distributed, (3) tagged synapses capture the PrPs under certain conditions, and (4) the tagged synapse is strengthened and consolidated. Importantly, most of the synapses that show LTP can also exhibit LTD (Citri & Malenka, 2008) which leads to the synapse becoming less effective and depotentiatied (Fujii et al.,1991).

Glutamate's role in LTP and LTD induction

As mentioned above, glutamate is an excitatory neurotransmitter in the mammalian central nervous system (Meldrum, 2000). This neurotransmitter has two different types of receptors, the ion-channel associated (ionotropic) and G-protein-coupled (metabotropic) receptors (Pin & Duvoisin, 1995). Ionotropic glutamate receptors (iGluRs) are classified as α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA), kainite, and N-methyl-D-aspartate (NMDA) receptors. Metabotropic glutamate receptors (mGluRs) are members of the G-protein-coupled receptor (GPCR), and they influence various intracellular second messenger systems that modulate, i.e., neuronal excitability and synaptic plasticity (Chen et al., 2011). The mGluRs have eight subtypes, which are divided into three subgroups: group I containing mGluR1 and mGluR5, group II including mGluR2 and mGluR3, and group III with mGluR4, mGluR6, mGluR7, and mGluR8 (Schoepp, Jane & Monn, 1999).

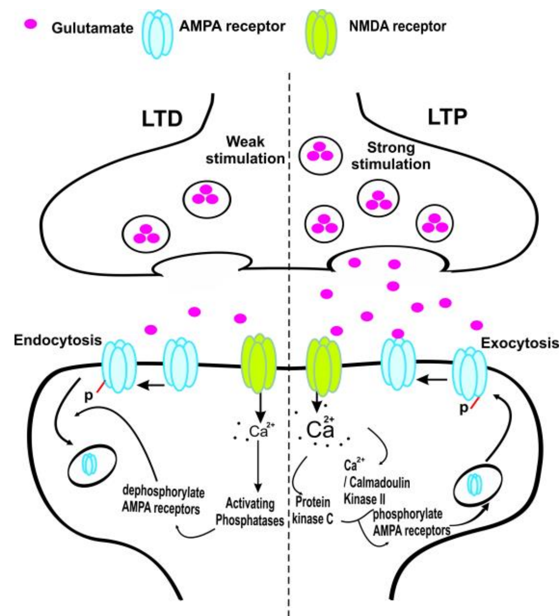

Figure 4. Molecular mechanisms underlying LTP and LTD induction. LTP occurring due to strong stimulation from the presynaptic neuron leads to strong depolarization and activates kinases, resulting in AMPA receptor exocytosis. LTD induction due to weak stimulation from presynaptic causes modest depolarization and phosphatase activation, resulting in AMPA receptor endocytosis.

It has been shown that for LTP induction, glutamate as the main excitatory neurotransmitter plays an important role (Collingridge and Bliss 1987) and mediates its effects via NMDA and AMPA receptors (Malenka & Nicoll, 1999). NMDA receptors consist of three families of subunits: NR1, NR2 including (NR2A, NR2B, NR2C, NR2D) and NR3A (Dingledine et al., 1999). Most of the NMDAR receptors contain NR2 subunits (Monyer et al., 1994). Importantly, most of the synapses which exhibit LTD also use glutamate receptors (Collingridge et al., 2009). Therefore both LTP and LTD require NMDA receptor activation (Bear & Malenka, 1994; Bliss & Collingridge, 1993). Among different subunits of NMDA receptors, it has been proposed that NR2A is important for LTP induction, while NR2B is crucial for LTD occurrence (Liu et al., 2004). Therefore, with manipulating the NMDA receptor subunits, plasticity could be manipulated in different directions. Importantly, LTD like LTP needs elevated postsynaptic Ca^{2+} entry via NMDA receptors (Mulkey & Malenka, 1992), but the receptor's gating for Ca^{2+} influx is complex.

At resting membrane potentials, Mg^{2+} ions block NMDA receptor permeability for Ca^{2+} influx. For opening the channel, NMDA receptors need to be co-activated by glutamate and a co-agonist, either glycine or D-serine (Kleckner & Dingledine, 1988; Mothet et al., 2000). Nevertheless, this is not enough for repelling the Mg^{2+} block and enabling the Ca^{2+} influx. Therefore, the postsynaptic membrane needs to be depolarized with activation of AMPA receptors, occurring upon the binding of glutamate, which is released due to stimulation from a presynaptic neuron in the synaptic cleft. Activation of AMPA receptors induces, among other cations, sodium influx through the connected ion channel and, if the activation is strong enough, it can depolarize the membrane. This depolarization releases the voltage-dependent Mg^{2+} block of the NMDA receptor, which allows Ca^{2+} to enter into the cell (Citri & Malenka, 2008). The Ca^{2+} influx activates a series of signalling cascades involving kinases and phosphatases. It has been hypothesized that the quantity of the postsynaptic calcium entry within the dendritic spines determines whether LTP or LTD is triggered. LTD needs a modest increase in Ca^{2+} (Cummings et al., 1996), while for LTP induction Ca^{2+} should increase above some critical threshold value (Malenka & Nicoll, 1993). Weak stimulation from presynaptic neurons leads to modest depolarization and smaller Ca^{2+} influx via NMDA receptors, which activate phosphatases that dephosphorylate AMPA receptors, resulting in promoting receptor endocytosis (Mulkey et al., 1993). Inversely, strong stimulation coupled with stronger depolarization inducing LTP via activating kinases resulting in AMPA receptor phosphorylation, and exocytosis (see Figure 4). Therefore, the strength of the depolarization, cytoplasmic Ca^{2+} concentration and associated enzymes activity will determine if more AMPA receptors are inserted into the membrane, which is the primary element for LTP induction, or if the existing AMPA receptors at the membrane are returned to the intracellular storage sites, which results in LTD (Borgdorff & Choquet, 2002; Henley & Wilkinson, 2013; Zhu et al., 2002; Sheng & Lee, 2001). However, recently, Nabavi et al. (2013) have shown that metabotropic action of the NMDAR, i.e., driving an ion-channel independent, is responsible for LTD in the hippocampus rather than Ca^{2+} influx through the channel. This study

showed that LTD induction just needs a basal level of Ca^{2+}, and metabotropic actions of NMDA-receptors can weaken active synapses without increasing the postsynaptic Ca^{2+} (Nabavi et al. 2013).

Glutamate receptors role in memory formation

The involvement of the glutamatergic system in memory processing in animals has been researched using 'one-trial' memory tasks. Here, NMDA receptors can be blocked before and/or after learning or just before retrieval to test its effect on retrieval later (Robbins & Murphy, 2006). In this regard, Bast et al. (2005), in a one-trial place memory test, have shown that hippocampal infusion of the NMDA receptor antagonist d-AP-5 blocked encoding and consolidation without affecting retrieval, while hippocampal infusion of the AMPA receptor antagonist (CNQX) impaired retrieval. Opposite to NMDA receptors, blockade of AMPA and kainate receptors with a selective antagonist disrupts encoding, consolidation, and retrieval of spatial memories – pointing to the general importance of the AMPA receptors for all of these processes (Riedel et al., 1999).

Neuromodulation of synaptic plasticity

The process of regulating nervous system activity by controlling the physiological levels of several neurotransmitters is known as neuromodulation. Neuromodulators are a subset of neurotransmitters, which are not involved directly in synaptic communication of the brain, but modulate it. These neuromodulators include acetylcholine, dopamine, noradrenaline, and serotonin, and their release can modulate synaptic plasticity in the hippocampus (Palacios-Filardo & Mellor, 2019).

The role of Dopamine

Dopamine is a major modulator of neuronal function and has several receptor subtypes in the mammalian brain. Five distinct but closely related receptors mediate the physiological actions of dopamine (Beaulieu & Gainetdinov, 2011; Andersen et al., 1990; Niznik & Van

Tol, 1992). Dopamine receptors have been grouped into two general families: D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptors (Andersen et al., 1990; Niznik & Van Tol, 1992). These receptors are metabotropic receptors, mostly but not only coupled to G proteins (Beaulieu & Gainetdinov, 2011).

The major dopamine-producing neurons are located in the Ventral Tegmental Area (VTA) and Substantia Nigra (SN) (Bjorklund & Dunnett, 2007). The SN projects to the dorsal striatum, while dopaminergic cells in the VTA project throughout the limbic system, including the hippocampus, amygdala, ventral striatum and prefrontal cortex (Fallon & Loughlin, 1995; Gasbarri et al., 1997; Asan, 1998; Wise, 2004; Wise, 2005; Chinta & Andersen, 2005). These areas receive dopamine in two modes, either "tonic" or “phasic” modes (Grace, 1991; Grace et al., 2007). The tonic mode provides a baseline amount of dopamine for the normal functioning of the neural network (Schultz, 2007), whereas, in the phasic mode, the firing rate of these neurons will sharply increase or decrease, which involves mainly learning processes (Schultz, 1998, 2007). Neuromodulators and specifically dopamine can influence the induction of LTP and/or LTD via specific changes in the initial levels of Ca^{2+} and cAMP which are the crucial regulators of LTP in the hippocampus, striatum and prefrontal cortex (Frey et al.,1993; Jay, et al., 1998; Spencer & Murphy, 2002; Gurden et al., 2000).

In the mammalian brain, dopamine is part of the reward circuitry and supposed to induce the adaptive effects of reward in the brain (Schultz, 2013; Schultz, 2000; Schultz, 2007; Wise, 2004; Wise & Rompre, 1989). Importantly it has been shown that dopaminergic system activity is important for learning novel and salient experiences (Duzel et al.,, 2010; Lisman & Grace, 2005) and also crucial for reward learning (Schultz, 1998, 2007; Ungless, 2004). Basically, information storage is prioritized based on relative novelty and reward value through dopaminergic signalling to the striatum and the hippocampus (Bromberg-Martin et al., 2010; Lisman & Grace, 2005).

It has been shown that dopamine release can modulate the strength of declarative memories in the hippocampus and this modulatory effect correlates with the extent of

VTA/SN activation (Adcock et al., 2006; Wittmann et al., 2005) and the level of the released dopamine in the hippocampus (Clausen et al., 2011; Hansen & Manahan-Vaughan, 2014). It has been suggested that the hippocampus-ventral-striatum-ventral-tegmental-area-hippocampus feedback loop plays an important role in declarative memory formation, in which dopamine input conveys the information about novelty and value of the stimulus to the hippocampus and determines which information enters to the long-term memory (Lisman & Grace, 2005). Probably, this dopamine signalling is also available during sleep, as ventral striatal reactivation, like hippocampal replay (Kudrimoti et al.,1999), is evident during SWS (Lansink et al., 2008; Lansink et al., 2009).

The role of dopamine has been investigated across all the memory stages in animals, for instance, infusion of dopamine antagonists to the hippocampus during or immediately after encoding disturbed the delayed recall in animals (Bethus et al., 2010; O'Carroll et al., 2006), indicating the benefit of dopaminergic activity in encoding and perhaps early consolidation. Increased dopamine levels within certain time points after learning can enhance memory consolidation; for example, infusing D1/D5 agonist to CA1 before learning has no effect while infusing after 3 or 6 hours post-learning increased performance at recall (Bernabeu et al., 1997). In older adult humans, levodopa– a dopamine precursor - was administered before learning, which showed no benefits on memory after 2 hours, but did show dose-dependent improvement in scene recognition after 6 hours (Chowdhury et al., 2012). The delayed positive effect of levodopa probably suggests that dopamine has an important role in late human memory consolidation.

1.3. What factors affect memory processing?

Different factors are known to have an effect on memory processing in humans, like physical and mental activity (Korol et al.,2013), stress (de Quervain et al., 2000), attention (Rees et al., 1999), hunger (Murphy et al., 1998), environmental context in which learning or recall

occurs (Mulligan, 2011), reward, which can modulate memory formation (Wittmann et al., 2011; Wittmann et al., 2008; Wittmann et al., 2005) and finally sleep. Studies have shown that sleeping immediately after learning can strengthen memory traces in the brain (Diekelmann et al., 2010; Takashima et al., 2006).

In addition to the already mentioned factors, memory will be affected by interference and time, which can cause forgetting and memory loss. Regarding the effect of time, it has been assumed that our memories are susceptible to passive processes of forgetting over time. This effect of time on forgetting goes back to Hermann Ebbinghaus (1885), who studied the dynamics of forgetting by using lists of none-sense-syllables pairs. He famously coined "the forgetting curve" showing that forgetting happens quickly during the first few hours after learning, but decelerates the longer the retention interval lasts. A recent study following his experiment successfully replicated these results (Murre & Dros, 2015).

The effect of interference, reward, and sleep will be discussed more in detail as they are relevant to the current work.

Interference effect on memory

It has been suggested that learning and memory are interacting, in which previously learned knowledge affects the learning of new knowledge (Krascum & Andrews, 1998; Murphy & Allopenna, 1994), and newly learned knowledge affects memory for already established knowledge (Roediger & Marsh, 2005). This interaction, in some cases, is facilitative; previous knowledge, or context, might serve as a schema that helps to understand and facilitates memory of new information, which is known as schema benefit on new learning (Preston & Eichenbaum, 2013). The concept of schema is introduced by Piaget (1929) and Bartlett (1932), and it is defined as a cognitive framework, representing an organized knowledge of some aspects of the world, which is obtained based on experience (Lewis & Durrant, 2011; Preston & Eichenbaum, 2013).

At the same time, the interactions between learning new information and the already existing memories can produce interference effects, for example, previously formed memories can reduce learning of new information, i.e., proactive interference (PI), while uptake of new information disturbs the recall of previously encoded information, i.e., retroactive interference (RI; Wixted., 2004). For instance, PI might happen for a teacher at the beginning of the semester when he/she finds it difficult to learn the new student's names since he/she has taught many students in the previous semester. In the case of RI, he/she might experience difficulty in remembering a particular student's name from the previous semester after learning new student's names (Darby & Sloutsky, 2015).

For over a century, researchers have designed experiments to examine the interference effect to reach a better understanding of the mechanisms of learning and memory (Anderson and Neely, 1996; Wixted, 2004). A model paradigm that is used to investigate the interference effect in experiments is the paired-associates learning task. In this task, participants have to study lists of paired items, i.e., a paired association between a cue (A) and a target (B), such as clock-church (referred to as AB list). After learning the AB list, participants have to learn a second list of pairs before testing the memory for both lists. The second list can be completely new, i.e., new cues and new targets (CD), or use cues from the first list coupled with new targets (AC), or cues and targets from the first list, which are paired differently (Wixted, 2004; Darby & Sloutsky, 2015). According to this framework, if participants learn a list of paired associates (A-B) and then later learn another list with the same cue words (A) but different targets (C). Then at later testing for the A-C the memory performance will be worse than if they did not have to learn the A-B list previously (so PI would be observed here). Darby and Sloutsky, (2015), performed an experiment on preschool-aged children and adults in order to gain developmental and mechanistic insights into retroactive and proactive interference effects. They found that PI and RI were present only for overlapping sets of information (such as in the described above AB-AC). The magnitude of PI was

comparable in children and adults, whereas retroactive interference reached a catastrophic level just in the children.

In the present work in order to investigate the proactive interference effect on new learning a associative word-pairs task was used in which participants were asked to learn two lists of word pairs (AB) in the evening after their arrival to the lab, and during the next day they had to again learn two lists of word pairs and one list had overlap with one of the first lists (AC) and the other one was completely new (CD).

Reward effect on memory

One of the factors that determine which experiences are remembered and which ones are forgotten is motivation (Shohamy & Adcock, 2010). Studies on healthy adults demonstrated that motivational states which are associated with anticipating and receiving a reward (i.e., money) could enhance memory. Importantly, cues which are associated with future reward are better remembered than neutral cues (Wittmann et al., 2011; Wittmann et al., 2008; Wittmann et al., 2005). This advantage can be extended to the information that is presented after the reward-signalling cue (Adcock et al., 2006; Kuhl et al., 2010). Both intentional memory formation (Adcock et al., 2006; Kuhl et al., 2010; Murty et al., 2011) and incidental memory formation (Bialleck et al., 2011; Mather & Schoeke, 2011; Murayama & Kuhbandner, 2011; Wittmann et al., 2011; Wittmann et al., 2008; Wittmann et al., 2005) are sensitive to reward. For example, in order to investigate the effect of reward associated cues in intentional memory formation, the current work has adapted the Motivated Learning Task (MLT) from prior work of Feld and colleagues (Feld et al.,2014) and required the participants to memorize 160 pictures of landscapes and living rooms. The presentation of half of these pictures (80) was preceded by a 1 Euro symbol. The other half (80) was preceded by a 2 Cents symbol. Participants were informed that they would receive the respective reward for every hit, 51 cents for a correct rejection, and they would lose 51 cents for a miss or a false alarm during the subsequent recognition test. In order to control for effects of encoding

depth, half of the pictures in each of the two reward conditions were presented for long and short duration, respectively. Recognition was tested twice, immediately after learning (after 15 min.) and in the evening of the next day (for more detail see, chapter 6. pages 72, 73, 74).

Sleep’s effect on memory

There is a long history in neuroscience, exploring the potential link between sleep and memory processes. Following Ebbinghaus (1885) pioneering work on forgetting curves, Jenkins and Dallenbach (1924), replicated his work and claimed that the rate of forgetting was slower after sleep. They attributed this to a reduction in the incoming sensory information during sleep and the corresponding decrease in interference. In this way, sleep can protect memories from forgetting. An alternative explanation for this would be a lower metabolism during sleep, which could prevent the neurobiological decay of memory traces (Thorndike, 1913). After the discovery of sleep structures and defining the sleep stages (Rechtschaffen & Kales, 1968), the sheltering interpretation of sleep against interference was challenged by showing that the memory retention for declarative memory was better over the first half of a night of sleep compared to the second half, which did not show superior retention compared to wakefulness (Yaroush et al.,1971). Later, studies suggested that declarative memories benefit more from SWS, while implicit memories mainly benefit from REM sleep (Plihal & Born, 1999; Plihal & Born, 1997). During recent years, the active effect of sleep on memory consolidation has been well-established (Diekelmann et al., 2010; Rasch & Born, 2013; Dudai, 2012).

Active system consolidation

Opposite to the passive role of sleep in protecting memories from forgetting, i.e., via less interfering information or slower metabolism, the recent studies consider the neural replay of memories during sleep as an indicator for an active role of sleep for memory consolidation (Rasch & Born, 2013; Dudai, 2012). The active system consolidation hypothesis explains the

role of sleep for long-term memory formation in the hippocampus-dependent memory system (Klinzing et al., 2019). Wilson and McNaughton (1994) recorded hippocampal place cell activity while rats performed a spatial behavioural task and also during SWS (before and after the task). The results showed that during post-task sleep, the likelihood for coincident firing of the hippocampal cells is higher for the cells which had correlated activity during wakefulness. This replay during SWS sleep also showed the same temporal order of firing as wakefulness (Ji & Wilson, 2007; Skaggs & McNaughton, 1996). A similar reactivation process is not evident in REM sleep (Kudrimoti et al., 1999). As mentioned before, active system consolidation is mainly related to hippocampus-dependent memories. However, a recent study on rats looking at sleep's effect on novel-object recognition memories showed that sleep is also relevant for 'non-hippocampus-dependent memories (Sawangjit et al., 2018). In humans, the causal role of hippocampal-dependent reactivation during SWS has been shown for declarative hippocampus-dependent memories (Rasch et al., 2007; Rudoy et al., 2009).

It is widely accepted that replay happening during the post-encoding sleep phase is involved in both system and synaptic consolidation of memories. During system consolidation, newly encoded memory traces are reactivated during SWS in the hippocampus and also the cortex (Feld & Diekelmann, 2015). Here the hippocampus resembles a trainer for the cortical long-term store, which is repeatedly reactivating the cortical memory representations. Due to those reactivations, the cortical connections will become strengthened and finally become hippocampus-independent (Feld & Diekelmann, 2015). Then, during the subsequent REM sleep, memories are stabilized via synaptic consolidation (Diekelmann et al., 2010).

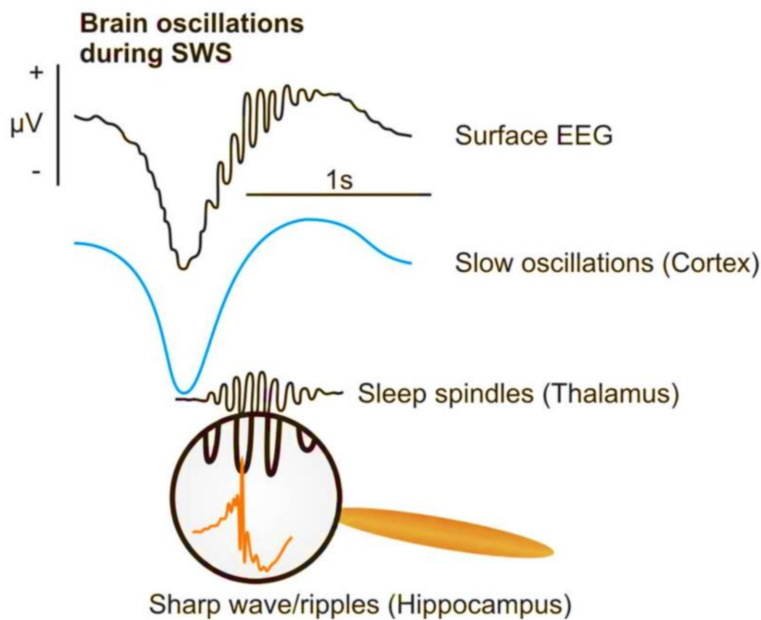

Figure 5. Schematic for the interplay between different oscillations during slow-wave sleep. A replay of memories in the hippocampus, in the form of sharp-wave ripples, mainly occurs during the up-state of slow oscillations. The coupling of fast spindles to the up-state leads to spindle-ripple event occurrence. This allows the reactivated memories to reach the cortex. Adapted from Feld and Diekelmann, 2015.

For successful system consolidation, slow oscillations (<1 Hz, generated in cortical areas), which are the hallmark oscillations of SWS, induce the replay of the recently encoded memories in the hippocampus in synchrony with sharp wave-ripples (generated in hippocampus) and thalamo-cortical spindles (12-15 Hz) (Mölle & Born, 2009, see Figure 5). Through this synchrony, slow oscillations support the formation of ripple-spindle events that act together to gradually transfer replayed memories from the hippocampus to the neocortex (Buzsaki, 1998; Mölle & Born, 2009). As spindle activity coincides with the depolarizing slow oscillation up-state, it prepares this network for further synaptic plastic changes (Bergmann et al., 2012; Mölle et al., 2011).

Basically, spindle activity during SWS primes the expression of the plasticity-related immediate early genes – the markers of synaptic potentiation – by increasing Ca^{2+} concentration in selected cortical neurons (Sejnowski & Destexhe, 2000; Rosanova & Ulrich, 2005), and this prepares these memory traces for synaptic strengthening during REM sleep. This

synaptic consolidation occurring during REM sleep can complement the action of systems consolidation during SWS (Diekelmann & Born, 2010).

Synaptic homeostasis hypothesis

Besides the theory of active systems consolidation, the synaptic homeostasis theory (SHY) proposed by Tononi & Cirelli (2006), suggests that sleep and SWS specifically promote the rebalancing and downscaling of synaptic weights, which has been unbalanced due to learning during prior wakefulness. Learning occurs based on Hebbian plasticity - for example, strengthening the connection between the neurons during encoding (Hebb, 1949), which results in a net increase in synaptic strength. This potentiation during wakefulness would increase space and energy demands. In order to avoid decreased signal to noise ratio (S/N) and saturation, renormalization of the synaptic strength is necessary, which happens during sleep since the synaptic inputs are not biased via sensory information (Tononi & Cirelli, 2014; Tononi & Cirelli, 2019). There are different markers of changing synaptic strength (Cirelli, 2017), which in general support these wake/sleep synaptic changes suggested by SHY. For example, the expression of excitatory glutamatergic AMPA receptors, measured at the synaptic level in the rat cerebral cortex and hippocampus of adult rats, is higher after wakefulness than sleep (Vyazovskiy et al., 2008).

The theoretical effectiveness of the slow-wave activity (SWA, 0.5 - 4.5 Hz) for renormalizing of synapses has been established by computer stimulations (Hill & Tononi, 2005; Esser et al., 2007; Sullivan & de Sa, 2008), and also empirically, by potentiating synapses via extended learning (Huber et al., 2004; Schmidt et al., 2006) or by transcranial magnetic stimulation (TMS) which is locally increasing the slow-wave activity (Huber et al., 2007; Huber et al., 2008). There is evidence suggesting that slow waves during NonREM sleep represent synaptic strength and possibly are responsible for synaptic downscaling (Massimini et al., 2009).

This SHY, in its first conceptualizations, disagrees with active systems consolidation theory, which suggests synaptic potentiation also occurs during sleep (Tononi & Cirelli, 2006). Here, the authors suggested that sleep benefits memory by increasing the S/N, which is generated from synaptic-downscaling (Tononi & Cirelli, 2006). The theory has been updated in order to show a unified concept considering the other functions of sleep: active systems consolidation. In the revised version, the concept of general downscaling is substituted by selective downscaling (Tononi & Cirelli, 2014), i.e., relevant representations, which are strengthened during wakefulness and fit to the existing circuits, might survive and the less activated and less well-fitting representations will be erased (Tononi & Cirelli, 2014).

Effect of relevance and reward on memory consolidation during sleep

Sleep's enhancement effect via active systems consolidation is selective: it mainly strengthens memories relevant for future behaviour. For example, Wilhelm et al. (2011) asked human subjects to learn word pairs before sleep or wakefulness and found, when participants were informed about the future retrieval test, their performance was superior after sleep compared to wakefulness. They also showed that expecting the retrieval could enhance sleep-associated consolidation of visuospatial and procedural motor memories. Future plans and expectations are important in long-term-retention of newly acquired information (Diekelmann et al., 2013; Shimizu, 1996; Szpunar et al., 2007), i.e., information that is relevant for future plans is easier to recall later. Importantly, the relevance of an information at encoding for the future can be signalled by reward (Miendlarzewska et al., 2016), which can increase the probability of these memories benefitting from sleep (Feld et al., 2014; Igloi et al., 2015). In this regard, Fischer & Born (2009), found that that participants who expected rewards for their performance after sleep showed stronger sleep–dependence for the rewarded memories.

