Dual Perspectives

Dual Perspectives Companion Paper: Sleep to Remember, by Susan J. Sara

Sleep Is for Forgetting

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It is possible that one of the essential functions of sleep is to take out the garbage, as it were, erasing and "forgetting" information built up throughout the day that would clutter the synaptic network that defines us. It may also be that this cleanup function of sleep is a general principle of neuroscience, applicable to every creature with a nervous system.

Key words: **depotentiation; development; mental health; noradrenaline; REM sleep; spindles; theta; TR sleep**

Introduction

In this article, I discuss and illustrate the importance of forgetting for development, for memory integration and updating, and for resetting sensory-motor synapses after intense use. I then introduce the mechanisms whereby sleep states and traits could serve this unique forgetting function separately for memory circuits within reach of the locus coeruleus (LC) and those formed and governed outside its noradrenergic net. Specifically, I talk about the role of rapid eye movement (REM) and transition-to-REM (TR) sleep for hippocampal and somatosensory memories and the role of slow-wave sleep (SWS) for memories guided by the dorsal striatum (e.g., motor and procedural learning). Finally, I talk about mental health disorders, such as schizophrenia, posttraumatic stress disorder (PTSD), and autism, memory disorders like Alzheimer's disease, and movement disorders, such as Parkinson's disease, in light of these important sleep-dependent forgetting functions and in light of treatment considerations.

Forgetting to avoid saturation

As pointed out in the article titled "Sleep to Remember" by Susan Sara in this issue, Jenkins and Dallenbach (1924) were the first to demonstrate experimentally that sleep preserved memory from gradual degradation over time. They called this gradual rate of forgetting "obliviscence." However, the type of forgetting we will discuss in this article is not passive obliviscence, but rather the active, targeted erasure of synapses. It is what Crick and Mitchison (1983) had in mind when they hypothesized that REM sleep was for forgetting useless tidbits of information learned throughout the day that, if not eliminated, would soon saturate the memory synaptic network with junk. Therefore, the type of forgetting we will discuss here is also not the global synaptic weight downscaling of the synaptic homeostasis hypothesis (SHY) (Tononi and Cirelli, 2003), although evidence from excellent experiments used to support the idea of sleep for synaptic homeostasis will be used to make points here. Instead, this article will present lines of evidence supporting the idea that, whereas synaptic strengthening underlying learning (long term potentiation, or LTP) can be accomplished either in waking or sleep (Bramham and Srebro, 1989), (1) it is the targeted erasure of synapses that is unique to sleep, (2) this targeted forgetting is necessary for efficient learning, and (3) deficits in this process may underlie various kinds of intellectual disabilities and mental health problems.

At a time when most studies regarding sleep and learning were supporting the function of REM sleep for remembering, Nobel laureate Francis Crick and his colleague Graham Mitchison published a speculative article (Crick and Mitchison, 1983) postulating that REM sleep might be for forgetting. They proposed that REM sleep is for forgetting all those extraneous things one learns during the day that, if not disposed of, would cloud and confuse cognitive access to the important knowledge we must use to survive. They argued that all the experiences of the day need not be remembered and that, indeed, if all were retained, they would create a white noise problem wherein all modifiable synapses would eventually saturate with LTP and any incoming input would cause excitation that would spread like wildfire from circuit to circuit without distinction. Their hypothesis was purely theoretical. Evidence will be presented here, from my own and other studies, that the ideas of Crick and Mitcheson were prescient and have been amply born out and expanded in multiple experiments.

Hippocampal activity for forgetting during REM sleep

One way to test whether Crick and Mitcheson were right that sleep was for forgetting, or whether instead, sleep was for remembering is to test the activity of hippocampal neurons during sleep. The hippocampus is a temporary rapid assembly area for mem-

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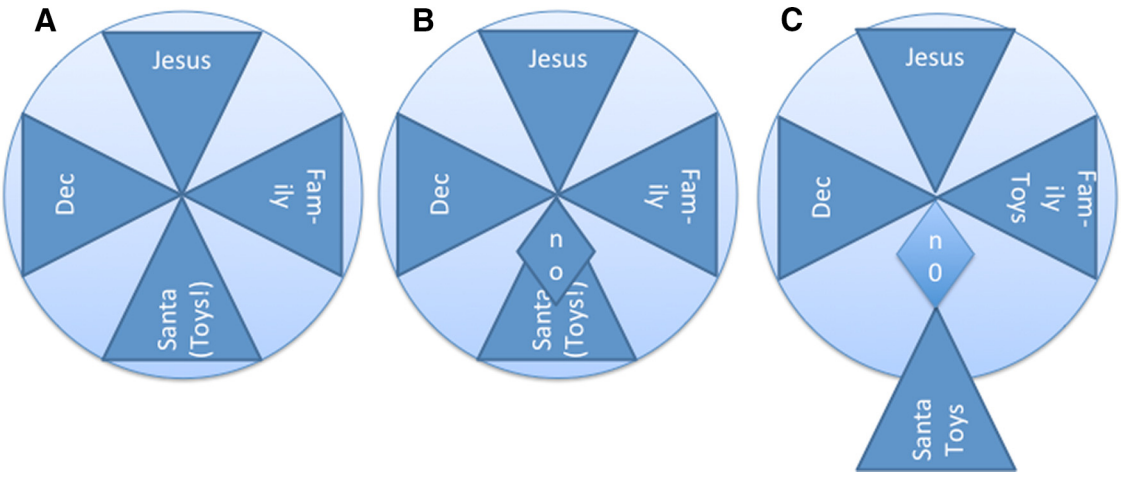

