CHAPTER

17

Functions and Circuits of REM Sleep

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I INTRODUCTION

Ever since its discovery by Aserinsky and Kleitman in 1953 (Aserinsky & Kleitman, 1953), the quest to understand the function of rapid eye movement (REM) sleep has inspired researchers. Experimental evidence implicates both non-rapid eye movement (NREM) and REM sleep in learning and memory consolidation (Boyce, Williams, & Adamantidis, 2017; Poe, 2017; Sara, 2017), although the underlying mechanisms remain unclear. It was suggested that REM sleep might provide a neural environment supporting processes essential to learning and cognition, including synaptic remodeling mechanisms such as long-term potentiation (LTP) and depotentiation or synaptic pruning of spines formed during previous wakefulness (Crick & Mitchison, 1983, 1995). Furthermore, the hypothesis "Sleep to remember, sleep to forget" posits that NREM sleep is important for the consolidation of newly formed memories, whereas the REM sleep state eliminates dispensable spines, thereby improving the signal-to-noise ratio in neural networks (Crick & Mitchison, 1983; Poe, 2017; Sara, 2017), the latter process often being referred to as an "unlearning" process that helps stabilize newly formed synapses and memories (Hopfield, Feinstein, & Palmer, 1983). In humans, REM sleep has frequently been associated with dreaming, which led to the hypothesis that REM sleep is important for the reactivation of emotional events that occurred during the previous waking period (Jouvet & Michel, 1959). Accordingly, the reactivation of brain regions linked to emotion regulation has been suggested to facilitate the consolidation of newly formed memories (Goldstein & Walker, 2014). Finally, the abundance of REM sleep during perinatal periods has supported the idea that REM sleep provides a context during which the development of neural circuits is facilitated (e.g., Blumberg, Marques, & Iida, 2013).

In this chapter, we will first provide a short overview of the circuits that regulate REM sleep and then discuss possible functions of REM sleep in learning and memory. We will further delineate how the reactivation of emotional—that is, aversive and rewarding—stimuli may support learning and memory mechanisms during REM sleep and highlight alternative functions of REM sleep occurring during development and brain maturation.

II REM SLEEP CIRCUITS

Pioneering studies on REM sleep regulation showed that cats with a transection at the caudal edge of the pons were still able to produce REM sleep with the typical low-amplitude, fast EEG activity but lost the REM-sleep-associated muscle atony (Jouvet, 1962). Conversely, transections at the pontomedullary junction resulted in the elimination of fast EEG activity during REM sleep but preserved muscle atony (Siegel, Nienhuis, & Tomaszewski, 1984). These findings have attracted the focus on pontine structures possibly underlying the generation of REM sleep. Historically, cholinergic pedunculopontine tegmental (PPT) and laterodorsal tegmental (LDT) neurons were thought to generate REM sleep, whereas monoaminergic nuclei, including the noradrenergic locus coeruleus and the serotonergic dorsal raphe nucleus, were considered as REM-suppressing nuclei (Scammell, Arrigoni, & Lipton, 2017). Accordingly, serotonin and noradrenaline

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inhibit cholinergic neurons in the PPT/LDT (Crochet & Sakai, 1999), and antidepressant drugs that enhance monoamine signaling often suppress REM sleep (McCarthy et al., 2016). On the other hand, cholinergic PPT/LDT neurons initiate firing just before a transition from NREM sleep into wakefulness or REM sleep (Boucetta et al., 2014). Optogenetic stimulation of these neurons facilitated the transition from NREM sleep to REM sleep, but did not extend REM sleep episode duration (Van Dort et al., 2015). However, in this study, wakefulness was also increased by the optogenetic stimulation of PPT/LDT neurons, suggesting that cholinergic PPT/LDT neurons might be modulators, rather than generators, of REM sleep.

Shortly after the pioneering discoveries by Jouvet and colleagues (Jouvet, 1962), the activity of glutamatergic neurons of the sublaterodorsal nucleus (SLD, or subcoeruleus; Fig. 17.1) was linked to the generation of muscle atony during REM sleep (Lu et al., 2006). Indeed, SLD neurons are highly active during REM sleep as demonstrated by c-fos immunoreactivity and single-unit recordings (Lu et al., 2006; Sakai, Crochet, & Onoe, 2001). Pharmacological activation of the SLD produces a REM-sleep-like state characterized by muscle atony and low-voltage theta-predominated EEG (Boissard et al., 2002). These neurons project to GABAergic/glycinergic neurons in the ventral gigantocellular (GiV) and alpha gigantocellular (GiA) nuclei of the ventromedial medulla (VMM) (Boissard et al., 2002, 2003), which in turn hyperpolarize motor neurons in the spinal cord (Luppi et al., 2012). Additionally, SLD neurons directly excite spinal interneurons that also lead to an inhibition of motor neurons (Lu et al., 2006). The SLD receives GABAergic projections from the ventrolateral periaqueductal gray (vlPAG) and lateral pontine tegmentum (LPT), both of which are largely inactive during REM sleep, as shown by c-fos immunoreactivity (Boissard et al., 2003; Sapin et al., 2009). Consistent with these results, pharmacological inactivation of the vlPAG/LPT disinhibited REM sleep (Lu et al., 2006; Sapin et al., 2009). Similarly, optogenetic activation of VMM GABAergic projections to the vlPAG increases REM sleep and triggers transitions from NREM to REM sleep (Weber et al., 2015). Importantly, the SLD also innervates the vlPAG/LPT and, together with SLD, may form a mutual inhibitory circuit that regulates the occurrence of REM sleep (Fig. 17.1).

In addition to pontine regulators of REM sleep, recent work suggests that brain regions of the fore- and midbrain are also involved in the regulation of REM sleep. For instance, optogenetic activation of melanin-concentrating hormone (MCH)-expressing neurons in the lateral hypothalamus (LH) increased REM sleep (Jego et al., 2013; Tsunematsu et al., 2014). These neurons may regulate REM sleep through their projections to the SLD, vlPAG, LC, and DRN (Jego et al., 2013; Scammell et al., 2017). In addition, optogenetic stimulation of MCH axons in the medial septum (MS) and tuberomammillary nucleus (TMN), but not DRN, also prolonged REM sleep (Jego et al., 2013). Interestingly, the MS contains GABAergic neurons that project to the dorsal hippocampus and are involved in the generation of REM sleep theta rhythm, but not REM sleep itself (Ford, Colom, & Bland, 1989; Hangya et al., 2009). Finally, it was recently proposed that the supramammillary nucleus, the claustrum, and the cholinergic neurons of the basal forebrain might be involved