Sleep's effects on interference

Studies have suggested that sleep can actively protect declarative memories against subsequent retroactive interference, occurring when the participants learn new yet overlapping information (interference learning) (Ellenbogen et al., 2009; Ellenbogen et al., 2006). In these studies, using the AB–AC word-pair learning paradigm (see page 18), interference disturbed memories much less following sleep compared to after a day of wakefulness. It seems memory consolidation transforms initially labile memories into more stable memories (e.g., Dudai, 2004) and due to this stabilization of memories after sleep (Rasch and Born 2013) they are less susceptible to retroactive interference (Ellenbogen et al., 2009; Ellenbogen et al., 2006).

Sleep’s effect on new learning

According to SHY, if extensive synaptic potentiation continued, the brain would reach its limit for encoding new information. Therefore renormalizing the synaptic weights is necessary during sleep to avoid this saturation (Tononi & Cirelli, 2006; Cirelli & Tononi, 2008; Tononi & Cirelli, 2014).

Synaptic downscaling during sleep should as a direct consequence, enhance learning after a period of sleep compared to a period of just wakefulness (McDermott et al., 2003). Mander and colleagues (Mander et al., 2011), in a nap study, asked their participants' to learn new information twice in one day, once at noon and a second time in the evening. One group of participants could take a nap in between the two learning sessions, and another group had to stay awake. Encoding ability declined across the day in the wake subjects, while the encoding performance of the participants in the nap group improved in the second session (Mander et al., 2011). This impairment in forming new memories was also demonstrated in sleep-deprived participants for a single night due to a deficit in hippocampal activity during encoding (Yoo et al., 2007). Regarding the importance of the slow-waves for synaptic homeostasis as suggested by SHY (Tononi & Cirelli, 2014), it has been

shown in elderly participants that decreasing in the SWA could reduce the participant's ability to encode novel images during the next morning (Van Der Werf et al., 2009).

1.4. Pharmacological influences on sleep-dependent memory consolidation

One of the potential strategies to better understand memory processes that occur during sleep at the molecular level is manipulating them with pharmacological agents. It has been shown that glutamatergic signalling is involved in sleep-dependent consolidation of sensory memory (Gais et al., 2008). In this study, healthy participants had to learn a procedural visual texture discrimination task, which relies on glutamatergic plasticity in the visual cortex. During the night of retention sleep, an AMPA receptor blocker, caroverine, and a NMDA receptor blocker, ketamine, were given to different groups of participants, respectively. Both blockers disturbed the performance on subsequent retrieval of the task. These findings are related to the non-declarative memories, which are essentially not relying on hippocampal networks. Declarative memory (hippocampal-dependent memories) consolidation during sleep involves reactivating neuronal ensembles that encoded these memories during wakefulness (Diekelmann & Born, 2010). Furthermore, the reactivation in hippocampal and neocortical networks would involve glutamatergic neurotransmission and is temporally coupled to hippocampal sharp wave-ripples and neocortical slow oscillations which is both supported by both, NMDA and AMPA receptor-related synaptic plasticity (Behrens et al., 2005; Chauvette et al., 2012; Csicsvari et al.,1999; Espinosa & Kavalali, 2009; King et al., 1999). Therefore, manipulating glutamatergic neurotransmission with specific drug like D-cycloserine (DCS) as a NMDA receptor co-agonist might affects sleep-dependent declarative memory consolidation as well. Of note, DCS is acting at the glycine-binding site of NMDA receptor and some evidences shows that it preferentially acts via NR2A containing receptors in order to enhance LTP (Kochlamazashvili et al, 2012; Sheinin et al., 2001). In this regards, in human subjects, the administration of DCS during retention sleep enhanced

hippocampus-dependent declarative memory consolidation (Feld et al., 2013). However, blocking NMDA and AMPA receptors with ketamine and caroverine, respectively, did not affect memory consolidation, which means the sleep-dependent consolidation probably does not simply depend on the AMPA and NMDA receptor reactivation, but glutamate nevertheless plays a crucial role.

It seems that the reward circuitry, in which dopamine plays a critical role (Miendlarzewska et al., 2016), might play a role for sleep-dependent consolidation. Studies in rats using reward learning tasks have shown that hippocampal replay during sleep was linked to ventral striatal replay (Lansink et al., 2009; Pennartz et al., 2004). This replay was also found in the VTA (Valdes et al., 2015). Importantly these areas, as mentioned before, are known to be involved in reward feedback loops (Lisman & Grace, 2005). Therefore, reactivation of these brain regions offers the possibility that replay in the hippocampus can access dopaminergic neuromodulation during sleep via the aforementioned feedback loop that acts similar to wake. Based on this, it seems manipulating the dopaminergic transmission during sleep can affect the consolidation of reward associated memories during sleep. In this regard, the administration of pramipexole, a D2-like receptor agonist, during sleep wiped out the difference in the consolidation of highly and lowly rewarded memories, and both memories benefited similarly from sleep-dependent reactivation (Feld et al., 2014).

1.5. Hypotheses and aims of the conducted studies

Sleep is an active process, and its dynamics can be affected by manipulating the brain's neurotransmitters. The effects of neurotransmitters are not just limited to sleep; their manipulation also affects different functions, like memory. Notably, sleep can benefit memory processes (Diekelmann & Born, 2010). One of sleep’s functions is benefiting memory by consolidating traces, which were encoded during prior wakefulness (Diekelmann & Born, 2010). Furthermore, it has been put forward that another function of sleep involves balancing processes of up and downscaling of synapses (Born & Feld, 2012). However, the neuro-

chemical processes underlying the synaptic up and downscaling in the hippocampus are not yet fully understood. In my current work, focusing on glutamate as the main excitatory and dopamine as the main modulatory neurotransmitter, I have explored how these neurotransmitters, which are known to be involved in memory formation during wakefulness, contribute to sleep-dependent memory processing.

The aim of the first study (see chapter 5, study I) was trying to influence glutamatergic transmission during sleep using DCS, a NMDA receptor co-agonist. As it has been shown that DCS can enhance declarative memory consolidation during sleep (Feld et al., 2013), we decided to test whether these consolidated memories proactively interfere with learning new information. To this end, we chose a word pairs task as our dependent variable. Participants had to learn two lists of word-pairs (original lists) in the evening after their arrival and then orally received the medication (DCS or placebo) before 8 hours of sleep. Sleep EEG was prepared, and polysomnography was recorded during sleep. The next evening, participants were asked to learn two lists of word-pairs again. One list consisted of entirely new word-pairs (new or no- interference list), while the other one used the cue words from one of the original lists and matched them with new target words (interference list). We hypothesized that new learning would decrease under DCS as the previously learned and consolidated memories under the drug would leave less space for new memories, and that this effect will even be facilitated by interference. To figure out whether the effect of DCS on new learning is sleep-dependent, we conducted a wake control study, where participants underwent the above described protocol but stayed awake until the new learning occurred.

My second study (see chapter 6 study II) attempts to influence the consolidation of reward-related memories during sleep. For this aim, the dependent variable was represented by a motivated learning task (MLT) (adapted from Adcock et al., 2006 and Feld et al., 2014), which relies on the interaction of the hippocampus and ventral striatum at encoding. We chose the D2-like receptor antagonist sulpiride to block dopaminergic signalling during sleep. Medication (sulpiride or placebo) was administered after the learning phase of the MLT and

before an 8-hour sleeping period. The retrieval phase for the task was scheduled the next evening to minimize the residual amount of drug circulating at retrieval testing. We hypothesized that reward contingencies are disturbed under sulpiride condition and that there will be no preference for consolidation of high versus low rewarded memories.

1.6. General discussion

Summary of the main results

To understand in more depths the sleep's neurochemical underpinnings that support memory processes, we decided to upregulate NMDA-receptor activity during sleep with its co-agonist DCS (study I). Additionally, we suppressed dopaminergic neurotransmission by using sulpiride, a dopamine D2-like receptor antagonist (study II).

In the first study, we found a trend-wise enhancement in learning new word-pairs after sleep than wakefulness, and DCS distinctly enhanced the learning of new word pairs compared to the placebo group. This effect was independent of sleep. This enhanced new learning effect under DCS, might point to the involvement of glutamate receptors in time-dependent forgetting in addition to sleep-dependent consolidation, as it had been shown by Feld et al., (2013). Furthermore, this study has shown that the performance in new learning phase (Run 1 and Run 3) for the no-interference list was positively correlated to time spent in sleep stage 4 in the placebo group. Unexpectedly, the interference list was generally learned better than the new (no-interference) list. This may be due to schemata formation, which is again probably time-dependent rather than sleep-dependent.

In the second study, using sulpiride, we found that at retrieval (after approximately 22-h retention interval in order to minimize residual drug effects), highly rewarded memories were retained better than lowly rewarded memories in both sulpiride and placebo conditions without any marked effect of treatment. This means that preferential consolidation of highly rewarded memories is benefiting from frequent replay, which may have been primed during

encoding due to the activation of dopaminergic neurotransmission. Furthermore, an effect of sulpiride on items with different depths of encoding might open the possibility for a critical role of dopaminergic neurotransmission for consolidation of memories, which are not associated with rewards during sleep. Of note, in the current study, half of the pictures which have been shown for a long time belonged to the high reward category, and half of them to the low reward category, the same is true for pictures of the short duration time. Therefore, they are not independent of the reward value. Another finding in this study demonstrates the positive and negative relationship of S4 with high reward and low rewarded representations in the placebo group, respectively.

Role of glutamate for new learning after sleep

In study I, the NMDA receptor was up regulated using DCS to explore whether enhanced memory consolidation under DCS during sleep (Feld et al., 2013) would decrease the subsequent new learning. The wake experiment was conducted to explore whether the effect of DCS on memory is sleep-dependent or not. The findings show that sleep and DCS are independently enhancing new learning performance. It has been shown that glutamate-mediated signalling via receptors such as NMDA and AMPA receptors plays an important role in regulating LTP and long term memory formation (Collingridge, 1987; Lynch & Baudry, 1984; Nicoll et al., 1988). Recently, the underlying mechanisms which are mediated by these glutamate receptors for the time-dependent forgetting has been clarified (Hardt et al., 2013; Migues et al., 2016; Sachser et al., 2016; Shinohara & Hata, 2014; Villarreal et al., 2002)..

According to Hardt et al., 2013, memory systems engage in acquiring memories irrespective of their later use, and only afterward, the brain actively decides which information is desired and is to be kept and which are unwanted and must be erased. It may, therefore, be a process of active decay that is employed after deciding about the value of already formed memory traces (Hardt et al., 2013). Interestingly, study I showed that new learning was significantly improved after both sleep and wakefulness, under DCS (NMDA receptor co-

agonist) administration. As proposed by SHY (Tononi & Cirelli, 2006), this result suggests that some kind of synaptic renormalization occurs. In the present case, this renormalization must be sleep independent and is possibly happening via a type of time-dependent decay-related forgetting (Hardt et al., 2013) and can add to the current knowledge about the importance of glutamate signalling for this time-dependent active decay.

Furthermore, study I showed, next to sleep-independent improved new learning under DCS, trend-wise enhanced new learning in the sleep compared to the wake group. This corresponds to earlier findings of enhanced encoding after sleep (Mander et al., 2011) and points to the benefit of sleep by providing new space for subsequent learning. Also, in support of an active role of sleep to enhanced encoding, study I found that time spent in S4 was positively related to new learning performance in the placebo condition. This finding can be explained well by the SHY hypothesis (see pages 23 and 24), suggesting that general renormalization occurs during sleep, which restores the capacity for further encoding (Tononi & Cirelli, 2006).

The better learning in the interference condition compared to the no-interference condition points to a schema benefit on new learning (Preston & Eichenbaum, 2013), which means the prior knowledge facilitates new learning. Therefore, in the current work, the interaction between previous knowledge and new information leads to proactive enhancement rather than PI. This enhancement in the interference condition was independent of sleep and DCS administration. Even though theoretically schema formation by abstracting the knowledge form episodes, has been suggested to be sleep-dependent (Lewis & Durrant, 2011) there exists empirical evidence supporting the time-dependency of establishing this knowledge base (Hennies et al., 2014), which is consistent with the current finding.

Role of dopamine in consolidation of reward-related memory during sleep

There are two possibilities for preferential retention of reward-associated memories after sleep. On the one hand, the reward circuitry which provides dopaminergic inputs at encoding

from the ventral tegmental area to the hippocampus via a feedback loop (during wakefulness) is reactivated during sleep. On the other hand, dopaminergic inputs to the hippocampus at encoding can increase the frequency of reactivation during retention sleep independent of this dopaminergic network. In rodent studies, evidence for both accounts has been found (Lansink et al., 2009; Pennartz et al., 2004; McNamara et al., 2014). In the current work, study II aimed at investigating whether dopaminergic neurotransmission is necessary for sleep's selective effect on rewarded memories.

Our findings in this study are showing that after sleep, highly rewarded memories were retained better than lowly rewarded memories in both sulpiride and placebo conditions. This finding demonstrates that highly rewarded memories might be benefiting from a tagging mechanism similar to the one suggested by the synaptic tagging and capture hypothesis (Redondo & Morris, 2011), which can serve as an example of dopamine-related tagging. This tagging for highly rewarded memories at encoding possibly leads to preferentially hippocampal reactivation during the following active system consolidation periods and better retention for the memories which are associated with high rewards compared to the low rewards (McNamara et al., 2014). Therefore it seems that reward-related specificity of active systems consolidation during sleep is promoted by fluctuation of reactivation frequency rather than involvement of dopaminergic neuromodulation.

Furthermore, in study II, time spent in S4 was positively correlated with the retention of highly rewarded memories whereas it was negatively correlated with retention of lowly rewarded memories (in the placebo group). The revised form of synaptic homeostasis (Tononi & Cirelli, 2014), which has the active systems consolidation embedded, can justify how S4 is playing a role in both consolidating highly relevant memories and forgetting the non-relevant ones.

One could assume that during NonREM replay, relevant memories (i.e., highly rewarded ones), are consolidated on the system level and might thereby be protected from forgetting, despite an overall downscaling mechanism. This might be occurring by a dual role

of NonREM oscillations, including slow oscillations, sleep spindles, and sharp wave-ripples. On the one hand, it has been proposed that a precise temporal coupling or nesting of these NonREM oscillations might lead to consolidation at the system level (Staresina et al., 2015; Maingret et al., 2016). On the other hand, the isolated activity of slow oscillations and sharp wave-ripples would lead to synaptic depotentiation, as both produce the low concentration of Ca^{2+} (Tononi & Cirelli, 2006; Norimoto et al., 2018) and possibly induce LTD for irrelevant memories.

Recently Kim et al. (2019) suggested an appealing scenario for this dual effect of NonREM sleep in memory consolidation and forgetting. They suggested a competing and dissociable role for slow oscillations (SOs) and delta waves for the dual function of sleep. The precise nesting of SOs and spindles is important for memory consolidation, possibly via driving and keeping the reactivation of awake experiences. However, delta wave-triggered processes promote weakening the reactivated memory traces, which is leading to forgetting, and it can also modulate the efficacy of SO-triggered processes. During NonREM sleep studies have found two separate classes of slow waves; one class is more global and has larger amplitudes and the other class is more local and has smaller amplitudes (Bernardi et al., 2018; Dang-Vu et al., 2008; Genzel et al., 2014; Mölle et al., 2002; Siclari et al., 2014). According to Kim et al., 2019, SOs are the large global slow waves, and delta waves are the local slow waves with smaller amplitude. Possibly, global SOs support systems consolidation (Genzel et al., 2014; Robertson, 2009). Oppositely, delta waves are just driving the local activity-dependent processes leading to weakening. Even though Kim et al., (2019), have suggested an active role for delta waves in weakening memories, it is plausible that delta waves mediate their effects just by reducing SO-related consolidation processes and nesting of spindles.

Importantly, unlike Feld et al., (2014), we were unable to show that sleep-dependent consolidation for rewarded memories benefits from VTA-hippocampal loop reactivation. In that study, they showed that using pramipexole (D2-like receptor agonist) during sleep wiped

out the differences between highly and lowly rewarded memories, while the highly rewarded memories were retained better in the placebo group (Feld et al., 2014). However, the findings from study II might give a clearer picture to what is occurring during the off-line retention intervals. Administrating dopaminergic system agonists (i.e., pramipexole) exert a dopamine effect on the existing receptors. Therefore this is not necessarily indicating endogenous dopaminergic signalling as a major player during reactivation for selectively consolidating the rewarded information. If there was an endogenous dopaminergic reactivation, then blocking the D2-like receptors should reverse those effects, which study II has shown it did not.

Role of an unexpected, new source of dopamine

In study II, even though we demonstrated that sulpiride administration during sleep did not disturb the consolidation of reward associated memories (pointing to the less important role for the dopaminergic system during sleep for reward-associated memories), we found that sulpiride, during sleep affected the consolidation of the memories based on their encoding depth regardless of their association with highly or lowly rewards (see chapter 6, pages 77 and 78). This finding might challenge the Lisman and Grace model (2005), which has proposed that following novelty detection the dopamine released from the VTA to the hippocampus would plays a major role in signalling novelty and enhanced LTP and learning. Based on this model processing of novelty and reward are interrelated in order to control the entry of behaviorally relevant information to the long term memory. Our findings might bring up the question of whether another source of dopamine is responsible for releasing dopamine following novelty for non-rewarded memories and might be available during sleep.

The model mentioned above suggests that the tyrosine-hydroxylase expressing (TH+) neurons in the VTA within the hippocampus would release dopamine following novelty or surprise (Lisman & Grace, 2005; Lisman et al., 2011). Of note, there are limited VTA-TH+ axons releasing dopamine in the hippocampus (Gasbarri et al., 1994; Gasbarri et al., 1997), which suggests the existence of another source of dopamine, like TH+ axons from the locus

coeruleus (LC) (Smith & Greene, 2012). TH+ axons from the LC are involved in novelty, arousal and cognition (Aston-Jones & Bloom, 1981; Harley, 1991; Sara, 2009), also, quite interestingly; LC activity can be regulated by the sleep slow oscillations (Eschenko et al., 2012). Although LC reactivation during sleep is not established, it might play an important role in the consolidation of memories from novel experiences during SWS. Presumably, there are two different types of novelty; 'environmental novelty' and 'reward-associated novelty' (Yamasaki & Takeuchi, 2017). It seems the LC-hippocampus system will mediate environmental novelty (Yamasaki & Takeuchi, 2017), as the dorsal hippocampus (important for spatial learning and memory) mainly receives dopamine from LC-TH+ neurons rather than the VTA (Takeuchi et al., 2016; Kempadoo et al., 2016). It has been suggested that LC dopamine release may increase attention to the salient features of the environment for spatial learning and memory (Kempadoo et al., 2016), and Takeuchi et al., 2016 have shown that optogenetic activation of LC-TH+ axons after encoding enhanced memory related to environmental novelty in the hippocampus. These findings suggested that LC possibly co-released dopamine with noradrenaline (NA) to the hippocampus. In support of this idea, it has been shown that chemical and electrical stimulation of LC triggers the release of both dopamine and noradrenaline in the hippocampus (Scatton et al., 1984; Quintin et al., 1986). The VTA-hippocampus system, which was previously proposed to signal the novelty of the experiences, might mediate reward-associated novelty (Yamasaki & Takeuchi, 2017) but not daily non-rewarded events. Interestingly, it has been proposed that it is plausible that the amount of dopamine released from LC might fluctuate depending on the level of its activation (Duszkiewicz et al., 2019), which can help to explain why pictures shown for longer durations might lead to sustained activation of LC and benefit more from the modulatory effect of dopamine.

Importantly, it has been suggested that in the hippocampus, novelty-induced memory enhancement depends on D1/D5 receptors (Yamasaki & Takeuchi, 2017). These are not the same receptors we have blocked, but some pieces of evidence have shown that blocking D2

receptors can suppress LTP induction (Price et al., 2014). Furthermore, D2-like receptors are enhancing excitatory activity via inhibiting the release of GABA (the predominant inhibitory neurotransmitter) and increasing glutamatergic transmission (Cooper & Stanford, 2001; Hu & White, 1997; Seamans et al., 2001; Smialowski & Bijak, 1987). Therefore, they might also be a candidate to affect novelty related plasticity in the hippocampus.

Conclusion

Glutamate and dopamine are involved in neuronal communication at learning during wakefulness (Collingridge & Bliss 1987; Robbins & Murphy, 2006; Bethus et al., 2010; McNamara et al., 2014; O'Carroll et al., 2006; Otmakhova & Lisman 1996). Regarding the findings from both studies, with manipulating glutamatergic and dopaminergic neurotransmission during sleep, it seems that these neurotransmitters are not necessarily taking a significant role in all sleep-dependent memory processing as it was expected. Specifically, upregulating the glutamatergic neurotransmission using DCS enhanced new learning rather than hampering it, and its effect on new learning was not sleep-dependent. Also, based on the findings using sulpiride as a D2-like receptors antagonist, it seems replay of memories in the hippocampus during sleep does not necessarily recruit the dopamine reward circuitry for preferential consolidation of highly rewarded memories. Since blocking the dopaminergic neurotransmission did not reduce the retention of highly rewarded memories.

The findings from current studies are adding to the two main fundamental theories, active systems consolidation and SHY, which have been proposed to explain the beneficial effects of sleep on learning and memory. Even though in study I, the new learning was generally enhanced after sleep due to renormalization based on SHY (Tononi & Cirelli, 2006). The distinct enhancement in new learning with upregulating the glutamatergic neurotransmission under DCS is suggested to stem from a kind of renormalization, which is time and glutamate-dependent (Hardt et al., 2013). Therefore, it seems, this sleep-independent active decay has a more pronounced role than the sleep-dependent synaptic homeostasis for the

enhanced new learning. Findings in study II, point to the idea that during sleep, parallel to the active systems consolidation of the relevant memories, there might be another brain mechanism which renormalizes the synaptic strength to erase the unwanted memories and provide more space for further learning (Feld & Born, 2012).

Critical appraisals, future directions, and application of the work

Although future studies may be able to correct some limitations and extend on the reported results, these present studies were conducted to a high standard. In both studies, I collected the data from male participants because sex affects memory consolidation (Genzel et al., 2012), and the responses to the monetary or social rewards (Wang et al., 2017). Therefore it would be beneficial to see if there is any difference when including female participants. In general, future research could go beyond the neurotransmitters used in the current work to manipulate memory during sleep. For example, it is possible that for reward modulation during sleep other less well-studied neurotransmitter systems, like the endocannabinoid system, are playing a major role as this system is involved in metaplastic processes in the hippocampus (Chevaleyre & Castillo, 2004; Xu et al., 2014) and also reward processing (Solinas et al., 2008). Recent discoveries points to the involvement of two distinct and parallel dopaminergic systems (VTA-hippocampus and LC-hippocampus) in mediating novelty and memory consolidation, depending on the nature of the novel experiences (Yamasaki & Takeuchi, 2017; Takeuchi et al., 2016). Therefore it would be interesting to study the cued reactivation of reward-related memories using functional magnetic resonance imaging (fMRI). This will provide information that activation of which of the two dopamine resources is mainly correlating with the better retention of reward-related memories.

Previously blocking the NMDA and AMPA receptors did not affect the consolidation of declarative memory during sleep (Feld et al., 2013). In the same vein, and the current work's finding with upregulating the NMDA receptor suggested that glutamatergic neurotransmission might not be playing a major role in memory processes during sleep. Thus it

will be helpful to block NMDA and metabotropic glutamate receptor 5 (mGluR5) at the same time to avoid any of them taking over the function of the other. For example, it has been shown that blockade of NMDA receptors with ketamine can be reversed with activating mGluR5 (Chen et al., 2011). Thus, in this way, one could make the role of the glutamatergic system crystal clear during sleep for consolidation and subsequent new learning.

In both studies, we tried to manipulate human cognitive functions using pharmacological agents. DCS might be effective for diseases associated with memory/learning deficits (e.g., dementia) or for therapies that rely on learning processes (e.g., exposure therapy in anxiety disorders; Schade & Paulus, 2016; Hofmann, Sawyer, & Asnaani, 2012). Regarding to potential clinical applications of DCS, it has been suggested that, for the effective use of DCS in exposure therapy, likely it is better to use the drug either immediately before or after the exposure session (Norberg et al., 2008). Previously, Feld et al., (2013) showed a positive effect of DCS on memory consolidation during sleep. Current results do not tackle memory consolidation but rather are showing DCS engagement in enhancing new learning via accelerating the forgetting. Therefore considering these findings and suggested clinical application mentioned above, we can suggest amplifying the learned behaviors at the successful exposure session by administrating DCS afterwards during sleep. Considering the improved new learning after DCS it can be further suggested to repeat the same exposure session during the next day to accelerate the effectiveness of treatment. Another feature that might influence the effectiveness of DCS is the dosage of the drug. First applications of DCS in exposure therapy have shown no difference reported for doses between 50 and 500 mg (Myers & Davis, 2007). In other studies, DCS also used at the doses of 50, 100 and 125 mg and all of these doses seems to be sufficient for enhancement of exposure therapy (Hofmann et al., 2013) and considering the possibility of acting as an antagonist at higher doses of DCS (i.e. > 500 mg) (Heresco-Levy et al., 2013), it seems our dose of 175 mg is close to the optimal dose.

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Findings from study II has shown that sulpiride did not affect the consolidation of reward associated memories. This finding hints at a minor role of the dopaminergic system in sleep-dependent memory consolidation. Although some previous human and animal studies point at such a dopaminergic pathway contribution (Feld et al., 2014; Lansink et al., 2009; Pennartz et al., 2004). Thus the translation of this finding in the current work using sulpiride to clinical application in humans does not seem evident.

