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Review

The role of rapid eye movement sleep for amygdala-related memory processing

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ABSTRACT

Over the years, rapid eye movement (REM) sleep has been associated with general memory consolidation, specific consolidation of perceptual, procedural, emotional and fear memories, brain maturation and preparation of waking consciousness. More recently, some of these associations (e.g., general and procedural memory consolidation) have been shown to be unlikely, while others (e.g., brain maturation and consciousness) remain inconclusive. In this review, we argue that both behavioral and neurophysiological evidence supports a role of REM sleep for amygdala-related memory processing: the amygdala–hippocampus–medial prefrontal cortex network involved in emotional processing, fear memory and valence consolidation shows strongest activity during REM sleep, in contrast to the hippocampus–medial prefrontal cortex only network which is more active during non-REM sleep. However, more research is needed to fully understand the mechanisms.

1. Introduction

Since the first empirical reports on the positive effects of post-learning sleep on memory consolidation (Jenkins Dellenbach, 1924), a large body of evidence has confirmed the sleep–memory relationship (Diekelmann Born, 2010). Sleep consists of a cyclic alternation between non-REM sleep (NREM), which can be subdivided into the stages 1 through 4 with stages 1 and 2 known as light sleep and 3 and 4 as slow wave sleep, and REM sleep. While evidence for the neural mechanisms occurring during non-REM (NREM) sleep – memory replay and downscaling – has been accumulating, the role of REM sleep still remains elusive. During NREM sleep, slow oscillations are thought to entrain hippocampal sharp wave ripples to enable replay in the hippocampus and prefrontal cortex, which is then followed by sleep spindles for local, cortical processing (Genzel, Kroes, Dresler, Battaglia, 2014). Sleep spindles may also occur independently, most likely to facilitate the consolidation of cortical networks independent of hippocampal led replay. This mechanism of active reprocessing of memories is then followed by a more general downscaling mechanism during the delta waves of deep sleep to enhance the signal to noise ratio (Genzel et al., 2014; Tononi Cirelli, 2014). Together the "push" of relevant memory traces during replay and "pull" of downscaling is thought to enable extraction of statistical overlap across different episodic memories leading to semanticized memories in the cortex (Battaglia, Borensztajn, Bod, 2012; Genzel et al., 2014). These consolidation processes in NREM are succeeded by REM sleep in the NREM/REM cycle, but it remains unknown for what purpose.

Initially, REM sleep was associated with brain maturation and general memory consolidation, potentially associated with dream mentation. Further, for several years the most dominant theory was that REM sleep supports the consolidation of procedural memories like motor skills while NREM sleep supports declarative memories like verbal information (Marshall Born, 2007). However, more recent studies failed to confirm this mapping between sleep stages and memory systems (Dresler et al., 2011a; Genzel, Dresler, Wehrle, Groezinger, & Steiger, 2009; Genzel et al., 2012; Rasch, Pommer, Diekelmann, & Born, 2009). In this paper, we will review the role of REM sleep for different memory systems and other functions in humans and non-human animals and provide existing evidence for and against each theory. Further, we will go on to show that the most conclusive and consistent evidence points toward a function of REM sleep in reprocessing of information in

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amygdala–hippocampal–medial prefrontal cortical networks, which may be enabled or mediated by the dominant oscillations (PGO-waves and theta) as well as elevated levels of acetylcholine and cortisol present in REM sleep. More specifically it seems that REM sleep may serve the purpose of emotional valence re-evaluation and adjustment, e.g., evaluating whether a stimulus is associated with a specific outcome and either up or down regulating the associated emotion encoded in the amygdala.

2. REM sleep dreaming and memory consolidation

One of the most striking features of REM sleep is its subjective phenomenology, i.e., dreaming. Dream-like mental activity can be observed during all sleep stages, however REM sleep dreams are particularly vivid and intense (Nielsen, 2000). Events and memories from waking life are sometimes incorporated into dreams, either as classical day-residues in the following night or after a "dream lag" of about 5–7 days (Blagrove, Henley-Einion, Barnett, Edwards, Seage, 2011; Nielsen, Kuiken, Alain, Stenstrom, Powell, 2004; Nielsen Powell, 1989). Such dream incorporations have been suggested to reflect processes of memory consolidation, and indeed some studies support this view by showing that items that were incorporated into dreams showed better memory retention (Cipolli, Fagioli, Mazzetti, Tuozzi, 2004; de Koninck, Christ, Hébert, Rinfret, 1990).

On the neurophysiological level, dream mentation has been suggested to represent the phenomenological reflection of a neural replay of activation patterns associated with recent learning experiences (Wamsley, 2014; Wamsley Stickgold, 2011; Wilson McNaughton, 1994). Although one study demonstrated such reactivations in REM sleep (Louie Wilson, 2001), the most advanced models of sleep-related memory consolidation propose that neural replay is orchestrated by an interaction of hippocampal sharp wave ripples, thalamo-cortical sleep spindles, and cortical slow oscillations during NREM sleep (Genzel et al., 2014; Molle Born, 2011). In line with this view, more recent studies found a positive effect of dream-incorporations of recent learning experiences on later memory performance to be associated mainly with NREM sleep (Wamsley, Perry, 2010; Wamsley, Tucker, 2010). Moreover, despite a majority of dream reports having been judged to reflect certain aspects of recent waking life experiences, an actual episodic replay of waking events was found in no more than 1–2% of the dream reports (Fosse, Fosse, Hobson, Stickgold, 2003), with NREM sleep dreams appearing to include more identifiable episodic memory sources than REM sleep dreams (Baylor Cavallero, 2001). However, it was suggested that particularly engaging learning experiences have a more robust influence on dream content, relative to more passive experiences which might lead to underestimations of experience-related dream incorporations (Wamsley, 2014). Nevertheless, the REM sleep dream narrative does not seem to reflect a simple replay of full episodic memories for the sake of consolidation.

