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The up and down of sleep: From molecules to electrophysiology

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ABSTRACT

Alternations of up and down can be seen across many different levels during sleep. Neural firing-rates, synaptic markers, molecular pathways, and gene expression all show differential up and down regulation across brain areas and sleep stages. And also the hallmarks of sleep – sleep stage specific oscillations – are characterized themselves by up and down as seen within the slow oscillation or theta cycles. In this review, we summarize the up and down of sleep covering molecules to electrophysiology and present different theories how this up and down could be regulated by the up and down of sleep oscillations. Further, we propose a tentative theory how this differential up and down could contribute to various outcomes of sleep related memory consolidation: enhancement of hippocampal representations of very novel memories and cortical consolidation of memories congruent with previous knowledge-networks.

1. Introduction

Sleep is characterized by a constant switching of up and down on many different levels: from molecules, firing rates of neurons to LFP oscillations. The most prominent up and down of sleep is the alternation of up and down states – periods of intense neural activity and silence that characterize NonREM sleep and underlie the slow oscillation (SO or K-complex) seen in LFP and EEG recordings. But also REM sleep has an up and down within its dominant LFP/EEG pattern theta. However, the up and down can also been seen as a result and perhaps function of sleep, with up and down regulation of synaptic strength, firing rates and other molecular or metabolic products seen across sleep.

Many studies report how different sleep stages can influence this up and down, but often do not consider other influencing factors or specificity to certain brain areas. However, to understand the function of the up and down of sleep it is critical to consider that different brain areas may show differential effects but also what type of behavior preceded sleep. The general idea is that the combined up and down leads to a "push–pull" action ("push" equals potentiating "important" memory traces and "pull" equals weakening irrelevant traces), which would together aid the construction and updating of memory networks via increased signal-to-noise ratio as well as eliminate unimportant memories (Genzel, Kroes, Dresler, & Battaglia, 2014). Further, especially the down component is thought to be critical for general homeostasis in the brain (Tononi and Cirelli, 2014).

In this review, we attempt to provide an overview of the ups and downs of sleep from electrophysiology to molecules, considering different brain areas as well as pre-sleep behaviors.

2. Firing rates

One proposed function of sleep is the regulation of neural activity, both for general homeostasis as well as memory consolidation. One way to measure neural activity is by examining firing rates of neurons; and firing rates have been shown to be modulated by sleep at least in some brain areas.

Grosmark, Mizuseki, Pastalkova, Diba, and Buzsaki (2012) focused on the hippocampus and could show that across sleep there was a total decrease in the firing rate of pyramidal cells; the across-sleep decrease was correlated with the neurons' preference to discharge during theta and gamma epochs in REM. Interestingly, within NonREM an increase in firing rates was observed in contrast to the decrease over REM. Miyawaki and Diba (2016) confirmed and extended these findings in the hippocampus and could show that the activity of the neurons during preceding NonREM spindles and ripples predicted the scaling seen during theta in REM. The across sleep decrease was stronger in neuron with low-firing rates than those with higher firing rates. Grosmark and Buzsaki (2016) have proposed that slow-firing neurons are more plastic and their activity experience dependent, while fast-firing neurons may present general network structure. Thus, it seems as if at least in the hippocampus there is an upscaling of firing rates during NonREM and downscaling during REM sleep with a net decrease across the whole sleep period.

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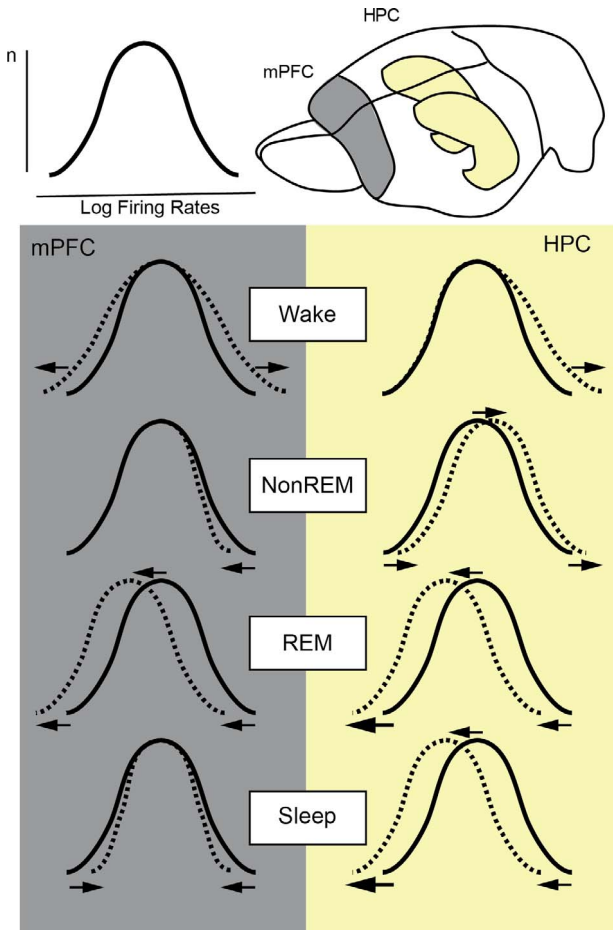