Figure 1. Graphic depiction of the importance of weakening synapses to incorporate new information into old schemas. ***A***, A simplified Christmas schema as might be presented to a small child. ***B***, When that child first learns that Santa is a myth and therefore cannot bring the toys, the new information is laid upon the schema during waking. ***C***, During sleep, the old schema is updated with the new information tying the gifts to the family members and inserting a "no" to the "Santa Toys" item information for an altered but singular schema of Christmas. Depotentiation of the old Santa belief is necessary to form this coherent new schema and make it accessible without confusion.

ory. Hippocampal synapse numbers are limited compared with those contained in the entire neocortical mantle, where long-term memories are thought to be stored in a parallel, distributed fashion (Lashley, 1950). The hippocampus forms initial associative memories and temporarily stores them until they are consolidated to the neocortex. It is logical, therefore, that the hippocampal network of weighted synapses involved with already consolidated memories should be recycled for future differential weighting, such that it is free to form new associative links during future learning involving other sets of hippocampal functional assemblies.

Hippocampal place cells form a functional assembly to map an animal's environment. Place cells are most active at the peaks of theta frequency (5–10 Hz) local field potential patterns during active waking. Such theta peak activity is consistent with strengthening synapses (LTP) during the learning process. Theta peaks correspond to the maximum depolarization phase of the cell membrane during the theta cycle, and such subthreshold membrane depolarization allows neuron to respond robustly to inputs, e.g., as the neuron discharges through the place field (Buzsáki et al., 1983; Fox et al., 1986). Pavlides et al. (1988) found that stimulation on the positive phase of the hippocampal theta rhythm induced LTP whereas stimulation at the opposite phase, the theta trough, induced a decrease in synaptic efficacy (depotentiation). Huerta and Lisman (1995) and others have replicated this robust finding. I hypothesized that, if REM sleep is for learning, then place cells should reactivate during REM sleep in a manner consistent with LTP, at theta peaks, as during a learning session. We found that neurons active in novel places did indeed discharge at the peaks of local theta oscillations in REM sleep (Poe et al., 2000) as they had in waking. If REM sleep were for forgetting, however, place cells should be active during REM sleep at the troughs of theta, which is the phase at which Pavlides et al. (1988) and Huerta and Lisman (1995) found that stimulation induced a decrease in synaptic efficacy (depotentiation). We found that, once the place became familiar to the animal, the place cells reversed their primary firing phase with respect to local theta oscillations during REM sleep (Poe et al., 2000).

The time course over which place cells switched from the novel peak firing pattern in REM sleep to the familiar trough firing pattern corresponded with the timescale of memory consolidation from the hippocampus to storage places outside the hippocampus as described by Kim and Fanselow (1992). Such theta trough firing could accomplish the refreshing of synapses that had encoded already-consolidated memories. However, not yet consolidated memories remain reactivated at theta peaks (Poe et al., 2000), consistent with a synaptic strengthening and remembering function of REM sleep for these memories that have not been "downloaded" to the neocortex. Thus, REM sleep would serve to maintain or strengthen memories until they are transferred outside the hippocampus whereupon they should be erased from that space-limited short-term memory factory, allowing those synapses to be used to encode new associative memories.

Forgetting necessary to incorporate novel information into established schema

Depotentiation, the reverse of LTP, is also induced by learning, such as during novel spatial exploration (Xu et al., 1998), and seems to be necessary to encode the introduction of new stimuli in a familiar contextual schema (Kemp and Manahan-Vaughan, 2004). The updating of schema, a term used here to represent related memory sets, such as the set of place memories associated with the concept of "home," is a function important for cognition (Manahan-Vaughan and Braunewell, 1999; Braunewell and Manahan-Vaughan, 2001; Nakao et al., 2002). The hypothesis that REM sleep is a unique time for forgetting would predict that any learning that requires depotentiation would be compromised by its disturbance. One type of learning that requires forgetting is reversal learning, requiring the update of schemas in light of new information. For example, the Christmas schema taught to children in Western culture is, broadly, that Christmas is Jesus' birthday, celebrated in December, involves family gathering, and Santa bringing toys (Figure 1). At some point, however, we must refine this schema to put a "Not" flag on the idea that Santa brings toys. Santa remains part of the schema, but the memory, the Christmas schema, must be refined and reworked when we learn that Santa bringing toys to all good girls and boys is a myth. If the loosening or weakening (depotentiation) of at least some synaptic connections encoding the original schema network does not occur after presentation of the new information, then we would be redundantly connected with conflicting information,

which can be imagined as short-circuiting during memory recall, rendering one prone to confusion as to what is true and what is myth.

Targeted forgetting is unique to sleep

Forgetting only possible without norepinephrine (NE)

The theta phase specificity of experience-dependent reactivation in the hippocampus revealed an elegant sleep-dependent memory function. Why would such an important a function as rewiring a memory schema not occur during waking? A coherent line of evidence replicated in multiple studies indicates that the depotentiation step in the rewiring process is only reliably induced in the absence of norepinephrine (NE). NE, working at both β ands α1 receptors, blocks depotentiation and enhances LTP (Thomas et al., 1996; Katsuki et al., 1997; Yang et al., 2002). Either stimulation of the nucleus that provides NE to the forebrain, the LC, or direct application of NE through intracerebroventricular infusion enhances and prolongs LTP (Almaguer-Melian et al., 2005). Tom O'Dell's work, recently reviewed in *Neuron* (O'Dell et al., 2015), shows in mechanistic detail how NE acts at β receptors to enhance LTP and prevent synaptic weakening. A few seconds of LC silence is enough to neutralize the effects of NE in the cell and allow depotentiation. In the following paragraph, I will introduce how sustained LC silence (for a few seconds or more) normally only occurs during sleep.