3. The role of REM sleep in memory integration and reorganization

Besides a mere strengthening of recently acquired memories, REM sleep has also been suggested to be involved in the integration of new information into existing knowledge structures, the reorganization of these structures, and the generalization of recently acquired memories. For example, auditory cues were associated during encoding with pictures of faces and were later delivered during REM sleep. The subjects later not only remembered previously presented faces better, but also related face pictures that have not been presented before (Sterpenich et al., 2014). This was not the case when the cues were delivered during NREM sleep or when the cues had not been associated with the face stimuli. Increased false recognition related to REM sleep reactivations was interpreted as a generalization and schematization of the encoded information.

In a similar vein, it has recently been proposed that REM sleep serves as a state of elaborative (re-)encoding, during which the hippocampus reorganizes and integrates recent episodic memory fragments into remote episodic memories (Llewellyn, 2013). This process was proposed to rely on principles that also underlie the mnemonic encoding strategies of ancient orators (hence dubbed ancient art of memory, AAOM) such as vivid, complex and often bizarre associative imagery, narratives with embodiment of oneself and associations with known locations, later serving as retrieval cues. Subjectively, this process would be experienced as the typical dream mentation with its hyper-associative and bizarre imagery. Despite intuitively appealing, several theoretical considerations and empirical results are inconsistent with the REM sleep/AAOM analogy. Theoretically, it might be seen as a mere matter of definition if a mnemonic reprocessing of previously gained information during REM sleep as proposed by the model is called 'encoding' (which might be confused with the initial information uptake) instead of 'consolidation' (as in standard nomenclature). Mnemonic strategies normally recode abstract information into episode-like structures, thereby providing easily assessable retrieval cues that enable later recall. However, episodic memories are already structured in an easily assessable form, which would, due to dream amnesia, hardly benefit from further mnemonic cues created during REM sleep dreaming. Empirically, neither expert users nor novices feel the use of mnemonic strategies to be dreamlike (Dresler Konrad, 2013). Also on the neurophysiological level, no difference in REM sleep duration and REM density could be found between expert mnemonic users and mnemonics-nave controls, neither in a baseline night nor after an intense learning session (Dresler Konrad, 2013). Investigating similarities of REM sleep and episodic memory processing using functional neuroimaging also does not support the model, as REM sleep only activates parts of the episodic memory network: the posterior cingulate, precuneus and adjacent areas even appear deactivated in REM sleep (Dang-Vu et al., 2007). In contrast, more and more evidence is accumulating that processes occurring during NREM sleep (replay and downscaling, see (Genzel et al., 2014)) have the properties that would allow for memory reorganization to occur. Interestingly, birds do not show memory reorganization across brain areas and also do not show NREM ripples and spindles, which are thought to underlie these consolidation processes (Rattenborg, Martinez-Gonzalez, Roth, Pravosudov, 2011). In contrast, both REM sleep and the amygdala are evolutionarily conserved in birds.

A particularly striking effect of memory integration and reorganization is the emergence of novel associations and cognitive insights. Numerous anecdotal reports on scientific discovery and artistic productivity suggest that creativity can be triggered or enhanced by sleep (Barrett, 2001), and a number of studies support this anecdotal evidence. For example, when subjects performed a cognitive task which could be solved much faster through applying a hidden rule, after a night of sleep more than twice as many subjects gained insight into the hidden rule as in a control group staying awake (Wagner, Gais, Haider, Verleger, Born, 2004). Similarly, subjects benefited in a remote associations creativity task from an afternoon nap containing REM sleep but not from pure NREM naps or time spent awake (Cai, Mednick, Harrison, Kanady, Mednick, 2009). In a different video game problem task, however, SWS rather than REM sleep was found to prompt creative insight (Beijamini et al., 2014). Parallel to the cued reactivation of newly learned information in classical memory studies, the likelihood to

solve a problem encountered before sleep can be increased by cued reactivations during sleep (Ritter, Strick, Bos, van Baaren, Dijksterhuis, 2012).

According to the classical stage model of creativity, creative insights may be described by a process consisting of several stages, of which the incubation phase appears to be most intimately associated with sleep and dreaming (Dresler, 2012; Ritter & Dijksterhuis, 2014). The most common psychological approaches support this view: Early models of creativity emphasize the psychoanalytical primary process concept, which is explicitly conceptualized as dream-like (Kris, 1952). Physiological models propose that variability in cortical arousal levels benefit creativity (Martindale, 1999), implicating that the NREM-REM cycle is an environment particularly suited for creative processes. In addition, low levels of norepinephrine are proposed to facilitate creativity (Heilman, Nadeau, Beversdorf, 2003), again speaking for a creativity-enhancing role of REM sleep. Cognitive models propose that flat association hierarchies and a state of defocused attention facilitate creativity (Mednick, 1962; Mendelsohn, 1976), for which the typical defocused and hyper-associative REM sleep mentation could be considered a prime example: The chaotic activation of the cortex in REM sleep through brain stem regions in absence of external sensory data leads to a much more radical renunciation from unsuccessful problem solving attempts, leading to co-activations of memories that are highly remote in waking life (Kahn, Combs, Krippner, 2002).