All in all, these direct administrations of medications and neurochemical manipulation of memory processes in humans enabled us to investigate the complexity of human behaviour. Furthermore, it provided the opportunity to interpret these findings without translating them from animal models even though animal research needs to complement the human work, for instance, in the cases to make use of substances not available in humans.

2. References

Abbott, A. (2005). Neuroscience: while you were sleeping. *Nature, 437*(7063), 1220-1222. doi: 10.1038/4371220a

Abraham, W. C., & Robins, A. (2005). Memory retention--the synaptic stability versus plasticity dilemma. *Trends Neurosci, 28*(2), 73-78. doi: 10.1016/j.tins.2004.12.003

Adcock, R. A., Thangavel, A., Whitfield-Gabrieli, S., Knutson, B., & Gabrieli, J. D. (2006). Reward-motivated learning: mesolimbic activation precedes memory formation. *Neuron, 50*(3), 507-517. doi: 10.1016/j.neuron.2006.03.036

Adler, C. H. (2005). Nonmotor complications in Parkinson's disease. *Mov Disord, 20 Suppl 11*, S23-29. doi: 10.1002/mds.20460

Andersen, P. H., Gingrich, J. A., Bates, M. D., Dearry, A., Falardeau, P., Senogles, S. E., & Caron, M. G. (1990). Dopamine receptor subtypes: beyond the D1/D2 classification. *Trends Pharmacol Sci, 11*(6), 231-236. https://doi.org/10.1016/0165-6147(90)90249-8

Anderson, MC.; Neely, JH. Interference and Inhibition in Memory Retrieval. In: A. Press. , editor. Memory Handbook of perception and cognition. 1996. p. 237-313.doi: https://www.sciencedirect.com/science/article/pii/B9780121025700500100

Asan, E., 1998. The catecholaminergic innervation of the rat amygdala. Adv. Anat. Embryol. Cell Biol. 142, 1?118. doi:10.1007/978-3-642-72085-7

Aserinsky, E., & Kleitman, N. (1953). Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science, 118*(3062), 273-274. doi: 10.1126/science.118.3062.273

Aston-Jones, G., & Bloom, F. E. (1981). Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *J Neurosci, 1*(8), 876-886. doi: 10.1523/JNEUROSCI.01-08-00876.1981

Bartlett, F.C. (1932). Remembering: A Study in Experimental and Social Psychology (CambridgeUniversityPress).http://nwkpsych.rutgers.edu/~jose/courses/578_mem_learn/2012/readings/Bartlett_1932.pdf

Bast, T., da Silva, B. M., & Morris, R. G. (2005). Distinct contributions of hippocampal NMDA and AMPA receptors to encoding and retrieval of one-trial place memory. *J Neurosci, 25*(25), 5845-5856. doi: 10.1523/JNEUROSCI.0698-05.2005

Battaglia, F. P., Benchenane, K., Sirota, A., Pennartz, C. M., & Wiener, S. I. (2011). The hippocampus: hub of brain network communication for memory. *Trends Cogn Sci, 15*(7), 310-318. doi: 10.1016/j.tics.2011.05.008

Bear, M. F., & Malenka, R. C. (1994). Synaptic plasticity: LTP and LTD. *Curr Opin Neurobiol, 4*(3), 389-399. DOI: 10.1016/0959-4388(94)90101-5

Beaulieu, J. M., & Gainetdinov, R. R. (2011). The physiology, signaling, and pharmacology of dopamine receptors. Pharmacol Rev, 63(1), 182-217. doi: 10.1124/pr.110.002642

Behrens, C. J., van den Boom, L. P., de Hoz, L., Friedman, A., & Heinemann, U. (2005). Induction of sharp wave-ripple complexes in vitro and reorganization of hippocampal networks. *Nat Neurosci, 8*(11), 1560-1567. doi: 10.1038/nn1571

Bergmann, T. O., Molle, M., Diedrichs, J., Born, J., & Siebner, H. R. (2012). Sleep spindle-related reactivation of category-specific cortical regions after learning face-scene associations. *Neuroimage, 59*(3), 2733-2742. doi: 10.1016/j.neuroimage.2011.10.036

Bernabeu, R., Bevilaqua, L., Ardenghi, P., Bromberg, E., Schmitz, P., Bianchin, M., . . . Medina, J. H. (1997). Involvement of hippocampal cAMP/cAMP-dependent protein kinase signaling pathways in a late memory consolidation phase of aversively motivated learning in rats. *Proc Natl Acad Sci U S A, 94*(13), 7041-7046. doi: 10.1073/pnas.94.13.7041

Bernardi, G., Siclari, F., Handjaras, G., Riedner, B. A., & Tononi, G. (2018). Local and Widespread Slow Waves in Stable NREM Sleep: Evidence for Distinct Regulation Mechanisms. *Front Hum Neurosci, 12*, 248. doi: 10.3389/fnhum.2018.00248

Bethus, I., Tse, D., & Morris, R. G. (2010). Dopamine and memory: modulation of the persistence of memory for novel hippocampal NMDA receptor-dependent paired associates. *J Neurosci, 30*(5), 1610-1618. doi: 10.1523/JNEUROSCI.2721-09.2010

Bialleck, K. A., Schaal, H. P., Kranz, T. A., Fell, J., Elger, C. E., & Axmacher, N. (2011). Ventromedial prefrontal cortex activation is associated with memory formation for predictable rewards. *PLoS One, 6*(2), e16695. doi: 10.1371/journal.pone.0016695

Bjorklund, A., & Dunnett, S. B. (2007). Dopamine neuron systems in the brain: an update. *Trends Neurosci, 30*(5), 194-202. doi: 10.1016/j.tins.2007.03.006

Bliss, T. V., & Collingridge, G. L. (1993). A synaptic model of memory: long-term potentiation in the hippocampus. *Nature, 361*(6407), 31-39. doi: 10.1038/361031a0

Bliss, T. V., & Lomo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol, 232*(2), 331-356. doi: 10.1113/jphysiol.1973.sp010273

Borgdorff, A. J., & Choquet, D. (2002). Regulation of AMPA receptor lateral movements. *Nature, 417*(6889), 649-653. doi: 10.1038/nature00780

Born, J., & Fehm, H. L. (1998). Hypothalamus-pituitary-adrenal activity during human sleep: a coordinating role for the limbic hippocampal system. *Exp Clin Endocrinol Diabetes, 106*(3), 153-163. doi: 10.1055/s-0029-1211969

Born, J., & Feld, G. B. (2012). Sleep to upscale, sleep to downscale: balancing homeostasis and plasticity. *Neuron, 75*(6), 933-935. doi: 10.1016/j.neuron.2012.09.007

Born, J., Lange, T., Hansen, K., Molle, M., & Fehm, H. L. (1997). Effects of sleep and circadian rhythm on human circulating immune cells. *J Immunol, 158*(9), 4454-4464.

Born, J., Rasch, B., & Gais, S. (2006). Sleep to remember. *Neuroscientist, 12*(5), 410-424. doi: 10.1177/1073858406292647

Bourtchouladze, R., Abel, T., Berman, N., Gordon, R., Lapidus, K., & Kandel, E. R. (1998). Different training procedures recruit either one or two critical periods for contextual memory consolidation, each of which requires protein synthesis and PKA. *Learn Mem, 5*(4-5), 365-374. doi:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC311273/

Bromberg-Martin, E. S., Hikosaka, O., & Nakamura, K. (2010). Coding of task reward value in the dorsal raphe nucleus. *J Neurosci, 30*(18), 6262-6272. doi: 10.1523/JNEUROSCI.0015-10.2010

Brown, R. E., Basheer, R., McKenna, J. T., Strecker, R. E., & McCarley, R. W. (2012). Control of sleep and wakefulness. *Physiol Rev, 92*(3), 1087-1187. doi: 10.1152/physrev.00032.2011

Buzsaki, G. (1998). Memory consolidation during sleep: a neurophysiological perspective. *J Sleep Res, 7 Suppl 1*, 17-23. doi: 10.1046/j.1365-2869.7.s1.3.x

Carlsson, A. (1987). Perspectives on the discovery of central monoaminergic neurotransmission. *Annu Rev Neurosci, 10*, 19-40. doi: 10.1146/annurev.ne.10.030187.000315

Carskadon, M. A., & Dement, W. C. . (2011). Normal human sleep: an overview. . *In M. H. Kryger, T. Roth & W. C. Dement (Eds.), Principles and practice of sleep medicine (5th ed., pp. 116-126). St. Louis, MI: Elsevier Saunders.* https://www.elsevier.com/books/principles-and-practice-of-sleep-medicine/kryger/978-1-4160-6645-3

Chauvette, S., Seigneur, J., & Timofeev, I. (2012). Sleep oscillations in the thalamocortical system induce long-term neuronal plasticity. *Neuron, 75*(6), 1105-1113. doi: 10.1016/j.neuron.2012.08.034

Chen, H. H., Liao, P. F., & Chan, M. H. (2011). mGluR5 positive modulators both potentiate activation and restore inhibition in NMDA receptors by PKC dependent pathway. *J Biomed Sci, 18*, 19. doi: 10.1186/1423-0127-18-19

Chevaleyre, V., & Castillo, P. E. (2004). Endocannabinoid-mediated metaplasticity in the hippocampus. *Neuron, 43*(6), 871-881. doi: 10.1016/j.neuron.2004.08.036

Chinta, S. J., & Andersen, J. K. (2005). Dopaminergic neurons. *Int J Biochem Cell Biol, 37*(5), 942-946. doi: 10.1016/j.biocel.2004.09.009

Chowdhury, R., Guitart-Masip, M., Bunzeck, N., Dolan, R. J., & Duzel, E. (2012). Dopamine modulates episodic memory persistence in old age. *J Neurosci, 32*(41), 14193-14204. doi: 10.1523/JNEUROSCI.1278-12.2012

Cirelli, C. (2017). Sleep, synaptic homeostasis and neuronal firing rates. *Curr Opin Neurobiol, 44*, 72-79. doi: 10.1016/j.conb.2017.03.016

Cirelli, C., & Tononi, G. (2008). Is sleep essential? *PLoS Biol, 6*(8), e216. doi: 10.1371/journal.pbio.0060216

Citri, A., & Malenka, R. C. (2008). Synaptic plasticity: multiple forms, functions, and mechanisms. *Neuropsychopharmacology, 33*(1), 18-41. doi: 10.1038/sj.npp.1301559

Clausen, B., Schachtman, T. R., Mark, L. T., Reinholdt, M., & Christoffersen, G. R. (2011). Impairments of exploration and memory after systemic or prelimbic D1-receptor antagonism in rats. *Behav Brain Res, 223*(2), 241-254. doi: 10.1016/j.bbr.2011.03.069

Collingridge, G. (1987). Synaptic plasticity. The role of NMDA receptors in learning and memory. *Nature, 330*(6149), 604-605. doi: 10.1038/330604a0

Collingridge, G. L., Olsen, R. W., Peters, J., & Spedding, M. (2009). A nomenclature for ligand-gated ion channels. *Neuropharmacology, 56*(1), 2-5. doi: 10.1016/j.neuropharm.2008.06.063

Collingridge, G. L., Peineau, S., Howland, J. G., & Wang, Y. T. (2010). Long-term depression in the CNS. *Nat Rev Neurosci, 11*(7), 459-473. doi: 10.1038/nrn2867

Cooper, A. J., & Stanford, I. M. (2001). Dopamine D2 receptor mediated presynaptic inhibition of striatopallidal GABA(A) IPSCs in vitro. *Neuropharmacology, 41*(1), 62-71. doi: 10.1016/s0028-3908(01)00038-7

Corkin, S. (2002). What's new with the amnesic patient H.M.? *Nat Rev Neurosci, 3*(2), 153-160. doi: 10.1038/nrn726

Csicsvari, J., Hirase, H., Czurko, A., Mamiya, A., & Buzsaki, G. (1999). Fast network oscillations in the hippocampal CA1 region of the behaving rat. *J Neurosci, 19*(16), RC20. doi: 10.1523/JNEUROSCI.19-16-j0001.1999

Cummings, J. A., Mulkey, R. M., Nicoll, R. A., & Malenka, R. C. (1996). Ca2+ signaling requirements for long-term depression in the hippocampus. *Neuron, 16*(4), 825-833. doi: 10.1016/s0896-6273(00)80102-6

Dang-Vu, T. T., Schabus, M., Desseilles, M., Albouy, G., Boly, M., Darsaud, A., . . . Maquet, P. (2008). Spontaneous neural activity during human slow wave sleep. *Proc Natl Acad Sci U S A, 105*(39), 15160-15165. doi: 10.1073/pnas.0801819105

Darby, K. P., & Sloutsky, V. M. (2015). The cost of learning: interference effects in memory development. *J Exp Psychol Gen, 144*(2), 410-431. doi: 10.1037/xge0000051

Dash, M. B., Douglas, C. L., Vyazovskiy, V. V., Cirelli, C., & Tononi, G. (2009). Long-term homeostasis of extracellular glutamate in the rat cerebral cortex across sleep and waking states. *J Neurosci, 29*(3), 620-629. doi: 10.1523/JNEUROSCI.5486-08.2009

de Quervain, D. J., Roozendaal, B., Nitsch, R. M., McGaugh, J. L., & Hock, C. (2000). Acute cortisone administration impairs retrieval of long-term declarative memory in humans. *Nat Neurosci, 3*(4), 313-314. doi: 10.1038/73873

Diekelmann, S., & Born, J. (2010). The memory function of sleep. *Nat Rev Neurosci, 11*(2), 114-126. doi: 10.1038/nrn2762

Diekelmann, S., Born, J., & Wagner, U. (2010). Sleep enhances false memories depending on general memory performance. *Behav Brain Res, 208*(2), 425-429. doi: 10.1016/j.bbr.2009.12.021

Diekelmann, S., Wilhelm, I., Wagner, U., & Born, J. (2013). Sleep to implement an intention. *Sleep, 36*(1), 149-153. doi: 10.5665/sleep.2322

Dingledine, R., Borges, K., Bowie, D., & Traynelis, S. F. (1999). The glutamate receptor ion channels. *Pharmacol Rev, 51*(1), 7-61. http://pharmrev.aspetjournals.org/content/51/1/7

Duclos, C., Beauregard, M. P., Bottari, C., Ouellet, M. C., & Gosselin, N. (2015). The impact of poor sleep on cognition and activities of daily living after traumatic brain injury: a review. *Aust Occup Ther J, 62*(1), 2-12. doi: 10.1111/1440-1630.12164

Dudai, Y. (2004). The neurobiology of consolidations, or, how stable is the engram? *Annu Rev Psychol, 55*, 51-86. doi: 10.1146/annurev.psych.55.090902.142050

Dudai, Y. (2012). The restless engram: consolidations never end. *Annu Rev Neurosci, 35*, 227-247. doi: 10.1146/annurev-neuro-062111-150500

Durmer, J. S., & Dinges, D. F. (2005). Neurocognitive consequences of sleep deprivation. *Semin Neurol, 25*(1), 117-129. doi: 10.1055/s-2005-867080

Duszkiewicz, A. J., McNamara, C. G., Takeuchi, T., & Genzel, L. (2019). Novelty and Dopaminergic Modulation of Memory Persistence: A Tale of Two Systems. *Trends Neurosci, 42*(2), 102-114. doi: 10.1016/j.tins.2018.10.002

Duzel, E., Bunzeck, N., Guitart-Masip, M., & Duzel, S. (2010). NOvelty-related motivation of anticipation and exploration by dopamine (NOMAD): implications for healthy aging. *Neurosci Biobehav Rev, 34*(5), 660-669. doi: 10.1016/j.neubiorev.2009.08.006

Dzirasa, K., Ribeiro, S., Costa, R., Santos, L. M., Lin, S. C., Grosmark, A., . . . Nicolelis, M. A. (2006). Dopaminergic control of sleep-wake states. *J Neurosci, 26*(41), 10577-10589. doi: 10.1523/JNEUROSCI.1767-06.2006

Ebbinghaus, M. (1885). Über das Gedächtnis. Leipzig: K. Buehler

Ekstrand, B. R. (1967). Effect of sleep on memory. *J Exp Psychol, 75*(1), 64-72. doi: 10.1037/h0024907

Ellenbogen, J. M., Hulbert, J. C., Jiang, Y., & Stickgold, R. (2009). The sleeping brain's influence on verbal memory: boosting resistance to interference. *PLoS One, 4*(1), e4117. doi: 10.1371/journal.pone.0004117

Ellenbogen, J. M., Payne, J. D., & Stickgold, R. (2006). The role of sleep in declarative memory consolidation: passive, permissive, active or none? *Curr Opin Neurobiol, 16*(6), 716-722. doi: 10.1016/j.conb.2006.10.006

Eschenko, O., Magri, C., Panzeri, S., & Sara, S. J. (2012). Noradrenergic neurons of the locus coeruleus are phase locked to cortical up-down states during sleep. *Cereb Cortex, 22*(2), 426-435. doi: 10.1093/cercor/bhr121

Espinosa, F., & Kavalali, E. T. (2009). NMDA receptor activation by spontaneous glutamatergic neurotransmission. *J Neurophysiol, 101*(5), 2290-2296. doi: 10.1152/jn.90754.2008

Esser, S. K., Hill, S. L., & Tononi, G. (2007). Sleep homeostasis and cortical synchronization: I. Modeling the effects of synaptic strength on sleep slow waves. *Sleep, 30*(12), 1617-1630. doi: 10.1093/sleep/30.12.1617

Fallon, J.H., Loughlin, S.E. (1995). Substantia nigra. In: Paxinos, G. (Ed.), The Rat Nervous System. *Academic Press, San Diego, CA., second ed.* doi: https://trove.nla.gov.au/work/7543011?q&versionId=46509888

Feenstra, M. G., Botterblom, M. H., & Mastenbroek, S. (2000). Dopamine and noradrenaline efflux in the prefrontal cortex in the light and dark period: effects of novelty and handling and comparison to the nucleus accumbens. *Neuroscience, 100*(4), 741-748. doi: 10.1016/s0306-4522(00)00319-5

Feld, G. B., Besedovsky, L., Kaida, K., Munte, T. F., & Born, J. (2014). Dopamine D2-like receptor activation wipes out preferential consolidation of high over low reward memories during human sleep. *J Cogn Neurosci, 26*(10), 2310-2320. doi: 10.1162/jocn_a_00629

Feld G. B. , Born, J. (2012). Sleep EEG Rhythms and System Consolidation of Memory. *Sleep and Brain Activity*, 187-226. doi: http://dx.doi.org/10.1016/B978-0-12-384995-3.00009-5

Feld, G. B., & Diekelmann, S. (2015). Sleep smart-optimizing sleep for declarative learning and memory. *Front Psychol, 6*, 622. doi: 10.3389/fpsyg.2015.00622

Feld, G. B., Lange, T., Gais, S., & Born, J. (2013). Sleep-dependent declarative memory consolidation--unaffected after blocking NMDA or AMPA receptors but enhanced by NMDA coagonist D-cycloserine. *Neuropsychopharmacology, 38*(13), 2688-2697. doi: 10.1038/npp.2013.179

Fischer, S., & Born, J. (2009). Anticipated reward enhances offline learning during sleep. *J Exp Psychol Learn Mem Cogn, 35*(6), 1586-1593. doi: 10.1037/a0017256

Frankland, P. W., & Bontempi, B. (2005). The organization of recent and remote memories. *Nat Rev Neurosci, 6*(2), 119-130. doi: 10.1038/nrn1607

Frey, U., Huang, Y. Y., & Kandel, E. R. (1993). Effects of cAMP simulate a late stage of LTP in hippocampal CA1 neurons. *Science, 260*(5114), 1661-1664. doi: 10.1126/science.8389057

Fujii, S., Saito, K., Miyakawa, H., Ito, K., & Kato, H. (1991). Reversal of long-term potentiation (depotentiation) induced by tetanus stimulation of the input to CA1 neurons of guinea pig hippocampal slices. *Brain Res, 555*(1), 112-122. doi: 10.1016/0006-8993(91)90867-u

Gagnon, J. F., Bedard, M. A., Fantini, M. L., Petit, D., Panisset, M., Rompre, S., . . . Montplaisir, J. (2002). REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. *Neurology, 59*(4), 585-589. doi: 10.1212/wnl.59.4.585

Gais, S., Plihal, W., Wagner, U., & Born, J. (2000). Early sleep triggers memory for early visual discrimination skills. *Nat Neurosci, 3*(12), 1335-1339. doi: 10.1038/81881

Gais, S., Rasch, B., Wagner, U., & Born, J. (2008). Visual-procedural memory consolidation during sleep blocked by glutamatergic receptor antagonists. *J Neurosci, 28*(21), 5513-5518. doi: 10.1523/JNEUROSCI.5374-07.2008

Gasbarri, A., Sulli, A., & Packard, M. G. (1997). The dopaminergic mesencephalic projections to the hippocampal formation in the rat. *Prog Neuropsychopharmacol Biol Psychiatry, 21*(1), 1-22. doi: 10.1016/s0278-5846(96)00157-1

Gasbarri, A., Verney, C., Innocenzi, R., Campana, E., & Pacitti, C. (1994). Mesolimbic dopaminergic neurons innervating the hippocampal formation in the rat: a combined retrograde tracing and immunohistochemical study. *Brain Res, 668*(1-2), 71-79. doi: 10.1016/0006-8993(94)90512-6

Genzel, L., Kiefer, T., Renner, L., Wehrle, R., Kluge, M., Grozinger, M., . . . Dresler, M. (2012). Sex and modulatory menstrual cycle effects on sleep related memory consolidation. *Psychoneuroendocrinology, 37*(7), 987-998. doi: 10.1016/j.psyneuen.2011.11.006

Genzel, L., Kroes, M. C., Dresler, M., & Battaglia, F. P. (2014). Light sleep versus slow wave sleep in memory consolidation: a question of global versus local processes? *Trends Neurosci, 37*(1), 10-19. doi: 10.1016/j.tins.2013.10.002

Gore, A. C. (1998). Diurnal rhythmicity of gonadotropin-releasing hormone gene expression in the rat. *Neuroendocrinology, 68*(4), 257-263. doi: 10.1159/000054373

Grace, A. A. (1991). Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience, 41*(1), 1-24. doi: 10.1016/0306-4522(91)90196-u

Grace, A. A., Floresco, S. B., Goto, Y., & Lodge, D. J. (2007). Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. *Trends Neurosci, 30*(5), 220-227. doi: 10.1016/j.tins.2007.03.003

Greenwood, T. A., Schork, N. J., Eskin, E., & Kelsoe, J. R. (2006). Identification of additional variants within the human dopamine transporter gene provides further evidence for

an association with bipolar disorder in two independent samples. *Mol Psychiatry, 11*(2), 125-133, 115. doi: 10.1038/sj.mp.4001764

Gurden, H., Takita, M., & Jay, T. M. (2000). Essential role of D1 but not D2 receptors in the NMDA receptor-dependent long-term potentiation at hippocampal-prefrontal cortex synapses in vivo. *J Neurosci, 20*(22), RC106.

Hansen, N., & Manahan-Vaughan, D. (2014). Dopamine D1/D5 receptors mediate informational saliency that promotes persistent hippocampal long-term plasticity. *Cereb Cortex, 24*(4), 845-858. doi: 10.1093/cercor/bhs362

Hardt, O., Nader, K., & Nadel, L. (2013). Decay happens: the role of active forgetting in memory. *Trends Cogn Sci, 17*(3), 111-120. doi: 10.1016/j.tics.2013.01.001

Harley, C. (1991). Noradrenergic and locus coeruleus modulation of the perforant path-evoked potential in rat dentate gyrus supports a role for the locus coeruleus in attentional and memorial processes. *Prog Brain Res, 88*, 307-321. doi: 10.1016/s0079-6123(08)63818-2

Hebb, D. O. (1949). The Organisation of Behaviour. . *New York, NY: John Wiley & Sons.* doi: http://s-f-walker.org.uk/pubsebooks/pdfs/The_Organization_of_Behavior-Donald_O._Hebb.pdf

Henley, J. M., & Wilkinson, K. A. (2013). AMPA receptor trafficking and the mechanisms underlying synaptic plasticity and cognitive aging. *Dialogues Clin Neurosci, 15*(1), 11-27. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3622464/

Hennies, N., Lewis, P. A., Durrant, S. J., Cousins, J. N., & Ralph, M. A. (2014). Time- but not sleep-dependent consolidation promotes the emergence of cross-modal conceptual representations. Neuropsychologia, 63, 116-123. doi: 10.1016/j.neuropsychologia.2014.08.021

Heresco-Levy, U., Gelfin, G., Bloch, B., Levin, R., Edelman, S., Javitt, D. C., & Kremer, I. (2013). A randomized add-on trial of high-dose D-cycloserine for treatment-resistant depression. *Int J Neuropsychopharmacol, 16*(3), 501-506. doi: 10.1017/S1461145712000910

Hill, S., & Tononi, G. (2005). Modeling sleep and wakefulness in the thalamocortical system. *J Neurophysiol, 93*(3), 1671-1698. doi: 10.1152/jn.00915.2004

Hofmann, S. G., Sawyer, A. T., & Asnaani, A. (2012). D-cycloserine as an augmentation strategy for cognitive behavioral therapy for anxiety disorders: an update. *Curr Pharm Des, 18*(35), 5659-5662. doi: 10.2174/138161212803530916

Hofmann, S. G., Smits, J. A., Rosenfield, D., Simon, N., Otto, M. W., Meuret, A. E., . . . Pollack, M. H. (2013). D-Cycloserine as an augmentation strategy with cognitive-behavioral therapy for social anxiety disorder. *Am J Psychiatry, 170*(7), 751-758. doi: 10.1176/appi.ajp.2013.12070974

Holst, S. C., & Landolt, H. P. (2018). Sleep-Wake Neurochemistry. *Sleep Med Clin, 13*(2), 137-146. doi: 10.1016/j.jsmc.2018.03.002

Hsieh, H., Boehm, J., Sato, C., Iwatsubo, T., Tomita, T., Sisodia, S., & Malinow, R. (2006). AMPAR removal underlies Abeta-induced synaptic depression and dendritic spine loss. *Neuron, 52*(5), 831-843. doi: 10.1016/j.neuron.2006.10.035

Hu, X. T., & White, F. J. (1997). Dopamine enhances glutamate-induced excitation of rat striatal neurons by cooperative activation of D1 and D2 class receptors. *Neurosci Lett, 224*(1), 61-65. doi: 10.1016/s0304-3940(97)13443-7

Huber, R., Esser, S. K., Ferrarelli, F., Massimini, M., Peterson, M. J., & Tononi, G. (2007). TMS-induced cortical potentiation during wakefulness locally increases slow wave activity during sleep. *PLoS One, 2*(3), e276. doi: 10.1371/journal.pone.0000276

Huber, R., Ghilardi, M. F., Massimini, M., & Tononi, G. (2004). Local sleep and learning. *Nature, 430*(6995), 78-81. doi: 10.1038/nature02663

Huber, R., Maatta, S., Esser, S. K., Sarasso, S., Ferrarelli, F., Watson, A., . . . Tononi, G. (2008). Measures of cortical plasticity after transcranial paired associative stimulation

predict changes in electroencephalogram slow-wave activity during subsequent sleep. *J Neurosci, 28*(31), 7911-7918. doi: 10.1523/JNEUROSCI.1636-08.2008

Igloi, K., Gaggioni, G., Sterpenich, V., & Schwartz, S. (2015). A nap to recap or how reward regulates hippocampal-prefrontal memory networks during daytime sleep in humans. *Elife, 4*. doi: 10.7554/eLife.07903

Jackson, M. L., Gunzelmann, G., Whitney, P., Hinson, J. M., Belenky, G., Rabat, A., & Van Dongen, H. P. (2013). Deconstructing and reconstructing cognitive performance in sleep deprivation. *Sleep Med Rev, 17*(3), 215-225. doi: 10.1016/j.smrv.2012.06.007

Jay, T. M., Gurden, H., & Yamaguchi, T. (1998). Rapid increase in PKA activity during long-term potentiation in the hippocampal afferent fibre system to the prefrontal cortex in vivo. *Eur J Neurosci, 10*(10), 3302-3306. doi: 10.1046/j.1460-9568.1998.00389.x

Jenkins JG, Dallenbach KM. 1924.Obliviscence during sleep and waking. Am J Psychol 35: 605–612.