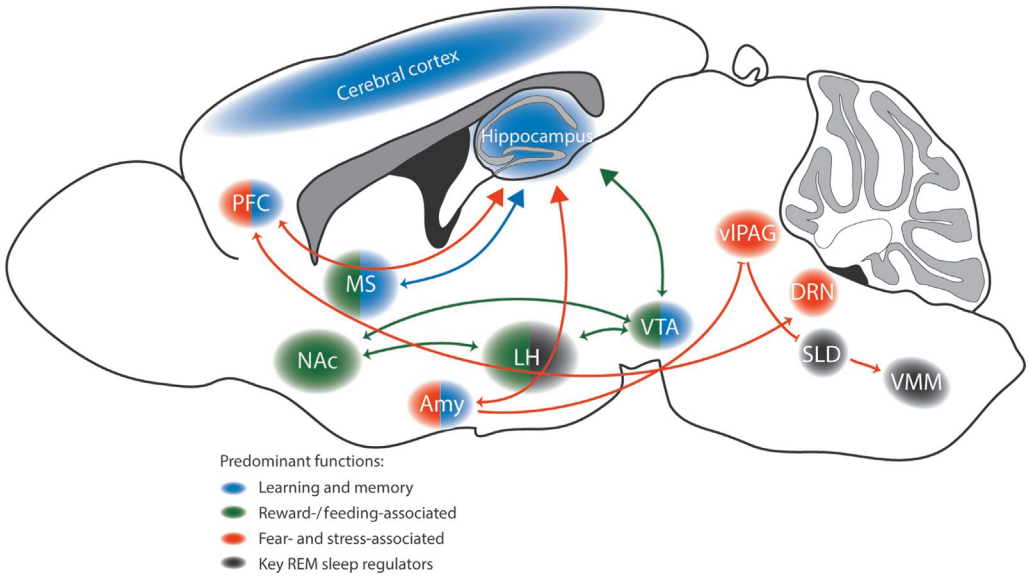

FIG. 17.1 Activated/reactivated brain regions and circuits during REM sleep. Brain regions implicated in memory and learning, reward and feeding, and fear and stress regulation are reactivated during REM sleep and interact with REM sleep regulating circuits. *Amy*, amygdala; *DRN*, dorsal raphe nucleus; *LH*, lateral hypothalamus; *MS*, medial septum; *NAc*, nucleus accumbens; *PFC*, prefrontal cortex; *SLD*, sublaterodorsal nucleus; *vlPAG*, ventrolateral periaqueductal gray; *VMM*, ventromedial medulla; and *VTA*, ventral tegmental area.

in the cortical activation during REM sleep (Renouard et al., 2015)′ (Irmak & de Lecea, 2014; Saper et al., 2010). Despite the fact that much has been learned about the regulation of REM sleep over the past decades, especially with respect to the generation of certain features of REM sleep, such as muscle atony and theta rhythm generation, several gaps in our understanding of the circuit level still exist. Moreover, despite the fact that numerous brain regions are active during REM sleep, many of them do not seem to contribute to the generation of REM sleep and likely serve other functions. We will review the possible functions of the activation of several brain regions during REM sleep in the following sections.

III REM SLEEP FUNCTIONS

A Memory Consolidation

The idea that memories are reexperienced and consolidated during REM sleep dates back to the discovery of REM sleep itself and originated mainly from the observation that dreams are frequently associated with REM sleep (Aserinsky & Kleitman, 1953; Jouvet & Michel, 1960). To date, an increasing number of studies support a role for REM sleep in the consolidation of newly formed memories (Boyce et al., 2016; Sara, 2017). The first evidence for the role of REM sleep in memory consolidation was provided by Leconte and Bloch, who showed that REM sleep deprivation in rats impaired memory consolidation in a conditioning task (Leconte & Bloch, 1970a, 1970b). Later on, the same group showed learning-dependent increases of REM sleep in rats (Leconte & Hennevin, 1971). Subsequent studies further supported Leconte and Bloch's work, suggesting that specific features of REM sleep underlie learning-related mechanisms, such as the predominant theta oscillations (5–10 Hz) and pontine waves (P-waves, in the rat) or ponto-geniculate-occipital waves (PGO waves) in the cat. For instance, using state-of-the-art optogenetic tools in mice, Boyce and colleagues recently provided the first causal evidence that theta-locked activity of MS GABA cells, which drives theta activity in the hippocampus during REM sleep, is essential for contextual memory consolidation (Boyce et al., 2016). In the next section, we will review the current evidence and strategies used to investigate the role of REM sleep in memory consolidation in mice, rats, and humans.

1 Correlative Studies

To elucidate the role of REM sleep in learning and memory, correlative studies have examined learning-induced changes in REM sleep quantity or learning-related effects on specific features of REM sleep, including theta oscillations and P-waves. In mice, learning of a new task (including appetitive and aversive conditioning) is followed by increased REM sleep quantity (Destrade et al., 1978; Smith et al., 1974; Smith, Young, & Young, 1980). REM sleep theta power has been associated with place cell activity in the hippocampus (Louie & Wilson, 2001; Mizuseki et al., 2011; Moser, Rowland, & Moser, 2015; Poe et al., 2000) and has therefore been linked to memory and learning. It was suggested that the theta rhythm might modulate LTP in the dentate gyrus and CA1 region of the hippocampus, as electrically stimulating the perforant path at the peak of the theta oscillation enhanced LTP, while stimulation at the theta trough led to long-term depression (LTD) (Huerta & Lisman, 1995; Pavlides et al., 1988). In addition, one study reported that place cell firing is reactivated during REM sleep (Poe et al., 2000), as seen during sharp-wave ripples occurring during NREM sleep (Roumis & Frank, 2015). Conversely, REM sleep theta power is enhanced after learning and might represent increased postlearning place cell firing (Fogel, Smith, & Beninger, 2009; Popa et al., 2010). P-waves are generated in the pons predominantly during REM sleep and to a lesser extent during NREM sleep. As is the case for REM sleep quantity and REM sleep theta power, P-waves are also enhanced after learning in rats (Datta, 2000; Datta, Li, & Auerbach, 2008; Datta & O'Malley, 2013; Ulloor & Datta, 2005). Interestingly, putative P-wave-generating cells in the subcoeruleus region (Datta et al., 1998) were shown to project to the hippocampus and amygdala, two brain regions that are highly active during REM sleep and implicated in learning and cognition (Davenne & Adrien, 1984; Renouard et al., 2015).

Similar to rodents, REM sleep quantity increases in humans after studying (Meienberg, 1977; Smith & Lapp, 1991), motor skill training (Buchegger et al., 1991; Buchegger & Meier-Koll, 1988), foreign language learning (De Koninck et al., 1989), and visual or auditory passage learning (Verschoor & Holdstock, 1984). In addition, increased REM intensity (total number of REM episodes and rapid eye movement densities) has been associated with learning in a procedural task (Smith, Nixon, & Nader, 2004). The improvements in procedural memory performance after a night of sleep were positively correlated with REM sleep quantity (Fischer et al., 2002). Furthermore, in studies that include a nap period between acquisition and recall of new information, the occurrence of a REM sleep episode in addition to NREM sleep improved performance, suggesting that the cycling of REM and NREM sleep is crucial for learning and memory (Grosmark et al., 2012; Mednick, Nakayama, & Stickgold, 2003). Indeed, along with changes in REM sleep, learning-related increases in NREM sleep amounts have also been reported in humans and in rodents (for review, see Sara, 2017). Interestingly, Buzsáki's group (Grosmark et al., 2012)

showed that the synchrony of hippocampal CA1 neuron firing increased during the course of sleep in rats, encompassing several cycles of NREM and REM sleep episodes. The increase in neural synchrony resulted from decreasing firing rate of hippocampal neurons during REM sleep episodes and correlated with REM sleep theta power. Conversely, the firing rate of these neurons increased within single NREM sleep episodes. These data further highlight that the cycling of NREM and REM sleep episodes is important for sleep-related neuronal plasticity (Grosmark et al., 2012).

2 Effects of REM Sleep Deprivation on Learning and Memory

To investigate whether REM sleep indeed plays a crucial role in learning and memory in rodents, previous studies employed the flowerpot method to selectively suppress the occurrence of REM sleep. In this procedure, the animal is placed on one or multiple small platforms over a water-filled arena and progressively adapts to not transition to REM sleep and the associated postural muscle atony to avoid falling in the water, while NREM sleep quantities remain mostly unaffected. However, NREM sleep continuity is frequently disrupted during this procedure, as the number of attempts to enter REM sleep increases over time. This method was successfully used to report decreased performance after REM sleep deprivation in more complex learning tasks such as two-way aversive conditioning, maze navigation in Morris water maze, and avoidance task in a two-compartment shuttle box (Beaulieu & Godbout, 2000; Danguir & Nicolaidis, 1976; Fishbein, 1971; Hars & Hennevin, 1983; Marti-Nicolovius, Portell-Cortes, & Morgado-Bernal, 1988; Ota et al., 2013; Pearlman, 1969, 1973, 1982; Pearlman & Becker, 1974; Smith & Butler, 1982; Smith & Rose, 1996; Youngblood et al., 1997). However, REM sleep deprivation failed to induce any changes as compared with the control groups in simpler tasks (Albert, Cicala, & Siegel, 1970; Bryden & Holdstock, 1973; Shiromani, Gutwein, & Fishbein, 1979; Sloan, 1972; Van Hulzen & Coenen, 1979). Moreover, REM sleep deprivation impaired the consolidation of the novel object recognition task, but did not affect its reconsolidation (Chen, Tian, & Ke, 2014). These effects have been attributed to reduced hippocampal LTP following REM sleep deprivation (Davis, Harding, & Wright, 2003; Marks & Wayner, 2005; McDermott et al., 2003, 2006; Ravassard et al., 2009); however, it is not clear whether the effects on memory performance are solely attributable to REM sleep deprivation or whether other factors such as alterations of energy metabolism or stress (see also Figs. 17.1 and 17.2, discussed in the following sections) represent confounding factors to these results.