NE's source (LC) off in REM and transition to REM sleep spindles

REM sleep is a time when noradrenergic cells in the LC are suppressed in rats and cats studied (Aston-Jones and Bloom, 1981; Nitz and Siegel, 1997). Noradrenergic neurons that provide NE to the forebrain are tonically active in all states except REM sleep (Aston-Jones and Bloom, 1981). The only other time when LC neurons are silent is during sleep spindles: 1- to 2-s-long spindle-shaped waveforms that appear during non-REM (NREM) sleep in the transition to REM (TR, called Stage 2 in human sleep records). Noradrenergic neurons fall silent in the second or more preceding each spindle (Aston-Jones and Bloom, 1981). Indeed, a second or two of LC silence during NREM sleep may be necessary to hyperpolarize the neurons that generate these sleep spindles. The absence of NE allows the reticular neurons in the thalamus to hyperpolarize (Lee and McCormick, 1996) until they emit Ca^{2+} spikes in the spindle frequency (11–16 Hz). Thus, these reticular neurons coordinate spindles (Gardner et al., 2013). The presence of spindles characterizes this TR state of NREM sleep. Because depotentiation requires the sustained absence of NE, it is likely that depotentiation may only be possible during these two NE free states: normal REM sleep and TR. This lack of NE is likely important for all learning that requires depotentiation (exception: motor learning, which is guided by the dorsal striatum—see Parkinson's disease, below). Thus, REM sleep and TR are perhaps the only times when synaptic circuits within reach of the LC could be refreshed and reset from the day's relentless accumulation of connectivity.

Sleep spindles allow hippocampal-cortical interactions to reshape schema

Romcy-Pereira and Pavlides (2004) and Wierzynski et al. (2009) found that transmission between the hippocampus and the medial prefrontal cortex is strongest during the TR sleep state. The two areas do not fire together during REM sleep; coherence timing of prefrontal activity in relation the hippocampus is relatively poor. Nor would consolidation-related transfer of information to the prefrontal cortex occur in the majority, nonspindle state of SWS as the prefrontal cortex is largely inactive except at the peaks of slow waves. Instead, waking and TR sleep states have the highest coherence between the hippocampus and prefrontal cortex (Siapas and Wilson, 1998; Wierzynski et al., 2009). If neuronal activity between the hippocampal output CA1/subiculum region and prefrontal cortex are coordinated during spindles or during theta/spindle complexes while NE is absent and serotonin levels are low (see Serotonin and reconsolidation), then the hippocampus could induce the same kind of targeted bidirectional synaptic reorganization in the prefrontal cortex during the NREM TR state that it accomplishes within itself during REM sleep.

Sleep spindles present a vulnerable time for schema modifications

During sleep spindle reactivations, however, when the LC is silent, overlapping memories are uniquely vulnerable to depotentiation. Perhaps the TR state is so short (10–20 s per sleep cycle in rats and ~30–60 s in humans) precisely because it is such a powerful time for bidirectional plasticity. Reactivation of memory circuits during spindles would leave other inactive memory traces that use some of the same neurons in different sets (orthogonally encoded memories) vulnerable to degradation through a process called heterosynaptic depotentiation (see Acetylcholine, spike timing-dependent plasticity). It is possible that the only networks reactivated during these highly plastic LC-free sleep spindles are those encoding schema that need to be altered by novel information acquired during prior waking. This possibility would be difficult to test, but one would hope it to be the case, as during a time of such metaplasticity, any reactivated or orthogonally encoded memory network would be inadvertently modified.

NE bursts may terminate sleep spindles and serve to bind novel and familiar schema elements

It could also be important that a burst of LC neuronal firing comes midway through spindle-associated reactivations (Aston-Jones and Bloom, 1981). Such burst-associated release of NE could deliver significant amounts of NE to active forebrain circuits and serve to reestablish LTP, rebinding the network that was made metaplastic by reactivation, knitting the old, loosened network together with new elements. If the mid-spindle LC burst is prevented (e.g., through degeneration or silencing LC noradrenergic neurons), then spindle-associated reactivations might fail to bind the new elements and more may be lost than gained. Detailed study of the specific timing of reactivated neuronal sequences and of orthogonally encoded memories over the course of the sleep spindle is warranted.

Targeted forgetting essential to developing circuits

Establishing experience-dependent memory circuits involves two sides of circuit formation: LTP and depotentiation, followed by pruning of unused or extraneous synapses at the close the critical period. Synapse elimination is essential in every developing circuit with experience-dependent refinement, including muscle innervation, imprinting, visual cortex development, etc. The loss of redundant or extraneous synapses that would have encoded other unreinforced stimuli occurs, according to the theory I am building here, during sleep after critical-period learning has occurred. I hypothesize that sleep-dependent depotentiation followed by pruning is likely a crucial part of the closing of the critical period, which probably also involves the collapse of the extracellular matrix over pruned axonal input paths.

Interestingly, REM sleep is especially abundant during early development. At birth, half or more of our sleep time is occupied by REM sleep, whereas it occupies <20% of sleep in adults

(Roffwarg et al., 1966). A 40%–50% decrease in dendritic spines occurs in zebra finches and mynah birds as they learn to vocalize songs or words (Rausch and Scheich, 1982; Wallhäusser-Franke et al., 1995). Derégnaucourt et al. (2005) found that in juveniles learning their song, sleep each night reduced song complexity that had built up over the day. In the morning, the noise that had invaded the song the day before was gone, whereas correct song elements were preserved. Shank and Margoliash (2009) confirmed and extended both of these findings, showing that the entropy in song elements that had built up during the day was cleared after high-frequency neural activity during the night's sleep.