In summary, while the sparse literature on creativity and insight processes indeed points to a role of REM sleep for such qualitative transformations of memories, the most convincing theoretical and empirical support for a role of sleep in more basal processes of memory integration and reorganization emphasizes NREM rather than REM sleep processes (see e.g., (Genzel et al., 2014; Lewis Durrant, 2011; Rasch Born, 2013)).

4. The role of REM sleep in the simulation and preparation of waking life

An alternative explanation for REM sleep dreaming that does not focus on the processing of recent experiences is the idea that REM mentation serves primarily preparational functions. Since REM sleep dominates the sleep episode more during early developmental periods in comparison to later in life (~50% vs. ~25%), some researchers have argued for a role of REM sleep in general brain maturation (Marks, Shaffery, Oksenberg, Speciale, Roffwarg, 1995; Mirmiran, 1995; Roffwarg, Muzio, Dement, 1966); however, also a life-long preparational function of REM sleep has been proposed. One of the first approaches in this direction was the hypothesis of Jouvet (1979), Jouvet (1998) that REM sleep serves as a genetic programming system for the brain. Based on the brain maturation hypothesis and Dewan's (1970) metaphor of the brain being a computer programmed during REM sleep, Jouvet (1979) suggested that innate behaviors are rehearsed during REM sleep to prepare for their application in waking life. He later revised his approach, now assuming that REM sleep constitutes an iterative genetic programming helping to maintain the process of psychological individuation (Jouvet, 1998). In a similar vein, Hobson (2009) proposed that REM sleep may constitute a 'protoconscious' state preparing for waking conscious experiences. The development of consciousness during ontogenetic development in this view is a gradual and lifelong process, building on the more primitive innate virtual reality generator, which is phenomenally experienced as dreaming. Based on the observation that during dreaming particularly threatening experiences are overrepresented, Revonsuo (2000) proposed the theory that a function of sleep is to simulate threatening events, and to rehearse threat perception and threat avoidance. Such a mechanism of simulating threats of waking life over and over again in various combinations would be valuable for the development and maintenance of threat-avoidance skills. Some empirical studies have supported threat simulation theory (for a review see Valli Revonsuo, 2009). Generally, however, evidence for a preparational function of REM sleep is still sparse.

5. The role of REM sleep in procedural memory consolidation

Independent from dream mentation, a role of REM sleep in memory consolidation has been studied since several decades. While many studies from the 1970s have been criticized as being heavily confounded by too stressful REM sleep deprivation procedures (Horne McGrath, 1984), in the 1990s a study demonstrating that a basic visual discrimination task improved after a normal night's sleep, but not after selective REM sleep deprivation (Karni, Tanne, Rubenstein, Askenasy, Sagi, 1994; see also Mednick, Nakayama, Stickgold, 2003), raised new interest in the role of REM sleep for memory consolidation. During the following years, a leading research aim in the field has been to identify which memory systems benefit from which coarse sleep stages.

Based on an approach first utilized by Barret Ekstrand (1972), a number of studies have experimentally exploited the fact that sleep stages are unevenly distributed across the night: While slow wave sleep (SWS) is present in the first half of the night and less so in the second, REM sleep is more pronounced in the second night half. On this background, subjects were either trained in the evening and retested in the middle of the night, or trained in the middle of the night and retested in the morning. Having sleep vs. sleep deprivation as a further variable of interest, subjects having slept during a period either rich in SWS or REM sleep could be compared with each other and with completely sleep-deprived subjects. Using this experimental paradigm, it was demonstrated that early sleep benefits declarative while late sleep supports procedural memories (Plihal Born, 1997; Plihal Born, 1999).

Further support for the role of REM sleep in procedural memory consolidation came from studies showing that REM sleep intensity (total number of REMs and REM densities) increased following procedural task acquisition (Smith, Nixon, Nader, 2004) and improvements in procedural memory performance after a night of sleep were proportional to the time spent in REM sleep (Fischer, Hallschmid, Elsner, Born, 2002). Moreover, brain areas activated during a procedural learning task were more active during REM sleep in subjects who were trained at the task, further support for the hypothesis that REM sleep is involved in the consolidation of procedural memory traces (Laureys et al., 2001; Maquet et al., 2000; Peigneux et al., 2003).

Recently the possibility of an active training of procedural skills during REM sleep has been suggested (Erlacher Schredl, 2010). While during normal dreaming the dreamer is typically unaware of his current state of mind, the phenomenon of lucid dreaming allows insight into and often even volitional control over the dream state (Dresler et al., 2014). Of note, actually executed and lucidly dreamed movements activate similar brain regions (Dresler et al., 2011b). Motor practice during lucid dreaming was therefore proposed as a novel type of mental rehearsal, comparable to mental practice during wakefulness, which is well established in sports science (Schmidt & Lee, 2011). Preliminary data demonstrate that dreamed training during lucid REM sleep might indeed improve previously learned motor skills (Erlacher & Schredl, 2010; Stumbrys, Erlacher, & Schredl, Personal Communication).