Fig. 1. A schematic for log firing rate changes in the medial prefrontal cortex (mPFC, grey) and hippocampus (HPC, yellow) (y axis: number of neurons). *Wake* leads to an increase of high firing rate neurons in both the mPFC and HPC, but in the mPFC the low firing rate neurons decrease firing. During *NonREM* general variance decreases in the mPFC and fast neurons getting slower; in contrast in the HPC all neurons increase their firing rates. In *REM* both mPFC and HPC show a decrease in firing rate across all neurons. In net *sleep decreases variability* in firing rates in the mPFC, while in the HPC a *general decrease* in firing rates for all neurons is seen with slow firing neurons showing a stronger decrease (Grosmark et al., 2012; Grosmark and Buzsaki, 2016; Miyawaki and Diba, 2016; Watson et al., 2016).

In contrast, the cortex shows a more complex picture; here periods of NonREM sleep reduced the activity of high firing-rate neurons and tended to upregulate firing of slow-firing neurons, almost the opposite effect as seen in the hippocampus. But as with the hippocampus REM reduced firing rates across all neurons (Watson, Levenstein, Greene, Gelinas, & Buzsaki, 2016) (see Fig. 1).

The above mentioned studies recorded sleep without any preceding significant learning experience or behavior, which could influence scaling effects. Gulati, Guo, Ramanathan, Bodepudi, and Ganguly (2017) recorded from the motor cortex after neuro-prosthetic learning and reported task-related rescaling. Specifically, they found that neurons that were non-causally involved in the task showed downscaling after NonREM in contrast to neurons that were causally involved in the task. Further, neural firing during slow oscillations was linked to this rescaling process; optogenetic suppression of neural activity during up-states of the slow oscillation prevented performance gains and re-scaling. Using a motor-sequence task the same group had already previously shown that the motor cortex shows active replay during NonREM sleep, which could lead to the differential rescaling effect for neurons involved in learning in contrast to neurons that are not (Ramanathan, Gulati, & Ganguly, 2015).

In sum, NonREM shows a differential effect on firing rates in the hippocampus (upregulation) and the prefrontal cortex (both up and down), while REM sleep is dominated by downscaling predicted by previous NonREM activity.

3. Synaptic strength and calcium

In addition to firing activity, sleep is thought to influence synaptic strength for both plasticity and homeostasis. Synaptic indicators are possible markers for this process, e.g. changes in synapse size and composition as well as tracking calcium signals. Calcium influx should result in the activation of molecular pathways and thus affect synaptic strength.

Vyazovskiy, Cirelli, Pfister-Genskow, Faraguna, and Tononi (2008) compared nocturnal wake with day-time sleep and could show that GluR1-containing AMPA receptors levels are high during wakefulness and low during sleep in both the hippocampus and cortex, which could indicate synaptic downscaling occurring during sleep. Following up on this finding de Vivo, Bellesi et al. (2017) used electron microscopy to show the axon-spine interface decrease after sleep in comparison to sleep deprivation with novelty and nocturnal wake; this scaling was selective for smaller synapses thought to be more plastic. Further, Diering, Nirujogi, Roth, Worley, Pandey, and Huganir (2017) replicated the decrease of mGluR1 receptors during sleep and associated this change with Homer1a signaling. In contrast, Havekes, Park et al. (2016) showed that 5 h of sleep deprivation lead to reduction in apical and basal CA1 hippocampal spine numbers as well as dendritic length. The studies above did not include any significant pre-sleep behavior and could not differentiate between NonREM and REM sleep effects, due to the comparison to total sleep deprivation needed for the histological analysis.

In order to increase time-resolution and specificity Li, Ma, Yang, and Gan (2017) used in vivo imaging in the motor cortex after motor learning and could show that REM sleep selectively pruned and maintained new synapses in development and learning. Interestingly only new post-synaptic dendritic spines are pruned or strengthened, and old spines remained unaffected as with de Vivo et al. (2017). Further, dendritic calcium spikes arising during REM sleep were important for this process.

Combining EEG and calcium imaging as well, Seibt, Richard et al. (2017) reported similar dendritic, calcium transients associated with spindle oscillation during NonREM, however the cell bodies of the same neurons did not show the same relationship. Mirroring the electrophysiological findings from Miyawaki and Diba (2016), Seibt et al. also reported that the dendritic calcium activity during NonREM sleep spindles predicted activity during REM sleep for a given animal. More recently, Norimoto et al. (2018) showed that silencing sharp-wave-ripples prevented the spontaneous downregulation of net synaptic weights as measured in slices and impaired later learning of an object-place task.