Recently, a study demonstrated that REM sleep provides the context during which the pruning of spurious spines can take place after learning of a new task (Li et al., 2017). In this study, newly formed spines in layer 5 of the motor cortex were identified by transcranial two-photon microscopy in mice that constitutively expressed yellow fluorescent protein (YFP) expression. Motor skill learning typically increases the number of spines in the motor cortex, as exemplified by training on an accelerated rotarod task in adult and adolescent mice (Li et al., 2017). Sleep deprivation studies demonstrated that a large amount of these spines gets eliminated during sleep (Maret et al., 2011; Yang et al., 2014; Yang & Gan, 2012). The authors showed that REM sleep

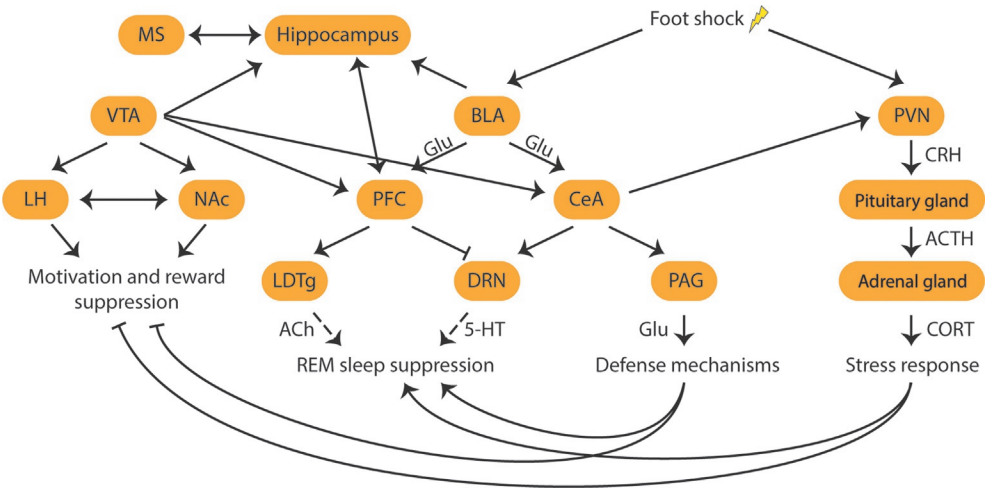

FIG. 17.2 Interactions between fear, stress, reward/feeding, and memory/learning networks. Foot-shock delivery activates a cascade of neural responses that impacts on multiple networks to facilitate the fight-or-flight response acutely, while other behaviors such as REM sleep and reward/feeding are suppressed. *5-HT*, serotonin; *ACh*, acetylcholine; *BLA*, basolateral amygdala; *CeA*, central nucleus of the amygdala; *CORT*, corticosterone/cortisol; *DRN*, dorsal raphe nucleus; *Glu*, glutamate; *LDT*, laterodorsal tegmental; *LH*, lateral hypothalamus; *MS*, medial septum; *NAc*, nucleus accumbens; *PAG*, periaqueductal gray; *PFC*, prefrontal cortex; *PVN*, paraventricular nucleus of the hypothalamus; *SLD*, sublaterodorsal nucleus; *VMM*, ventromedial medulla; and *VTA*, ventral tegmental area.

deprivation by gentle handling (over 8 h) significantly halts the process of spine elimination after motor training. The elimination was specific to newly formed spines and did not significantly affect preexisting spines. Furthermore, disrupting NREM sleep did not alter the elimination rate of spines and yielded amounts comparable with control mice that were not disturbed during their sleep. Interestingly, those newly formed spines that were not eliminated during REM sleep exhibited an increase in size when animals were allowed to spend time in REM sleep, but not in those animals that were REM sleep deprived, suggesting that REM sleep supports the strengthening of newly formed spines. This mechanism may support the elimination of spurious spines and to free up space for new spine generation, which likely functions to enhance the signal-to-noise ratio of neural activity relevant to newly learned tasks and allowing the storage of new memories (Li et al., 2017). However, it is not known whether and how REM sleep characteristics, including the hippocampal theta rhythm and cortical asynchrony, regulate REM-associated spine elimination.

In line with the aforementioned role of REM sleep in motor learning in rodents, REM sleep has often been associated with the consolidation of procedural memories in humans. To assess the effects of REM sleep loss in humans, previous studies have made use of the different distributions of NREM and REM sleep across the night; the first half of the night is rich in NREM sleep, while most REM sleep occurs during the second half of the night. Depriving humans of their sleep during the first half of the night (NREM-sleep-rich) or the second half of the night (REM-sleep-rich) yields different effects; the NREM-sleep-rich period was crucial to the consolidation of memory trained in a spatial rotation task (Plihal & Born, 1999) and a simple word-pair learning task (Fowler, Sullivan, & Ekstrand, 1973; Plihal & Born, 1997), whereas the REM-sleep-rich period improved the recall of episodic memory (Rauchs et al., 2004) and procedural memory components (Plihal & Born, 1997, 1999). Based on these findings, REM sleep was initially associated with procedural learning, whereas declarative memory was proposed to benefit from NREM sleep (dual-process hypothesis) (Plihal & Born, 1997, 1999). However, the role of REM sleep is not strictly limited to procedural memory consolidation; learning impairment after REM sleep deprivation was also observed in tasks involving learning of emotionally threatening words, procedural visual discrimination, and story learning (Grieser, Greenberg, & Harrison, 1972; Karni et al., 1994; Tilley & Empson, 1978). Learning of simple word pairs or sequential finger tapping was not impaired by REM sleep deprivation (Chernik, 1972; Ekstrand et al., 1971), confirming a role for REM sleep in more complex tasks.

3 Pharmacological Suppression of REM Sleep in Learning and Memory

REM sleep can be potently suppressed by antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) (McCarthy et al., 2016; Vertes & Eastman, 2000; Wichniak et al., 2017). These drugs enhance the activity of neurotransmitter systems that are typically turned OFF during REM sleep, including the serotonergic and noradrenergic systems. Administration of REM-suppressing drugs disrupted spatial memory and learning of complex rules in rodents (Bridoux et al., 2013; Pearlman & Becker, 1975; Sass & Wortwein, 2012; Watts et al., 2012). However, other groups have provided conflicting results; administration of SSRIs either did not impair memory consolidation (Feltmann et al., 2015), or even improved memory (Flood & Cherkin, 1987; Marwari & Dawe, 2018; Mork et al., 2013). Further, the administration of drugs targeting the noradrenergic system produced improvements in memory consolidation in a recognition memory task (Feltmann et al., 2015), suggesting that the effects on memory consolidation might also depend on the drug molecules used.