Ji, D., & Wilson, M. A. (2007). Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nat Neurosci, 10*(1), 100-107. doi: 10.1038/nn1825

Jones, B. E. (2005). From waking to sleeping: neuronal and chemical substrates. *Trends Pharmacol Sci, 26*(11), 578-586. doi: 10.1016/j.tips.2005.09.009

Kempadoo, K. A., Mosharov, E. V., Choi, S. J., Sulzer, D., & Kandel, E. R. (2016). Dopamine release from the locus coeruleus to the dorsal hippocampus promotes spatial learning and memory. *Proc Natl Acad Sci U S A, 113*(51), 14835-14840. doi: 10.1073/pnas.1616515114

Killgore, W. D. (2010). Effects of sleep deprivation on cognition. *Prog Brain Res, 185*, 105-129. doi: 10.1016/B978-0-444-53702-7.00007-5

Kim, J., Gulati, T., & Ganguly, K. (2019). Competing Roles of Slow Oscillations and Delta Waves in Memory Consolidation versus Forgetting. *Cell, 179*(2), 514-526 e513. doi: 10.1016/j.cell.2019.08.040

King, C., Henze, D. A., Leinekugel, X., & Buzsaki, G. (1999). Hebbian modification of a hippocampal population pattern in the rat. *J Physiol, 521 Pt 1*, 159-167. doi: 10.1111/j.1469-7793.1999.00159.x

Kleckner, N. W., & Dingledine, R. (1988). Requirement for glycine in activation of NMDA-receptors expressed in Xenopus oocytes. *Science, 241*(4867), 835-837. doi: 10.1126/science.2841759

Klinzing, J. G., Niethard, N., & Born, J. (2019). Mechanisms of systems memory consolidation during sleep. *Nat Neurosci, 22*(10), 1598-1610. doi: 10.1038/s41593-019-0467-3

Kochlamazashvili, G., Bukalo, O., Senkov, O., Salmen, B., Gerardy-Schahn, R., Engel, A. K., Dityatev, A. (2012). Restoration of synaptic plasticity and learning in young and aged NCAM-deficient mice by enhancing neurotransmission mediated by GluN2A-containing NMDA receptors. J Neurosci, 32(7), 2263-2275. doi: 10.1523/JNEUROSCI.5103-11.2012

Korol, D. L., Gold, P. E., & Scavuzzo, C. J. (2013). Use it and boost it with physical and mental activity. *Hippocampus, 23*(11), 1125-1135. doi: 10.1002/hipo.22197

Krascum, R. M., & Andrews, S. (1998). The effects of theories on children's acquisition of family-resemblance categories. *Child Dev, 69*(2), 333-346. https://srcd.onlinelibrary.wiley.com/doi/abs/10.1111/j.1467-8624.1998.tb06192.x

Kudrimoti, H. S., Barnes, C. A., & McNaughton, B. L. (1999). Reactivation of hippocampal cell assemblies: effects of behavioral state, experience, and EEG dynamics. *J Neurosci, 19*(10), 4090-4101. doi: 10.1523/JNEUROSCI.19-10-04090.1999

Kuhl, B. A., Shah, A. T., DuBrow, S., & Wagner, A. D. (2010). Resistance to forgetting associated with hippocampus-mediated reactivation during new learning. *Nat Neurosci, 13*(4), 501-506. doi: 10.1038/nn.2498

Kuriyama, K., Stickgold, R., & Walker, M. P. (2004). Sleep-dependent learning and motor-skill complexity. *Learn Mem, 11*(6), 705-713. doi: 10.1101/lm.76304

Lansink, C. S., Goltstein, P. M., Lankelma, J. V., Joosten, R. N., McNaughton, B. L., & Pennartz, C. M. (2008). Preferential reactivation of motivationally relevant information in the ventral striatum. *J Neurosci, 28*(25), 6372-6382. doi: 10.1523/JNEUROSCI.1054-08.2008

Lansink, C. S., Goltstein, P. M., Lankelma, J. V., McNaughton, B. L., & Pennartz, C. M. (2009). Hippocampus leads ventral striatum in replay of place-reward information. *PLoS Biol, 7*(8), e1000173. doi: 10.1371/journal.pbio.1000173

Lechner, H. A., Squire, L. R., & Byrne, J. H. (1999). 100 years of consolidation--remembering Muller and Pilzecker. *Learn Mem, 6*(2), 77-87. doi: 10.1101/lm.6.2.77

Lena, I., Parrot, S., Deschaux, O., Muffat-Joly, S., Sauvinet, V., Renaud, B., . . . Gottesmann, C. (2005). Variations in extracellular levels of dopamine, noradrenaline, glutamate, and aspartate across the sleep--wake cycle in the medial prefrontal cortex and nucleus accumbens of freely moving rats. *J Neurosci Res, 81*(6), 891-899. doi: 10.1002/jnr.20602

Lewis, P. A., & Durrant, S. J. (2011). Overlapping memory replay during sleep builds cognitive schemata. *Trends Cogn Sci, 15*(8), 343-351. doi: 10.1016/j.tics.2011.06.004

Lisman, J. E., & Grace, A. A. (2005). The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron, 46*(5), 703-713. doi: 10.1016/j.neuron.2005.05.002

Lisman, J., Grace, A. A., & Duzel, E. (2011). A neoHebbian framework for episodic memory; role of dopamine-dependent late LTP. *Trends Neurosci, 34*(10), 536-547. doi: 10.1016/j.tins.2011.07.006

Liu, L., Wong, T. P., Pozza, M. F., Lingenhoehl, K., Wang, Y., Sheng, M., . . . Wang, Y. T. (2004). Role of NMDA receptor subtypes in governing the direction of hippocampal synaptic plasticity. *Science, 304*(5673), 1021-1024. doi: 10.1126/science.1096615

Luppi, P. H., & Fort, P. (2019). Neuroanatomical and Neurochemical Bases of Vigilance States. *Handb Exp Pharmacol, 253*, 35-58. doi: 10.1007/164_2017_84

Lynch, G., & Baudry, M. (1984). The biochemistry of memory: a new and specific hypothesis. *Science, 224*(4653), 1057-1063. doi: 10.1126/science.6144182

Maggini C, Guazzelli M, Pieri M, Lattanzi L, Ciapparelli A, Massimetti G, Rossi G (1986). REM latency in psychiatric disorders: polygraphic study on major depression, bipolar disorder-manic, and schizophrenic disorder. *New Trends Exp Clin Psychiatry, 2:93–101*. doi: https://psycnet.apa.org/record/1988-14045-001

Maingret, N., Girardeau, G., Todorova, R., Goutierre, M., & Zugaro, M. (2016). Hippocampo-cortical coupling mediates memory consolidation during sleep. *Nat Neurosci, 19*(7), 959-964. doi: 10.1038/nn.4304

Malenka, R. C., & Nicoll, R. A. (1993). NMDA-receptor-dependent synaptic plasticity: multiple forms and mechanisms. *Trends Neurosci, 16*(12), 521-527. doi: 10.1016/0166-2236(93)90197-t

Malenka, R. C., & Nicoll, R. A. (1999). Long-term potentiation--a decade of progress? *Science, 285*(5435), 1870-1874. doi: 10.1126/science.285.5435.1870

Mander, B. A., Santhanam, S., Saletin, J. M., & Walker, M. P. (2011). Wake deterioration and sleep restoration of human learning. *Curr Biol, 21*(5), R183-184. doi: 10.1016/j.cub.2011.01.019

Marr, D. (1971). Simple memory: a theory for archicortex. *Philos Trans R Soc Lond B Biol Sci, 262*(841), 23-81. doi: 10.1098/rstb.1971.0078

Marrosu, F., Portas, C., Mascia, M. S., Casu, M. A., Fa, M., Giagheddu, M., . . . Gessa, G. L. (1995). Microdialysis measurement of cortical and hippocampal acetylcholine release during sleep-wake cycle in freely moving cats. *Brain Res, 671*(2), 329-332. doi: 10.1016/0006-8993(94)01399-3

Massimini, M., Tononi, G., & Huber, R. (2009). Slow waves, synaptic plasticity and information processing: insights from transcranial magnetic stimulation and high-

density EEG experiments. *Eur J Neurosci, 29*(9), 1761-1770. doi: 10.1111/j.1460-9568.2009.06720.x
Mather, M., & Schoeke, A. (2011). Positive outcomes enhance incidental learning for both younger and older adults. *Front Neurosci, 5*, 129. doi: 10.3389/fnins.2011.00129
Mazei-Robison, M. S., Couch, R. S., Shelton, R. C., Stein, M. A., & Blakely, R. D. (2005). Sequence variation in the human dopamine transporter gene in children with attention deficit hyperactivity disorder. *Neuropharmacology, 49*(6), 724-736. doi: 10.1016/j.neuropharm.2005.08.003
McClelland, J. L., McNaughton, B. L., & O'Reilly, R. C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol Rev, 102*(3), 419-457. doi: 10.1037/0033-295X.102.3.419
McDermott, C. M., LaHoste, G. J., Chen, C., Musto, A., Bazan, N. G., & Magee, J. C. (2003). Sleep deprivation causes behavioral, synaptic, and membrane excitability alterations in hippocampal neurons. *J Neurosci, 23*(29), 9687-9695. doi: 10.1523/JNEUROSCI.23-29-09687.2003.
McGaugh, J. L. (2000). Memory--a century of consolidation. *Science, 287*(5451), 248-251. doi: 10.1126/science.287.5451.248
McGeoch, JA. (1932). Forgetting and the law of disuse. *Psychol. , Rev. 39:352–70.*
McNamara, C. G., Tejero-Cantero, A., Trouche, S., Campo-Urriza, N., & Dupret, D. (2014). Dopaminergic neurons promote hippocampal reactivation and spatial memory persistence. *Nat Neurosci, 17*(12), 1658-1660. doi: 10.1038/nn.3843
Meldrum, B. S. (2000). Glutamate as a neurotransmitter in the brain: review of physiology and pathology. *J Nutr, 130*(4S Suppl), 1007S-1015S. doi: 10.1093/jn/130.4.1007S
Miendlarzewska, E. A., Bavelier, D., & Schwartz, S. (2016). Influence of reward motivation on human declarative memory. *Neurosci Biobehav Rev, 61*, 156-176. doi: 10.1016/j.neubiorev.2015.11.015
Migues, P. V., Liu, L., Archbold, G. E., Einarsson, E. O., Wong, J., Bonasia, K., . . . Hardt, O. (2016). Blocking Synaptic Removal of GluA2-Containing AMPA Receptors Prevents the Natural Forgetting of Long-Term Memories. *J Neurosci, 36*(12), 3481-3494. doi: 10.1523/JNEUROSCI.3333-15.2016
Milner, B. in Physiologie de l'Hippocampe (ed. Passouant, P.) 257–272 (CNRS, Paris, 1962)
Molle, M., Bergmann, T. O., Marshall, L., & Born, J. (2011). Fast and slow spindles during the sleep slow oscillation: disparate coalescence and engagement in memory processing. *Sleep, 34*(10), 1411-1421. doi: 10.5665/SLEEP.1290
Mölle, M., & Born, J. (2009). Hippocampus whispering in deep sleep to prefrontal cortex--for good memories? *Neuron, 61*(4), 496-498. doi: 10.1016/j.neuron.2009.02.002
Mölle, M., Marshall, L., Gais, S., & Born, J. (2002). Grouping of spindle activity during slow oscillations in human non-rapid eye movement sleep. *J Neurosci, 22*(24), 10941-10947. DOI: https://doi.org/10.1523/JNEUROSCI.22-24-10941.2002
Monyer, H., Burnashev, N., Laurie, D. J., Sakmann, B., & Seeburg, P. H. (1994). Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. *Neuron, 12*(3), 529-540. doi: 10.1016/0896-6273(94)90210-0
Mothet, J. P., Parent, A. T., Wolosker, H., Brady, R. O., Jr., Linden, D. J., Ferris, C. D., . . . Snyder, S. H. (2000). D-serine is an endogenous ligand for the glycine site of the N-methyl-D-aspartate receptor. *Proc Natl Acad Sci U S A, 97*(9), 4926-4931. doi: 10.1073/pnas.97.9.4926
Muller, G.E., and Pilzecker, A. (1900). Experimentelle Beitrage zur Lehre vom Gedachtnis. Z. Psychol. Z. Angew. Psychol. 1, S1–S300
Mulkey, R. M., Herron, C. E., & Malenka, R. C. (1993). An essential role for protein phosphatases in hippocampal long-term depression. *Science, 261*(5124), 1051-1055. doi: 10.1126/science.8394601

Mulkey, R. M., & Malenka, R. C. (1992). Mechanisms underlying induction of homosynaptic long-term depression in area CA1 of the hippocampus. *Neuron, 9*(5), 967-975. doi: 10.1016/0896-6273(92)90248-c

Mulligan, N. W. (2011). Conceptual implicit memory and environmental context. *Conscious Cogn, 20*(3), 737-744. doi: 10.1016/j.concog.2010.11.008

Murayama, K., & Kuhbandner, C. (2011). Money enhances memory consolidation--but only for boring material. *Cognition, 119*(1), 120-124. doi: 10.1016/j.cognition.2011.01.001

Murphy, G. L., & Allopenna, P. D. (1994). The locus of knowledge effects in concept learning. *J Exp Psychol Learn Mem Cogn, 20*(4), 904-919. doi: 10.1037//0278-7393.20.4.904

Murphy, J. M., Pagano, M. E., Nachmani, J., Sperling, P., Kane, S., & Kleinman, R. E. (1998). The relationship of school breakfast to psychosocial and academic functioning: cross-sectional and longitudinal observations in an inner-city school sample. *Arch Pediatr Adolesc Med, 152*(9), 899-907. doi: 10.1001/archpedi.152.9.899

Murre, J. M., & Dros, J. (2015). Replication and Analysis of Ebbinghaus' Forgetting Curve. *PLoS One, 10*(7), e0120644. doi: 10.1371/journal.pone.0120644

Murty, V. P., LaBar, K. S., Hamilton, D. A., & Adcock, R. A. (2011). Is all motivation good for learning? Dissociable influences of approach and avoidance motivation in declarative memory. *Learn Mem, 18*(11), 712-717. doi: 10.1101/lm.023549.111

Myers, K. M., & Davis, M. (2007). Mechanisms of fear extinction. *Mol Psychiatry, 12*(2), 120-150. doi: 10.1038/sj.mp.4001939

Nabavi, S., Kessels, H. W., Alfonso, S., Aow, J., Fox, R., & Malinow, R. (2013). Metabotropic NMDA receptor function is required for NMDA receptor-dependent long-term depression. *Proc Natl Acad Sci U S A, 110*(10), 4027-4032. doi: 10.1073/pnas.1219454110

Nicoll, R. A., Kauer, J. A., & Malenka, R. C. (1988). The current excitement in long-term potentiation. *Neuron, 1*(2), 97-103. doi: 10.1016/0896-6273(88)90193-6

Niznik, H. B., & Van Tol, H. H. (1992). Dopamine receptor genes: new tools for molecular psychiatry. *J Psychiatry Neurosci, 17*(4), 158-180. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1188440/

Norberg, M. M., Krystal, J. H., & Tolin, D. F. (2008). A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. *Biol Psychiatry, 63*(12), 1118-1126. doi: 10.1016/j.biopsych.2008.01.012

Norimoto, H., Makino, K., Gao, M., Shikano, Y., Okamoto, K., Ishikawa, T., . . . Ikegaya, Y. (2018). Hippocampal ripples down-regulate synapses. *Science, 359*(6383), 1524-1527. doi: 10.1126/science.aao0702

O'Carroll, C. M., Martin, S. J., Sandin, J., Frenguelli, B., & Morris, R. G. (2006). Dopaminergic modulation of the persistence of one-trial hippocampus-dependent memory. *Learn Mem, 13*(6), 760-769. doi: 10.1101/lm.321006

Otmakhova NA, Lisman JE (1996) D1/ D5 dopamine receptor activa-tion increases the magnitude of early long-term potentiation at CA1hippocampal synapses. J Neurosci 16:7478 –7486. https://www.ncbi.nlm.nih.gov/pubmed/8922403

Palacios-Filardo, J., & Mellor, J. R. (2019). Neuromodulation of hippocampal long-term synaptic plasticity. *Curr Opin Neurobiol, 54*, 37-43. doi: 10.1016/j.conb.2018.08.009

Pennartz, C. M., Lee, E., Verheul, J., Lipa, P., Barnes, C. A., & McNaughton, B. L. (2004). The ventral striatum in off-line processing: ensemble reactivation during sleep and modulation by hippocampal ripples. *J Neurosci, 24*(29), 6446-6456. doi: 10.1523/JNEUROSCI.0575-04.2004

Piaget, J. (1929). The Child's Conception of the World (Adams: Littlefield) https://psycnet.apa.org/record/1961-00657-000

Pin, J. P., & Duvoisin, R. (1995). The metabotropic glutamate receptors: structure and functions. *Neuropharmacology, 34*(1), 1-26. doi: 10.1016/0028-3908(94)00129-g

Plihal, W., & Born, J. (1997). Effects of early and late nocturnal sleep on declarative and procedural memory. *J Cogn Neurosci, 9*(4), 534-547. doi: 10.1162/jocn.1997.9.4.534

Plihal, W., & Born, J. (1999). Memory consolidation in human sleep depends on inhibition of glucocorticoid release. *Neuroreport, 10*(13), 2741-2747. doi: 10.1097/00001756-199909090-00009

Preston, A. R., & Eichenbaum, H. (2013). Interplay of hippocampus and prefrontal cortex in memory. Curr Biol, 23(17), R764-773. doi: 10.1016/j.cub.2013.05.041

Price, R., Salavati, B., Graff-Guerrero, A., Blumberger, D. M., Mulsant, B. H., Daskalakis, Z. J., & Rajji, T. K. (2014). Effects of antipsychotic D2 antagonists on long-term potentiation in animals and implications for human studies. *Prog Neuropsychopharmacol Biol Psychiatry, 54*, 83-91. doi: 10.1016/j.pnpbp.2014.05.001

Quintin, L., Hilaire, G., & Pujol, J. F. (1986). Variations in 3,4-dihydroxyphenylacetic acid concentration are correlated to single cell firing changes in the rat locus coeruleus. *Neuroscience, 18*(4), 889-899. doi: 10.1016/0306-4522(86)90107-7

Rasch, B., & Born, J. (2013). About sleep's role in memory. *Physiol Rev, 93*(2), 681-766. doi: 10.1152/physrev.00032.2012

Rasch, B., Buchel, C., Gais, S., & Born, J. (2007). Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science, 315*(5817), 1426-1429. doi: 10.1126/science.1138581

Rasch, B., Gais, S., & Born, J. (2009). Impaired off-line consolidation of motor memories after combined blockade of cholinergic receptors during REM sleep-rich sleep. *Neuropsychopharmacology, 34*(7), 1843-1853. doi: 10.1038/npp.2009.6

Rechtschaffen A, Kales A. (1968). A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. *Bethesda, MD: US Depart- ment of Health, Education and Welfare*. https://www.scribd.com/doc/51728449/Rechtschaffen-Kales-A-Manual-of-Standardized-Terminology-Techniques-and-Scoring-System-for-Sleep-Stages-of-Human-Subjects

Rechtschaffen, A., & Bergmann, B. M. (1995). Sleep deprivation in the rat by the disk-over-water method. *Behav Brain Res, 69*(1-2), 55-63. doi: 10.1016/0166-4328(95)00020-t

Redondo, R. L., & Morris, R. G. (2011). Making memories last: the synaptic tagging and capture hypothesis. *Nat Rev Neurosci, 12*(1), 17-30. doi: 10.1038/nrn2963

Rees, G., Russell, C., Frith, C. D., & Driver, J. (1999). Inattentional blindness versus inattentional amnesia for fixated but ignored words. *Science, 286*(5449), 2504-2507. doi: 10.1126/science.286.5449.2504

Reimund, E. (1994). The free radical flux theory of sleep. *Med Hypotheses, 43*(4), 231-233. doi: 10.1016/0306-9877(94)90071-x

Riedel, G., Micheau, J., Lam, A. G., Roloff, E. L., Martin, S. J., Bridge, H., . . . Morris, R. G. (1999). Reversible neural inactivation reveals hippocampal participation in several memory processes. *Nat Neurosci, 2*(10), 898-905. doi: 10.1038/13202

Robertson, E. M. (2009). From creation to consolidation: a novel framework for memory processing. *PLoS Biol, 7*(1), e19. doi: 10.1371/journal.pbio.1000019

Roediger, H. L., 3rd, & Marsh, E. J. (2005). The positive and negative consequences of multiple-choice testing. *J Exp Psychol Learn Mem Cogn, 31*(5), 1155-1159. doi: 10.1037/0278-7393.31.5.1155

Robbins TW, Murphy ER (2006) Behavioural pharmacology: 40C years of progress, with a focus on glutamate receptors and cognition. TIPS 27:141–148. doi:10.1016/j.tips.2006.01.009

Rosanova, M., & Ulrich, D. (2005). Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. *J Neurosci, 25*(41), 9398-9405. doi: 10.1523/JNEUROSCI.2149-05.2005

Roth, T. C., 2nd, Rattenborg, N. C., & Pravosudov, V. V. (2010). The ecological relevance of sleep: the trade-off between sleep, memory and energy conservation. *Philos Trans R Soc Lond B Biol Sci, 365*(1542), 945-959. doi: 10.1098/rstb.2009.0209

Rudoy, J. D., Voss, J. L., Westerberg, C. E., & Paller, K. A. (2009). Strengthening individual memories by reactivating them during sleep. *Science, 326*(5956), 1079. doi: 10.1126/science.1179013

Sachser, R. M., Santana, F., Crestani, A. P., Lunardi, P., Pedraza, L. K., Quillfeldt, J. A., . . . Alvares Lde, O. (2016). Forgetting of long-term memory requires activation of NMDA receptors, L-type voltage-dependent Ca2+ channels, and calcineurin. *Sci Rep, 6*, 22771. doi: 10.1038/srep22771

Saper, C. B., & Fuller, P. M. (2017). Wake-sleep circuitry: an overview. *Curr Opin Neurobiol, 44*, 186-192. doi: 10.1016/j.conb.2017.03.021

Sara, S. J. (2009). The locus coeruleus and noradrenergic modulation of cognition. *Nat Rev Neurosci, 10*(3), 211-223. doi: 10.1038/nrn2573

Sawangjit, A., Oyanedel, C. N., Niethard, N., Salazar, C., Born, J., & Inostroza, M. (2018). The hippocampus is crucial for forming non-hippocampal long-term memory during sleep. *Nature, 564*(7734), 109-113. doi: 10.1038/s41586-018-0716-8

Scatton, B., Dennis, T., & Curet, O. (1984). Increase in dopamine and DOPAC levels in noradrenergic terminals after electrical stimulation of the ascending noradrenergic pathways. *Brain Res, 298*(1), 193-196. doi: 10.1016/0006-8993(84)91169-7

Schade, S., & Paulus, W. (2016). D-Cycloserine in Neuropsychiatric Diseases: A Systematic Review. *Int J Neuropsychopharmacol, 19*(4). doi: 10.1093/ijnp/pyv102

Schoepp DD, Jane DE, Monn JA: Pharmacological agents acting at subtypes of metabotropic glutamate receptors. Neuropharmacology 1999, 38(10):1431-76. doi: 10.1016/s0028-3908(99)00092-1

Schmidt, C., Peigneux, P., Muto, V., Schenkel, M., Knoblauch, V., Munch, M., . . . Cajochen, C. (2006). Encoding difficulty promotes postlearning changes in sleep spindle activity during napping. *J Neurosci, 26*(35), 8976-8982. doi: 10.1523/JNEUROSCI.2464-06.2006