In conclusion, synaptic markers also show both up and down depending on previous learning. Overall downregulation is seen across sleep, with learning specific strengthening – in a motor task – seen in the cortex during REM sleep. Interestingly, again mirroring effects seen in electrophysiology, the differential REM sleep effect was predicted by NonREM activity during spindles.

4. Molecular signaling pathway

How molecular and cellular mechanisms are effected by the up and down of sleep after learning remains as a mystery and more studies are required to understand how neuronal activity changes induced by cascade molecular signaling correlate with the LFP recordings observed during sleep related memory consolidation. However, so far different research groups have made effort to shed light on the molecular mechanism underlying sleep regulation process and consequently in memory consolidation through the study of up or down regulated

proteins during sleep and sleep deprivation.

The adenylyl cyclases, mitogen-activated protein kinase (MAPK), and cAMP response element-binding protein (CREB)-mediated transcriptional pathway are implicated in the consolidation of hippocampus-dependent memory (Abel, Nguyen, Barad, Deuel, Kandel, & Bourtchouladze, 1997; Athos, Impey, Pineda, Chen, & Storm, 2002), also during sleep (Vecsey, Baillie et al., 2009; Hernandez and Abel, 2011; Luo, Phan, Yang, Garelick, & Storm, 2013; Havekes, Bruinenberg, 2014). High levels of cAMP, phospho-p44/42 MAPK, and phosphorylated form of CREB were found in the hippocampus (CA1 and dentate gyrus) during REM compared with wake and NonREM (Luo, Phan, Yang, Garelick, & Storm, 2013). In addition, mice lacking calmodulin-stimulated adenylyl cyclases did not show this peak activity during REM and performed worse in hippocampus-dependent behavioral task (contextual fear conditioning and passive avoidance) compared with wild types (Luo et al., 2013). Five hours of sleep deprivation after contextual fear conditioning disrupted the cAMP signaling pathway and impeded memory consolidation (Vecsey, Baillie et al., 2009). Low levels of cAMP as a consequence of sleep deprivation were due to an increase of the isoform phosphodiesterase-4A5 (PDE4A5) (Vecsey, Baillie et al., 2009; Havekes, Bruinenberg et al., 2014). The degradation of cAMP suppresses activity of the cAMP-protein kinase A (PKA) LIM kinase domain protein (LIMK) pathway with the consequent increase in cofilin activity in the hippocampus. Cofilin is a regulator of actin filament dynamics, and its ability to bind and depolymerize actin is abolished by phosphorylation at Ser 3 by LIMK (Agnew, Minamide, & Bamburg, 1995; Welch, Mallavarapu, Rosenblatt, & Mitchiso, 1997; Yang, Higuchi, 1998). These changes in the cytoskeleton are implicated in the reduction in the spine number and dendrite length of hippocampal CA1 excitatory neurons and memory impairment's observed because of sleep deprivation (Havekes, Vecsey, Peixoto et al., 2012; Havekes, Bruinenberg et al., 2014; Havekes, Park et al. 2016). Interestingly, the memory deficit in an object-in-place recognition task observed in sleep-deprived animals was restored by increasing levels of cAMP in the excitatory neurons in the hippocampus (Havekes, Bruinenberg et al, 2014).

The cAMP-PKA signaling pathway is also implicated in the activation of CREB (Mellon, Clegg, Correll, & McKnight, 1989), therefore, low levels of cAMP as a consequence of sleep deprivation, reduces levels of p-CREB (active form) and consequently CREB-mediated gene transcription, implicated in synaptic plasticity and memory consolidation (Alberini, 2009; Bailey, Kandel, & Harris, 2015; Datta, Knapp, Koul-Tiwari, & Barnes, 2015). Recent findings suggest that CREB modulates memory allocation to specific neurons (neuronal allocation), perhaps by regulating the transcription of channels that control neuronal excitability (Won and Silva, 2008; Rogerson, Jayaprakash, 2016). CREB is a transcription factor for brain-derivated neurotrophic factor (bdnf) (Tao, Finkbeiner, Arnold, Shaywitz, & Greenberg, 1998), and the levels of both are reduced after sleep deprivation in the hippocampus but not in the neocortex (Guzman-Marin, Ying, 2006). Recently, it has been demonstrated that an increase in the number of REM sleep transitions induced by a short period (< 90 min) of selective REM sleep restriction (Datta, Knapp, Koul-Tiwari, & Barnes, 2015; Barnes, Koul-Tiwari, Garner, Geist, & Datta, 2017) induced the activation of extracellular-signal-regulated kinase 1 and 2 (ERK1/2) and BDNF expression in the pedunculopontine tegmentum (PPT, one of the REM sleep generating areas) (Datta and Oliver, 2017). In addition, the homeostatic regulation of REM transitions involves the activation of TrKB receptor signaling pathway through the binding of BDNF in this brain area (Barnes, Koul-Tiwari, Garner, Geist, & Datta, 2017), which may activate several intracellular signaling pathways, including ERK1/2 transduction pathway (Andero, Choi, Ressler, 2014); this in turn induces transcription of bdnf through the activation of CREB (Andero et al., 2014). Furthermore, ERK1/2 signaling may increase BDNF release in the brain in a positive feedback loop (Alonso, Medina, & Pozzo-Miller, 2004). The increase in pontine-wave density during post-training (active avoidance) REM sleep is positively correlated with the increased levels of CREB, BDNF, and Arc protein in the dorsal hippocampus (Ulloor and Datta, 2005). Therefore, it is possible that pontine waves play a key role in the up regulation of immediately early gene (IEG) expression during sleep in the dorsal hippocampus (Ribeiro and Nicolelis, 2004; Ulloor and Datta, 2005), which will be address in the following section.