Similarly, in humans, application of these drugs led to conflicting results; in one study, REM-sleep-suppressing drugs improved performance in a motor skill task with a concomitant increase in spindle-rich NREM sleep stage 2 in healthy subjects (Rasch et al., 2009). Conversely, other studies reported neither beneficial nor detrimental effects of antidepressant medication in healthy subjects or depressed patients (Akindele, Evans, & Oswald, 1970; Georgotas, Reisberg, & Ferris, 1983; Joiner, 2016; Siegel, 2001; Vertes & Eastman, 2000; Wyatt et al., 1971). On the other hand, antidepressant drugs with different mechanisms of action might impact differently on memory consolidation; for example, antidepressants that target both the serotonergic and the noradrenergic system seem to improve memory (Li, Sanchez, & Gulinello, 2017; Herrera-Guzman et al., 2009; Papakostas, 2015). It is worth mentioning that these drugs not only do reduce REM sleep but also are associated with potentially confounding effects, including delaying sleep onset, sleep fragmentation, alterations of cholinergic neurotransmission, and brain plasticity mechanisms (Wichniak et al., 2017). Therefore, it is difficult to directly address REM-sleep-specific effects by means of pharmacological manipulations.

4 Optogenetic Suppression of Theta Activity During REM Sleep

The methodological confounds associated with the administration of antidepressants or the use of REM sleep

deprivation to suppress REM sleep are numerous and involve multifaceted effects, including impact on stress, thermoregulation, and energy expenditure. With the advent of optogenetic tools, we can now overcome these confounds that may mask the specific role of REM sleep in memory and learning. Using optogenetics, the activity of specific neuronal populations in a preselected brain region can be stimulated or silenced with a high spatial and temporal precision (Yizhar et al., 2011). Boyce and colleagues employed optogenetic tools to modulate REM sleep theta rhythm to address its role in REM-sleep-related learning and memory (Boyce et al., 2016). The authors genetically targeted silencing opsin to GABAergic cells in the medial septum (MS), which project to the hippocampus and are involved in the generation of the theta rhythm, but not in the generation of REM sleep itself. Optogenetic silencing of MS GABA neurons during REM sleep immediately after learning significantly impaired the memory consolidation of a previous object place in a novel object recognition task and contextual memory in a fear conditioning paradigm, as compared with various controls. These data demonstrate that the activity of MS GABA neurons enables theta activity during REM sleep, which, in turn, is key to the consolidation of two different types of memory that involve the hippocampal formation. This study provides the first experimental proof for the importance of MS GABA neuron activity and possibly REM sleep theta power, in spatial and contextual memory consolidation. Given the increasing synchrony between CA1 neurons during the course of a single REM bout and across several REM sleep episodes (Grosmark et al., 2012), MS GABA neuron activity during REM sleep and thereby theta oscillations might be crucial to facilitate plasticity-related mechanisms in the hippocampus that are necessary for the consolidation of newly formed memories. One may speculate that disrupting theta-related LTP and LTD in CA1 neurons (Huerta & Lisman, 1995) likely results in impairments of memory consolidation. In addition, recent evidence suggests that the activity of parvalbumin-expressing interneurons is crucial for memory consolidation after fear conditioning; pharmacogenetic inhibition of parvalbumin neurons in the CA1 region of the hippocampus impaired fear learning by reducing postlearning increases in theta power (among other effects) and by interfering with CA1 network coherence (Ognjanovski et al., 2017). Furthermore, during REM sleep, theta-gamma (gamma frequency band: 30–90 Hz) coherence is higher than during wakefulness (Montgomery, Sirota, & Buzsaki, 2008) and is thought to contribute to learning (Belluscio et al., 2012). Inhibition of the septal GABAergic input to the hippocampus impedes on theta-gamma coupling and theta coherence (Bandarabadi et al., 2017), an effect that might underlie the learning impairments shown by Boyce and colleagues (Boyce et al., 2016).

B Emotional Processing and Stress

Memories associated with negative or positive emotions are encoded more strongly and persist longer than neutral ones (McGaugh, 2004; Phelps, 2004). Several studies have shown activation and reactivation of brain regions that are important for emotional memory processing during REM sleep (Fig. 17.1). In rodents, such reactivation mostly involves the amygdalar-hippocampal network and neocortical structures (Girardeau, Inema, & Buzsaki, 2017; Hutchison & Rathore, 2015; Tempesta et al., 2018). Similarly, in humans, emotional memory-related brain regions are highly active during REM sleep as revealed by functional imaging studies (Dang-Vu et al., 2010; Maquet et al., 1996; Miyauchi et al., 2009; Nofzinger, 2005; Wehrle et al., 2007). Those brain regions include the amygdala, striatum, hippocampus, medial prefrontal cortex, and insula, together forming the limbic system (Cahill, 2000; McGaugh, 2004). The limbic activation during tasks that trigger an emotional response and their reactivation during REM sleep have inspired the hypothesis that REM sleep is implicated in the selective strengthening of emotional memories. In rodents, the number of studies dissociating the function of REM sleep in neutral versus emotional memories is sparse. It is known that rodents learn to discriminate stimuli that are associated with positive or negative outcomes. However, learning paradigms in rodents usually contain an emotional component. For example, appetitive tasks involve the presentation of rewarding stimuli to ensure that the mouse or rat will participate in the task, while fear conditioning paradigms involve aversive foot shocks that are delivered to the animal. In contrast, in humans, emotional memories can be assessed more easily with tasks that require learning positive or negative stimuli (e.g., texts or pictures). Human studies showed that the amount of REM sleep predicted the ability to recall emotional text (Wagner, Gais, & Born, 2001), the discrimination of negative and positive facial expressions (Wagner et al., 2007), and the recall of negative (but not neutral) emotional pictures (Groch et al., 2013; Nishida et al., 2009); importantly, the longer the participants spent in REM sleep during their daytime nap, the better they could recall the negative emotional pictures (Nishida et al., 2009). Thus, the results from human studies suggest that REM sleep promotes the consolidation of memories that are associated with emotional load (Hutchison & Rathore, 2015).

1 Fear Responses and Emotional Memory

Emotional memory in rodents is usually assessed in the context of fear responses or motivated/rewarding behaviors (detailed below). Acquisition, consolidation, and extinction of emotional memories in rodents are usually modeled using a conventional fear conditioning

paradigm. In this paradigm, the rodent is placed in a neutral, sound-attenuated chamber (context), where unexpected, noxious, inescapable foot shocks (unconditioned stimulus) are delivered. Foot-shock delivery is frequently paired with a tone, which then becomes the conditioned stimulus and is remembered in association with foot-shock delivery. Hence, the presentation of the conditioned stimulus or the context alone can trigger a fear response. Fear extinction paradigms usually require the presentation of the conditioned stimulus without the noxious stimulus for several trials to extinguish the fear response. Extinction learning does not depend upon unlearning of the fear response, but rather on the generation of a novel memory trace (Duvarci & Pare, 2014). Interestingly, exposure to an acute, inescapable shock reduced REM sleep in animals (Kant et al., 1995; Machida et al., 2017; Palma, Suchecki, & Tufik, 2000; Pawlyk et al., 2005, 2008; Vazquez-Palacios & Velazquez-Moctezuma, 2000). Fear conditioning further increased REM sleep latency and further reduces the number of REM sleep bouts (Jha et al., 2005; Pawlyk et al., 2005; Sanford et al., 2001; Silvestri, 2005). In contrast, in a mouse model of posttraumatic stress disorder (PTSD), an increased number of REM sleep episodes at baseline and immediately after the traumatic experience (i.e., two unexpected foot shocks) predicted the degree by which mice would develop a PTSD-like phenotype, as measured by the acoustic startle response (equivalent to human hyperarousal symptoms), reexposure to the shock context (avoidance symptoms), and a novel context (generalized fear). However, only low REM sleep continuity (short REM sleep episodes and frequent transitions to wakefulness), but not REM sleep amount, predicted the PTSD-like phenotype (Polta et al., 2013), although the interpretation of this latter study should take into consideration the differences in the number, intensity, and duration of the foot shocks as compared with previous ones (Jha et al., 2005; Kant et al., 1995; Machida et al., 2017; Palma et al., 2000; Pawlyk et al., 2005, 2008; Sanford et al., 2001; Silvestri, 2005; Vazquez-Palacios & Velazquez-Moctezuma, 2000).