Similarly, when imprinting occurs, a young animal must learn the features of the parent, and prune multiple other synaptic connections not associated with features of the parent (Bock and Braun, 1998). Such process of imprinting is followed by immediate and impressive increases in REM sleep (Solodkin et al., 1985). Sir Gabriel Horn's laboratory performed an arduous experiment gently disturbing the sleep of chicks in the hours immediately following their imprinting experience. Behavioral data showed that the chicks did not selectively imprint on the features of the presented stimulus. Electrophysiological data were consistent with the idea presented here that without proper REM and TR sleep, neurons remained overconnected in the imprinting circuitry (Jackson et al., 2008). If pruning fails, the synapses encoding alternate features remain in place and the animal will remain open to imprinting on features of other individuals (e.g., strangers or predators) and would follow them indiscriminately. Imprinting is a good example of the importance of targeted forgetting for survival.

Targeted forgetting essential throughout the lifespan

Depotentiation is essential in every circuit that continues to be refined by experience throughout the lifespan. Both REM and TR sleep rise during intensive learning periods (Datta et al., 2004; Mavanji et al., 2004). Sleep also serves a critical role in resetting the synaptic weights of primary sensory areas undergoing continuous amplification during waking. Sleep processes of targeted depotentiation can reset these circuits after waking overuse, maintaining and restoring them to their postcritical period baseline strength, and thereby restoring the network. David Blake and Fabrizio Strata, working in Michael Merzenich's laboratory, observed that when monkeys who were learning a cortical receptive field somatosensory task (Blake et al., 2005) fell asleep in the recording chair, receptive fields would reset to pretraining baseline representation only after the occurrence of REM sleep; NREM sleep left the enlarged representation of the trained fingertips unchanged (Blake and Merzenich, 2002). Many studies have shown that wakefulness spanning the time from training to testing, without intervening sleep, interferes with memory performance (e.g., Wamsley et al., 2010; Jenkins and Dallenbach, 1924). If only LTP is possible during wakefulness, confusion is inevitable. Perhaps, indeed, the "obliviscence" induced by extended wakefulness is actually due to a buildup of interference, rather than slow forgetting due to synaptic weakening. Slowly saturating circuits would result in a loss of specificity and clarity of information traces.

It is possible that, without such nightly reset, better imagined as a nightly noise reduction session, each day's experience, including acquired errors, would overly influence future perception and behavior. Need for a protected time away from waking sensory interference to emboss memories (Ribeiro and Nicolelis, 2004), raising important memories above the noise by eliminating noise, was proposed by Jenkins and Dallenbach in 1924 (Jenkins and Dallenbach, 1924) and by Melton and Irwin in 1940 (Melton and Irwin, 1940).

The mechanisms for such memory circuit distinction, or embossing, have been explored by Winson (1990), McClelland et al. (1995), Dave and Margoliash (2000), and Ribeiro et al. (1999, 2002; Ribeiro and Nicolelis, 2004), among others. One example of the importance of sleep to reset erroneous learning was an ingenious experiment (Hoedlmoser et al., 2015) wherein experienced bicycle riders were trained to ride a bicycle with a reversed handle bar steering system, training in three 15 min sessions. If the riders were allowed a 2 h window to nap after this oddball 3-session experience (enough time for a full sleep cycle, including REM), the subjects were more likely to forget the oddball training, erasing the sensorimotor learning gains, than those who did not sleep. Furthermore, the amount of REM sleep obtained and the density of sleep spindles in the nap group correlated with their performance "decrement": they reset to default (nonreversed) steering techniques. The authors interpret their findings to mean that REM and TR sleep spindles might protect everyday, needed skills like riding a bicycle by forgetting the interfering, irrelevant material acquired in the oddball experience before sleep.

Preventing forgetting during reconsolidation interferes with schema

In a study looking at rats' ability to disambiguate between two similar contexts, we found that the presence of NE during sleep corrupted the familiar schema as well as interfered with consolidation of the new experience (Watts et al., 2012). We hypothesize that this learning deficit was due to the inability to depotentiate critical synapses, causing confusion between the two schemas. This memory network corruption was proportional to the amount of time spent in the TR state with NE present. As mentioned earlier, this TR state, when the hippocampus and cortex uniquely synchronize during sleep spindles to transfer of memory from the hippocampus to the neocortex (Siapas and Wilson, 1998; Wierzynski et al., 2009), is a vulnerable period when memories can be modified. When memory reactivation occurs during sleep spindles without the ability to depotentiate synapses, circuits requiring reconsolidation become entangled.

A schematic of this disambiguation process during reconsolidation is shown in Figure 2. Imagine you just met your child's teacher, who is named Gwen. The name Gwen, however, is firmly associated in your memory networks with your grandmother, who is also named Gwen. Your grandmother's looks, facts about her life, experiences with her, and her personality traits have been firmly consolidated. When you are consolidating the new contact Gwen during sleep, the name is reactivated with the newly established memory network (semantic facts about the teacher Gwen), but your grandmother's network would only be partially coactivated. Without noradrenaline, synapses to and from the name Gwen to the silent components of the memory associated with your grandmother would be at risk through heterosynaptic potentiation. Noradrenaline preserves the memory network associated with your grandmother even while it allows the new network to be consolidated.