In short, it seems that there is an increase in the cAMP-PKA- CREB pathway activation in the hippocampus during REM but not NonREM, which may play an important role in the synapses remodeling and memory consolidation during sleep. This upregulation is not seen in the cortex; however this may be task related since most experiments used fear or novelty related paradigms.

5. Gene expression

The importance of sleep in memory consolidation, a process which requires protein synthesis (Hernandez and Abel, 2008), has led to different research groups to study waves of gene expression and protein synthesis during sleep and sleep deprivation. In general, gene expression is reduced during sleep, when compared to wakefulness. Systematic studies using microarrays in total cortex demonstrated that approximately 5% of all transcript studied were differentially expressed between sleep and sleep deprivation (Cirelli and Tononi, 2004). Wakefulness was related with heat shot protein genes, genes implicated in the metabolism and synthesis of glutamate; and level of transcripts related to GABAergic neurotransmission or potassium channels and genes implicated in synaptic plasticity are differentially expressed during sleep (McCormick and Bal, 1997; Cirelli and Tononi, 2004). In addition, differential expression of immediately early genes (IEG) have been observed after sleep deprivation (Cirelli and Tononi, 2004; Wang, Liu, Briesemann, & Yan, 2010; Genzel, Rossato et al., 2017).

The wave of IEG expression, such as c-fos, Arc, Zif-268, implicated in the production of plasticity-related proteins (Frey and Morris, 1998; Romcy-Pereira and Erraji-Benchekroun, 2009) and memory consolidation (Redondo and Morris, 2011) has been studied during sleep and sleep deprivation in the hippocampus and cortex. Levels of Arc and Zif268 gene transcription were studied during sleep-wake cycle after a novel spatio-tactile stimulation experience (exposure to four different objects in darkness for 20 min). Immediately after the experience an increase in IEGs was seen in both the hippocampus and somatosensorial cortex (S1). However, after four hours IEG expression was specifically upregulated during REM sleep in the cortex, but not in the hippocampus (Ribeiro, Shi et al., 2007). Romcy-Pereira and Erraji-Benchekroun (2009), also observed a cortical up regulation *zif268* during REM sleep as a consequence of hippocampal long-term potentiation (LTP) prior to sleep. In particular in early REM, *zif268* upregulation was observed in the auditory and entorhinal cortices, and in late REM (at least 2 h after) high levels of zif268 were observed in the temporal, motor and somatosensory cortices, besides the amygdala. Recently, the expression of IEG (arc, c-fos and zif268) during sleep and sleep deprivation combined with novelty after watermaze training was investigated in order to shed light on the molecular mechanism underlying the dynamic interaction between hippocampus and the cortex for memory storage during sleep (Genzel, Rossato et al., 2017). An increase in the three IEGs studied, but especially in c-fos, was observed in both brain areas 30 min after learning. However 5 h after task, hippocampus showed lower levels of the expression, while mPFC kept high levels in contrast to animals that slept without a learning experience indicating a memory consolidation specific effect. In case of novelty with sleep deprivation, the prefrontal cortex showed a significant decrease in the expression of these genes post-learning. Interestingly, when animals that slept were contrasted to home cage controls a significant, linear decrease over time in gene expression was observed especially in PFC. In contrast high expression of the same genes were observed in the condition of novelty with sleep deprivation in both brain areas (Genzel, Rossato et al., 2017).