Unlike fear conditioning, "safety conditioning" (placing the animal into an environment that they have learned to be safe) or shuttle-box avoidance training (offers an escape from the foot-shock compartment to a safe compartment) enhances posttraining REM sleep and might reflect learning-induced enhancement of REM sleep (see the previous section) (Fogel et al., 2011; Pawlyk et al., 2005, 2008), suggesting that controllable (escapable) and inescapable stressors have opposite effects on REM sleep. Indeed, milder stressors such as immobilization- or restraint-related stress for 1 or up to 4 h, cage changes, or exposure to an open field frequently increase REM sleep amount in mice and rats (Adrien, Dugovic, & Martin, 1991; Dewasmes et al., 2004; Meerlo et al., 2001; Pawlyk et al., 2008; Rampin et al., 1991; Tang, Yang, & Sanford, 2005, 2007; Vazquez-Palacios & Velazquez-Moctezuma, 2000). Conversely, selective REM sleep deprivation enhances anxiety-related behavior and activates the stress axis (da Silva Rocha-Lopes, Machado, & Suchecki, 2018). Altogether, these results suggest a role of REM sleep in stress-induced emotional processing.

In humans, the amount of REM sleep during a daytime nap following a fear extinction paradigm correlated with the skin conductance response, an indirect measure of sympathetic autonomic activity that is triggered by negative or positive emotional load (Bradley et al., 2001); the amount of REM sleep during the nap after fear extinction was inversely correlated with the autonomic arousal response to the conditioned stimulus (Spoormaker et al., 2010). Furthermore, fear extinction was impaired when participants were REM sleep deprived during the night, but not when they were deprived of NREM sleep (Spoormaker et al., 2012). In addition, REM sleep after fear extinction reengaged the ventromedial prefrontal cortex, which provides top-down inhibition of the amygdala and is required for fear extinction learning (Phelps, 2004; Spoormaker et al., 2012).

Given the relationship between REM sleep quantities and emotional memory, previous studies employed REM sleep deprivation to study the role of REM sleep in emotional memory consolidation. Surprisingly, REM sleep deprivation in rodents did not impact fear memory acquisition or consolidation (Bueno et al., 1994), whereas the loss of REM sleep impaired fear extinction (Fu et al., 2007; Landmann et al., 2014; Silvestri, 2005). Conversely, increasing REM sleep quantity to preshock levels by optogenetic activation of the basolateral amygdala (see below) during training did not impact fear memory recall, suggesting that REM sleep quantity immediately after fear memory acquisition did not affect the outcome on learning and memory and that some of the effects seen in other work might be a by-product of defense mechanisms or stress responses (Machida et al., 2017). In addition, amygdala-hippocampal reactivation after an aversive task occurred primarily during NREM sleep, but not during REM sleep (Girardeau et al., 2017). On the other hand, REM sleep deprivation prior to training impaired avoidance learning in the rat, suggesting a task-specific modulation of emotional memory in rodents (Gruart-Masso et al., 1995). In humans, on the other hand, REM sleep deprivation after fear conditioning impaired memory consolidation (Menz et al., 2013); REM sleep deprivation prior to the training interfered with the acquisition of fear conditioning (Menz et al., 2013), whereas REM sleep deprivation after fear conditioning interfered with the retention of fear memory (McGrath & Cohen, 1978). These results suggest that sufficient REM sleep in humans and rodents is crucial for the

acquisition of novel memories, as well as their consolidation and extinction in humans, whereas most studies in rodents have not found a causal relationship between REM sleep and emotional memory formation.

From a clinical perspective, REM sleep disturbances have been described as a hallmark of posttraumatic stress disorder (PTSD) almost three decades ago (Ross et al., 1989). PTSD patients show discontinued REM sleep with shorter but more frequent REM sleep bouts, increased rapid eye movement density, and an elevated number of transitions to other states (to wakefulness and NREM stage 1) (Breslau et al., 2004; Insana, Kolko, & Germain, 2012; Mellman, 1997; Mellman et al., 1995; Ross et al., 1989). These REM sleep disturbances likely result from sustained nightmares, dream enactment, and distressing awakenings resulting thereof (Habukawa et al., 2007; Mellman et al., 2007). However, these findings are rather inconsistent among PTSD patients and require further exploration (Engdahl et al., 2000; Germain, 2013; Mellman et al., 1995; Ross et al., 1994; Woodward et al., 2000).

REM sleep disinhibition is also a characteristic symptom in major depressive disorder (MDD); patients show a decreased latency to enter REM sleep after sleep onset, an increase in time spent in REM sleep, and an increase in the density of rapid eye movements (Palagini et al., 2013; Steiger & Kimura, 2010). These alterations in REM sleep expression might be part of a maladaptive stress reaction resulting from increased allostatic load due to chronic emotional stress (Palagini et al., 2013). Interestingly, total or partial sleep deprivation or selective REM sleep restriction in MDD patients leads to a temporary improvement in mood. However, any subsequent sleep counteracts this effect (Cluydts, 2003). Treatment of MDD often involves the use of antidepressant drugs that target the monoaminergic system by selectively inhibiting serotonin or noradrenergic reuptake. In patients that respond to SSRI/SNRI treatment, an improvement in mood and depression scores become evident after 2–4 weeks of treatment (Pigott et al., 2010). As mentioned above, it is a well-known fact that many antidepressant drugs including SSRIs and SNRIs suppress REM sleep in patients with MDD immediately upon treatment onset, that is, even before a treatment effect becomes evident (Palagini et al., 2013). This suppression might last for up to 1 year (Wyatt et al., 1971), thereby questioning the necessity of REM sleep in emotional processing. However, it should be noted that depression is a pathological state, in which changes to REM sleep might be essential to the recovery process (Horne, 2013).

Taken together, these results indicate that REM sleep, at least in humans, might "recalibrate" the sensitivity of the brain to emotional experiences during the preceding waking period, the so-called REM sleep emotional homeostasis hypothesis (Goldstein & Walker, 2014; Gujar et al., 2011; Horne, 2013). According to Goldstein and Walker (Goldstein & Walker, 2014), "the unique neurobiological state of REM sleep supports decoupling of emotion from memory such that we sleep to forget the emotional tone, yet sleep to remember the memory of that experience." Thereby, REM sleep provides a form of *overnight therapy* (Goldstein & Walker, 2014) that reduces the emotional strength of a newly acquired memory (Goldstein & Walker, 2014) and may be required for cognitive flexibility and creativity (reviewed inLandmann et al., 2014 ; Landmann et al., 2015). Hence, chronic disturbances in REM sleep might contribute to the pathophysiology of mood disorders ranging from PTSD and anxiety to depressive disorders. Chronic disturbances to either of these processes can manifest in psychiatric conditions, in which emotionality and REM sleep are disturbed. However, causal evidence for a role of REM sleep in the regulation of emotions and a reconciliation between human and rodent studies are still missing (Landmann et al., 2014, 2015) and need to be addressed in future studies. Furthermore, it might be worth exploring whether modulating REM sleep can provide new windows to the prevention and treatment of mental disorders.