Despite several supporting studies, the idea of a major role of REM sleep in procedural memory consolidation has occasionally faced fierce criticism (Siegel, 1995; Siegel, 2001; Vertes, 2004;

Vertes Eastman, 2000; Vertes Siegel, 2005). Among other arguments, it was emphasized that many patients with major depression receive antidepressant medication with strong REM-suppressing effects, without apparently impairing memory functions thereby. While many studies in fact do show memory impairments in depressed patients for the declarative domains (Zakzanis, Leach, Kaplan, 1998), sleep-related aspects of procedural memory consolidation have not been investigated until recently. Today, several studies have demonstrated impaired procedural memory consolidation in depressed patients (Dresler, Kluge, Genzel, Schüssler, & Steiger, 2010; Dresler et al., 2011a; Genzel, Ali, Dresler, Steiger, & Tesfaye, 2011; Genzel, Dresler, et al., 2015). Surprisingly however, this procedural memory consolidation impairment was not related to the markedly reduced time spent in REM sleep: Despite ample variance, REM sleep amount did not correlate with memory consolidation, and patients with REM-suppressive medication did not experience stronger consolidation impairments compared to patients without REM-suppressing medication (Dresler, Kluge, Genzel, Schüssler, & Steiger, 2010; Dresler et al., 2011a). These findings are in line with studies in healthy volunteers: sleep-related procedural learning was improved rather than impaired by pharmacological REM sleep deprivation in healthy young subjects (Rasch et al., 2009), and also manual REM sleep deprivation had no effects on procedural and declarative memory consolidation in young (Genzel et al., 2009; Saxvig et al., 2008) or older (Hornung, Regen, Danker-Hopfe, Schredl, Heuser, 2007) subjects. Moreover, a nap without any REM sleep has been shown to benefit procedural and declarative learning (Genzel et al., 2012; however, see also Tucker et al., 2006). Instead the deficits in memory consolidation seen in psychiatric patients are most likely due to deficient hippocampal-medial prefrontal cortex communication during encoding and NREM slow oscillations, sharp wave ripples and spindles (Genzel, Dresler, et al., 2015; Phillips et al., 2012; Suh, Foster, Davoudi, Wilson, Tonegawa, 2013).

Reasons for the inconsistencies in the literature regarding the role of REM sleep in non-declarative memory consolidation might lie in different methodologies (see Table 1). Positive findings were mainly achieved with visuo-motor adaptation or perceptual tasks such as mirror tracing or visual discrimination, whereas studies with negative findings mainly used a sequential finger-tapping task. Sleep-related memory consolidation for the latter has been shown to involve hippocampal contributions, perhaps due to the sequential component (Albouy et al., 2008; Genzel, Dresler, et al., 2015), which might rely on other sleep-related processes (i.e., sharp wave ripple-related replay) than in hippocampus-independent tasks. However, recently researchers using a motor adaptation task in animals could show cortical replay during NREM resulting in specific dendritic branch spine formation (Yang et al., 2014). Another potential source of variance is the method of REM manipulation: Naps without REM sleep might involve other processes than night sleep with pharmacological or manual REM sleep suppression, which in turn might involve other processes than depriving early vs. late sleep. The night-half paradigm is highly confounded by hormonal changes, as early and late sleep coincide not only with different amounts of REM sleep, but also with the daily peak and nadir of several hormones such as growth hormone and cortisol (Steiger, 2007; Steiger, Dresler, Kluge, Schussler, 2013). In particular glucocorticoids have repeatedly been shown to be involved in sleep-related memory consolidation (Dresler, Genzel, 2010; Wagner Born, 2008) and cortisol given during sleep seems to enhance the effects on emotional memory usually attributed to REM sleep (van Marle, Hermans, Qin, Overeem, Fernandez, 2013).

In summary, while the connection between REM sleep and motor memory consolidation seems to be refuted, it may still play a role in other non-declarative memory processes as e.g., perceptual tasks.

6. The role of REM sleep in emotional memory consolidation

Whereas the idea that REM sleep supports procedural memory consolidation could not be confirmed, in recent years, evidence has added up for an important role of REM sleep in emotional memory consolidation. Already early content analyses of REM sleep dreams noticed that many dreams are highly emotional, with unpleasant emotions prevailing (Hall Van de Castle, 1966; Snyder, 1970). This is in line with neuroimaging studies of REM sleep, demonstrating

Table 1
Methodological approaches to REM sleep in humans.

Design	Description	Control	Caveats	Examples
Half-night paradigm	Contrasts the two night halves using the dominance of SWS during the first half of the night and REM sleep during the second half (encoding before and retrieval after the respective night half)	The other half of the night	Difference in encoding/retrieval conditions (early evening/middle of the night/early morning), hormone levels (growth hormone, cortisol)	Plihal and Born (1997)
Selective sleep deprivation – manual	Subject's sleep is scored online and they are awoken as soon as the respective sleep stage is reached	Control wakening condition (other sleep stage e.g., SWS or random), undisturbed night	Can be stressful	Genzel et al. (2009)
Selective sleep deprivation – pharmacological	Certain antidepressants (e.g., SNRI) show REM sleep suppressed effects	Other anitdepressants (e.g., SSRI)	Confounding effects of medication	Rasch et al. (2009)
Nap	Short daytime naps (60 min) usually contain little or no REM sleep, while longer naps (90 min) do	Wake control during the same time period	Day time naps may not be the same as night sleep in regard to hormones e.g., cortisol. Further usually only very little REM sleep is achieved (15 min)	Genzel et al. (2012)
Effects of learning on sleep	Sleep with and without previous learning is compared	Sometimes similar encoding experience but without memory component	Unspecific effects of the encoding experience often not controlled for	Fogel et al. (2011)
Correlational analysis	REM sleep amount, REM density or REM spectral power are correlated with learning measures	None	Correlational, often not controlled for multiple comparison (e.g., the different sleep stages) and correlation for state (memory consolidation) can be confounded by trait	Peters, Smith, and Smith (2007)