Transcriptional regulators seem to be up regulated during wakefulness, while sleep could promote translation process needed for memory consolidation (Cirelli and Tononi, 2004; Naidoo, Giang, Galante, & Pack, 2005; Tudor, Davis et al, 2016). High levels mRNA of translational promoters, the eukaryotic translation elongation factors 2 and initiation factor 4AII were found in rat cortex during sleep (no specifications about REM or NonREM) (Cirelli and Tononi, 2004). Also, it has been demonstrated that 5-h sleep deprived mice showed reduced levels of the mammalian target of rapamycin complex 1 (mTOR-1) in the hippocampus and spatial memory impartment (Vecsey, Peixoto et al., 2012; Tudor, Davis et al., 2016). The mTORC1 stimulates protein synthesis by phosphorylating and inhibiting the translational repressor the eukaryotic translation initiation factor 4E–binding protein 2 (4EBP2) (Banko, Poulin, Hou, DeMaria, Sonenberg, Klann, 2005). The rescuing of protein synthesis in these mice by the viral expression of 4EBP2 in the hippocampus was sufficient to prevent this memory deficit induced by sleep deprivation (Tudor, Davis et al., 2016), which indicates the importance of protein synthesis for memory consolidation during sleep.

In sum, gene expression can show both an up and down regulation across sleep stages and brain areas, dependent on previous behavior and contrast used in the analysis. In general sleep leads to a reduction in gene expression, but after learning upregulation can be seen in the cortex which may be REM sleep related.

6. Slow oscillations and theta

Sleep clearly influences the up and down of molecules, synaptic strength and firing rates, but how does this take place? The up and down seen within sleep oscillations may have this function. Both NonREM and REM sleep are dominated by up and down transitions in their dominant oscillations: the slow oscillations in NonREM and theta in REM. Both could contribute to up and down regulation of neural activity.

Recently, Levenstein, Watson, Rinzel, Buzsaki (2017) proposed how slow oscillations during NonREM could contribute to both specific memory-related strengthening of synapses as well as general homeostatic downregulation, depending on which phase of the slow oscillation neurons fire in. Neurons fire in a statistically reliable sequence at the down to up transition of the slow oscillation (Luczak, Barthó, Marguet, Buzsáki, Harris, 2007), and this pattern of neuronal firing could provide a putative mechanisms for the homeostatic function of sleep. In cortical slice, an LTP protocol during the onset of the up state was found to effectively facilitate synaptic potentiation following a Spike-Timing-Dependent-Plasticity rule. Because high firing rate neurons tend to fire earlier than low firing rate neurons at the down to up transition Spike-Timing-Dependent-Plasticity will tend to increase synaptic weights from high firing rate to low firing rate units, while decreasing weights from low firing rate to high firing rate units. This redistribution of synaptic weight from high to low firing rate neurons would pull both ends of the firing rate distribution closer to the mean and thus regulate firing-rate homeostasis (Levenstein et al., 2017).

However, memory replay during sharp-wave ripples (see below) can perturb this sequence by enabling neurons associated with the learning experience to fire earlier in the sequence and slow oscillation phase. According to Spike-Timing-Dependent-Plasticity rules this would lead to increase synaptic weights for these memory related neurons. Thus, replay-induced perturbation of the sequential activation of neurons at the down to up transition could present a window of opportunity for memory consolidation of neurons tagged by hippocampal replay events. In this way, the coupling of mnemonic and homeostatic function at the down to up transition of slow oscillations could act as a vehicle for the interaction between local and global plasticity (Levenstein et al., 2017).

Bartram et al. (2017) confirmed this idea experimentally in acute slices and could show that spontaneous pattern of up state spiking can induce synaptic weakening while pairing synaptic inputs with postsynaptic spiking during up states maintained synaptic strength and appeared to protect against subsequent synaptic weakening. Converging with this idea, Poe (2017) has pointed out that during NonREM LC neurons fire in bursts 120 ms before the peak of the slow oscillation (Eschenko, Magri, Panzeri, Sara, 2012), perhaps timed to deliver significant amounts of noradrenalin to the forebrain synapses just as sharp-wave-ripples reactivate neurons, which could lead to the strengthening instead of weakening of those neurons (see Fig. 2)