2 *Neurotransmitters and Neuropeptides Involved in Emotional REM Sleep Regulation*

The neural substrates of fear-induced acute suppression of REM sleep have been addressed in several studies. Muscimol (a $GABA_A$ receptor agonist) administration to the basolateral amygdala (BLA) during foot-shock delivery prevented freezing and postshock REM sleep suppression (Wellman et al., 2014). On the other hand, muscimol administration to the BLA immediately after fear conditioning did not block freezing behavior during subsequent reexposure to the shock context, but successfully blocked REM sleep suppression following the foot shocks (Wellman et al., 2013). Conversely, optogenetic inactivation of glutamatergic neurons of the BLA during NREM and REM sleep extended REM sleep duration in nonfear conditions and when the inactivation occurred during foot-shock delivery (Machida et al., 2017). Inactivation of glutamatergic BLA neurons resulted in an increased activation of the central nucleus of the amygdala (CeA), suggesting its disinhibition by the BLA during fear conditioning (as measured by the number of cells expressing the immediate early gene c-fos (Milanovic et al., 1998). CeA activity is required to produce fear behavior including freezing and physiological responses (Duvarci, Popa, & Pare, 2011), but might not be sufficient to suppress REM sleep after fear acquisition (Machida et al., 2017). Furthermore, REM sleep regulatory regions were differentially modulated by BLA inactivation; the dorsal raphe nucleus (DRN) exhibited less c-fos-immunoreactive

cells after BLA inactivation coupled to foot-shock delivery, whereas the lateral dorsal tegmental nucleus (LDTg) and medial prefrontal cortex (mPFC) contained more c-fos-expressing cells than foot-shocked control animals (Fig. 17.2). The authors suggested that BLA inactivation indirectly activated the mPFC and CeA, which might exert a top-down control over the DRN and LDTg, in turn controlling REM sleep (Machida et al., 2017).

In addition, stress systems including the DRN and paraventricular nucleus (PVN) of the hypothalamus are activated by various types of stressors. The DRN and its major neurotransmitter serotonin are activated by prolonged immobilization or foot-shock stress (Chaouloff, Berton, & Mormede, 1999; Dazzi et al., 2005; Gardner et al., 2005; McEwen, 2004) and might suppress REM sleep in the first few hours after stress. In parallel, acute stressors also trigger the activity of the hypothalamic-pituitary-adrenal (HPA) axis, by first activating corticotropin-releasing hormone (CRH)-expressing neurons of the PVN and subsequently releasing adrenocorticotropic hormone (ACTH) from the pituitary gland to stimulate the secretion of glucocorticoids (cortisol in humans and corticosterone in rodents) from the adrenal glands (Fig. 17.2). In this regard, centrally (intracerebroventricularly) injected CRH inhibited REM sleep and increased wakefulness in mice in a dose-dependent manner (Romanowski et al., 2010). The CRH receptor 1 was necessary to mediate the wake-promoting effects of CRH, but not the REM-suppressing effects. Conversely, the administration of a CRH receptor 1 antagonist (astressin) reduced the time spent awake, but did not influence REM sleep, after restraint stress (Chang & Opp, 2002). The authors argue that peripheral effects, such as enhanced corticosterone and immunomodulator actions (Chang & Opp, 2001), might mediate REM sleep suppression. Systemic administration of corticosterone, on the other hand, did not alter immobilization-induced REM sleep increases significantly (Vazquez-Palacios & Velazquez-Moctezuma, 2000), suggesting a specific role for CRH in REM sleep alterations following acute stress.

In summary, multiple neurotransmitter systems are activated by acute stressors, many of which are directly required to promote wakefulness and suppress REM sleep. REM sleep suppression following acute inescapable stressors or REM sleep enhancement after mild stressors may represent forms of coping mechanisms that are triggered by an intricate activation cascade of different neurotransmitter systems recruiting CRH neurons in the PVN, serotonergic neurons of the DRN, glutamatergic neurons of the BLA, and many more. The necessity of these neurotransmitter systems for emotional processing during REM sleep is still open for future investigations.

C Reward System and Energy Homeostasis

Chronic sleep curtailment is strongly associated with increased weight gain (Kim et al., 2015; Laposky et al., 2008; Taheri et al., 2004; Watanabe et al., 2010), which likely results from changes in energy expenditure (Calvin et al., 2013; Markwald et al., 2013) and the related hormonal regulation and changes in the reward system (Chen et al., 2015) and late-night snacking (Markwald et al., 2013). Selective REM sleep loss in humans led to higher hunger ratings and increases in fat consumption proportional to the amount of lost REM sleep (Gonnissen et al., 2013; Shechter et al., 2012). Similarly, in rodents, REM sleep deprivation produces hyperphagia, even though it is unclear whether this effect can be attributed specifically to the loss of REM sleep or to the accompanying stress response by the flowerpot method (Hanlon et al., 2005; Shaw, Bergmann, & Rechtschaffen, 1998), during which animals lose a significant part of their body weight. On the other hand, fasting reduces REM sleep time in rodents (Sato et al., 2015; Willie et al., 2008; Yamanaka et al., 2003) and humans (Bahammam et al., 2014; MacFadyen, Oswald, & Lewis, 1973; Qasrawi, Pandi-Perumal, & BaHammam, 2017). Recent studies have addressed the participation of hedonic and homeostatic feeding brain centers, such as the mesolimbic dopamine pathway and lateral hypothalamic area, respectively, in the regulation of sleep-wake behavior. Disturbed neurotransmission in these areas is observed in humans and rodents with pathological overweight (i.e., obesity) and might be, at least in part, responsible for the sleep disorders that frequently accompany this condition. In the following section, we will review the role of REM sleep in the reactivation of mesolimbic dopamine and lateral hypothalamic neurotransmission and how this might relate to food intake and reward-related behaviors.

1 Lateral Hypothalamus (LH)

Early studies showed that lesions of the LH resulted in death by starvation and dehydration, leading to the designation of the LH as a "feeding center" (Anand & Brobeck, 1951a, 1951b; Morrison, Barrnett, & Mayer, 1958). Supporting this idea, electric stimulation of the LH stimulated food intake and increased physical activity (Delgado & Anand, 1953; Mogenson & Morgan, 1967). In addition, the LH plays a central role in arousal; pharmacological inhibition of the LH by LH-specific injections of the $GABA_A$ agonist muscimol reduced wakefulness in rats (Cerri et al., 2014). In fact, proper functioning of the LH is necessary for fasting-induced arousal, thus highlighting the important role of the LH in integrating metabolism and sleep (Adamantidis & de Lecea, 2008; Yamanaka et al., 2003). Interestingly, the loss of hypocretin/orexin neurons in the LH causes narcolepsy, a condition characterized by hypersomnolence,

sleep-wake fragmentation, increased REM sleep (including sleep-onset REM sleep), and cataplexy. Cataplexy is often triggered by emotional stimuli and results in a sudden loss of muscle tone, reminiscent of muscle atony during REM sleep (Pintwala & Peever, 2017; Scammell, 2003). Furthermore, orexin knockout mice and narcoleptic patients are often overweight or obese (Nixon et al., 2015). Among the diversity of neurotransmitters and neuropeptide contained by the LH, MCH- and Vgat-expressing (GABAergic) neurons were shown to fire actively during REM sleep (Hassani et al., 2010; Hassani, Lee, & Jones, 2009). While optogenetic activation of MCH neurons prolonged REM sleep episodes and facilitated the transition from NREM to REM sleep (Jego et al., 2013; Tsunematsu et al., 2014), optogenetic stimulation of Vgat neurons in the LH during NREM or REM sleep led to an immediate arousal (Herrera et al., 2016); this suggests that MCH plays a role in the regulation of REM sleep, while Vgat neurons do not. Taken together, these findings indicate that neurons in the LH play a significant role in both food intake and REM sleep regulation, a phenomenon that has been previously referred to as the "multitasking" capabilities of the LH (Herrera et al., 2016). However, the causal relationship between sleep-wake and feeding behaviors is not yet fully understood.