that neural areas involved in emotion regulation like the amygdala, medial prefrontal cortex and anterior cingulate cortex are highly activated during REM sleep (Nir Tononi, 2010). Several REM sleep characteristics differ between healthy subjects scoring low in depression scales and those with higher, but still sub-clinical depression scores (Cartwright, Luten, Young, Mercer, Bears, 1998). While certain kinds of mild stressors tend to increase REM sleep duration probably via prolactinergic and serotonergic pathways (Suchecki, Tiba, Machado, 2012), more intense stress disturbs REM sleep (Kim Dimsdale, 2007). After life events like divorce, REM sleep changes can be observed in those subjects that react with symptoms of depression (Cartwright, 1983), and dreams of depressed subjects differ from patients in remission (Cartwright, Agargun, Kirkby, Friedman, 2006). Changes in REM sleep are symptomatic of affective disorders including depression and PTSD (Dresler et al., 2014), and the sleep-memory relationship is altered in these diseases (Dresler, Genzel, 2010; Dresler, Kluge, Genzel, Schüssler, & Steiger, 2010; Dresler et al., 2011a; Genzel et al., 2011; Genzel, Dresler, et al., 2015; van Liempt, 2012; van Liempt, van Zuiden, Westenberg, Super, & Vermetten, 2013; van Liempt, Vermetten, Lentjes, Arends, & Westenberg, 2011). In healthy subjects, the consolidation of emotional texts (Wagner, Gais, Born, 2001) or pictures (Hu, Stylos-Allan, Walker, 2006; Nishida, Pearsall, Buckner, Walker, 2009) is enhanced through REM sleep, an effect that has been shown to last for several years (Wagner, Hallschmid, Rasch, Born, 2006). Of note, in addition to negative emotions, also the consolidation of reward information was proposed to be associated with REM sleep, suggesting the processing of memories of high emotional and motivational relevance in general to be a major function of REM sleep (Perogamvros Schwartz, 2012, 2014).

While on first sight it might look as if REM sleep unequivocally strengthens emotional memory processes, some studies suggest a more complex picture: Referring to the fact that emotional experiences are remembered better than neutral ones, however their emotional tone during retrieval decreases with time, it was proposed that REM sleep serves an emotional decoupling function: We sleep to remember emotionally tagged information yet sleep to forget the associated the emotional tone (Walker van der Helm, 2009). While some studies support this model (Hu et al., 2006; Nishida et al., 2009), other studies suggest that the affective tone of emotional memories is preserved rather than reduced during REM sleep (Groch, Wilhelm, Diekelmann, Born, 2013). Further, cortisol given during the sleep period enhances the difference between emotional and neutral consolidated memory, effectively prioritizing emotional memory consolidation. On a neural level, cortisol reduces amygdala reactivity related to the retrieval of these same consolidated, negative items (van Marle et al., 2013). These findings show that the effect attributed to REM sleep may be mediated or confounded by cortisol, which shows a natural interrelationship with REM sleep (Steiger, 2007; Steiger et al., 2013). Further indication for a complex interaction between REM sleep, amygdala related processing and cortisol is seen in patients with depression, in which all three seem to be concurrently affected (Drevets, 2000; Steiger Kimura, 2010; Steiger et al., 2013).

To sum up, evidence of some relationship between emotional memory and REM sleep is accumulating. However, it is at the moment unclear, which aspects of the memory–emotion association are strengthened and which are weakened through REM sleep. Does REM sleep consolidate the actual memory engram of emotionally tagged memories or is only the emotional tag re-evaluated and adapted as needed (either toning the emotional value up or down)? And is this effect actually a result of the oscillatory phenomena in REM sleep or effected by cortisol, or perhaps even a combination of both?

7. The role of REM sleep in fear extinction

To be able to investigate basic mechanisms via interventional studies as well as the behavior effect in humans, good translational models are needed. While it is difficult to find these for procedural and emotional memories not to mention dream mentation, in recent years, fear extinction has become an important model for the study of fear and anxiety in both animal and human research (Pape Pare, 2010; Rauch, Shin, Phelps, 2006). Neuroscientific work has demonstrated striking analogies between rodents and humans in research methodology (e.g., pairing between neutral stimuli and electric shocks in a specific context) and associated neural circuitry (Milad Quirk, 2012), including amygdala, hippocampus and ventromedial prefrontal cortex (vmPFC). The close overlap between methodology and neural circuitry of such a basic across-species process like associative learning has led to the proposition that fear extinction itself may be a model for how translational neuroscience could work and bridge the gap between preclinical and clinical work (Milad Quirk, 2012).