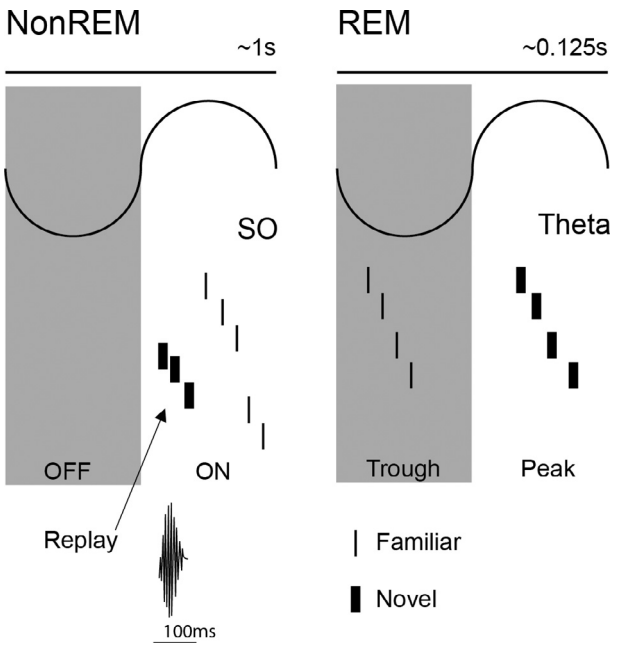

Fig. 2. A schematic for possible NonREM and REM sleep mechanisms. NonREM sleep is dominated by the down (OFF states, neural silence) to up (ON states, neural activity) transitions of the slow oscillations (SO). By default neurons fire in a fixed sequence in the ON, leading to weakening of synaptic strength. Memory replay during sharp-wave-ripples leads to earlier firing in the SO phase, which could strengthen those synapses (Levenstein et al., 2017). In contrast, REM sleep is dominated by the up and down or waxing and waning of theta oscillations. Neurons of familiar experiences have been shown to be played in the theta trough (Poe et al., 2000), which could lead to synaptic weakening (Pavlides et al., 1988). On the other hand, novel experiences are played in the theta peak (Poe et al., 2000) leading to synaptic strengthening (Pavlides et al., 1988). Thus in both NonREM and REM mechanisms for both strengthening and weakening of synapses could be present. Of note, peaks and troughs are according to intracranial LFP recordings and may differ in the EEG.

During REM sleep similar differential up and down regulation of synaptic strength could be achieved by different theta phases (Poe, 2017). In anesthetized rats stimulation on the positive phase of theta induced LTP, whereas stimulation at the opposite phase induced depotentiation (Pavlides, Greenstein, Grudman, & Winson, 1988). Interestingly, Poe, Nitz, McNaughton, and Barnes (2000) reported that cells in the hippocampus shifted their preferred theta-phase of firing over the course of learning with cells active in familiar or novel environments showing a 180 degree phase difference. These findings fit the hypothesis that circuits may be restructured during REM sleep by selectively strengthening very new memories and weakening older ones at least in the hippocampus (Poe, 2017) (see Fig. 2)

Not only the phase in which cells fire may play a role, but also how different brain areas are related to each other. Recently Totty et al. (2017) could show that the mean phase difference between the lateral amygdala and the ventral hippocampus during REM sleep predicted changes in freezing after cued fear extinction; a 180 degree difference was associated with decreases in freezing whereas no phase lag was associated with increases mirroring the findings seen within the hippocampus (Poe et al., 2000).

7. Memory replay

During sleep, replay of patterns of neural activity initially recorded during waking behavior may serve as a mechanism of strengthening the memory trace (Girardeau, Benchenane, Wiener, & G. Buzs ki and M. B. Zugaro, 2009; Sadowski, Jones, & Mellor, 2016) or preserving it from downscaling (Tononi and Cirelli, 2014; Gulati, Guo, Ramanathan, Bodepudi, & Ganguly, 2017; Li, Ma, Yang, & Gan, 2017) as well as integrating the new experience in existing memory networks (Genzel et al., 2014). This phenomenon is usually measured as a statistical increase in the reactivation of behavior-associated neuronal spike timing patterns seen after that behavioral experience relative to before (Wilson and McNaughton, 1994) with novel and significant experiences showing preferred reactivations (Dupret, O'Neill, Pleydell-Bouverie, & Csicsvari, 2010; McNamara, Tejero-Cantero, Trouche, Campo-Urriza, & Dupret, 2014). This replay is seen brain-wide often even coordinated across a wide range of brain areas, e.g. prefrontal, motor, auditory, visual, medial enthorhinal cortex, hippocampus, striatum, amygdala, VTA (Ji and Wilson, 2007; Peyrache, Battaglia, & Destexhe, 2009; Dupret, O'Neill, Pleydell-Bouverie, & Csicsvari, 2010; Gomperts, Kloosterman, & Wilson, 2015; Ramanathan, Gulati, & Ganguly, 2015; Grosmark and Buzsaki, 2016; Lansink et al., 2016; Olafsdottir, Carpenter, & Barry, 2016; Girardeau, Inema, & Buzsaki, 2017; Rothschild, Eban, & Frank, 2017; Tang, Shin, Frank, & Jadhav, 2017); usually during NonREM and influenced by previous behavior. Replay is most commonly measured during sharp-wave-ripples in the hippocampus and with a slight delay (~40 ms) in other brain areas such as the prefrontal cortex (Peyrache et al., 2009). However, in areas such as the mPFC, ACC and auditory cortex activity preceding hippocampal sharp-wave-ripples has been reported (Wang and Ikemoto, 2016; Rothschild et al., 2017; Tang et al., 2017), indicating that perhaps the selection of which memories are to be replayed during NonREM sharp-wave-ripples is done by the cortex and not the hippocampus. Possibly, the selected memories could be those memories that fit into preexisting cortical networks (e.g. schema) (Tse, Langston et al., 2007; Tse, Takeuchi et al., 2011; Wang, Tse, & Morris, 2012).