2 *Reward System Activation During REM Sleep*

The mesolimbic dopamine (ML-DA) pathway originates in the ventral tegmental area (VTA) of the midbrain and projects to the lateral hypothalamus, the nucleus accumbens (NAc), the olfactory tubercle of the ventral striatum (VS), the bed nucleus of the stria terminalis (BNST), the lateral septum (LS), the hippocampus, the amygdala, the PFC, and the anterior cingulate cortex (ACC) (Figs. 17.1 and 17.2) (Alcaro, Huber, & Panksepp, 2007). The ML-DA system plays an essential role in goal-directed behaviors, reward processing, reinforcement, and learning (Adcock et al., 2006; Alcaro et al., 2007; Ikemoto, 2007). Several studies have shown that the ML-DA pathway is activated during sleep, especially during REM sleep; the VTA exhibits increased bursting (phasic) activity during REM sleep, which produces a large synaptic dopamine release at terminal region, including the NAc shell (Dahan et al., 2007; Eban-Rothschild et al., 2016; Maloney, Mainville, & Jones, 2002; Miller et al., 1983). The enhanced activation of VTA dopamine neurons during REM sleep indicates that these neurons are possibly involved in the regulation of this state. However, despite their high activity during REM sleep (Dahan et al., 2007; Eban-Rothschild et al., 2016), the optogenetic activation of VTA dopamine neurons specifically during NREM and REM sleep produced arousal and shortened REM sleep duration, respectively (Eban-Rothschild et al., 2016). This suggests that VTA dopamine neurons might not be involved in the maintenance of REM sleep. Interestingly, the bursting activity of VTA dopamine neurons during REM sleep resembled the activity seen during the consumption of palatable foods, leading the authors to suggest that dopamine might participate in the memory consolidation of novel or rewarding stimuli during REM sleep (Dahan et al., 2007). Two projection targets of the VTA, namely, the NAc and mPFC, show enhanced dopamine release during both wakefulness and REM sleep (Lena et al., 2005), raising the possibility that dopamine recruits these two brain regions to exert its effects on memory consolidation during REM sleep.

Based on the reactivation of reward pathways delineated above, Perogamvros and Schwartz (Perogamvros & Schwartz, 2012) proposed a "reward activation model" (RAM) of the ML-DA pathway during REM sleep. The RAM proposes that the ML-DA pathway is reactivated during REM sleep to (a) consolidate memory traces by prioritizing information with high emotional and/or motivational valence, (b) modulate REM sleep by the activation of REM-related terminal regions such as the SLD, and (c) contribute to the generation of dreams. In this model, the VTA and the hippocampus form a functional loop that supports the entry of newly acquired, relevant information into long-term memory storage (Lisman & Grace, 2005). Thereby, novel, salient information is first relayed by the hippocampus (Pennartz et al., 2011) and the PPT (Pan & Hyland, 2005), which indirectly disinhibits dopaminergic neurons in the VTA via the NAc and VP when salient stimuli are encountered during wakefulness (Floresco & Grace, 2003; Holmstrand & Sesack, 2011; Lisman & Grace, 2005). This activation pattern is spontaneously reactivated at the end of an NREM episode at the transition to REM sleep (Perogamvros & Schwartz, 2012). In turn, the dopaminergic input to the hippocampus promotes synaptic plasticity, most likely by enhancing LTP (Adcock et al., 2006). Other reward-related brain regions that are activated by salient and novel stimuli, such as the amygdala, PFC, VS/NAc, and the ACC, also receive projections from the VTA and might contribute to RAM (Bush et al., 2002; Haber & Knutson, 2010; Knutson et al., 2001; Takenouchi et al., 1999). Thereby, VTA activation during REM sleep might promote "the reprocessing of memories with a high emotional or motivational relevance" by off-line replay of recent memory traces. This mechanism could facilitate the interaction of systems underlying reward processing and memory consolidation during sleep in the absence of associated contextual cues from wakefulness (Lansink et al., 2009; Perogamvros & Schwartz, 2012). It has been suggested that the reactivation of motivation and reward circuits, as well as the limbic system, reflects the sensations that are generated during dreaming in humans (Perogamvros & Schwartz, 2012). Accordingly, hyperactivation of dopaminergic activity by administration of L-DOPA, amphetamines, or dopamine

receptor agonists induces vivid dreamlike experiences in humans (Nausieda et al., 1982; Pinter, Pogarell, & Oertel, 1999; Sharf et al., 1978; Thompson & Pierce, 1999). On the other hand, hypoactivity of the dopaminergic system reduces vivid dreams (Gaillard & Moneme, 1977), suggesting that the activity of the dopaminergic system facilitates dreaming (see also Perogamvros & Schwartz, 2012).

In an attempt to provide causal evidence for the activity of reward-associated brain regions during REM sleep underlying hedonic eating, McEown and colleagues combined chemogenetic inhibition of the mPFC and REM sleep deprivation and measured the consumption of palatable foods in mice (McEown et al., 2016). REM sleep deprivation was achieved by housing mice on a wire-mesh-grid device (WMGD), which reduced REM sleep specifically during the dark (active) period by approximately 50% over the 3 deprivation days. NREM sleep amount was not significantly changed by the procedure. However, exposure to the WMGD produced a significant sleep fragmentation. With respect to hedonic feeding, REM sleep loss resulted in an enhanced consumption of palatable foods in a choice paradigm, where white chocolate, a high-fat diet with 60% fat content, and standard laboratory chow were available ad libitum. In turn, chemogenetic inactivation (Lerchner et al., 2007) of the mPFC reversed the effect of REM sleep loss on the consumption of highly palatable foods, especially by decreasing the consumption of sucrose-rich foods (fat consumption was not altered) (McEown et al., 2016). This study demonstrates that REM sleep is required to limit appetitive drives toward highly palatable, energy-dense foods. The mPFC seems to regulate food choices when REM sleep curtailment prevails. Yet, one should note that pharmacogenetic silencing of the mPFC independent of REM sleep or (the possible rescue of) sleep fragmentation may induce similar effects on food choice.

3 REM Sleep for the Preparation of Ensuing Wakefulness

In contrast to the proposed "reactivation/replay" function of REM sleep discussed above, Jouvet and later Horne suggested that REM sleep might be suited to prepare for ensuing wakefulness, rather than to consolidate experiences acquired during prior wakefulness. This idea stems from the conspicuous similarities between REM sleep and wakefulness. The most predominant common features are the increase in hippocampal theta (Jones, 1998; Kramis, Vanderwolf, & Bland, 1975) and hippocampal and neocortical gamma activity (Cantero et al., 2004; Montgomery et al., 2008) during both REM sleep and wake-associated exploratory and feeding activities. In this respect, it was shown that gamma oscillations generated in the medial septum entrain the activity of LH neurons to promote food seeking during wakefulness (Carus-Cadavieco et al., 2017). Considering that REM sleep is characterized by high-gamma activity (in addition to the predominant theta rhythm), it might be worth exploring a possible role of REM sleep gamma oscillations in the reactivation of such pathways that control food intake. Further, the prominent rapid eye movements during REM sleep are reminiscent of saccadic eye movements during wakefulness (Hong et al., 2009) and default mode network activity (Horne, 2013, 2015). It was argued that REM sleep might serve as a rehearsal of exploratory strategies (e.g., foraging) and that the motor output that is required for these strategies would be blocked by the REM-sleep-associated atony. Interestingly, in humans, REM sleep accumulates toward the end of the night, when sleep pressure is low and the individual has already undergone considerable physiological fasting since the last meal. Hence, it was suggested that REM sleep may play a role during physiological fasting by suppressing appetite at the end of the night, possibly through mechanisms involving orexin/hypocretin in the LH and peripheral satiety hormones, such as leptin (Nishiyama et al., 2000). However, if sleep curtailment prevails, such as in short sleepers, and the last REM episodes are lost and replaced by wakefulness, the REM-sleep-mediated satiety signaling might be blocked and feeding activity facilitated, as suggested by Horne (Horne, 2015). Together with the loss of emotional recalibration capabilities, this alternative view could explain the propensity of short sleepers to develop overweight or even obesity (Kim et al., 2015; Laposky et al., 2008; Taheri et al., 2004; Watanabe et al., 2010). However, whether REM sleep actively facilitates satiety signaling is still questionable and requires careful investigation. Furthermore, the idea that REM sleep promotes a rehearsal of feeding circuits aligns with the aforementioned study by McEown and colleagues, demonstrating that selective REM sleep loss promoted feeding on palatable, energy-dense foods (McEown et al., 2016). Therefore, REM sleep could "fine tune and help updating these behavioral (cognitive and emotional), locomotor and physiological processes to enable the animal to engage in efficient, safe exploration" (Horne, 2015). However, definite experimental proof in favor of the rehearsal hypothesis is still missing, and it will be a challenging task to dissociate the function of REM sleep in rehearsal/preplay versus reactivation/consolidation.