As a formal definition, fear conditioning is the (often repeated) pairing of a conditioned stimulus (CS+) with an aversive event such as electric shocks (unconditioned stimulus, US), because of which the CS+ alone comes to elicit an anticipatory fear response manifest in physiological (skin conductance, startle eye-blink electromyography) or behavioral (e.g., freezing) recordings (Steckle, 1933; Switzer, 1934). Fear extinction then comprises the (again often repeated) presentation of CS+ without any pairings with the US, the reduction of the fear response over nonreinforced stimulus presentation is the extinction readout/slope.

Consolidation of extinction is then typically assessed 24 h or 7 days later, when the extinguished conditioned stimulus (CS_E) is presented again without shock. Fear conditioning is often performed in a particular context, and extinction and extinction consolidation can be tested in a different context (e.g., context order A–B–B) to assess context-specificity of the learned associations (not to be confused with contextual fear conditioning in which the context itself can be viewed as a complex, multicompound CS). Note that after extinction, the original fear response to the extinguished stimulus can spontaneously reappear (spontaneous recovery), can reappear in a new context (renewal) or can be reinstated by repeated spontaneous shock administration (reinstatement). This indicated that extinction is not erasure of the original fear memory (CS–US), but the acquisition of a new extinction memory (CS–no US) through inhibitory mechanisms. Interestingly, whereas the CS–US pairing during fear conditioning appears to involve plasticity in the basolateral amygdala, extinction learning and recall additionally involves the vmPFC, which has projections to the inhibitory GABAergic intercalated cells in the amygdala, among others, which inhibit the fear response in the centromedial nucleus of the amygdala (Milad Quirk, 2002; Milad Quirk, 2012; Milad et al., 2007; Pitman et al., 2012). The hippocampal contribution may consist of appropriate cue and context recognition for triggering the vmPFC and inhibiting the fear response in the centromedial nucleus of the amygdala (Pitman et al., 2012).

Initial work in rodents a decade ago has shown that specific REM sleep deprivation impairs cued but not contextual extinction learning (Silvestri, 2005) and a subsequent rodent study additionally observed that REM sleep deprivation impairs cued (but not contextual) extinction consolidation, i.e., a hippocampus independent process, when performed in a time-window of 0–6 h after extinction learning (Fu et al., 2007). In the mean-time, theoretical work started to address the cognitive and neural mechanisms of the potential role for sleep and REM sleep in the acquisition and consolidation of fear extinction (Germain, Buysse, Nofzinger,

2008; Levin Nielsen, 2007). Here it should be noted that neuroimaging works has revealed that vmPFC and amygdala show increased activity in association with both fear extinction (Etkin Wager, 2007) and REM sleep (Braun et al., 1997; Maquet et al., 1996) in humans. The same applies to other regions in the 'fear network', such as insula, thalamus and dorsal anterior cingulate, although findings on whether hippocampus shows increased activity in REM sleep are not as unequivocal (Spoormaker, Czisch, Holsboer, 2013).

Initial work on the role of sleep in fear extinction in humans observed that sleep (compared to wake) only had a small and non-significant effect on extinction consolidation (Cohen's $D \sim 0.3$), and instead reduced the fear response to the unextinguished stimulus (i.e., a second CS+ that was not extinguished), which was interpreted as generalization of extinction (Pace-Schott et al., 2009). Employing a long afternoon nap paradigm, individual differences in physiological and brainstem habituation were observed to affect (REM) sleep disruption and subsequent extinction recall (Spoormaker et al., 2010). Moreover, overnight REM sleep deprivation versus control awakenings in NREM sleep specifically impaired extinction consolidation, which was associated with altered activity in the left temporal lobe (middle temporal gyrus) (Spoormaker et al., 2012). Such findings bear relevance for clinical extinction augmentation, and two pioneering studies have shown beneficial effects of a brief nap after exposure therapy for fear of spiders (Kleim et al., 2014; Pace-Schott, Verga, Bennett, Spencer, 2012). Intriguingly, recent animal work has revealed that successful fear extinction consolidation was strongly associated with pontine wave quality (corresponding to PGO waves in cats) during REM sleep (Datta O'Malley, 2013).

Unclear is yet whether there are long-term extinction consolidation effects of (REM) sleep deprivation, and not all studies have observed an effect of sleep on extinction consolidation, instead finding effects on fear memory consolidation and recall of safety (Menz et al., 2013). The latter finding has also been observed in studies on rodents showing impaired fear memory consolidation after sleep deprivation (Cohen et al., 2012). This opened up the intriguing possibility that sleep deprivation immediately after fear learning (or exposure to a traumatic event) may prevent fear memory consolidation and long-term memory consolidation, but an initial study in healthy subjects has shown that this relationship may be much more complex in humans with (thought) suppression as a potential major confound (Kuriyama, Honma, Yoshiike, Kim, 2013). Although sleep could be relevant for both fear memory and extinction memory consolidation, differences between studies in humans might further be due to varying methodologies, i.e., whether fear extinction follows immediately on the fear conditioning run or whether there is a 24-h delay to separate fear and extinction memory consolidation. Moreover, an individual shock titration procedure (to find the right shock level) before an extinction or recall session may to some extent comprise reinstatement, which would make an extinction recall session technically a re-extinction session. This would point to an effect of REM sleep on extinction learning in both rodents and humans (Silvestri, 2005; Spoormaker et al., 2012), although the individual shock titration in a controlled interaction with the experimenter may not have the same effects as administering unpredicted shocks with maximal intensity as in a typical reinstatement procedure (Hermans et al., 2005).