Memory reactivations are most often seen to co-occur with the hippocampal sharp-wave-ripple oscillation (Buzsaki, 2015). However, how other oscillations are related to replay is less clear, partly due to the cyclic nature and difference in time-scales of length and occurrence of these oscillations; making assumptions of directionality, co-occurrence and "who comes first" difficult. During NonREM sleep a complex interaction of slow oscillations, spindles and hippocampal sharp-wave-ripples is seen, which can change depending on pre-sleep experiences. In the PFC the sequence of a sharp-wave-ripple at the down to up transition of the slow oscillation followed by a spindle is seen and the causal importance of this sequence for memory consolidation was elegantly demonstrated by Maingret, Girardeau, Toderova, Goutiere, and Zugaro (2016); however, by default this accounts for less than 5% of sharp-wave-ripples and even pre-sleep learning only increases this to < 10% (Maingret et al., 2016). Others report of sharp-wave-ripples occurring in the trough of the spindles, however these are individual ripples occurring during a single spindle (again < 5% of ripples) (Sullivan, Mizuseki, Sorgi, & Buzsaki, 2014; Staresina, Bergmann, 2015) not ripples occurring at each trough as sometimes depicted in schemes. Sharp-wave-ripples are much more frequent (~1 per sec) and much shorter (~100 ms) than spindles (length ~ 1.5 s), thus very likely to occur before, during and after the spindle.

However, the difference is ripple-spindle coordination could also be explained by the type of spindle investigated; especially in humans a difference between frontal, slower spindles and parietal, faster spindles can be seen (Adamczyk, Genzel, Dresler, Steiger, & Friess, 2015). Frontal spindles occur after the sharp-wave-ripple and seem to deafferent the cortex from hippocampal inputs (Peyrache, Battaglia, & Destexhe, 2011) and in the cortex only dendritic spikes are seen that do not reach the cell body (Seibt et al., 2017); in contrast parietal spindles may have an individual sharp-wave-ripple nested in their troughs (Staresina et al., 2015). This difference could also explain why replay in the prefrontal cortex is seen before the spindle (Peyrache et al., 2009), while motor cortex replay is seen during the spindle (Genzel and Robertson, 2015; Ramanathan et al., 2015).

8. A possible function of NonREM's and REM's up and down

During sleep with seem to "clean up" our brain, from simply washing out metabolic by-products (Xie, Kang et al., 2013) to a more complex process of tidying up our memory system. Every night we (or our brains) need to sort through our day and decide which experience to integrate into our long-term storage, which memories to keep in detail and which we can discard and forget. The complex up and down during sleep across different brain areas and sleep stages most likely contributes to this process.

Brain-wide reactivations would allow for the comparison of new memories to other or older experiences and knowledge. Thus perhaps allowing the integration of such new memories into pre-existing memory networks. This could be the mechanisms already described by Marr (1971) and modelled by McClelland, McNaughton, and O'Reilly (1995) and McClelland (2013) as interleaved learning to avoid catastrophic interference. Memories are thought to be consolidated from the short-term, temporally organized storage in the hippocampus to a long-term cortical, semantic memory network organized by content instead of time (Wang and Morris, 2009; Squire, Genzel, Wixted, & Morris, 2015; Genzel and Wixted, 2017). However, unique events that do not fit in any pre-existing networks may be tagged to not undergo this process to avoid catastrophic interference. Such unique events instead would be retained in the hippocampus in its detailed form. But how would such sorting take place during sleep?

Events that can be incorporated into pre-existing networks may be tagged by VTA activation to be replayed during NonREM sleep (McNamara et al., 2014) under cortical guidance (Wang and Ikemoto, 2016; Rothschild et al., 2017) and thus integrated by interleaved learning into cortical networks (McClelland, 2013). Memories processed in such a way for long-term storage during NonREM ripples and spindles would then undergo downscaling in the hippocampus during REM sleep by being played in the theta trough (Miyawaki and Diba, 2016). In contrast new and unique memories possibly tagged by LC activation (Takeuchi, Duszkiewicz, 2016), could be retained in the hippocampus (Genzel, Rossato et al., 2017) by the preferred firing during theta peaks in REM sleep (Poe et al., 2000).