Schultz, W. (1998). Predictive reward signal of dopamine neurons. *J Neurophysiol, 80*(1), 1-27. doi: 10.1152/jn.1998.80.1.1

Schultz, W. (2000). Multiple reward signals in the brain. *Nat Rev Neurosci, 1*(3), 199-207. doi: 10.1038/35044563

Schultz, W. (2007). Multiple dopamine functions at different time courses. *Annu Rev Neurosci, 30*, 259-288. doi: 10.1146/annurev.neuro.28.061604.135722

Schultz, W. (2013). Updating dopamine reward signals. *Curr Opin Neurobiol, 23*(2), 229-238. doi: 10.1016/j.conb.2012.11.012

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry, 20*(1), 11-21. doi: 10.1136/jnnp.20.1.11

Seamans, J. K., Gorelova, N., Durstewitz, D., & Yang, C. R. (2001). Bidirectional dopamine modulation of GABAergic inhibition in prefrontal cortical pyramidal neurons. *J Neurosci, 21*(10), 3628-3638. DOI: https://doi.org/10.1523/JNEUROSCI.21-10-03628.2001

Sejnowski, T. J., & Destexhe, A. (2000). Why do we sleep? *Brain Res, 886*(1-2), 208-223. doi: 10.1016/s0006-8993(00)03007-9

Sheinin, A., Shavit, S., & Benveniste, M. (2001). Subunit specificity and mechanism of action of NMDA partial agonist D-cycloserine. *Neuropharmacology, 41*(2), 151-158. doi: 10.1016/s0028-3908(01)00073-9

Sheng, M., & Lee, S. H. (2001). AMPA receptor trafficking and the control of synaptic transmission. *Cell, 105*(7), 825-828. doi: 10.1016/s0092-8674(01)00406-8

Shimizu, H. (1996). Rehearsal strategies, test expectancy, and memory monitoring in free recall. *Memory, 4*(3), 265-287. doi: 10.1080/096582196388951

Shinohara, K., & Hata, T. (2014). [Post-training N-methyl-D-aspartate receptor blockade facilitates retention of acquired spatial memory in rats]. *Shinrigaku Kenkyu, 84*(6), 618-624. doi: 10.4992/jjpsy.84.618

Shohamy, D., & Adcock, R. A. (2010). Dopamine and adaptive memory. *Trends Cogn Sci, 14*(10), 464-472. doi: 10.1016/j.tics.2010.08.002

Siclari, F., Bernardi, G., Riedner, B. A., LaRocque, J. J., Benca, R. M., & Tononi, G. (2014). Two distinct synchronization processes in the transition to sleep: a high-density electroencephalographic study. *Sleep, 37*(10), 1621-1637. doi: 10.5665/sleep.4070

Silber, M. H., Ancoli-Israel, S., Bonnet, M. H., Chokroverty, S., Grigg-Damberger, M. M., Hirshkowitz, M., . . . Iber, C. (2007). The visual scoring of sleep in adults. *J Clin Sleep Med, 3*(2), 121-131. https://www.ncbi.nlm.nih.gov/pubmed/17557422

Skaggs, W. E., & McNaughton, B. L. (1996). Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science, 271*(5257), 1870-1873. doi: 10.1126/science.271.5257.1870

Smialowski, A., & Bijak, M. (1987). Excitatory and inhibitory action of dopamine on hippocampal neurons in vitro. Involvement of D2 and D1 receptors. *Neuroscience, 23*(1), 95-101. doi: 10.1016/0306-4522(87)90274-0

Smith, C. C., & Greene, R. W. (2012). CNS dopamine transmission mediated by noradrenergic innervation. *J Neurosci, 32*(18), 6072-6080. doi: 10.1523/JNEUROSCI.6486-11.2012

Solinas, M., Goldberg, S. R., & Piomelli, D. (2008). The endocannabinoid system in brain reward processes. *Br J Pharmacol, 154*(2), 369-383. doi: 10.1038/bjp.2008.130

Sowers, J. R., & Vlachakis, N. (1984). Circadian variation in plasma dopamine levels in man. *J Endocrinol Invest, 7*(4), 341-345. doi: 10.1007/BF03351014

Spencer, J. P., & Murphy, K. P. (2002). Activation of cyclic AMP-dependent protein kinase is required for long-term enhancement at corticostriatal synapses in rats. *Neurosci Lett, 329*(2), 217-221. doi: 10.1016/s0304-3940(02)00659-6

Squire, L. R., & Dede, A. J. (2015). Conscious and unconscious memory systems. *Cold Spring Harb Perspect Biol, 7*(3), a021667. doi: 10.1101/cshperspect.a021667

Squire, L. R., Knowlton, B., & Musen, G. (1993). The structure and organization of memory. *Annu Rev Psychol, 44*, 453-495. doi: 10.1146/annurev.ps.44.020193.002321

Squire, L. R., & Wixted, J. T. (2011). The cognitive neuroscience of human memory since H.M. *Annu Rev Neurosci, 34*, 259-288. doi: 10.1146/annurev-neuro-061010-113720

Squire, L. R., & Zola, S. M. (1996). Structure and function of declarative and nondeclarative memory systems. *Proc Natl Acad Sci U S A, 93*(24), 13515-13522. doi: 10.1073/pnas.93.24.13515

Staresina, B. P., Bergmann, T. O., Bonnefond, M., van der Meij, R., Jensen, O., Deuker, L., . . . Fell, J. (2015). Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. *Nat Neurosci, 18*(11), 1679-1686. doi: 10.1038/nn.4119

Sullivan, T. J., & de Sa, V. R. (2008). Sleeping our way to weight normalization and stable learning. *Neural Comput, 20*(12), 3111-3130. doi: 10.1162/neco.2008.04-07-502

Szpunar, K. K., McDermott, K. B., & Roediger, H. L., 3rd. (2007). Expectation of a final cumulative test enhances long-term retention. *Mem Cognit, 35*(5), 1007-1013. https://link.springer.com/article/10.3758/BF03193473

Takashima, A., Petersson, K. M., Rutters, F., Tendolkar, I., Jensen, O., Zwarts, M. J., . . . Fernandez, G. (2006). Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. *Proc Natl Acad Sci U S A, 103*(3), 756-761. doi: 10.1073/pnas.0507774103

Takeuchi, T., Duszkiewicz, A. J., Sonneborn, A., Spooner, P. A., Yamasaki, M., Watanabe, M., . . . Morris, R. G. (2016). Locus coeruleus and dopaminergic consolidation of everyday memory. *Nature, 537*(7620), 357-362. doi: 10.1038/nature19325

Thorndike, E. L. (1913). *Educational psychology: Vol. 2. The psychology of learning*. New York: Teachers College Press.
Tononi, G., & Cirelli, C. (2006). Sleep function and synaptic homeostasis. *Sleep Med Rev, 10*(1), 49-62. doi: 10.1016/j.smrv.2005.05.002
Tononi, G., & Cirelli, C. (2014). Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. *Neuron, 81*(1), 12-34. doi: 10.1016/j.neuron.2013.12.025
Tononi, G., & Cirelli, C. (2019). Sleep and synaptic down-selection. *Eur J Neurosci*. doi: 10.1111/ejn.14335
Tulving, E. (2005). “Episodic memory and autonoesis: uniquely human?” in The Missing Link in Cognition, eds H. S. Terrace, and J. Metcalfe (Oxford: Oxford University Press), 3–56. doi: https://alicekim.ca/ema.pdf
Ungless, M. A. (2004). Dopamine: the salient issue. *Trends Neurosci, 27*(12), 702-706. doi: 10.1016/j.tins.2004.10.001
Valdes, J. L., McNaughton, B. L., & Fellous, J. M. (2015). Offline reactivation of experience-dependent neuronal firing patterns in the rat ventral tegmental area. *J Neurophysiol, 114*(2), 1183-1195. doi: 10.1152/jn.00758.2014
Van Der Werf, Y. D., Altena, E., Schoonheim, M. M., Sanz-Arigita, E. J., Vis, J. C., De Rijke, W., & Van Someren, E. J. (2009). Sleep benefits subsequent hippocampal functioning. *Nat Neurosci, 12*(2), 122-123. doi: 10.1038/nn.2253
Villarreal, D. M., Do, V., Haddad, E., & Derrick, B. E. (2002). NMDA receptor antagonists sustain LTP and spatial memory: active processes mediate LTP decay. *Nat Neurosci, 5*(1), 48-52. doi: 10.1038/nn776
Vorster, A. P., & Born, J. (2015). Sleep and memory in mammals, birds and invertebrates. *Neurosci Biobehav Rev, 50*, 103-119. doi: 10.1016/j.neubiorev.2014.09.020
Vyazovskiy, V. V., Cirelli, C., Pfister-Genskow, M., Faraguna, U., & Tononi, G. (2008). Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. *Nat Neurosci, 11*(2), 200-208. doi: 10.1038/nn2035
Walker, M. P., Brakefield, T., Morgan, A., Hobson, J. A., & Stickgold, R. (2002). Practice with sleep makes perfect: sleep-dependent motor skill learning. *Neuron, 35*(1), 205-211. doi: 10.1016/s0896-6273(02)00746-8
Wang, D., Liu, T., & Shi, J. (2017). Development of Monetary and Social Reward Processes. *Sci Rep, 7*(1), 11128. doi: 10.1038/s41598-017-11558-6
Weitzman, E. D., Fukushima, D., Nogeire, C., Roffwarg, H., Gallagher, T. F., & Hellman, L. (1971). Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. *J Clin Endocrinol Metab, 33*(1), 14-22. doi: 10.1210/jcem-33-1-14
Wilhelm, I., Diekelmann, S., Molzow, I., Ayoub, A., Molle, M., & Born, J. (2011). Sleep selectively enhances memory expected to be of future relevance. *J Neurosci, 31*(5), 1563-1569. doi: 10.1523/JNEUROSCI.3575-10.2011
Wilson, M. A., & McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science, 265*(5172), 676-679. doi: 10.1126/science.8036517
Winocur, G., Moscovitch, M., & Bontempi, B. (2010). Memory formation and long-term retention in humans and animals: convergence towards a transformation account of hippocampal-neocortical interactions. *Neuropsychologia, 48*(8), 2339-2356. doi: 10.1016/j.neuropsychologia.2010.04.016
Wise, R. A. (2004). Dopamine, learning and motivation. *Nat Rev Neurosci, 5*(6), 483-494. doi: 10.1038/nrn1406
Wise, R. A. (2005). Forebrain substrates of reward and motivation. *J Comp Neurol, 493*(1), 115-121. doi: 10.1002/cne.20689
Wise, R. A., & Rompre, P. P. (1989). Brain dopamine and reward. *Annu Rev Psychol, 40*, 191-225. doi: 10.1146/annurev.ps.40.020189.001203

Wittmann, B. C., Dolan, R. J., & Duzel, E. (2011). Behavioral specifications of reward-associated long-term memory enhancement in humans. *Learn Mem, 18*(5), 296-300. doi: 10.1101/lm.1996811

Wittmann, B. C., Schiltz, K., Boehler, C. N., & Duzel, E. (2008). Mesolimbic interaction of emotional valence and reward improves memory formation. *Neuropsychologia, 46*(4), 1000-1008. doi: 10.1016/j.neuropsychologia.2007.11.020

Wittmann, B. C., Schott, B. H., Guderian, S., Frey, J. U., Heinze, H. J., & Duzel, E. (2005). Reward-related FMRI activation of dopaminergic midbrain is associated with enhanced hippocampus-dependent long-term memory formation. *Neuron, 45*(3), 459-467. doi: 10.1016/j.neuron.2005.01.010

Wixted, J. T. (2004). The psychology and neuroscience of forgetting. *Annu Rev Psychol, 55*, 235-269. doi: 10.1146/annurev.psych.55.090902.141555

Xia, S. Z., Feng, C. H., & Guo, A. K. (1998). Multiple-phase model of memory consolidation confirmed by behavioral and pharmacological analyses of operant conditioning in Drosophila. *Pharmacol Biochem Behav, 60*(4), 809-816. doi: 10.1016/s0091-3057(98)00060-4

Xu, J., Antion, M. D., Nomura, T., Kraniotis, S., Zhu, Y., & Contractor, A. (2014). Hippocampal metaplasticity is required for the formation of temporal associative memories. *J Neurosci, 34*(50), 16762-16773. doi: 10.1523/JNEUROSCI.2869-13.2014

Yamasaki, M., & Takeuchi, T. (2017). Locus Coeruleus and Dopamine-Dependent Memory Consolidation. *Neural Plast, 2017*, 8602690. doi: 10.1155/2017/8602690

Yaroush, R., Sullivan, M. J., & Ekstrand, B. R. (1971). Effect of sleep on memory. II. Differential effect of the first and second half of the night. *J Exp Psychol, 88*(3), 361-366. doi: 10.1037/h0030914

Yeragani, V. K., Tancer, M., Chokka, P., & Baker, G. B. (2010). Arvid Carlsson, and the story of dopamine. Indian J Psychiatry, 52(1), 87-88. doi: 10.4103/0019-5545.58907

Yoo, S. S., Hu, P. T., Gujar, N., Jolesz, F. A., & Walker, M. P. (2007). A deficit in the ability to form new human memories without sleep. *Nat Neurosci, 10*(3), 385-392. doi: 10.1038/nn1851

Zhu, J. J., Qin, Y., Zhao, M., Van Aelst, L., & Malinow, R. (2002). Ras and Rap control AMPA receptor trafficking during synaptic plasticity. *Cell, 110*(4), 443-455. doi: 10.1016/s0092-8674(02)00897-8

3. List of appended papers

Alizadeh Asfestani, M., Braganza, E., Schwidetzky, J., Santiago, J., Soekadar, S., Born, J., & Feld, G. B. (2018). Overnight memory consolidation facilitates rather than interferes with new learning of similar materials-a study probing NMDA receptors. Neuropsychopharmacology, 43(11), 2292-2298. doi:10.1038/s41386-018-0139-0

Alizadeh Asfestani, M., Brechtmann, V., Santiago, J. C. P., Born, J., & Feld, G. B. (2019). Consolidation of reward memory during sleep does not require dopaminergic activation.

bioRxiv. doi:10.1101/703132

4. Statement of contribution

Study I: Overnight memory consolidation facilitates rather than interferes with new learning of similar materials-a study probing NMDA receptors.

Sleep phase of study I, was designed and planned by GB. Feld and J. Born. Wake phase of study I was designed and planned by me, GB. Feld and J. Born. I conducted both of the experiments for data collection and supervised the doctoral students. I analysed the data, created the figures, and wrote the first draft of the manuscript. The manuscript was edited by G.Feld and J. Born. The data collection was done together with doctoral students Elena Braganza, Jan Schwidetzky.

This study was published as: Alizadeh Asfestani, M., Braganza, E., Schwidetzky, J., Santiago, J., Soekadar, S., Born, J., & Feld, G. B. (2018). Overnight memory consolidation facilitates rather than interferes with new learning of similar materials-a study probing NMDA receptors. Neuropsychopharmacology, 43(11), 2292-2298. doi:10.1038/s41386-018-0139-0

Study II: Consolidation of reward memory during sleep does not require dopaminergic activation.

Study II was designed and planned by G.Feld and J. Born. I supervised the doctoral student for data collection and analysed the data, created the figures, and wrote the first draft of the manuscript. The manuscript was edited by G.Feld and J. Born. The data collection was done together with doctoral student Valentin Brechtmann.

This study is submitted as: Alizadeh Asfestani, M., Brechtmann, V., Santiago, J. C. P., Born, J., & Feld, G. B. (2019). Consolidation of reward memory during sleep does not require dopaminergic activation. bioRxiv. doi:10.1101/703132

5. Study I: Overnight memory consolidation facilitates rather than interferes with new learning of similar materials - a study probing NMDA-receptors

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ARTICLE

Overnight memory consolidation facilitates rather than interferes with new learning of similar materials—a study probing NMDA receptors

M. Alizadeh Asfestani[1], E. Braganza[1], J. Schwidetzky[1], J. Santiago[1,2,3], S. Soekadar[4], J. Born[1,5] and G. B. Feld[1,6,7]

Although sleep-dependent consolidation and its neurochemical underpinnings have been strongly researched, less is known about how consolidation during sleep affects subsequent learning. Since sleep enhances memory, it can be expected to pro-actively interfere with learning after sleep, in particular of similar materials. This pro-active interference should be enhanced by substances that benefit consolidation during sleep, such as D-cycloserine. We tested this hypothesis in two groups (Sleep, Wake) of young healthy participants receiving on one occasion D-cycloserine (175 mg) and on another occasion placebo, according to a double-blind balanced crossover design. Treatment was administered after participants had learned a set of word pairs (A–B list) and before nocturnal retention periods of sleep vs. wakefulness. After D-cycloserine blood plasma levels had dropped to negligible amounts, i.e., the next day in the evening, participants learned, in three sequential runs, new sets of word pairs. One list—to enhance interference—consisted of the same cue words as the original set paired with a new target word (A–C list) and the other of completely new cue words (D–E set). Unexpectedly, during post-retention learning the A–C interference list was generally better learned than the completely new D–E list, which suggests that consolidation of previously encoded similar material enhances memory integration rather than pro-active interference. Consistent with this view, new learning of word pairs was better after sleep than wakefulness. Similarly, D-cycloserine generally enhanced learning of new word pairs, compared to placebo. This effect being independent of sleep or wakefulness, leads us to speculate that D-cycloserine, in addition to enhancing sleep-dependent consolidation, might mediate a time-dependent process of active forgetting.

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INTRODUCTION

The relationship between sleep and memory maintenance has received detailed attention in the last 20 years [1, 2] and there is widespread interest in enhancing this beneficial effect of sleep on memory [3], e.g., by enhancing neuronal oscillations [4, 5] or externally cueing replay [6, 7] i.e., processes that support sleep-dependent memory. We recently demonstrated that the *N*-methyl-D-aspartate (NMDA) receptor co-agonist D-cycloserine powerfully enhances sleep-dependent declarative memory consolidation when administered before sleep [8]. It is, however, completely unclear, how this enhancement affects the subtle balance of encoding and memory maintenance in the brain [9]. This is especially interesting as sleep has been suggested to also benefit new learning [10].

One of the first reports investigating the effect of sleep on memory was by Jenkins and Dallenbach [11], who famously hypothesized that sleep enhances memory not via an active process but by shielding it from interference, a line of argument that remains popular [12]. However, since this proposal it has been convincingly shown across species, modalities and paradigms that during sleep, memory is actively strengthened by the repeated replay of traces that were encoded during prior phases of wakefulness [6, 7, 13–15]. Intriguingly, it has also been shown that this sleep-dependent consolidations makes memory traces more robust towards retro-active interference [16], i.e., to the interfering influence of learning new information that deteriorates the original trace even if it had previously been successfully encoded [17]. When participants in this experiment learned a set of word pairs (A–B) before sleep and had to learn a retro-actively interfering set of word pairs (A–C) after sleep (but before retrieval), the effect of sleep on memory retention was enhanced. Moreover, in a study where participants encoded while exposed to the smell of roses, re-exposing them to this odor cue during sleep made the associated memory robust to retro-active interference and the same treatment during wakefulness had the opposite effect [18]. These findings pose the intriguing question whether the reduction in memories' susceptibility to retro-active interference during sleep is due to a strengthening of the original trace that would be accompanied by enhanced pro-active interference, i.e., whether new memory traces are harder to establish if they overlap with these stronger old memory traces [17]

[1]Institute of Medical Psychology and Behavioural Neurobiology, University of Tübingen, Tübingen, Germany; [2]German Center for Diabetes Research (DZD), Tübingen, Germany; [3]Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the Eberhard Karls University Tübingen, Tübingen, Germany; [4]Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany; [5]Center for Integrative Neuroscience, University of Tübingen, Tübingen, Germany; [6]Division of Psychology and Language Sciences, University College London, London, UK; [7]Present address: Department of Experimental Psychology, Division of Psychology and Language Science, Institute of Behavioural Neuroscience, University College London, 26 Bedford Way, London WC1H 0AP, UK
Correspondence: M. Alizadeh Asfestani (marjan.alizadeh-asfestani@uni-tuebingen.de) or G. B. Feld (g.feld@ucl.ac.uk)

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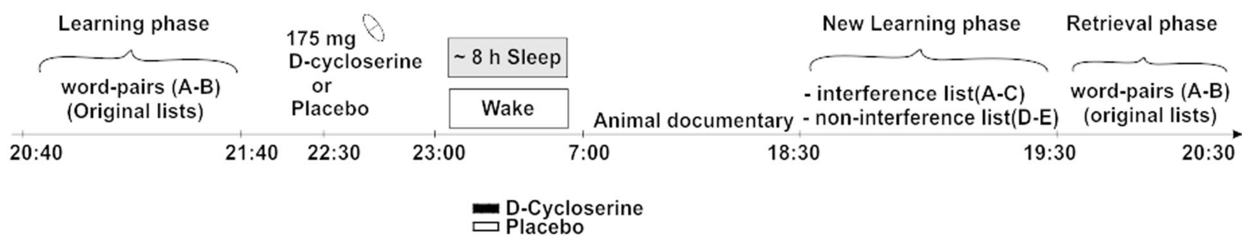
The oscillatory properties of sleep that support the consolidation process [19] are ideally suited to drive the strengthening of memory traces via long-term potentiation (LTP) [20], which occurs mainly at glutamatergic synapses and is mediated by NMDA receptors [21, 22]. Accordingly, we administered D-cycloserine, a drug that supports NMDA receptor activation by binding to its glycine-binding site [23], to participants after they learned word pairs, so that peak plasma concentration occurred during the first half of the sleep phase [8]. Enhancing NMDA receptor activation benefited the sleep-dependent consolidation specifically of the word pairs if given during sleep and thus represents the ideal model to test whether memory traces enhanced by sleep introduce detrimental pro-active interference on new learning.

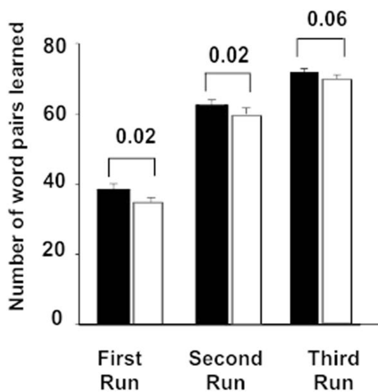
To test this we asked participants to learn a list of word pairs (A–B) and then enhanced sleep-dependent consolidation of these memories by administering D-cycloserine [8]. We expected that, when participants learned a new list of word pairs (A–C) the next evening (i.e., after twice the drug half-life), performance would be reduced under treatment compared to placebo due to enhanced pro-active interference of the more strongly consolidated memory. To specify whether this effect depends on the item specificity of pro-active interference, participants also learned new word pairs that did not overlap with the original list (D–E) and we expected that performance on this list would not be affected by treatment. We also tested a group of participants that did not sleep during the retention interval to test our hypothesis that these effects are mediated by processes active only during sleep.

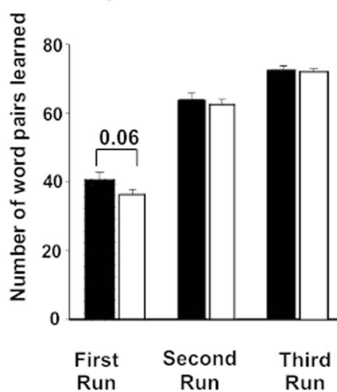
METHODS

Participants

Fifty-one participants completed the study in the sleep ($n = 30$) and the Wake ($n = 21$) conditions. Participants were healthy, non-smoking, native German speaking men, age range between 18 and 30 years old, with a body mass index between 19 and 26 kg/m^2. This narrow range of inclusion criteria was chosen to test our hypothesis in a homogenous sample thereby limiting the amount of noise from variables of non-interest. Before starting the study a routine medical examination was performed for all the participants to exclude any psychiatric, neurological or endocrine diseases, participants who took regular medication were also excluded. The medical screening relied on a structured interview asking for current or past diagnosed conditions, a physical examination as well as a blood pressure and blood-screening test (white cells, red cells, hemoglobin, sodium, potassium, calcium, chloride, glucose, bilirubin, alanine transaminase, alkaline phosphatase, gamma-glutamyltransferase, C-reactive protein, prothrombin time, partial thromboplastin time) and only healthy participants were included. Participants were pre-screened via telephone making sure they did not take any acute medication at the time of the experiments and that they reported a normal sleep–wake cycle, no shift work, night work or intercontinental flights (>4 h time difference) for at least 6 weeks before the experiments. They were instructed to keep a steady sleep schedule in the week before the experiment (approximately sleeping from 23:00 to 07:00 each night), to go to bed at 23:00 the night before experiments, to get up at 07:00 on experimental days and, during these days, not to take any naps, no caffeine-containing drinks after 13:00 and also not to consume alcohol starting one day before the experimental nights. Adherence to these rules was assessed with a questionnaire at the very beginning of each experimental condition and experiments were aborted and rescheduled, if gross deviation from this plan was found. This questionnaire also asked about acute medication and drug use as well as stressful events. Before the sleep experiment, participants took part in an adaptation night under conditions of







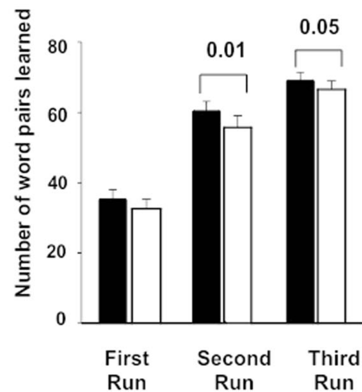


Fig. 1 **a** Participants first learned 80 word pairs (A–B) up to a criterion of 60%, by a repeated cued recall procedure (see Methods section for details). Afterwards at ~22:30, they took 175 mg D-cycloserine or placebo. At 23:00 the participants in the Sleep group went to bed and polysomnographic recording was performed, whereas the Wake participants watched documentaries about planets. All participants received breakfast at 07:45 and watched animal documentaries until 18:00. Afterwards, at 18:30, the participants learned 80 new word pairs in three consecutive runs and finally retrieved the original 80 word pairs. **b** Mean and standard error of the mean (SEM) of the amount of correctly recalled word pairs in total, **c** in the Sleep experiment, and **d** in the Wake experiment during the three runs of the New Learning phase are shown

the experiment, which included the placement of electrodes for polysomnographic recordings. The experiments were approved by the ethics committee of the University of Tübingen. We obtained written informed consent from all participants before their participation.