Serotonin and reconsolidation

To round out the picture for targeted forgetting, the absence of serotonin during REM sleep may be as important as the absence of NE to the process of synapse-specific memory reformation during REM sleep. Serotonin is present in the hip-

pocampus in all states but is vastly diminished in REM sleep (Park et al., 1999), when dorsal raphe serotonergic neurons are inactive (McGinty and Harper, 1976). Kemp and Manahan-Vaughan (2004) found that both depotentiation and habituation to an environment were inhibited by serotonin receptor ($5\text{-}HT_4$) agonist application. Another study showed that $5\text{-}HT_4$ agonist improved acquisition but post-training activation of $5\text{-}HT_4$ receptors impaired memory consolidation (Meneses and Hong, 1997), suggesting that the natural sharp reduction in serotonin during the post-training sleep consolidation period was essential.

One of the many functions of serotonin is to increase conductance through hyperpolarization-activated cyclic nucleotide-gated (HCN) potassium leak channels (I_h) present in abundance along distal dendrites (Gasparini and DiFrancesco, 1999; Migliore et al., 2004; Nolan et al., 2004). In the hippocampus, reduction of serotonin during REM sleep could allow depotentiation by reducing the HCN potassium leak and thus increasing the influence of distal inputs on the activity of neurons. Because such distal inputs arriving from layer 3 of the entorhinal cortex are familiarity-encoding (Vinogradova, 2001) and arrive at opposite phases of theta as the novelty-encoding proximal inputs, REM sleep reductions in serotonin would allow the CA1 neurons to fire action potentials at odd times in relation to the usually dominant proximal novelty-encoding inputs. When CA1 postsynaptic cells fire while their CA3 novelty-encoding inputs are silent, heterosynaptic depotentiation of novelty-encoding pathways can occur. This mistimed CA3-CA1 firing is more likely once the synapses at distal inputs have been strengthened through the memory consolidation process (Booth and Poe, 2006). This consolidation-dependent strengthening of distal inputs is a candidate "tag" that a memory is familiar within the hippocampal circuit and can therefore be depotentiated in the novelty-encoding CA3-CA1 synapses. Indeed, strengthening of distal inputs combined with the absence of serotonin is the signal allowing the theta trough activity that (in the absence of NE) induces such depotentiation. Such proximal-distal dendritic spatial distribution patterns of serotonin-sensitive HCN channels also occurs throughout the cortex. Thus, the loss of serotonin in REM sleep may complement the loss of NE to serve a similar depotentiation function globally in forebrain circuits reached by the LC and dorsal raphe.

Can targeted forgetting occur in SWS?

We have spent time discussing mechanisms occurring during TR and REM sleep that would allow targeted forgetting, or depotentiation. Now we will explore whether the other NREM sleep state, SWS, could serve, under normal circumstances, to downscale potentiated synapses, as has been proposed by Tononi and Cirelli (2003). Their well-considered and heavily evidenced SHY hypothesis is in direct opposition to a strong line of research findings indicating that NREM sleep serves to reactivate prior waking memory circuits to strengthen them, as is covered by Dr. Sara in the "Sleep to Remember" article in this issue.

Depotentiation-related gene expression rises and LTP-related gene expression drops during sleep (Cirelli et al., 2004; Cirelli and Tononi, 2000a, b). A period of sleep also reduces the amplitude of slow waves, perhaps because fewer neurons synchronously fire at the peaks of each slow wave (e.g., Vyazovskiy et al., 2000; Steriade, 2004; Hanlon et al., 2009). Esser et al. (2006) showed a decline in evoked potentials across sleep, which they conclude is due to general synaptic downscaling. However, it is possible that this downscaling can occur during the TR and REM sleep times between SWS periods, and the reduction in slow-wave activity (SWA) from cycle to cycle may be due to the above discussed depotentiation function of these two states. Wilson and others (Wilson and McNaughton, 1994; Kudrimoti et al., 1999) have found that the highly correlated neuronal firing resulting from spatial learning on a maze decreases across the first 20–40 min of the start of SWA. However, the rodent sleep cycle is ~6 min long, and periods of TR have not generally been considered separate from SWS, with researchers lumping them together. Thus, such decrement in cross-correlated activity across 20–40 min may still be due to short periods of TR or REM sleep. Indeed, Buzsáki's group (Grosmark et al., 2012) showed that hippocampal firing rates increase across SWS and decrease across REM sleep, a result more consistent with depotentiation occurring in REM sleep. It is safe to say that whether slow waves serve a depotentiation or potentiation function remains unresolved and requires closer study, perhaps paying particular attention to TR sleep spindles and brain regions (see Striatocortical consolidation differences).

Would low acetylcholine, low Ca^{2+} influx, and backward reactivation cause forgetting in SWS?

One mechanism whereby slow-wave coincident reactivation could lead to synaptic downscaling or depotentiation consistent with the synaptic homeostasis hypothesis of Tononi and Cirelli, (2003) is the finding that slow waves activate voltage gated Ca^{2+} channels, allowing small amounts of calcium to enter. This small rise in intracellular Ca^{2+} would lead to depotentiation if not augmented by simultaneous presynaptic and postsynaptic depolarization. The majority of neuronal activity during slow waves does not contain a forward-ordered replay of the specific memory under study, and whether every burst of neural activity during every slow wave contains the ordered replay of some other memory is unknown (Foster and Wilson, 2006; Karlsson and Frank, 2009). However, a disordered replay (the majority of replays from the perspective of any one memory trace) would, in the absence of NE, cause heterosynaptic depotentiation through asynchronous activation of postsynaptic-then-presynaptic elements according to the rules of spike timing-dependent plasticity (Bi and Poo, 1998).