D Other REM Sleep Functions

1 REM Sleep and Development

A notable feature of sleep across the animal kingdom is its disproportionate abundance in the perinatal period. Indeed, newborns of all species studied thus far—from humans to fruit flies—sleep more than adults (Blumberg et al., 2014; Jouvet-Mounier, Astic, & Lacote, 1970;

Kayser & Biron, 2016; Roffwarg, Muzio, & Dement, 1966). Why do neonates sleep so much? The fundamental observation by Roffwarg and colleagues that human infants spend more than 50% of their time asleep in REM (or active) sleep (AS) inspired the so-called ontogenetic hypothesis (Marks et al., 1995; Roffwarg et al., 1966). According to this hypothesis, the brain stem mechanisms that generate REM sleep provide the developing nervous system with substantial neural stimulation during critical periods of plasticity when wake-related activity is limited. The ontogenetic hypothesis rests on the notion that spontaneous, endogenous neural activity during REM sleep plays a fundamental role in brain development and plasticity, as primarily demonstrated in the visual system (Davenne & Adrien, 1984) (see Chapter 27, this volume). Crucially, the role of REM sleep in the development of neural circuits is likely to extend beyond the visual system. In the sensorimotor system, for instance, the elimination of newly formed spines in the primary motor cortex of juvenile mice (in turn necessary for building up functional circuits) requires REM sleep (Li et al., 2017). In addition, sensory feedback from myoclonic twitches of limbs and facial muscles during REM sleep is a potent driver of neural activity across cortical and subcortical areas in the sensorimotor system of neonatal rats (e.g., Del Rio-Bermudez et al., 2017; Khazipov et al., 2004; Mohns & Blumberg, 2008; Sokoloff, Uitermarkt, & Blumberg, 2015; Tiriac, Del Rio-Bermudez, & Blumberg, 2014) and humans (Milh et al., 2007), thus contributing to activity-dependent brain development (Blumberg, 2010; Blumberg et al., 2013; Del Rio-Bermudez & Blumberg, 2018).

The importance of REM sleep in development is also illustrated by the deleterious effects of early REM sleep deprivation. In rat pups, for instance, early studies demonstrated that administration of pharmacological agents that suppress REM sleep (e.g., SSRIs and SNRIs such as clomipramine) causes a variety of behavioral (e.g., increased anxiety and impaired social interactions), morphological (reduced cortical size), and physiological (e.g., sleep disturbances) deficits that persist into adulthood (Mirmiran et al., 1981, 1983; Mirmiran, Uylings, & Corner, 1983). However, the reported effects of pharmacological disruption of early REM sleep must be interpreted with caution, since it is difficult to dissociate the relative impact of sleep disruption from that caused by merely altering monoaminergic transmission during sensitive developmental periods (Frank, 2011). More selective approaches have focused on disrupting specific features of neonatal REM sleep. For instance, suppression of the aforementioned REM-sleep-related PGO waves in kittens by mesencephalic lesions results in atypical morphological and functional development of the lateral geniculate nucleus (LGN) in the visual system (Davenne & Adrien, 1984; Davenne et al., 1989). These results suggest that typical brain and behavioral development likely depend on early REM sleep.

Finally, REM sleep disturbances are one of the most common and prevalent symptoms in a wide variety of neurodevelopmental disorders (Picchioni et al., 2014). The interplay between the lack of sleep and atypical development is difficult to assess experimentally; however, the discussed role of REM sleep in learning and memory, emotional processing, and brain development suggests that REM sleep disruption or deprivation during critical periods in these children likely exacerbates the cognitive and behavioral symptoms associated with these disorders.

In summary, further research is needed to elucidate the specific roles of REM (and NREM) sleep across ontogeny. However, existing experimental and clinical evidence indicates that REM sleep is likely to play a pivotal role in brain development by promoting neural plasticity and providing a suitable context for the activity-dependent development of the nervous system.

2 *Jouvet's Genetic Reprogramming Theory of REM Sleep*

Almost three decades ago, Jouvet suggested that REM sleep facilitates a process of genetic reprogramming that he termed "psychological individuation" (Jouvet, 1991, 1998). The reprogramming would depend on plastic changes in the adult brain (as opposed to the developing brain that has the ability of neurogenesis) and might involve epigenetic mechanisms. His idea was based on Bouchard's observation that homozygous (genetically similar) twins, who were raised at different environments after birth, "conserved identical psychological profiles" in adulthood (Bouchard et al., 1990). Jouvet therefore concluded that there must be a mechanism, by which the genetic programming of the CNS is reinforced ("iterative genetic programming"). In ectothermic vertebrates and in some cases also in birds, programming might be achieved by neurogenesis. However, in homeothermic vertebrates, neurogenesis ceases shortly after the developmental period (with the exception of adult neurogenic niches in the subgranular zone and subventricular zone; Shohayeb et al., 2018), leaving only plasticity mechanisms in place. Jouvet believed that REM sleep must provide the context for such a mechanism; he argued that REM sleep only occurs after the CNS ceases to produce new neurons and might provide the setting necessary for endogenous programming, which integrates both genetic and cortical information. In this sense, REM sleep would activate an endogenous system of stimulation to achieve "endogenous genetic learning," which could reinforce or erase the synaptic circuitry that had been established during prior waking experience. He suggested that hippocampal theta and cholinergic

activity during REM sleep might be crucial for the CNS to access the newly established synaptic circuitry and that PGO activity underlies longer-term "genetic reprogramming" (epigenesis) of the brain (Jouvet, 1978, 1998) (reviewed by Horne, 2015). In light of the above-discussed functions of REM sleep, Jouvet's idea presents many parallels to the plasticity-related mechanisms by which memory consolidation and emotional/reward circuit reactivation during REM sleep are achieved. However, it is still not clear whether and how reprogramming during REM sleep is achieved and whether psychological individuation is indeed programmed during REM sleep. Moreover, as we know now, neurogenesis continues in adulthood, contradicting Jouvet's idea that REM sleep occurs after the cessation of neurogenesis.

IV CONCLUSION/SUMMARY

Since its discovery in the 1950s, many different functions have been attributed to REM sleep. It has become clear that REM sleep is important for learning and memory by facilitating theta power-dependent processes in the hippocampus (for contextual and spatial memories) and by enabling synaptic depotentiation and strengthening in the cortex (to improve the signal-to-noise ratio of newly formed memories in procedural learning task). Concomitantly, REM sleep is altered by stress-related and traumatic experiences and has been proposed to serve emotional processing by reactivating the limbic system. Therefore, it has been proposed that dreams during REM sleep are much more vivid and bizarre than during any other state. However, causal evidence for the role of REM sleep in emotional reactivation is still missing. Similarly, motivation, reward, and feeding circuits are highly active during REM sleep, suggesting either their reactivation to consolidate prior wake experiences or their rehearsal for ensuing wakefulness. In addition, REM sleep seems to play a crucial role in early life by promoting neural plasticity and providing a suitable context for the activity-dependent development of neural circuits. Hence, REM sleep is a multifaceted state with complex salient features such as PGO/P-waves and theta and gamma oscillations that likely supports many different functions, the details of which require further exploration.

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