Thus the up and down seen during NonREM slow oscillations with ripples and spindles and REM theta could be a possible brain-wide mechanism to consolidate information and reset the brain for the next day. By influencing the timing of neural firing in the ups and downs of the oscillations during both sleep stages the differential needs of experience-dependent consolidation and homeostatic regulation could be met. The representation of old memories or general network structure would be played during later phases of the slow oscillation in NonREM and in the REM theta troughs resulting in the their maintenance or downscaling for general homeostatic regulation. Semi-new memories could be integrated into whole brain pre-existing networks. This could be achieved by sharp-wave-ripple related whole-brain replay leading to earlier firing in the down to up transition of the NonREM slow oscillation and strengthening of the cortical representation; subsequently activation in the REM theta trough would weaken the hippocampal representation after the cortical memory update has occurred. New and unique memories would be played in the REM theta peak, strengthening the hippocampal representation. Further, depending on the phase shift between e.g. the hippocampus and the amygdala during REM the valence of the memory may be adapted (Genzel, Spoormaker, Konrad, & Dresler, 2015; Totty, Chesney, Geist, & Datta, 2017) (see Fig. 3).

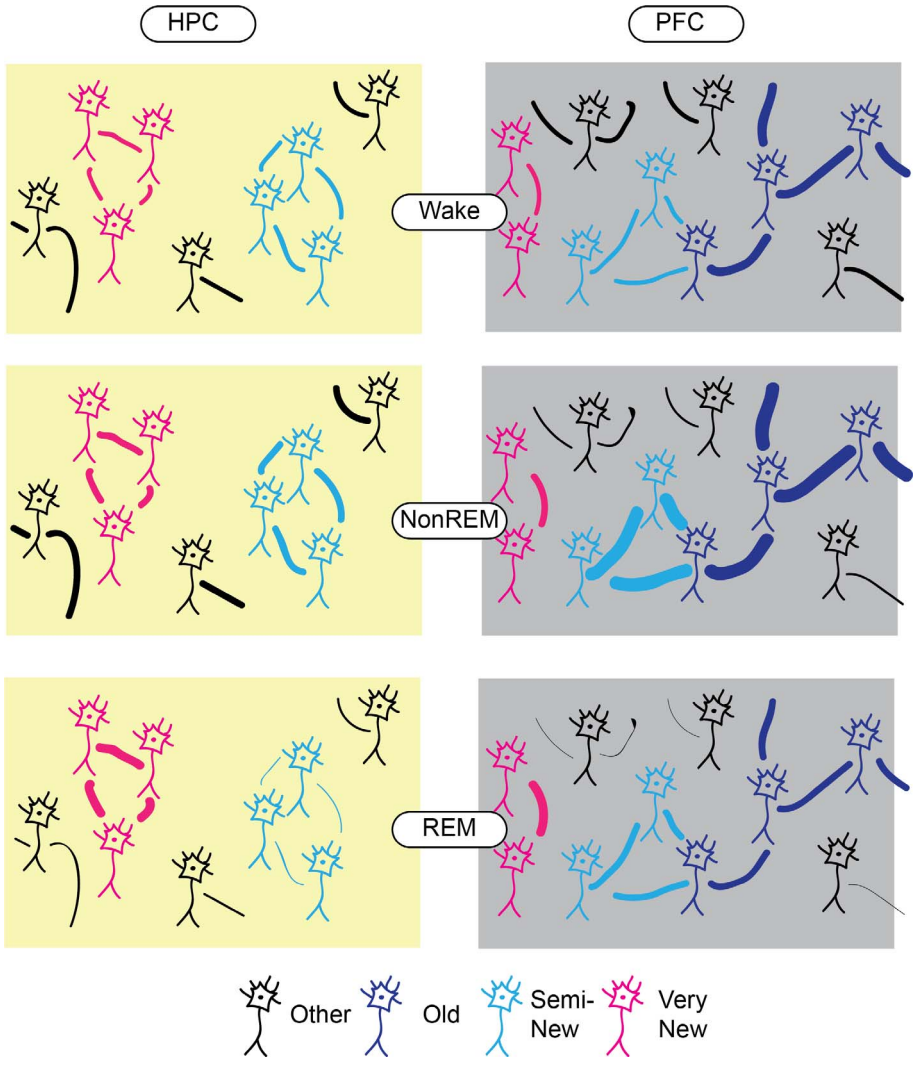

Fig. 3. A schematic of a possible NonREM and REM effect on memory. During the day we encode many new experiences; some are semi-new (light blue) and fit into our previous experiences and memory networks (old, dark blue), others may be very new (pink) and do not fit into any previous network. During NonREM hippocampal replay would strengthen these new memories and the cortex would bias replay to those events which resonate with previous experiences and can be integrated into cortical networks. During REM sleep overall downscaling would take place due to activity in the theta troughs; the exception would be very new memories, which by being played in the theta peaks, would be strengthened. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

9. Conclusion

Altogether the up and down of sleep oscillation could provide a flexible system how to consolidate memories across whole brain networks; strengthening and weakening individual nodes such as the hippocampus and prefrontal cortex, while also allowing for general network maintenance. To test this hypothesis more systematic approaches covering multiple brain areas and different pre-sleep behaviors are needed. Especially how novel a pre-sleep behavior is, should be considered to correctly predict in which brain area and sleep stage an effect is to be expected.

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