Acetylcholine is important to the induction of LTP in the intact animal and to learning in the hippocampus (Winson, 1978; Mizumori et al., 1990; Hasselmo and Bower, 1993; Givens, 1996; Rashidy-Pour et al., 1996a, b). If postsynaptic activity is also not amplified by muscarinic acetylcholine receptor activation during NREM sleep, then the intracellular cascade, absent a strong activation of β adrenergic receptors, would be set up to produce depotentiation instead of LTP. Indeed, cholinergic cells supplying the forebrain are off during NREM sleep, and acetylcholine levels plummet to all time lows during this state (Marrosu et al., 1995; Hassani et al., 2009). Without the intracellular LTP boost from acetylcholine, small rises in intracellular Ca^{2+} would set into motion a cascade of events that leads to depotentiation rather than LTP (for review, see Blitzer et al., 2005; O'Dell et al., 2015). Thus, through disordered reactivation of most memory traces on most slow waves and the absence of acetylcholine during SWS, the SHY hypothesis function of SWS is hypothetically possible except that for most animals studied the LC does not turn off during SWS, and remains as active as during quiet wakefulness. Thus, memory traces stored in areas of the forebrain guarded by the LC would not be vulnerable to depotentiation during SWS (although they would during TR and REM sleep, as explained above).

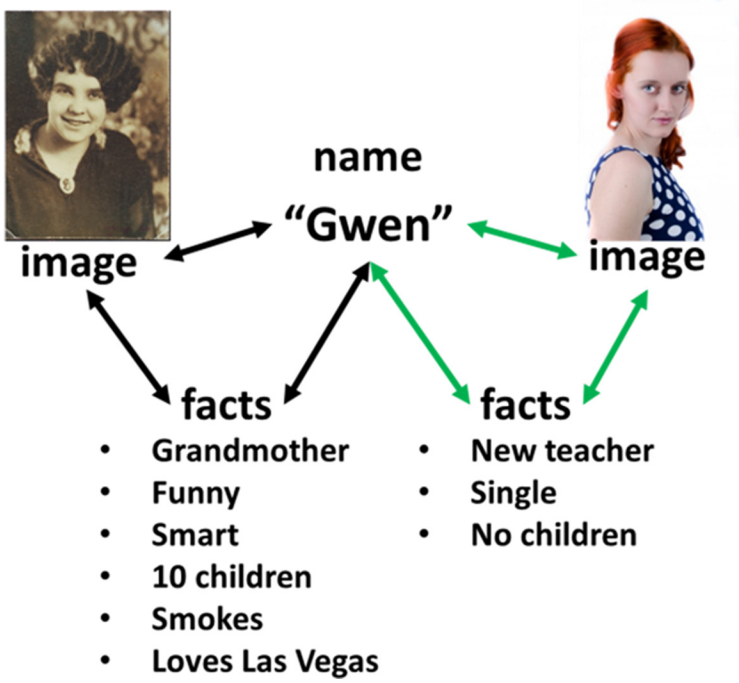

Figure 2. Disambiguating the teacher Gwen from the grandmother Gwen requires sleep-dependent consolidation of the novel information while protecting the grandmother schema.

NE could protect against spurious forgetting in SWS

A strong argument against the role of SWS in forgetting is the fact that noradrenergic neurons of the LC burst fire on the rising phase of each slow wave (Eschenko et al., 2012). Such burst, occurring ~120 ms before the peak of the slow wave, is precisely timed to deliver significant amounts of NE to forebrain synapses just as sharp-wave ripples reactivate neurons. The depotentiation-preventing action of NE would likely block synaptic downscaling of memories under the reach of the LC during SWA. The significance of this memory-guarding function of the LC in preventing memory loss will later be discussed in the context of Alzheimer's disease.

Dorsal striatal regulated memories may allow forgetting in SWS

The past few paragraphs have argued against the role of SWS in forgetting due to the presence of NE. However, there is one important circuit in the forebrain that lacks noradrenergic receptors and inputs from the LC: the dorsal striatum (Jones et al., 1977). Interestingly, dorsal striatal-dependent learning (e.g., motor learning and procedural memory) is also not affected by REM sleep disturbances and is instead dependent on SWS. Thus, SWS sleep may be able to function for forgetting in the dorsal striatum and related cortical targets, such as the motor cortex. Furthermore, dopamine has a similar effect of promoting LTP as does NE. Whereas somatosensory learning and hippocampal associative learning require REM and TR sleep for depotentiation, striatal-dependent learning may require a dip in dopamine as seen only during SWS (Léna et al., 2005).

Parkinson's disease treatment-related dykinesia may be prevented by cessation of L-dopa treatment during sleep

Long term L-dopa treatments for Parkinson's disease have resulted in dyskinesia movement disorders (Suarez et al., 2016) that could reflect a prevention of sleep-dependent depotentiation in the dorsal striatum. Inappropriate dopamine delivery to the dorsal striatum during this NREM sleep state could cause the same type of hypertrophic connectivity and accumulation of spurious synapses or abnormal enlarging of synapses as described in the section on monkey somatosensory learning, above. Future treatments for Parkinsons's disease may benefit from consideration of the synaptic strength reduction function of normal state-dependent drops in dopamine during sleep in the dorsal striatum.

Animal studies supporting a SHY hypothesis function of SWS use motor learning tasks under the regulation of the dorsal striatum. Dorsal striatal and somatosensory and hippocampal associative learning strategies are complementary learning systems. It is fascinating to think that destruction of neither the dopaminergic nor noradrenergic systems, or destruction of SWS or TR and REM sleep would entirely wipe out the ability for an animal to preserve or modify all memories. Such complementary redundancy in the survival-critical process of learning and memory is highly adaptive.