In any case, current translational evidence seems to converge that sleep, and in particular REM sleep, is involved in the consolidation of fear- and safety-relevant information, which fits with more general models on the potential role for sleep in emotional processing and homeostasis (Walker van der Helm, 2009). Eventually, such experimental translational work may help to assess the causality of disturbed sleep in pathological anxiety such as posttraumatic stress disorder (Germain, 2013; Spoormaker Montgomery, 2008), and as a consequence, inform clinicians about the need to specifically treat objective and subjective sleep symptoms in the course of stress-related disorders.

8. Methodological issues in assessing the role of REM sleep in animal studies

Although these findings on a role of REM sleep in the processing of fear extinction and safety learning seem to be converging across species, albeit still tentative, one should be careful in extrapolating such findings to other types of emotional or non-emotional memory. Cued fear conditioning and extinction procedures are standard in human studies but not in animal research, which regularly employs contextual fear conditioning, often without any other cue. This particularly holds for sleep research in rodents, and such procedures cannot disentangle whether emotional and/or spatial elements of the memory were affected by an experimental manipulation. A further issue is that contextual fear conditioning and avoidance tasks require the additional consolidation of a spatial memory, which is to be associated with an aversive event.

In such cases (Maren, Phan, Liberzon, 2013; Redondo et al., 2014), the neutral stimulus has been shown to be encoded in the hippocampus while the valence is stored in the amygdala, both independently in need of consolidation processes. Interestingly, using an optogenetic approach Redondo et al. (2014) could show that the neutral spatial, hippocampal engram can be associated with a new valence stored in the amygdala.

Currently most animal studies concerning REM sleep and memory either use avoidance or contextual fear learning, with both tasks including multiple memory aspects i.e., spatial and fear (Alvarenga et al., 2008; Cowdin, Kobayashi, Mellman, 2014; Datta, 2000; Datta, Mavanji, Ulloor, Patterson, 2004; Fogel, Smith, Beninger, 2009; Fogel, Smith, Beninger, 2010; Fogel, Smith, Higginson, Beninger, 2011; Graves, Heller, Pack, Abel, 2003; Hellman Abel, 2007; Jha, Brennan, Pawlyk, Ross, Morrison, 2005; Luo, Phan, Yang, Garelick, Storm, 2013; Mavanji Datta, 2003; Mavanji, Ulloor, Saha, Datta, 2004; Ognjanovski, Maruyama, Lashner, Zochowski, Aton, 2014; Pinho et al., 2013; Portell-Cortés, Martí-Nicolovius, Segura-Torres, Morgado-Bernal, 1989; Saha Datta, 2005; Silva, Chehin, 2004; Silvestri Root, 2008; Tian et al., 2009; Ulloor Datta, 2005; Vanderheyden, Poe, Liberzon, 2014; Wellman, Fitzpatrick, Machida, Sanford, 2014; Wetzel, Wagner, Balschun, 2003). Thus effects of e.g., REM sleep deprivation observed on performance on these types of tasks may represent a change in emotional valence as well as a change in spatial memory strength itself. Nonetheless, many authors claim an effect of REM sleep on spatial memory based on such a multi-compound procedure.

Furthermore, classic REM sleep deprivation techniques (Alvarenga et al., 2008; Chen, Tian, Ke, 2014; Datta et al., 2004; Fu et al., 2007; Graves et al., 2003; Legault, Smith, Beninger, 2004; Lima, de Bruin, Rios, de Bruin, 2014; Lipinska, Timol, Kaminer, Thomas, 2014; Morgenthaler et al., 2014; Pinho et al., 2013; Romcy-Pereira Pavlides, 2004; Sei, Saitoh, Yamamoto, Morita, Morita, 2000; Silva, Chehin, 2004; Silva, Kameda, 2004; Silvestri, 2005; Silvestri Root, 2008; Smith, Conway, Rose, 1998; Tian et al., 2009; Wetzel et al., 2003) are quite stressful themselves – the animal is placed on an overturned flower pot as platform in the middle of a water bucket thus falling into the water every time it reaches REM sleep with muscle atonia – creating a crucial confound via cortisol, which can produce the same effects as those associated with REM sleep itself (van Marle et al., 2013). Comparable control procedures in a balanced experimental design are therefore critical, such as the use of a control group undergoing the exact same sleep deprivation procedure but with a different latency after learning (Fu et al., 2007); however, even then the

potential effect of the stress on consolidation may also be different during different consolidation periods thus still creating a possible confounder. Instead other methods more similar to human study designs should be used, e.g., automatic online REM sleep scoring combined with gentle handling.