Design and procedures

The experiments followed a double-blind, placebo-controlled, within-subject crossover design, with Sleep vs. Wake between-subjects groups. Within each group, participants took part in two identical experimental sessions with the exception of administration of D-cycloserine or placebo (D-cycloserine: Cycloserine Capsules®, 175 mg, the Chao Center for Industrial Pharmacy & Contract Manufacturing, USA, plasma halftime: 10 h, plasma maximum: 1–2 h; Fig. 1 summarizes study design). The dose of D-cycloserine was chosen to be the same as in our previous study [8], which effectively enhanced sleep-dependent consolidation of word pairs. D-cycloserine was applied at 22:30, i.e., 30 min before lights off in the Sleep group. This timing was chosen to maximize drug levels during the slow wave sleep rich first half of the night, which has been shown to be beneficial for the consolidation of word pairs. New learning of word pairs was scheduled the next evening, i.e., as late as possible without adding an additional night of sleep, in an attempt to minimize direct effects of the drug. The two experimental sessions were scheduled at least 14 days apart.

Participants arrived at 20:00 for each experimental night and first filled out questionnaires. In the Sleep group, polysomnography was prepared by applying electrodes. In the Wake group no polysomnography was assessed. Next, they learned the first set of declarative word pairs (original word pairs) between 20:40 and 21:40. Participants were informed that the word pairs would be recalled immediately and also the next evening, as well as, that they would learn new word pairs during the next evening. This was done to match expectations on the first session to those on the second session, where these essential procedures would be known by the participant. After learning they filled in questionnaires measuring mood and sleepiness and performed a reaction time task to measure vigilance (psychomotor vigilance task). At 22:30, Participants received the medication (D-cycloserine or placebo). At 23:00, the electrodes were connected to the amplifiers and lights were turned off, in the Sleep group. The Wake group watched astronomy documentaries while sitting in a comfy chair (two counterbalanced lists of films, one for each session) in the lab during this time and were monitored by the investigator through cameras at all times, who prevented them falling asleep unintentionally. Approximately every 1.5 h, participants took a short walk together with the investigator to enhance wakefulness. After ~8 h (between 06:45 and 07:15), the Sleep group was woken up (if possible from sleep stage 1 or 2). All participants first answered questionnaires measuring their mood and sleepiness and, afterwards, received a standardized breakfast and the Sleep group was allowed to shower to clean the electrode gel off their head. During the day, participants followed a tight protocol watching animal documentaries (two counterbalanced lists of films, one for each session) for ~1½ h at a time (two episodes), where the investigator checked in on them every 15 min to ensure wakefulness. Each of these episodes was followed by a break to take a walk around the campus and participants received two snacks in the afternoons. This was done for 10 h only interrupted by lunch at the local canteen together with the investigator. This protocol was chosen to standardize the experience of the participants after drug application and to minimize the opportunity of newly encoding written words. This strategy included that participants were not allowed to use their mobile devices and the internet or read books and magazines during the experiment. Please note, however, that we cannot completely exclude that participants encoded new words. We chose not to completely deprive the participants from all sensory input, which would have minimized these opportunities even more, as it would have been nearly impossible to keep them awake at the same time. At 18:30, participants learned new word pairs and immediately recalled them. Next they recalled original word pairs they learned the day before. Finally, we again measured mood, sleepiness, and vigilance, as well as, word generation.

Word-pair tasks

Consolidation was measured using 80 slightly associated word pairs (A–B list, e.g., Democracy–System) in two lists (original lists). The word pairs were presented on a computer screen for 4 s each with a 1 s inter-stimulus interval (ISI). After presenting both lists, the participant's memory was tested in a cued recall procedure by presenting only the first word and asking the participant to produce the associated word. This was done for each list individually. If the participant did not reach the criterion of 60% correct responses on one (or both) of the lists, only this list (or both lists) was presented again completely (3 s per pair) and cued recall was repeated. This was done until he reached the criterion. The amount of word pairs recalled during the last cued recall was used as measure of learning performance. The cued recall procedure as described above was performed again at the very end of the Retrieval phase (after the New Learning phase—see below). This was done, so that the participants formed the intention to retain the word pairs across each of the two sessions, which may have been undercut, if delayed retrieval did not take place in the first session. The intention to retain word pairs has previously been shown to be an essential factor driving sleep-dependent memory consolidation [24]. Data from this retrieval were not analyzed as they are confounded by the prior new learning.

During the next evening, participants were presented a new set of 80 word pairs in two separate lists. One list with 40 word pairs (A–C list, Democracy–Equality) interfered with the original list, i.e., they contained a new sec word (C) paired with a cue word (A) of the original list (interference list), the other also consisting of 40 word pairs (D–E list, e.g., Painter–Pianist) was completely new (no-interference list). These two word-pair lists were also learned back to back in a balanced order and each pair was shown for 4 s (1 s ISI). The cued recall procedure described above was performed three times (run 1–run 3) and after runs 1 and 2 the word pairs were shown again for 3 s each. Note that we constructed six pairs of A–B and corresponding A–C lists with 40 word pairs each. We counterbalanced which of the lists was used for the interference (two pairs per participant, A–B and corresponding A–C version) and non-interference conditions (four lists per participant, i.e., only the A–B or the A–C version of the remaining four pairs, referred to as D–E lists below to convey that they were non-overlapping).

Polysomnography, sleep analysis, and EEG power 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 0.03 and 35 Hz, and sampled at a rate of 250 Hz using a Brain Amp 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 [25]. Scoring was performed by an experienced technician who was blind to the assigned treatment (an additional expert was consulted for ambiguous epochs). For each night, total sleep time (TST), i.e., the time between the first detection of transition from sleep stage 1 to 2 and lights on, and time spent in the different sleep stages, i.e., wake; sleep stages 1, 2, 3, 4; SWS (defined by the sum of sleep stage 3 and 4) and rapid eye movement (REM) sleep was calculated in minutes.

Table 1. Mean (SEM) correctly recalled word pairs in the New Learning phase for the interference and no-interference conditions

	Sleep				Wake			
	D-cycloserine		Placebo		D-cycloserine		Placebo	
Interference								
First run	21.42	(1.12)	19.00	(0.93)	19.38	(1.32)	16.67	(1.49)
Second run	31.85	(0.82)	31.27	(1.00)	30.76	(1.25)	27.57	(1.57)
Third run	36.08	(0.53)	36.31	(0.59)	35.10	(1.13)	33.00	(1.22)
No-interference								
First run	19.27	(1.28)	17.38	(0.98)	15.95	(1.61)	16.00	(1.62)
Second run	32.23	(1.20)	31.31	(0.99)	29.67	(1.62)	28.19	(1.97)
Third run	36.73	(0.62)	35.81	(0.65)	34.00	(1.34)	33.57	(1.26)

Control measures—vigilance, sleepiness, and mood ratings and test of encoding

Participant's sleepiness and mood was assessed using self-report measures. The Stanford Sleepiness Scale (SSS) [26] measures subjective sleepiness with one item and eight answer options ranging from one = "Feeling active, vital, alert, or wide awake" to eight = "Asleep" (provided as an anchor). We assessed the participant's mood using the multidimensional mood questionnaire at three time points per session [27]. This questionnaire produces the three scales positive mood (high is positive), tiredness (low is tired), and calmness (high is calm). Objective vigilance was additionally tested using the psychomotor vigilance task (PVT; [28]. This 5-min version of the PVT 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 reaction time. General capabilities of long-term memory retrieval were tested using a word generation task, which, e.g., has been used to diagnose such long-term memory capabilities in very mild dementia [29], but also requires executive function that is affected by total sleep deprivation [30]. Participants had to produce as many words as possible starting with a certain letter (P or M) or belonging to a defined category (hobby or profession) during a time of 2 min each (Regensburger Wortflüssigkeitstest [WFT]; [31]). At the end of each session all participants were asked if they believed to have received the active agent or placebo.

Data reduction and statistical analysis

In the Sleep group two participants were excluded because of their extremely low learning performance (below seven word pairs in more than one list). After checking the sleep scoring, two participants were excluded because of disrupted sleep. Statistical analyses generally relied on analyses of variance (GLM; SPSS version 21.0.0 for Windows) including the repeated-measures factors Substance (D-cycloserine vs. placebo), Interference (interference vs. no-interference) and, where appropriate, the factor Runs (1,2,3) pertaining to the three recalls during the New Learning phase, as well as, the between-subjects factor Sleep/Wake. Greenhouse-Geisser correction of degrees of freedom was applied where necessary. Significant interactions were followed up by lower-level ANOVAs and post hoc *t* tests.

RESULTS

Word pairs

Concerning the New Learning phase of word pairs on the second evening of each session, the interference list was learned significantly better than the no-interference list, with this effect being predominant on the first run (Interference × Run: $F_{(2,90)} = 9.035$, $p = 0.001$, First run: $F_{(1,45)} = 9.492$, $p = 0.004$; Table 1). Trivially, performance improved across the three runs ($F_{(2,90)} = 832.695$, $p \leq 0.001$). We also found a trend towards the Sleep group learning more new word pairs than the Wake group ($F_{(1,45)} = 3.447$, $p = 0.070$, for main effect of the Sleep/Wake factor, i.e., not different between A–C and D–E lists). D-cycloserine distinctly enhanced new learning of word pairs 20 h after administration ($F_{(1,45)} = 6.512$, $p = 0.014$, for main effect of Substance). On average participants learned 2.7 more new word pairs in the D-cycloserine condition than in the Placebo condition (D-cycloserine: 57.30 ± 1.40, Placebo: 54.63 ± 1.43).

We also identified a three-way interaction of Substance × Run × Sleep/Wake ($F_{(2,90)} = 3.514$, $p = 0.034$). This effect was mainly driven by word pairs being learned more in the Sleep group after D-cycloserine during the first run ($t_{(25)} = 1.964$, $p = 0.061$), whereas word pairs being learned more in the Wake group after D-cycloserine during the second ($t_{(20)} = 2.880$, $p = 0.009$) and third ($t_{(20)} = 2.102$, $p = 0.048$) runs. All the other effects and interactions were non-significant (All $p \geq 0.114$; Table 1).

Sleep stages

Under D-cycloserine participants spent significantly more time (in minutes) in wakefulness and sleep stage 1 (Wake: $t_{(25)} = -2.737$ $p = 0.011$; stage 1: $t_{(25)} = -2.661$ $p = 0.013$, descriptive statistics are provided in Fig. 2) and less time in REM sleep ($t_{(25)} = 2.768$, $p = 0.010$). We also found a trend towards reduced time in sleep stage 2 in the D-cycloserine condition in comparison to placebo ($t_{(25)} = 1.795$, $p = 0.085$), but there was no significant difference between the treatments in time spent in the other sleep stages (all $t \geq -0.356$, $p \geq 0.451$) or total sleep time ($t_{(25)} = -0.509$, $p = 0.615$). Time spent in sleep stage 4 was positively correlated to performance during Run 1 and Run 3 of the New Learning phase for the no interference list in the placebo condition ($r = 0.34$, $p = 0.091$ and $r = 0.42$, $p = 0.032$, respectively). Conversely, time spent awake was negatively related to performance during Run 3 of the New Learning phase for the no interference list in the placebo condition ($p = 0.017$, $r = 0.47$). Of note, the reported correlation is not evident, if sleep stages 3 and 4 are combined to SWS (all $p \geq 0.23$).

Control measures

As can be expected, in the Wake group, sleep deprivation led to increased subjective sleepiness (measured by Stanford Sleepiness Scale) in the morning and at retrieval ($F_{(1,45)} = 41.07$, $p \leq 0.001$ and $F_{(1,45)} = 52.74$, $p \leq 0.001$, respectively), as well as, reduced objective vigilance (measured by PVT) at retrieval ($F_{(1,45)} = 4.03$, $p = 0.051$) compared to the Sleep group. However, in both groups

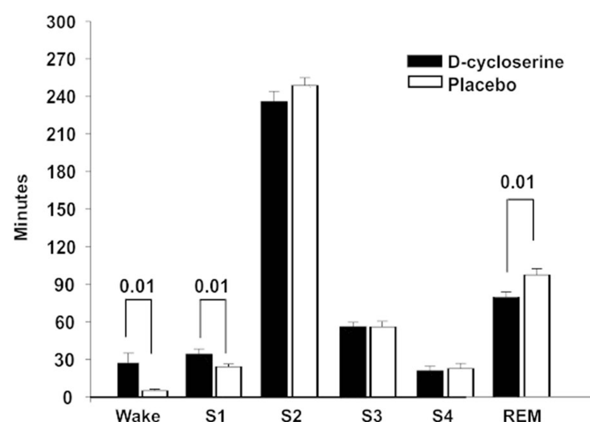


Fig. 2 Mean (SEM) time spent in the different sleep stages Wake, S1 (sleep stage 1), S2 (sleep stage 2), S3 (sleep stage 3), S4 (sleep stage 4), and REM (rapid eye movement sleep) sleep in minutes

Table 2. Means (SEM) of performance are given for the control measures

	Sleep				Wake			
	D-cycloserine		Placebo		D-cycloserine		Placebo	
Stanford Sleepiness Scale								
Learning	3.23	(0.17)	3.77	(0.21)	2.81	(0.25)	2.95	(0.26)
Morning	3.65	(0.26)	3.42	(0.17)	5.05	(0.23)	5.38	(0.22)
Retrieval	2.81	(0.24)	2.92	(0.23)	5.43	(0.28)	5.14	(0.29)
Psychomotor vigilance task								
Learning	3.74	(0.07)	3.70	(0.07)	3.73	(0.09)	3.74	(0.09)
Retrieval	3.82	(0.08)	3.78	(0.07)	3.60	(0.09)	3.55	(0.08)
Multidimensional mood questionnaire								
Learning								
Positive mood	16.88	(0.51)	16.46	(0.66)	17.29	(0.44)	17.05	(0.41)
Tiredness	12.19	(0.47)	11.07	(0.58)	13.90	(0.64)	13.14	(0.60)
Calmness	16.69	(0.38)	15.85	(0.68)	16.00	(0.56)	15.57	(0.62)
Morning								
Positive mood	16.08	(0.66)	17.00	(0.50)	13.19	(0.65)	11.76	(0.73)
Tiredness	12.46	(0.77)	14.08	(0.59)	8.19	(0.74)	6.90	(0.64)
Calmness	15.96	(0.55)	16.62	(0.52)	13.19	(0.68)	12.67	(0.70)
Retrieval								
Positive mood	16.15	(0.84)	15.92	(0.76)	13.48	(0.75)	13.24	(0.70)
Tiredness	12.85	(0.81)	13.08	(0.70)	7.00	(0.69)	6.67	(0.64)
Calmness	14.27	(0.80)	14.46	(0.74)	12.00	(0.75)	12.24	(0.69)
Word fluency task								
Category	19.35	(1.27)	18.58	(0.95)	16.71	(0.98)	17.24	(0.98)
Letter	17.96	(0.85)	18.35	(1.01)	15.14	(1.14)	15.67	(0.79)

Subjective sleepiness (Stanford Sleepiness Scale), objective vigilance (Psychomotor Vigilance Task), mood (Multidimensional mood questionnaire), and general retrieval performance (Word Fluency Test). Learning (after the original Learning phase), Morning (at ~07:15), Retrieval (after the Retrieval phase).

we found no differences between the treatments in the psychomotor vigilance task (PVT, all $p \geq 0.196$). In the Sleep group, subjective "tiredness" in the morning after nocturnal sleep, was enhanced in the D-cycloserine group ($t_{(25)} = -2.534$, $p = 0.018$; Table 2). In the Wake group, subjects in the morning after D-cycloserine showed trend-wise higher "good mood" and less "tiredness" ("tiredness": $t_{(20)} = 1.910$, $p = 0.071$, "good mood": $t_{(20)} = 1.805$, $p = 0.086$; Table 2) than after placebo. Sleepiness (on the SSS did not differ between substance conditions at all times (all $p \geq 0.167$). Also, we did not have any significant differences between substance conditions in the general retrieval performance as measured by the word generation task within any of the groups (all $p \geq 0.503$), however, the Sleep group produced more words compared to the Wake group in an overall analysis ($F_{(1,45)} = 5.02$, $p = 0.030$). Participants in both groups were not able to discriminate between D-cycloserine and placebo (McNemars' exact test: $p \geq 0.774$).

DISCUSSION

We expected that learning of new word pairs will be decreased after sleep under D-cycloserine in comparison to placebo, due to enhanced pro-active interference by the consolidated memory. This effect was predicted to be facilitated, if the new word pairs shared the consolidated word-pair's cue word. In contrast, we found that sharing a cue word with the original list enhanced new learning rather than impaired it. Also, our results provide evidence that new learning was generally facilitated by sleep and by D-cycloserine. Notably the enhancing effect of D-cycloserine was independent of whether it was given before sleep or wakefulness, which was also unexpected. The effects of D-cycloserine on sleep architecture replicated earlier findings of increased wake and light sleep while REM sleep was reduced [8], suggesting a robust albeit mild alerting effect of the drug. Generally, these findings suggest that pro-active interference that is predominant immediately after learning does not carry over to longer retention intervals but rather is reversed by consolidation to aid new learning. Accordingly, enhancing sleep-dependent consolidation of memory traces appears to pro-actively support new learning. Moreover, the effect of D-cycloserine being independent of sleep and associated consolidation, suggests additional time-dependent mechanisms supporting new learning perhaps by inducing active forgetting.

Our finding of better encoding in the interference condition than in the no-interference condition indicates that rather than producing pro-active interference and thereby impairing new learning our interference condition enhanced new learning. This cannot be explained by the initial memory merely decaying across time and thereby reducing its pro-active influence, as this would not enhance performance on the interference above and beyond the no-interference condition. It has been proposed that new information can be learned more easily, if it can be integrated with existing knowledge [32]. Theoretically consolidation during sleep may derive such knowledge by abstracting from episodes [33]. However, empiric evidence suggests that knowledge may be built in a time-dependent rather than a sleep-dependent manner [34], which is consistent with our data revealing that improved learning of interfering materials is independent of prior sleep or wakefulness. Intriguingly, work in rodents suggests, that after a schema is established, new learning is facilitated [35] and subsequent work has shown that such schema-dependent encoding may access the cortical store directly [36]. Alternatively, the present effect may rely on map-like representations of concepts established within the entorhinal grid code [37], which has been shown to encode complex associative memories [38]. Essentially, this question needs to be addressed by additional experiments that go beyond the scope of the current study and establish when pro-active interference is overridden by knowledge abstraction.

The trend-wise enhanced encoding in the Sleep versus the Wake group, corresponds to earlier findings of enhanced encoding after sleep [10], however, this effect may also have been due to sleep deprivation leading to reduced performance in the Wake group. The absence of a more pronounced difference in encoding performance between the sleep and the wake group could also be indicative of a ceiling effect, which would be most pronounced in the third run of the New Learning phase. In support of an active contribution of sleep to improved encoding, we found that time spent in sleep stage 4 was positively related to New Learning phase performance in the placebo condition. While this is in line with causal experiments that showed that boosting slow wave activity can enhance the encoding of declarative memories after sleep [39], an important function may also be performed by sleep spindles during sleep stage 2 [10]. In contrast to findings that suggest REM sleep down-scales synaptic weights in the hippocampus [40], we found improved encoding after D-cycloserine combined with the drug's substantial suppression of REM. Interestingly, we found that there was a significant three-way interaction (between Substance, Sleep/Wake, and Runs), which appeared to mainly reflect that in the Sleep group D-cycloserine-enhanced new learning on run 1, whereas in the Wake group the NMDA receptor co-agonist-enhanced learning on runs 2 and 3.

This can be interpreted as the Sleep group already reaching ceiling levels after run 1, because of the additional boost in learning through sleep. The Wake group on the other hand had more opportunity to increase learning later on in the task. In essence, we suggest that this interaction effect is mediated by sleep-dependent increases in new learning that are independent of the increases in new learning induced by D-cyloserine.

Thus, unexpectedly, D-cycloserine not only enhanced new learning when administered before sleep but also when administered before a wake retention period. This is difficult to integrate. We suspect that this effect might reflect an involvement of NMDA receptor activation in sleep-independent processes that renormalize synaptic weights and generally free capacity for novel encoding (see refs. [41, 42] for opposing remarks) that have recently been shown to also occur during wakefulness [43]. Active decay is a form of renormalization that has been suggested to occur at glutamatergic synapses [44]. Studies of object-location and associative memories in rats have shown that such decay can be prevented by blocking the removal of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors from the synapse [45]. Similarly, blocking NMDA receptors for prolonged periods impaired forgetting of spatial memory in rats [46]. As activating the NMDA receptor in specific ways induces AMPA-receptor endocytosis [47], it is tempting to speculate that the present finding of a generally enhanced encoding (after wake as well as sleep retention periods) involves D-cycloserine sensitizing NMDA receptors to ambient glutamate levels [48], which drives forgetting and frees up capacity for new learning. It is important to note that although we aimed to minimize direct effects of D-cycloserine on encoding by timing New Learning as late as possible, i.e., after two times the half-life of the drug, the drug has also been shown to directly enhance performance when administered before learning [49], and a residual direct influence on new learning cannot be ruled out completely. Remarkably, D-cycloserine's effect on memory has been suggested to rely on lower-level, automatic mechanisms rather than directly affecting high-level processes such as declarative learning [50], which nicely aligns with drug effects in the present study and our previous report [8] affecting processing not under immediate explicit control, i.e., forgetting and consolidation, respectively.

Since sleep-dependent memory consolidation might be influenced by sex and sex hormones [51] the present study is limited, inasmuch as, only men were investigated, which was done to limit risks of the drug to unborn life and reduce noise by assessing a homogenous sample. Also, we only considered a high-level declarative learning task in this study and sleep has been shown also to re-process, e.g., motor sequence memories [52]. However, no effect of sleep on subsequent encoding was found for this task in a nap study [10]. Similarly, we did not manipulate the difficulty of our memory task, which has been shown to modulate the effects of sleep-dependent memory consolidation [16, 53], and thus may have influenced the degree of sleep related interference produced by our lists.

In conclusion, we found that overnight retention periods after learning facilitated new learning in particular of interfering materials. Sleep as well as D-cycloserine generally enhanced new learning, and these effects might partly originate from their consolidating influence of the originally learned A–B word pairs, that might facilitate transfer learning of new wordlists (including A–C and D–E lists). The effect of D-cycloserine likewise observed after wake periods also suggests a contribution of NMDA receptor-mediated active decay [44] that is established as a form of sleep-independent synaptic renormalization [42, 43]. Examining how this form of forgetting interacts with sleep-dependent forms of synaptic renormalization [41] and sleep-dependent memory consolidation [2], will be of essence to understand how consolidation and forgetting sustain long-term memory and new learning [54].

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ADDITIONAL INFORMATION

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REFERENCES

1. Rasch B, Born J. About sleep's role in memory. Physiol Rev. 2013;93:681–766. https://doi.org/10.1152/physrev.00032.2012
2. Diekelmann S, Born J. The memory function of sleep. Nat Rev Neurosci. 2010;11:114–26. https://doi.org/10.1038/nrn2762
3. Feld GB, Diekelmann S. Sleep smart-optimizing sleep for declarative learning and memory. Front Psychol. 2015;6:622 https://doi.org/10.3389/fpsyg.2015.00622
4. Marshall L, Molle M, Hallschmid M, Born J. Transcranial direct current stimulation during sleep improves declarative memory. J Neurosci. 2004;24:9985–92. https://doi.org/10.1523/JNEUROSCI.2725-04.2004
5. Ngo HV, Martinetz T, Born J, Molle M. Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. Neuron. 2013;78:545–53. https://doi.org/10.1016/j.neuron.2013.03.006
6. Rasch B, Buchel C, Gais S, Born J. Odor cues during slow-wave sleep prompt declarative memory consolidation. Science. 2007;315:1426–9. https://doi.org/10.1126/science.1138581
7. Rudoy JD, Voss JL, Westerberg CE, Paller KA. Strengthening individual memories by reactivating them during sleep. Science. 2009;326:1079 https://doi.org/10.1126/science.1179013
8. Feld GB, Lange T, Gais S, Born J. Sleep-dependent declarative memory consolidation-unaffected after blocking NMDA or AMPA receptors but enhanced by NMDA coagonist D-cycloserine. Neuropsychopharmacology. 2013;38:2688–97. https://doi.org/10.1038/npp.2013.179
9. Richards BA, Frankland PW. The persistence and transience of memory. Neuron. 2017;94:1071–84. https://doi.org/10.1016/j.neuron.2017.04.037
10. Mander BA, Santhanam S, Saletin JM, Walker MP. Wake deterioration and sleep restoration of human learning. Curr Biol. 2011;21:R183–4. https://doi.org/10.1016/j.cub.2011.01.019
11. Jenkins JG, Dallenbach KM. Obliviscence during sleep and waking. Am J Psychol. 1924;35:605–12.
12. Mednick SC, Cai DJ, Shuman T, Anagnostaras S, Wixted JT. An opportunistic theory of cellular and systems consolidation. Trends Neurosci. 2011;34:504–14. https://doi.org/10.1016/j.tins.2011.06.003
13. Sadowski JH, Jones MW, Mellor JR. Sharp-wave ripples orchestrate the induction of synaptic plasticity during reactivation of place cell firing patterns in the hippocampus. Cell Rep. 2016;14:1916–29. https://doi.org/10.1016/j.celrep.2016.01.061
14. van de Ven GM, Trouche S, McNamara CG, Allen K, Dupret D. Hippocampal offline reactivation consolidates recently formed cell assembly patterns during sharp wave-ripples. Neuron. 2016;92:968–74. https://doi.org/10.1016/j.neuron.2016.10.020
15. Wilson MA, McNaughton BL. Reactivation of hippocampal ensemble memories during sleep. Science. 1994;265:676–9.
16. Ellenbogen JM, Hulbert JC, Stickgold R, Dinges DF, Thompson-Schill SL. Interfering with theories of sleep and memory: sleep, declarative memory, and associative interference. Curr Biol. 2006;16:1290–4. https://doi.org/10.1016/j.cub.2006.05.024
17. Osgood CE. An investigation into the causes of retroactive interference. J Exp Psychol. 1948;38:132–54.
18. Diekelmann S, Wilhelm I, Wagner U, Born J. Elevated cortisol at retrieval suppresses false memories in parallel with correct memories. J Cogn Neurosci. 2011;23:772–81. https://doi.org/10.1162/jocn.2010.21493
19. Staresina BP, Bergmann TO, Bonnefond M, van der Meij R, Jensen O, Deuker L, et al. Hierarchical nesting of slow oscillations,spindles and ripples in the human hippocampus during sleep. Nat Neurosci. 2015;18:1679–86. https://doi.org/10.1038/nn.4119
20. King C, Henze DA, Leinekugel X, Buzsaki G. Hebbian modification of a hippocampal population pattern in the rat. J Physiol. 1999;521:159–67.

21. Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. Neuron. 2004;44:5–21. https://doi.org/10.1016/j.neuron.2004.09.012
22. Malenka RC, Nicoll RA. Long-term potentiation-a decade of progress? Science. 1999;285:1870–4.
23. Sheinin A, Shavit S, Benveniste M. Subunit specificity and mechanism of action of NMDA partial agonist D-cycloserine. Neuropharmacology. 2001;41:151–8.
24. Wilhelm I, Diekelmann S, Molzow I, Ayoub A, Molle M, Born J, et al. Sleep selectively enhances memory expected to be of future relevance. J Neurosci. 2011;31:1563–9. https://doi.org/10.1523/JNEUROSCI.3575-10.2011
25. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Bethesda, MD: US Department of Health, Education and Welfare (1968). https://www.ncbi.nlm.nih.gov/nlmcatalog/?term=Rechtschaffen%20A,%20Kales%20A%20%281968%29
26. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of sleepiness: a new approach. Psychophysiology. 1973;10:431–6.
27. Hinz A, Daig I, Petrowski K, Brahler E. [Mood in the German population: norms of the Multidimensional Mood Questionnaire MDBF]. Psychother Psychosom Med Psychol. 2012;62:52–7. https://doi.org/10.1055/s-0031-1297960
28. Dinges DF, Pack F, Williams K, Gillen KA, Powell JW, Ott GE, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 h per night. Sleep. 1997;20:267–77.
29. Gomez RG, White DA. Using verbal fluency to detect very mild dementia of the Alzheimer type. Arch Clin Neuropsych. 2006;21:771–5. https://doi.org/10.1016/j.acn.2006.06.012
30. Jones K, Harrison Y. Frontal lobe function, sleep loss and fragmented sleep. Sleep Med Rev. 2001;5:463–75.
31. Aschenbrenner A, Tucha O, Lange K. RWT Regensburger Wortflüssigkeits-Test. Handanweisung. Göttingen: Hogrefe Verlag; 2000.
32. van Kesteren MT, Rijpkema M, Ruiter DJ, Morris RG, Fernandez G. Building on prior knowledge: schema-dependent encoding processes relate to academic performance. J Cogn Neurosci. 2014;26:2250–61. https://doi.org/10.1162/jocn_a_00630
33. Lewis PA, Durrant SJ. Overlapping memory replay during sleep builds cognitive schemata. Trends Cogn Sci. 2011;15:343–51. https://doi.org/10.1016/j.tics.2011.06.004
34. Hennies N, Lewis PA, Durrant SJ, Cousins JN, Ralph MA. Time- but not sleep-dependent consolidation promotes the emergence of cross-modal conceptual representations. Neuropsychologia. 2014;63:116–23. https://doi.org/10.1016/j.neuropsychologia.2014.08.021
35. Tse D, Langston RF, Kakeyama M, Bethus I, Spooner PA, Wood ER, et al. Schemas and memory consolidation. Science. 2007;316:76–82. https://doi.org/10.1126/science.1135935
36. Tse D, Takeuchi T, Kakeyama M, Kajii Y, Okuno H, Tohyama C, et al. Schema-dependent gene activation and memory encoding in neocortex. Science. 2011;333:891–5. https://doi.org/10.1126/science.1205274
37. Constantinescu AO, O'Reilly JX, Behrens TEJ. Organizing conceptual knowledge in humans with a gridlike code. Science. 2016;352:1464–8. https://doi.org/10.1126/science.aaf0941
38. Garvert MM, Dolan RJ, Behrens TE. A map of abstract relational knowledge in the human hippocampal-entorhinal cortex. eLife. 2017;6:e17086. https://doi.org/10.7554/eLife.17086
39. Antonenko D, Diekelmann S, Olsen C, Born J, Molle M. Napping to renew learning capacity: enhanced encoding after stimulation of sleep slow oscillations. Eur J Neurosci. 2013;37:1142–52. https://doi.org/10.1111/ejn.12118
40. Grosmark AD, Mizuseki K, Pastalkova E, Diba K, Buzsaki G. REM sleep reorganizes hippocampal excitability. Neuron. 2012;75:1001–7. https://doi.org/10.1016/j.neuron.2012.08.015
41. Tononi G, Cirelli C. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron. 2014;81:12–34. https://doi.org/10.1016/j.neuron.2013.12.025
42. Frank MG. Erasing synapses in sleep: is it time to be SHY? Neural Plast. 2012;2012:264378 https://doi.org/10.1155/2012/264378
43. Hengen KB, Torrado Pacheco A, McGregor JN, Van Hooser SD, Turrigiano GG. Neuronal firing rate homeostasis is inhibited by sleep and promoted by wake. Cell. 2016;165:180–91. https://doi.org/10.1016/j.cell.2016.01.046
44. Hardt O, Nader K, Nadel L. Decay happens: the role of active forgetting in memory. Trends Cogn Sci. 2013;17:111–20. https://doi.org/10.1016/j.tics.2013.01.001
45. Migues PV, Liu L, Archbold GE, Einarsson EO, Wong J, Bonasia K, et al. Blocking synaptic removal of GluA2-containing AMPA receptors prevents the natural forgetting of long-term memories. J Neurosci. 2016;36:3481–94. https://doi.org/10.1523/JNEUROSCI.3333-15.2016
46. Villarreal DM, Do V, Haddad E, Derrick BE. NMDA receptor antagonists sustain LTP and spatial memory: active processes mediate LTP decay. Nat Neurosci. 2002;5:48–52. https://doi.org/10.1038/nn776
47. Beattie EC, Carroll RC, Yu X, Morishita W, Yasuda H, von Zastrow M, et al. Regulation of AMPA receptor endocytosis by a signaling mechanism shared with LTD. Nat Neurosci. 2000;3:1291–300. https://doi.org/10.1038/81823
48. Featherstone DE, Shippy SA. Regulation of synaptic transmission by ambient extracellular glutamate. Neuroscientist. 2008;14:171–81. https://doi.org/10.1177/1073858407308518
49. Ledgerwood L, Richardson R, Cranney J. Effects of D-cycloserine on extinction of conditioned freezing. Behav Neurosci. 2003;117:341–9.
50. Grillon C. D-cycloserine facilitation of fear extinction and exposure-based therapy might rely on lower-level, automatic mechanisms. Biol Psychiatry. 2009;66:636–41. https://doi.org/10.1016/j.biopsych.2009.04.017
51. Genzel L, Kiefer T, Renner L, Wehrle R, Kluge M, Grozinger M, et al. Sex and modulatory menstrual cycle effects on sleep related memory consolidation. Psychoneuroendocrinology. 2012;37:987–98. https://doi.org/10.1016/j.psyneuen.2011.11.006
52. Walker MP, Brakefield T, Seidman J, Morgan A, Hobson JA, Stickgold R, et al. Sleep and the time course of motor skill learning. Learn & Mem. 2003;10:275–84. https://doi.org/10.1101/lm.58503
53. Drosopoulos S, Schulze C, Fischer S, Born J. Sleep's function in the spontaneous recovery and consolidation of memories. J Exp Psychol General. 2007;136:169–83. https://doi.org/10.1037/0096-3445.136.2.169
54. Feld GB, Born J. Sculpting memory during sleep:concurrent consolidation and forgetting. Curr Opin Neurobiol. 2017;44:20–7. https://doi.org/10.1016/j.conb.2017.02.012

6. Study II: Consolidation of reward memory during sleep does not require dopaminergic activation

(Manuscript Under review)

Alizadeh Asfestani, M., Brechtmann, V., Santiago, J. C. P., Born, J., & Feld, G. B.

Consolidation of reward memory during sleep does not require dopaminergic activation

Alizadeh Asfestani M[1], Brechtmann V[1], Santiago J[1,2,3], Peter A[2,3,4], Born J[1,2,3,5], Feld GB[1,6 *]

1 Institute of Medical Psychology and Behavioural Neurobiology, University of Tübingen, Tübingen, Germany

2 German Center for Diabetes Research (DZD), Tübingen, Germany

3 Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the Eberhard Karls University Tübingen, Tübingen, Germany

4 Department of Internal Medicine, Division of Endocrinology, Diabetology, Angiology, Nephrology and Clinical Chemistry, University Hospital of Tübingen, Tübingen, Germany

5 Center for Integrative Neuroscience, University of Tübingen, Tübingen, Germany

6 Clinical Psychology, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany

* Correspondence: Email: gordon.feld@zi-mannheim.de

Gordon Feld, Central Institute of Mental Health, J5, 68159 Mannheim, Germany, Tel. +49 621 1703 6540, Fax +49 621 1703 6505.

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 the present study, we scrutinize the idea that dopamine is needed for the preferential consolidation of rewarded information. We blocked 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 20 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 ms) and a long duration (1500 ms), respectively, which enabled to dissociate effects of reward on sleep-associated consolidation from those of mere encoding depth. Retrieval was tested after a retention interval of 20 h that included 8 h 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 blocking dopaminergic neurotransmission with sulpiride during sleep on this differential retention of rewarded information. This result indicates that dopaminergic activation 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 centres, i.e., 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 behaviour (Schultz, 2007). However, while it seems clear that sleep plays an important role for the preferential consolidation of highly (over lowly) rewarded information (Fischer & Born, 2009; Igloi, Gaggioni, Sterpenich, & Schwartz, 2015; Studte, Bridger, & Mecklinger, 2017), 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, Buchel, 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, Munte, & 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 (Valdes, 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 post-encoding wakefulness and vanished during post-encoding sleep (Gomperts, Kloosterman, & Wilson, 2015). Thus, an alternative view assumes that rather than directly participating in sleep-dependent consolidation

processes, dopamine activity 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, sleep has been confirmed to preferentially consolidate memory for high rewarded pictures over low rewarded pictures (Feld et al., 2014). Based on this evidence, here, 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 on average 25.30 years (18-30 years) 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, regular excessive alcohol consumption (regularly more than two bottles of beer per day), 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, a physical examination as well as a blood pressure and a routine blood screening test (including haemoglobin, sodium, potassium, calcium, chloride, glucose, bilirubin,

glutamate pyruvate transaminase, alkaline phosphatase, Gamma-glutamyl-trans-peptidase, C-reactive protein, Partial thromboplastin time) and only healthy participants were included. In addition, participants reported a normal sleep-wake cycle, no shift work, night work or intercontinental flights (>4 h 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, to get up at 07:00 on experimental days and, during these days, not to take any naps, not to drink caffeine-containing drinks after 13:00 and also not to consume alcohol starting one 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 of the experiment, which included the placement of the electrodes for polysomnographic recordings and of the cannula for the blood drawing. The ethics committee of the University of Tübingen approved the experiments. We obtained written informed consent from all participants before their participation.

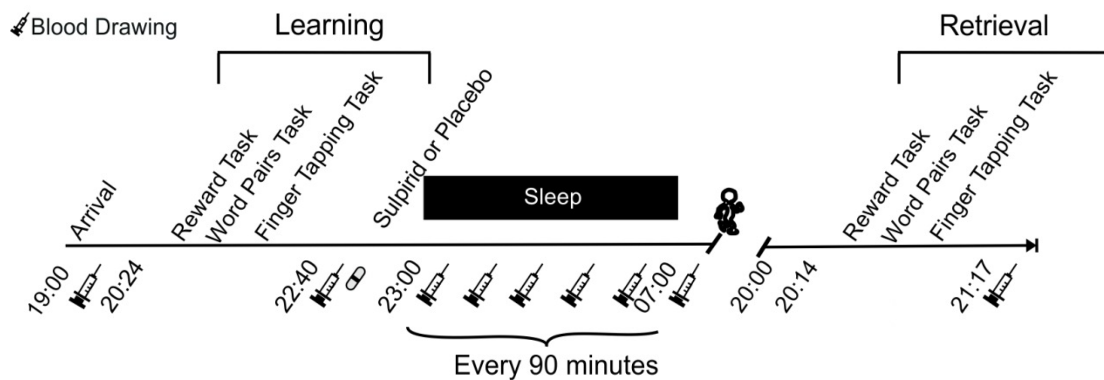
Design and procedures

The study followed a balanced, double-blind, placebo-controlled, within-subject crossover design (Figure 1A). Participants took part in two identical experimental sessions with the exception of administration of either sulpiride (4 Dogmatil Forte, sulpiride 200 mg, Sanofi Aventis, Germany) or placebo and parallel versions of the behavioural tasks where necessary, with at least two weeks interval between the sessions. The dose of 800 mg sulpiride (p.o., plasma maximum: 3-6 h, plasma half-life: 6-10 h) 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, i.e., 15min before lights off. We chose this

timing in order to maximize drug levels during the slow wave sleep (SWS) rich first half of the night and thereby maximise the effects during occurrence of replay. The Retrieval Phase for the reward task was scheduled the next evening, i.e., as late as possible to minimize the residual amount of drug circulating at retrieval testing.

On the experimental nights (for an overview see Figure 1A), participants arrived at 19:00 filled a general questionnaire and then an intravenous cannula was placed for drawing blood. Afterwards, electrodes were applied for polysomnographic recordings. Next, they filled in the questionnaires on mood and sleepiness. About one hour after cannula placement, the first blood sample was taken and then the behavioural 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. Afterwards they again preformed the vigilance task 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 h 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 (2 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. Afterwards, 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 lab.



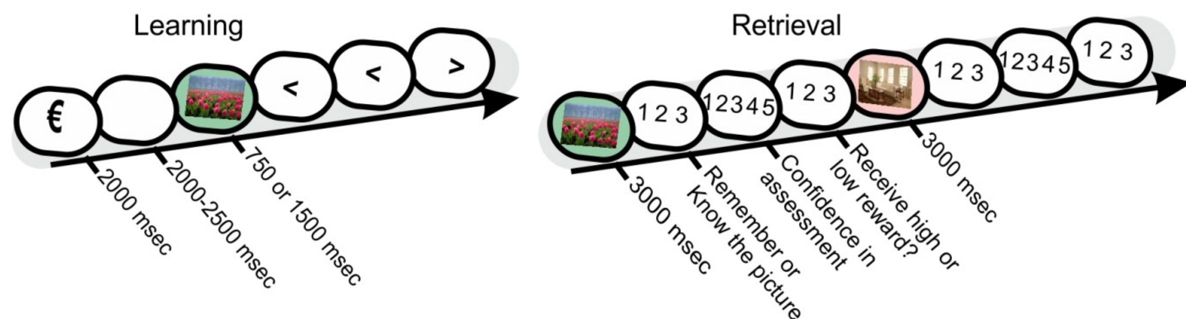


Figure 1. (A) Participants took part in two identical experimental sessions, but for the administration of placebo or sulpiride. They started the session at around 7:00 pm, after preparing for blood sampling and sleep EEG, the Learning Phase started. Thereafter at 23:00, the capsules (Sulpirid or placebo) were orally administered. Participants were awakened at 7:15 the next morning. The retention interval was approximately 22 h, and retrieval was tested in the evening at approximately 20:00. Blood was drawn before and after learning, after retrieval, and in 1.5-h 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 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 (Learning Phase) and delayed recognition (Retrieval Phase) testing, participants were shown different sets of 80 new and 80 old pictures and had to identify them correctly, which earned them their reward (see Methods for details).

Motivated Learning Task

The Motivated Learning Task was adapted from prior work 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 to 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 pseudo-random 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 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, 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. 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

Behaviour. To control effects of the drug on declarative and procedural memory we used a word-pair task and a finger sequence tapping (Walker, 2003) task, 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 5-element sequence (e.g., 4-1-3-2-4 or 4-2-3-1-4) with the fingers of their non-dominant hand as fast and as 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 difference between the Retrieval Phase and performance in the Learning Phase was 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 Wortflüssigkeits test [WFT]; Aschenbrenner A, 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 minutes 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, Eschborn, Germany. The inter-assay coefficients of variation were 5% for Cortisol and 2.5% for Prolactin. The area under curve was calculated as the weighted mean of the inter-interval approximation (time point n + time point (n + 1) / 2 x interval duration) for five time points, which occurred between lights out and waking, i.e., from 00:30 until 6:30.

Polysomnography and sleep scoring

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 Brain Amp DC (Brain Products 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.

Data reduction and statistical analysis

Three participants were excluded from the analysis, two of them for insufficient sleep and one for low levels of sleep and extremely long sleep latency. During blood sampling 73 draws (20.3 % of the total) were missed due to blockage of the tubing (occurring typically when the participant bends his arm during sleep). Singular missing values were replaced by interpolating between the neighbouring 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 measure factor for the Learning and Retrieval Phases as different stimuli were used for immediate and delayed recognition. 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. Greenhous-Geisser correction of degrees of freedom was used, if data violated the assumption of homoscedacity.

Results

Motivated Learning Task

During the Learning Phase, highly rewarded pictures were recognized better than lowly rewarded pictures (main effect of reward: $F_{(1,16)} = 25.03$, $p \leq 0.001$, Table 1 and Figure 2) and long duration pictures were recognized better than short duration pictures (main effect of duration: $F_{(1,16)} = 6.75$, $p = 0.019$). There were no significant interaction effects and no main effect of treatment in this analysis (all $p > 0.511$).

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: $F_{(1,16)} = 8.94$, $P = 0.009$; main effect of duration: $F_{(1,16)} = 20.54$, $p \leq 0.001$). However, there was no evidence of sulpiride affecting the recognition performance in general (main effect of treatment: $F_{(1,16)} = 0.02$, $p = 0.892$) or recognition performance in the reward conditions differentially (Treatment × Reward: ($F_{(1,16)} = 0.59$, $p = 0.454$). 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: $F_{(1,32)} = 0.57$, $p = 0.460$). Rather we found that sulpiride diminished the performance difference between long and short duration pictures during the Retrieval Phase (Treatment× Duration: $F_{(1,16)} = 11.06$, $p = 0.004$). 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, $t_{(16)} = 6.23$, $p \leq 0.001$), which was not true for the sulpiride condition (Long Duration: mean = 1.33, SD = 0.77 , Short Duration: mean = 1.20, SD = 0.57, $t_{(16)} = 1.44$, $p = 0.170$, Figure 2).

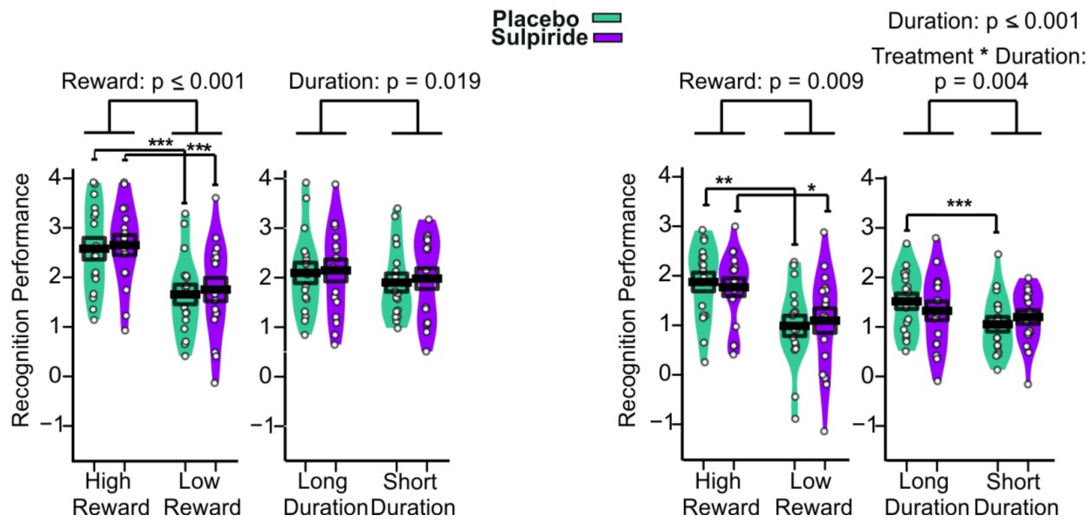


Figure 2. (A) Performance on the motivated learning task for the immediate recognition test during the Learning Phase before sleep and (B) delayed recognition test during the Retrieval Phase after sleep for the sulpiride (purple) and the placebo (green) conditions. Mean (±SEM) performance is indicated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

To determine response strategies we calculated the response bias, i.e., the negative mean of the z-value of the hit- and of the false-alarm rate. In both recognition phases participants' reactions were more conservative for the high-reward pictures (Learning Phase: $F_{(1,16)} = 18.18$, $p \leq 0.001$, Retrieval Phase: $F_{(1,16)} = 6.39$, $p = 0.022$, Table 2). None of the other contrasts were significant (all $p > 0.189$).

We also separately analysed hit rates and false alarm rate, which largely paralleled data for the sensitivity index. Hit rates were higher for longer duration pictures (Learning Phase: $F_{(1,16)} = 7.39$, $p = 0.015$, Retrieval Phase: $F_{(1,16)} = 21.69$, $p \leq 0.001$) and highly rewarded pictures (Learning Phase: $F_{(1,16)} = 7.10$, $p = 0.017$) and at learning and retrieval false alarms were reduced for highly rewarded pictures (Learning Phase: $F_{(1,16)} = 12.59$, $p = 0.003$, Retrieval Phase: $F_{(1,16)} = 6.34$, $p = 0.023$). For the hit rate, we also found that sulpiride differentially affected performance for long and short duration items, during the Retrieval Phase (Treatment × Duration: $F_{(1,16)} = 12.02$, $p = 0.003$; see Table 2).

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 = 0.729). Under sulpiride, participants recalled significantly less word-pairs during the Retrieval Phase than during the Learning Phase ($t_{(16)}$ = 2.56, p = 0.021). However, this difference was already apparent during the Learning Phase ($t_{(16)}$ = -2.10, p = 0.052, Table1). There was no difference between the treatments regarding the amount of runs needed to reach the learning criterion ($t_{(16)}$ = -1.38, p = 0.188).

In the finger tapping task, there was a trend wise effect for error rates decreasing more in the sulpiride condition across the retention interval ($t_{(16)}$ = 2.03, p = 0.059). However, this was from a trend wise higher baseline in the Learning Phase ($t_{(16)}$ = -1.81, p = 0.089). For the correctly tapped sequences we found a trend wise effect for participants tapping less correct sequences in the sulpiride condition during the Retrieval Phase ($t_{(16)}$ = 1.95, p = 0.069). There was no effect of sulpiride on the control sequence only performed during the Retrieval Phase (correct sequences: $t_{(16)}$ = - 0.02, p = 0.982; error rates: $t_{(16)}$ = 0.25, p = 0.809).

Word fluency, vigilance, mood, and subjective sleepiness. Descriptive data can be found in Table 3. We did not find any significant differences in long-term memory retrieval performance (as measured by the word fluency task, all p≥ 0.868). In the vigilance task (PVT) we found significantly higher reaction speed (i.e., reaction time-1) in the Placebo condition after the Retrieval Phase ($t_{(16)}$ = 3.13, p = 0.006, all other p ≥ 0.637). In the placebo condition compared to the sulpiride condition, the mood questionnaire (PANAS) showed significantly higher positive mood before the Retrieval phase ($t_{(16)}$ = 2.25, p = 0.039) and a trend toward more negative mood after the Learning Phase ($t_{(16)}$ = 2.06, p = 0.056). 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 = 0.014) and a trend toward increased sleepiness before the Retrieval Phase ($t_{(16)}$ = -1.81, p = 0.090). Participants were not able to discriminate between sulpiride and placebo (McNemars' exact test: p ≥ 0.791).

Cortisol and prolactin. We found no evidence of sulpiride affecting cortisol levels in general (Treatment: F = 1.65, p = 0.22) or at specific time points (Treatment x Time point: $F_{(1,16)}$ = 0.92, p = 0.45). However, prolactin levels were increased in the sulpiride condition at some time points (Treatment: $F_{(1,16)}$ = 227.00, p ≤ 0.001, Time point: $F_{(1,16)}$ = 40.49, p ≤ 0.001, Treatment × Time point: $F_{(1,16)}$ = 37.32, p ≤ 0.001). This was true for all samples from 00:30 until 21:30 (post-hoc t-test all p ≤ 0.001) as well as in an analysis of the area under the curve (AUC) from 00:30 until 06:30 ($t_{(16)}$ = -16.81, p ≤ 0.001,see Figure 3 C). This effect can be explained by Dopamine having a strong inhibitory effect on prolactin secretion (Fitzgerald & Dinan, 2008). Since 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. Since 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 p ≥ 0.199, 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 = 0.58, p = 0.014), whereas this relationship was negative for lowly reward pictures (r = -0.54, p = 0.025). 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 =0.50, p = 0.041, lowly rewarded pictures: r = -0.48, p = 0.053).