Mental health and neurological consequences when targeted forgetting fails

What we have reviewed thus far is that, for better or for worse, sleep that is characterized by a loss of noradrenergic and serotonergic tone (i.e., REM sleep and spindle-rich TR sleep) uniquely allows forgetting, or depotentiation, specifically in activated circuits targeted by the LC. In dorsal striatal-dependent learning and memory consolidation, SWS and dopamine likely replace TR/REM sleep and NE. Thus, under normal circumstances, particular states of sleep are required to achieve a balanced, carefully restructured memory network through a reconsolidation process that includes weakening of some synapses as well as strengthening others, and this balance cannot be achieved through waking rehearsal (mental practice) or waking restfulness (mental breaks) because of the neurochemical requirements associated with depotentiation.

Next, we will explore how the lack of this important depotentiation, or "forgetting," capability of sleep could lead to mental health and memory disorders. A number of mental health conditions and neurological diseases can be viewed in the light of a sleep forgetting function failure, with possible pathological consequences.

Schizophrenia

Schizophrenia is marked by a significant loss of sleep spindles (Ferrarelli et al., 2007; Wamsley et al., 2012). In an inspired experiment, Manoach and colleagues (Wamsley et al., 2012) reintroduced sleep spindles to schizophrenic patients through the use of ezsopiclone and tested whether their sleep-dependent memory consolidation would improve. They found that eszopiclone helped these schizophrenic patients to benefit from sleep consolidation. Given the mechanistic framework presented thus far, I propose that restoration of normal Stage 2 (TR in animals) sleep spindle function in these patients could help both negative (memory impairments) and positive (thought disorders) symptoms, especially when nightly normalized sleep is maintained in combination with daily therapy establishing what is real from what is not. Such treatment combination could also help those suffering from schizophrenia to update their in-

sight into their condition and increase their likelihood to seek and comply with treatments. It could also move them from Figure 1*B*, to *C*, disambiguating their schema of the world to render them more lucid and able to discern the real from the formerly believed.

Other psychiatric conditions are marked by large increases in TR sleep; whereas in normal human sleep, transitions are scored at <10%, under some conditions of psychiatric illness it can comprise up to 40% of total sleep time (Akindele et al., 1970; Nielsen, 2000). Very little overall time in any state may be necessary to accomplish depotentiation. Single bursts (lasting <100 ms) of stimuli timed to the troughs of ongoing theta have been shown to cause depotentiation (Huerta and Lisman, 1995). Effective forgetting could thus be obtained in only a few seconds of memory reactivation in the proper phase. Too much unguarded, indiscriminate depotentiation during the vulnerable bidirectionally plastic sleep phases could lead to unwanted disconnects and may, for example, explain the growing memory deficit pattern associated with Alzheimer's disease (see below).

PTSD and forgetting

Normally, the LC is active for 2–5 h after significant novel (nontraumatic) experiences. There is a plethora of secondary evidence of a hyper-reactive LC system during sleep in those suffering from PTSD (e.g., Mellman et al., 1995; Sara, 2009; van Liempt et al., 2013). Could PTSD be considered a failure of targeted forgetting while attempting to update schema? What would happen if the LC remained active during REM and TR sleep after a traumatic experience?

We measured sleep changes in rats that were, in the end, resilient to trauma exposure and did not display the PTSD phenotype (Vanderheyden et al., 2015). Susceptible rats showed an initial increase in REM within a few hours after the traumatic exposure, whereas resilient animals displayed initial insomnia during this period of high LC activity. Susceptible animals also showed a later reduction in REM sleep theta power, much like humans who were not resilient to trauma (Cowdin et al., 2014). Susceptible animals also developed reduced spindle frequency power and spindle counts in TR sleep. Interestingly, a gene variant that binds NE for less time at the β receptor is associated with resilience to PTSD (Liberzon et al., 2014). A gene that binds NE longer would likely not allow the few seconds of LC silence needed to unblock depotentiation mechanisms. Thus TR sleep could monolithically, unidirectionally potentiate recently activated trauma memory circuits, preventing the coherent incorporation of fear extinction information. Description of such a positive feedback loop involving memory reinforcement and saturation with LC overactivation can be found in Vanderheyden et al. (2014, their Fig. 2). PTSD, then, could be a problem of a hyperactive LC during sleep preventing the targeted forgetting function of normal sleep.

Autism-related failures to prune

Even autism, characterized by an overabundance of local dendrites that have not been pruned away, may have its roots in a lack of sleep-dependent pruning. Certainly, sleep disturbance in children with autism is one of the most prominent complaints voiced by the parents (Limoges et al., 2005; Veatch et al., 2015). Recently, a research group at Vanderbilt University found that autism is characterized by high sympathetic (NE) drive during sleep, as revealed in increased heart rate during sleep (Harder et al., 2016).

LC activity during NREM sleep guards against memory destruction

Given the possible high-NE related problems with sleep-dependent forgetting in PTSD, autism, and schizophrenia, why not suppress the LC during all sleep (e.g., as a prevention against PTSD and adding to the behavioral treatment regimen for autism)? One reason for caution is that the depotentiation of synapses is a dangerous capability within the circuits of our highly plastic brains. The behavioral states imbuing such capability need be tightly regulated, as must be the brain activity that occurs during those states, to avoid unnecessary losses. As mentioned above, normal SWS sees a spontaneous bursts in LC neurons precisely timed to the rising phase of the slow wave (Eschenko et al., 2012). Thus, LC firing precedes sharp-wave ripple memory circuit reactivation at the peaks of slow waves by ~120 ms. Such advance LC firing is perfectly timed to deliver NE to the forebrain at the onset of memory circuit reactivations, and through its depotentiation-preventing actions, such activity could serve to preserve orthogonally coded memories (using some of the same neurons) from spurious heterosynaptic depotentiation. In other words, LC bursts at critical moments during sleep would function to guard our schema in the face of many different patterns of activation during SWS.

An inappropriate loss of noradrenaline during stages of sleep when it should be present (i.e., SWS) could, for example, contribute significantly to the gradual loss of memory during Alzheimer's disease. Indeed, the LC is the first brain nucleus to exhibit degeneration in early stages of Alzheimer's disease (e.g., Mann et al., 1980; Tomlinson et al., 1981; Bondareff et al., 1982). As the LC protects against depotentiation, reactivation of memory networks outside the one we are measuring during learning (the "other" ordered reactivations, which constitute the majority of hippocampal activity patterns during NREM sleep) normally does no damage to the rest of our memory networks. However, sleep lacking timely NE presence could erase our memories, our knowledge base built up over our lifetime, and could prove maladaptive and even harmful to the constellation of everything we know.

Exogenous interventions to protect and serve schema during sleep

This problem of unwanted, inappropriate bidirectional plasticity could be ameliorated by interventions that stimulate what few noradrenergic neurons remain. During wakefulness, loud noises stimulate LC neuronal activity. Auditory afferents, like others, excite midline reticular cells that, in turn, activate LC neurons and pericoerulear neurons. During TR and REM sleep, loud sounds increase the density of ponto-geniculo-occipital (PGO) waves (Ball et al., 1989). Thus, auditory stimuli that would produce a startle reflex during wakefulness should, during sleep, activate the same arousal systems in which the LC is integral. It has not yet been ascertained whether such loud sounds also activate the LC during sleep. If so, auditory stimulation timed to the rising phase of slow waves could serve to protect and preserve memories.

Currently, several groups (e.g., Cousins et al., 2014) are proposing to use auditory stimulation during SWS to improve memory because it has been shown to increase the amplitude of slow waves, which declines with aging. If memory reactivations are increased without the presence of LC protective action, however, as when the LC is already degenerated, the effect of increasing slow-wave amplitude could be the opposite of what is intended: instead of increasing memory consolidation in a particular recently learned and thus more highly reactivated pathway, the intervention could increase heterosynaptic depotentiation in all orthogonal memory circuits, hastening memory declines. Thus, treatments designed to increase memory function should be care-

fully evaluated in light of what neuromodulatory systems remain in each individual patient.

In conclusion, although sleep may have a function for remembering or strengthening memory circuits as so well presented in "Sleep to Remember," this memory strengthening role may be as well served by more waking practice. Instead, the role of sleep for forgetting seems to be entirely unique and cannot be substituted by any other state. Thus, although sleep may serve to remember, sleep is essential for the targeted, careful forgetting necessary for experience-dependent synaptic circuit reshaping during development and throughout the lifespan.

Response from Dual Perspective Companion Author–Susan J. Sara

Francis Crick intuitively proposed that the function of "dream" sleep was to forget insignificant or noisy memories (Crick and Mitchison, 1983). Gina Poe has provided a convincing conceptual framework and supporting evidence for this view that REM sleep might be for the weakening of memories. There was little experimental evidence for this largely intuitive hypothesis until Poe recorded hippocampal place cells active during REM sleep (Poe et al., 2000). She describes this landmark study in the present review; her data are essentially the basis for her conclusion that "Sleep is for forgetting." The evidence is indirect, relying on interpretation of the functional significance of the switch from theta-peak-to-theta-trough replay firing of place cell assemblies during REM sleep, as the rat learns about the environment. Poe argues that, together with imposed silence of the locus coeruleus noradrenergic neurons during REM, the stage is set for opportunistic depotentiation of the synapses within the assemblies coding for the familiar. This will provide synaptic space for consolidation of newly encoded novel information. Her replay data are robust and irrefutable, but nonetheless somewhat puzzling.

There are no behavioral data relating synaptic depotentiation to loss of memory. Indeed, the theta peak-to-trough transition does not always weaken memories. Instead, this transition seems to be an important step in consolidation when rats are learning a new rule on a maze. In a recent study, it was found that, during the course of learning, neurons of the frontal cortex reorganize their firing phase to the troughs of hippocampal theta, resulting in emergence and strengthening of frontal cell assemblies in high coherence with hippocampal activity. Importantly, this reorganization of firing of frontal neurons in relation to hippocampal theta troughs is positively correlated with behavioral performance (Peyrache et al., 2009; Benchenane et al., 2010).

This raises another question: if, indeed, spontaneous depotentiation does occur at the synapses of those cell assemblies activated on the trough of the theta peaks in the absence of norepinephrine, can it be shown that it results in behavioral forgetting? William James (1890) reminds us that a putative "memory trace" can only be inferred from its retrieval and expression in behavior: "the only proof of there being retention is that recall takes place." So when we talk about remembering or forgetting, it must always refer to a behavioral performance or verbal report (for discussion, see Sara, 2000; Sara and Hars, 2006). The argument here from Gina Poe, in my view, is not really that sleep is for forgetting, but that memories are acquired and maintained by constant synaptic pruning and REM sleep provides ideal conditions for this process. Behavioral studies combined with measures of sleep-related changes in synaptic strengthwould greatly contribute to resolving this issue of the functional role of different sleep states.

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