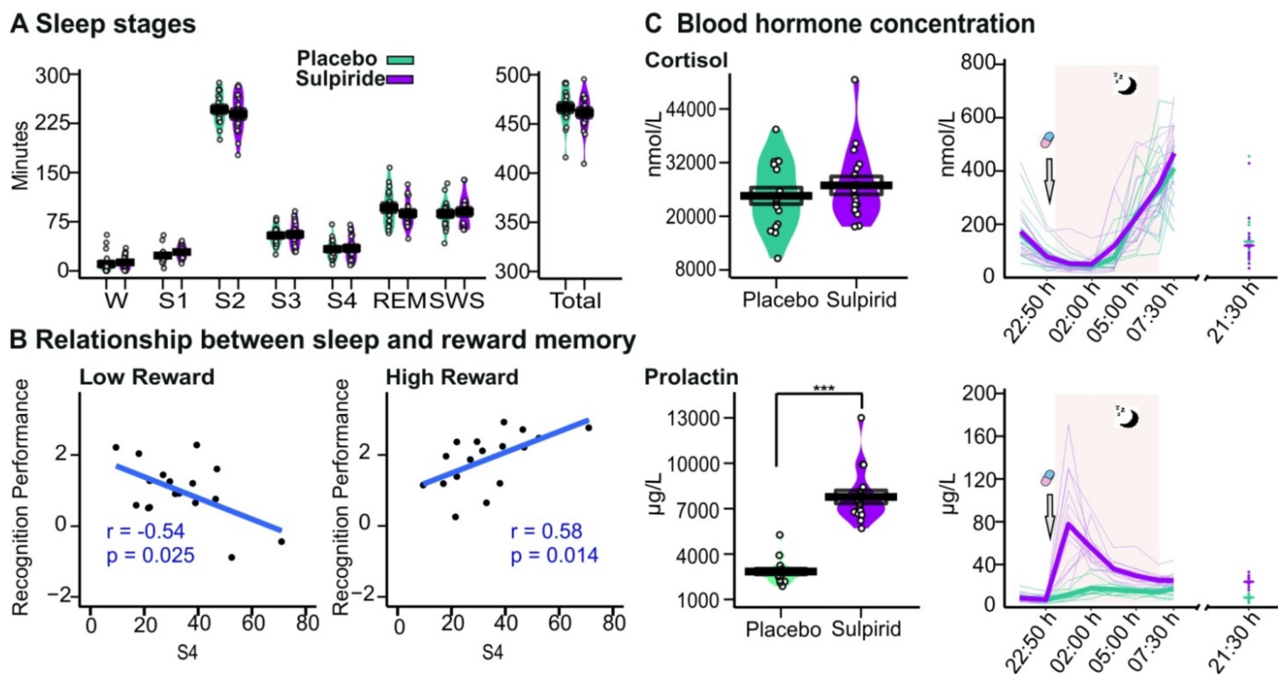


Figure 3. (A) Sleep stages. Mean (±SEM) time (in minutes) spent in non-REM Sleep Stages S1, S2, S3, and S4; in REM sleep; in SWS (i.e., the sum of S3 and S4) and total sleep time, are provided for the sulpiride (purple) and placebo (green) conditions. (B) Correlation, across placebo condition between 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) area under the curve (AUC) (from 00:30 until 06:30) is shown on the left and mean (thick lines) and individual data (thin lines) per time point is shown on the right. The sulpiride condition is shown in purple and placebo is shown in green. ***p ≤ .001

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 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 concurs with earlier reports (Adcock et al., 2006; Feld et al., 2014) and is also in line 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 exclude a causal contribution of dopaminergic activation during sleep to the preferential consolidation of reward-associated memory.

Both in the sulpiride and the placebo condition, 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, Angeles, Keshavan, & Gabrieli, 2018; Spaniol, Schain, & Bowen, 2014; Wolosin, Zeithamova, & Preston, 2012), which is eventually necessary for sleep to selectively enhance highly rewarded information (Igloi et al., 2015; Fischer & Born, 2009; Studte et al., 2017). There is overwhelming evidence that this sleep-dependent consolidation relies on the replay of neuronal memory traces during slow wave sleep (e.g., Bendor & Wilson, 2012; Rasch et al., 2007; Rudoy, Voss, Westerberg, & Paller, 2009; Wilson & McNaughton, 1994). In addition, some studies suggested that the reward circuitry of the brain, i.e., the hippocampus-ventral striatum-ventral tegmental area-hippocampus loop, participates in this replay (Lansink et al., 2008; Lansink et al., 2009; Pennartz et al., 2004; Valdes et al., 2015). However, as our data revealed, a potent block 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 slow wave sleep. Another study in rats showed that dopaminergic activation during learning can enhance replay during sleep even in the absence of a behavioural effect at learning (McNamara et al., 2014). Those findings in combination with the present data, support the idea that augmented neuronal replay, rather than co-activation of dopaminergic neurotransmission, is the mayor 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, optogentically activating dopaminergic neurons of the VTA was found to promote wakefulness, whereas inhibition of the same cells supressed 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 non-physiological, i.e., 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 slow wave sleep (i.e., sleep stage 4) positively correlated with recognition performance of highly rewarded pictures, but negatively with performance on low-reward pictures. Replay has been especially connected to consolidation during slow wave sleep 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 (Clemens et al., 2007; Diekelmann & Born, 2010; Staresina et al., 2015). Ripples together with spindles are likely the oscillations, which promote the neuroplasticity that strengthens memory traces in this process (Girardeau, Cei, & Zugaro, 2014; Khodagholy, Gelinas, & Buzsaki, 2017; Sadowski, Jones, & Mellor, 2016; van de Ven, Trouche, McNamara, Allen, & Dupret, 2016). Importantly, hippocampal ripples appear to be simultaneously involved in processes of synaptic downscaling and forgetting (Feld & Born, 2017; Norimoto et al., 2018; 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.

Our finding that the enhanced recognition of highly rewarded pictures was already strongly evident at immediate recall, during the Learning Phase, points towards 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 (Feld et al., 2014; Murayama & Kuhbandner, 2011; Patil, Murty, Dunsmoor, Phelps, & Davachi, 2017; 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 a 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 post-encoding memory enhancement of novel stimuli by release of dopamine in the hippocampus that is mediated by the locus coeruleus (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 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; Ikemoto, Glazier, Murphy, & McBride, 1997; Manahan-Vaughan & Kulla, 2003; Wilkerson & Levin, 1999)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 conclusion, our data challenge the idea that replay during sleep engages dopaminergic inputs to the hippocampus via a feedback loop consisting of the brain's reward

centres 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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Refrences:

Adcock, R. A., Thangavel, A., Whitfield-Gabrieli, S., Knutson, B., & Gabrieli, J. D. (2006). Reward-motivated learning: mesolimbic activation precedes memory formation. *Neuron, 50*(3), 507-517. doi: 10.1016/j.neuron.2006.03.036

Aschenbrenner A, Tucha O, Lange K. RWT. (2000). RWT Regensburger Wortflüssigkeits-Test. Handanweisung. Göttingen:. *Göttingen: Hogrefe Verlag; 2000.* doi: https://m.portal.hogrefe.com/dorsch/regensburger-wortfluessigskeitstest-rwt/

Bendor, D., & Wilson, M. A. (2012). Biasing the content of hippocampal replay during sleep. *Nat Neurosci, 15*(10), 1439-1444. doi: 10.1038/nn.3203

Clemens, Z., Molle, M., Eross, L., Barsi, P., Halasz, P., & Born, J. (2007). Temporal coupling of parahippocampal ripples, sleep spindles and slow oscillations in humans. *Brain, 130*(Pt 11), 2868-2878. doi: 10.1093/brain/awm146

Diekelmann, S., & Born, J. (2010). The memory function of sleep. *Nat Rev Neurosci, 11*(2), 114-126. doi: 10.1038/nrn2762

Dinges, D. F., Pack, F., Williams, K., Gillen, K. A., Powell, J. W., Ott, G. E., . . . Pack, A. I. (1997). Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. *Sleep, 20*(4), 267-277.

Eban-Rothschild, A., Rothschild, G., Giardino, W. J., Jones, J. R., & de Lecea, L. (2016). VTA dopaminergic neurons regulate ethologically relevant sleep-wake behaviors. *Nat Neurosci, 19*(10), 1356-1366. doi: 10.1038/nn.4377

Eschenko, O., Magri, C., Panzeri, S., & Sara, S. J. (2012). Noradrenergic neurons of the locus coeruleus are phase locked to cortical up-down states during sleep. *Cereb Cortex, 22*(2), 426-435. doi: 10.1093/cercor/bhr121

Feld, G. B., Besedovsky, L., Kaida, K., Munte, T. F., & Born, J. (2014). Dopamine D2-like receptor activation wipes out preferential consolidation of high over low reward memories during human sleep. *J Cogn Neurosci, 26*(10), 2310-2320. doi: 10.1162/jocn_a_00629

Feld, G. B., & Born, J. (2017). Sculpting memory during sleep: concurrent consolidation and forgetting. *Curr Opin Neurobiol, 44*, 20-27. doi: 10.1016/j.conb.2017.02.012

Fischer, S., & Born, J. (2009). Anticipated reward enhances offline learning during sleep. *J Exp Psychol Learn Mem Cogn, 35*(6), 1586-1593. doi: 10.1037/a0017256

Fitzgerald, P., & Dinan, T. G. (2008). Prolactin and dopamine: what is the connection? A review article. *J Psychopharmacol, 22*(2 Suppl), 12-19. doi: 10.1177/0269216307087148

Geddes, M. R., Mattfeld, A. T., Angeles, C. L., Keshavan, A., & Gabrieli, J. D. E. (2018). Human aging reduces the neurobehavioral influence of motivation on episodic memory. *Neuroimage, 171*, 296-310. doi: 10.1016/j.neuroimage.2017.12.053

Girardeau, G., Cei, A., & Zugaro, M. (2014). Learning-induced plasticity regulates hippocampal sharp wave-ripple drive. *J Neurosci, 34*(15), 5176-5183. doi: 10.1523/JNEUROSCI.4288-13.2014

Gomperts, S. N., Kloosterman, F., & Wilson, M. A. (2015). VTA neurons coordinate with the hippocampal reactivation of spatial experience. *Elife, 4*. doi: 10.7554/eLife.05360

Hoddes, E., Zarcone, V., Smythe, H., Phillips, R., & Dement, W. C. (1973). Quantification of sleepiness: a new approach. *Psychophysiology, 10*(4), 431-436.

Hopf, F. W., Cascini, M. G., Gordon, A. S., Diamond, I., & Bonci, A. (2003). Cooperative activation of dopamine D1 and D2 receptors increases spike firing of nucleus accumbens neurons via G-protein betagamma subunits. *J Neurosci, 23*(12), 5079-5087.

Igloi, K., Gaggioni, G., Sterpenich, V., & Schwartz, S. (2015). A nap to recap or how reward regulates hippocampal-prefrontal memory networks during daytime sleep in humans. *Elife, 4*. doi: 10.7554/eLife.07903

Ikemoto, S., Glazier, B. S., Murphy, J. M., & McBride, W. J. (1997). Role of dopamine D1 and D2 receptors in the nucleus accumbens in mediating reward. *J Neurosci, 17*(21), 8580-8587.

Ji, D., & Wilson, M. A. (2007). Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nat Neurosci, 10*(1), 100-107. doi: 10.1038/nn1825

Khodagholy, D., Gelinas, J. N., & Buzsaki, G. (2017). Learning-enhanced coupling between ripple oscillations in association cortices and hippocampus. *Science, 358*(6361), 369-372. doi: 10.1126/science.aan6203

Lansink, C. S., Goltstein, P. M., Lankelma, J. V., Joosten, R. N., McNaughton, B. L., & Pennartz, C. M. (2008). Preferential reactivation of motivationally relevant information in the ventral striatum. *J Neurosci, 28*(25), 6372-6382. doi: 10.1523/JNEUROSCI.1054-08.2008

Lansink, C. S., Goltstein, P. M., Lankelma, J. V., McNaughton, B. L., & Pennartz, C. M. (2009). Hippocampus leads ventral striatum in replay of place-reward information. *PLoS Biol, 7*(8), e1000173. doi: 10.1371/journal.pbio.1000173

Lisman, J. E., & Grace, A. A. (2005). The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron, 46*(5), 703-713. doi: 10.1016/j.neuron.2005.05.002

Manahan-Vaughan, D., & Kulla, A. (2003). Regulation of depotentiation and long-term potentiation in the dentate gyrus of freely moving rats by dopamine D2-like receptors. *Cereb Cortex, 13*(2), 123-135.

McNamara, C. G., Tejero-Cantero, A., Trouche, S., Campo-Urriza, N., & Dupret, D. (2014). Dopaminergic neurons promote hippocampal reactivation and spatial memory persistence. *Nat Neurosci, 17*(12), 1658-1660. doi: 10.1038/nn.3843

Miendlarzewska, E. A., Bavelier, D., & Schwartz, S. (2016). Influence of reward motivation on human declarative memory. *Neurosci Biobehav Rev, 61*, 156-176. doi: 10.1016/j.neubiorev.2015.11.015

Montgomery, A. J., McTavish, S. F., Cowen, P. J., & Grasby, P. M. (2003). Reduction of brain dopamine concentration with dietary tyrosine plus phenylalanine depletion: an [11C]raclopride PET study. *Am J Psychiatry, 160*(10), 1887-1889. doi: 10.1176/appi.ajp.160.10.1887

Murayama, K., & Kuhbandner, C. (2011). Money enhances memory consolidation--but only for boring material. *Cognition, 119*(1), 120-124. doi: 10.1016/j.cognition.2011.01.001

Norimoto, H., Makino, K., Gao, M., Shikano, Y., Okamoto, K., Ishikawa, T., . . . Ikegaya, Y. (2018). Hippocampal ripples down-regulate synapses. *Science, 359*(6383), 1524-1527. doi: 10.1126/science.aao0702

Patil, A., Murty, V. P., Dunsmoor, J. E., Phelps, E. A., & Davachi, L. (2017). Reward retroactively enhances memory consolidation for related items. *Learn Mem, 24*(1), 65-69. doi: 10.1101/lm.042978.116

Pennartz, C. M., Lee, E., Verheul, J., Lipa, P., Barnes, C. A., & McNaughton, B. L. (2004). The ventral striatum in off-line processing: ensemble reactivation during sleep and modulation by hippocampal ripples. *J Neurosci, 24*(29), 6446-6456. doi: 10.1523/JNEUROSCI.0575-04.2004

Rasch, B., Buchel, C., Gais, S., & Born, J. (2007). Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science, 315*(5817), 1426-1429. doi: 10.1126/science.1138581

Rechtschaffen A, Kales A. (1968). A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. *Bethesda, MD: US Depart- ment of Health, Education and Welfare.*

Rudoy, J. D., Voss, J. L., Westerberg, C. E., & Paller, K. A. (2009). Strengthening individual memories by reactivating them during sleep. *Science, 326*(5956), 1079. doi: 10.1126/science.1179013

Sadowski, J. H., Jones, M. W., & Mellor, J. R. (2016). Sharp-Wave Ripples Orchestrate the Induction of Synaptic Plasticity during Reactivation of Place Cell Firing Patterns in the Hippocampus. *Cell Rep, 14*(8), 1916-1929. doi: 10.1016/j.celrep.2016.01.061

Schultz, W. (2007). Multiple dopamine functions at different time courses. *Annu Rev Neurosci, 30*, 259-288. doi: 10.1146/annurev.neuro.28.061604.135722

Spaniol, J., Schain, C., & Bowen, H. J. (2014). Reward-enhanced memory in younger and older adults. *J Gerontol B Psychol Sci Soc Sci, 69*(5), 730-740. doi: 10.1093/geronb/gbt044

Staresina, B. P., Bergmann, T. O., Bonnefond, M., van der Meij, R., Jensen, O., Deuker, L., . . . Fell, J. (2015). Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. *Nat Neurosci, 18*(11), 1679-1686. doi: 10.1038/nn.4119

Studte, S., Bridger, E., & Mecklinger, A. (2017). Sleep spindles during a nap correlate with post sleep memory performance for highly rewarded word-pairs. *Brain Lang, 167*, 28-35. doi: 10.1016/j.bandl.2016.03.003

Takano, A., Suhara, T., Yasuno, F., Suzuki, K., Takahashi, H., Morimoto, T., . . . Okubo, Y. (2006). The antipsychotic sultopride is overdosed--a PET study of drug-induced receptor occupancy in comparison with sulpiride. *Int J Neuropsychopharmacol, 9*(5), 539-545. doi: 10.1017/S1461145705006103

Takeuchi, T., Duszkiewicz, A. J., Sonneborn, A., Spooner, P. A., Yamasaki, M., Watanabe, M., . . . Morris, R. G. (2016). Locus coeruleus and dopaminergic consolidation of everyday memory. *Nature, 537*(7620), 357-362. doi: 10.1038/nature19325

Tononi, G., & Cirelli, C. (2014). Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. *Neuron, 81*(1), 12-34. doi: 10.1016/j.neuron.2013.12.025

Valdes, J. L., McNaughton, B. L., & Fellous, J. M. (2015). Offline reactivation of experience-dependent neuronal firing patterns in the rat ventral tegmental area. *J Neurophysiol, 114*(2), 1183-1195. doi: 10.1152/jn.00758.2014

van de Ven, G. M., Trouche, S., McNamara, C. G., Allen, K., & Dupret, D. (2016). Hippocampal Offline Reactivation Consolidates Recently Formed Cell Assembly Patterns during Sharp Wave-Ripples. *Neuron, 92*(5), 968-974. doi: 10.1016/j.neuron.2016.10.020

Walker, M. P., Brakefield, T., Seidman, J., Morgan, A., Hobson, J. A., & Stickgold, R. (2003). Sleep and the time course of motor skill learning. *Learning and Memory, 10*, 275–284.

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol, 54*(6), 1063-1070.

Wilhelm, I., Diekelmann, S., Molzow, I., Ayoub, A., Molle, M., & Born, J. (2011). Sleep selectively enhances memory expected to be of future relevance. *J Neurosci, 31*(5), 1563-1569. doi: 10.1523/JNEUROSCI.3575-10.2011

Wilkerson, A., & Levin, E. D. (1999). Ventral hippocampal dopamine D1 and D2 systems and spatial working memory in rats. *Neuroscience, 89*(3), 743-749.

Wilson, M. A., & McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science, 265*(5172), 676-679. doi: 10.1126/science.8036517

Wittmann, B. C., Schott, B. H., Guderian, S., Frey, J. U., Heinze, H. J., & Duzel, E. (2005). Reward-related FMRI activation of dopaminergic midbrain is associated with enhanced hippocampus-dependent long-term memory formation. *Neuron, 45*(3), 459-467. doi: 10.1016/j.neuron.2005.01.010

Wolosin, S. M., Zeithamova, D., & Preston, A. R. (2012). Reward modulation of hippocampal subfield activation during successful associative encoding and retrieval. *J Cogn Neurosci, 24*(7), 1532-1547. doi: 10.1162/jocn_a_00237

Tables

Table 1. Memory Tasks. Mean (±SEM) values are provided for the sulpiride and placebo conditions. Motivated Learning Task (MLT): d-prime 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 percent 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. Additionally, the absolute difference (Retrieval-Learning) and percent of learning (Retrieval/Learningx100) are provided. Word-pair task: total amount of recalled words is given for the criterion trial during the Learning Phase and the recall trial during the Retrieval Phase. Also, the absolute difference (Retrieval-Learning) and percent of learning (Retrieval/Learningx100) are provided: **ns: p > .10.**

	Placebo		Sulpiride		P-value
MLT Learning Phase					
High reward	2.58	(0.22)	2.65	(0.20)	ns
Low reward	1.66	(0.20)	1.75	(0.24)	ns
Long duration	2.10	(0.21)	2.15	(0.22)	ns
Short duration	1.90	(0.18)	1.98	(0.21)	ns
MLT Retrieval Phase					
High reward	1.87	(0.19)	1.77	(0.18)	ns
Low reward	0.99	(0.20)	1.09	(0.25)	ns
Long duration	1.52	(0.16)	1.33	(0.19)	ns
Short duration	1.05	(0.15)	1.20	(0.14)	ns
Finger Tapping					
Correctly tapped sequences					
Learning Phase	22.63	(1.40)	21.01	(1.51)	ns
Retrieval Phase	26.00	(1.71)	23.41	(1.72)	0.069
Absolute Difference	3.37	(0.83)	2.40	(0.68)	ns
% of Learning	115.47%	(3.72%)	112.18%	(3.63%)	ns
Error rates					
Learning Phase	0.07	(0.02)	0.13	(0.03)	0.089
Retrieval Phase	0.09	(0.02)	0.07	(0.01)	ns
Absolute difference	1.71	(2.08)	-5.71	(2.61)	0.059
Control Sequence					
Correct Sequences	18.65	(1.70)	18.69	(1.46)	ns
Error rate in percent	9.85%	(1.68)	9.31%	(1.76)	ns
Word-pairs					
Blocks to criterion	1.59	(0.17)	1.76	(0.16)	ns
Learning Phase	29.59	(0.96)	31.47	(0.88)	0.052
Retrieval Phase	28.06	(1.59)	29.47	(1.22)	ns
Absolut Difference	-1.53	(0.98)	-2.00	(0.78)	ns
% of Learning	94.09%	(3.57%)	93.57%	(2.61%)	ns

Table 2. Motivated Learning Task Additional Response Information. 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. ns: p > .10.

	Placebo		Sulpiride		P-value
Hits					
Learning Phase					
High reward	0.79	(0.04)	0.82	(0.03)	ns
Low reward	0.76	(0.04)	0.79	(0.03)	ns
Long duration	0.80	(0.03)	0.82	(0.03)	ns
Short duration	0.75	(0.04)	0.78	(0.03)	ns
Retrieval Phase					
High reward	0.69	(0.05)	0.63	(0.04)	ns
Low reward	0.64	(0.04)	0.64	(0.04)	ns
Long duration	0.73	(0.04)	0.65	(0.05)	0.028
Short duration	0.59	(0.05)	0.62	(0.04)	ns
False Alarms					
Learning Phase					
High reward	0.07	(0.02)	0.09	(0.03)	ns
Low reward	0.23	(0.05)	0.25	(0.05)	ns
Retrieval Phase					
High reward	0.14	(0.03)	0.12	(0.03)	ns
Low reward	0.31	(0.06)	0.29	(0.06)	ns
Response Bias					
Learning Phase					
High reward	0.37	(0.08)	0.29	(0.09)	ns
Low reward	0.02	(0.11)	-0.01	(0.11)	ns
Retrieval Phase					
High reward	0.36	(0.13)	0.50	(0.11)	ns
Low reward	0.09	(0.13)	0.15	(0.11)	ns

Table 3. Control Measures. Mean (±SEM) values are provided for the sulpiride 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) long-term retrieval capabilities**. ns: p > .10.**

	Placebo		Sulpirid		P-value
SSS					
Before Learning	2.94	(0.16)	2.94	(0.26)	ns
After Learning	3.71	(0.27)	4.47	(0.26)	0.014
Before retrieval	2.29	(0.22)	3.00	(0.32)	0.090
After Retrieval	2.71	(0.19)	3.00	(0.33)	ns
Positive Affect (PANAS)					
Before Learning	2.42	(0.09)	2.48	(0.13)	ns
After Learning	1.91	(0.15)	1.77	(0.13)	ns
Before retrieval	2.58	(0.16)	2.18	(0.15)	0.039
After Retrieval	2.32	(0.12)	2.15	(0.14)	ns
Negative Affect (PANAS)					
Before Learning	1.08	(0.03)	1.06	(0.04)	ns
After Learning	1.04	(0.01)	1.01	(0.01)	0.056
Before retrieval	1.02	(0.01)	1.01	(0.01)	ns
After Retrieval	1.02	(0.03)	1.01	(0.01)	ns
PVT					
Before Learning	3.56	(0.09)	3.59	(0.07)	ns
After Learning	3.45	(0.10)	3.45	(0.09)	ns
Before retrieval	3.54	(0.10)	3.55	(0.08)	ns
After Retrieval	3.53	(0.10)	3.33	(0.07)	0.006
WFT					
Category	20.18	(0.91)	20.24	(1.26)	ns
Letter	19.94	(1.01)	20.12	(1.39)	ns

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Curriculum vitae

Marjan Alizadeh Asfestani

INFO:
Address: Schönbuchweg7, Kusterdingen, 72127 Germany
Telephone: (+49)17672181482
Email: marjan.alizadeh-asfestani@uni-tuebingen.de

Education

Ph.D. in Neuroscience, 2013-2019
University of Tübingen, Germany
Dissertation:
Neurochemical mechanisms underlying sleep-dependent memory processing.
Supervisors: Prof. Dr. Jan Born and Dr. Gordon. B Feld

M.Sc. of General Psychology, 2008-2011
Tarbiat Modares University, Tehran, Iran
GPA : 18.6/20.
- Honored as top student

B.Sc. of Clinical Psychology 2002-2007
Science and Culture University, Tehran, Iran

Publications

Alizadeh Asfestani, M. Braganza, E.Schwidetzky, J.Santiago, J.Soekadar, S.Born, J.Feld, G. B.(2018).Overnight memory consolidation facilitates rather than interferes with new learning of similar materials — a study probing NMDA receptors.Neuropsychopharmacology, vol.43, issue 11. doi: https://www.nature.com/articles/s41386-018-0139-0

Alizadeh Asfestani, M. Brechtman,V. Santiago, J. Inostroza, M. Born, J. Feld, GB(2019). Consolidation of reward memory during sleep does not require dopaminergic activation. Submitted Pre-print available on bioRxiv.
https://www.biorxiv.org/content/10.1101/703132v1?rss=1

Feld, GB. Bergmann, T. **Alizadeh Asfestani, M.** Stuke, Wriede, Soekadar, J. Born, J. Blocking metabotropic glutamate receptor 5 during sleep in humans alters sleep-specific oscillatory activity, but leaves memory intact. Manuscript in preparation.

Accomplished Projects

Surveying Sleep Dependent Memory Consolidation in Patients with REM sleep Behaviour Disorder (RBD).

Exploring the environmental context effect on new learning.