A similar issue applies to those studies measuring a change in REM sleep due to these learning tasks by comparing post-learning sleep to a non-learning baseline sleep recording (Adrien, Dugovic, Martin, 1991; Datta, 2000; Datta, Saha, Prutzman, Mullins, Mavanji, 2005; Fogel et al., 2009; Fogel et al., 2010; Fogel et al., 2011; Hegde, Jayakrishnan, Chattarji, Kutty, Laxmi, 2011; Hegde et al., 2008; Jha et al., 2005; Mavanji Datta, 2003; Popa, Duvarci, Popescu, Lena, Pare, 2010; Portell-Cortés et al., 1989; Schiffelholz, 2002; Ulloor Datta, 2005); it remains unclear whether this is caused by the emotional versus the other, mostly spatial elements of the memory. Recent work has shown that these post-training changes in REM sleep are mediated by the amygdala (Wellman et al., 2014), which would indicate that specifically the emotional aspects may be responsible for the observed effects, in line with previous claims (Datta O'Malley, 2013).

Further evidence is seen in a study showing that different types of avoidance behaviors in individual rats (active avoiders, non-learning, and escape failures) correspond to dissociated REM responses (Fogel et al., 2011). This interrelationship between emotional response patterns and REM sleep seems reminiscent of the interrelationship between REM sleep and psychiatric diseases (see above). Stress induces similar REM sleep changes (Hegde et al., 2008; Hegde et al., 2011) and general sleep deprivation has been shown to have an anxiogenic effect (Silva et al., 2004b). Another argument for the notion that REM sleep is relevant for emotional processing comes from the observation that animal studies have shown both disrupted REM sleep after fear conditioning (DaSilva et al., 2011; Jha et al., 2005; Kumar Jha, 2012; Sanford, Yang, Tang, 2003) and improved sleep (including REM sleep) after extinction learning (Wellman, Yang, Tang, Sanford, 2008).

The sleep of a helpless rat is quite similar to the sleep of a depressed rat. So perhaps changes in sleep due to learning in some tasks are created by inducing learned helplessness instead of effects of memory consolidation (Adrien et al., 1991). Recently evidence for this was provided, by investigating the sleep and memory patterns of rats stressed via maternal separation and isolation during postnatal days 5–7. The stressed rats showed increased time in REM sleep, increased theta oscillations in the hippocampus, amygdala and cortical circuits as well as increased fear memory and increased fear generalization (Sampath et al., 2014).

A further caveat, which should be considered when translating animal work to humans, is the issue of sex. Most animal research is done in males, while human research uses both male and female participants, which can affect results (Genzel et al., 2012; Genzel, Bäurle et al., 2015).

While due to these issues of methodology conclusions on REM sleep and spatial memory in animal research should be viewed with caution, they do convey the fact that there is an interrelationship between REM sleep and tasks with emotional or fear memory.

9. REM sleep for amygdala related memory processing

The behavior approaches in animals have not provided the one true answer for a function of REM sleep; however, newer techniques may be able to provide more insights. Some studies have reported increased protein expression and increased CREB and cAMP phosphorylation in the amygdala after REM sleep (Luo et al., 2013; Pinho et al., 2013; Ribeiro, 1999; Ribeiro et al., 2002; Saha Datta, 2005), but again it remains unclear if this is really due to learning or stress since the platform technique as a stressful confounder was used during a fear conditioning task. However, an electrophysiological study on the mechanisms underlying the potential relationship between REM sleep and fear memory consolidation revealed that that bidirectional changes in fear memory were selectively correlated with modifications in theta coherence between the amygdala and the medial prefrontal cortex as well as the hippocampus during REM sleep (Popa et al., 2010). More recently Girardeau, Inema, Fernandez Ruiz, and Buzsaki (2014)

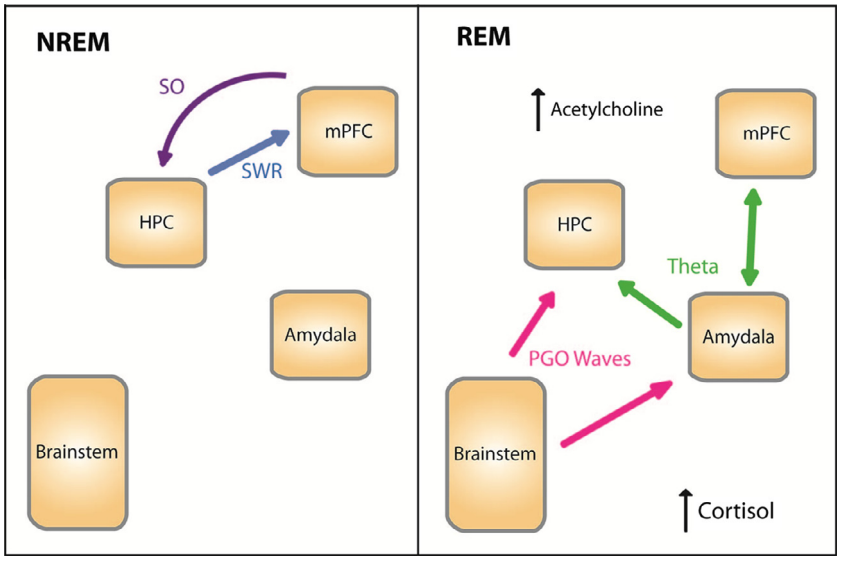

Fig. 1. NREM and REM sleep related network activity. As see in the left panel during Non-REM (NREM) sleep there is a bidirectional dialogue between the cortex and hippocampus, which is initiated via the slow oscillation (SO) in the cortex, which travels to the hippocampus and there it entrains the sharp wave ripple. During sharp wave ripples memory replay is seen in the hippocampus and the prefrontal cortex, which is then followed by a sleep spindle for local, cortical processing. During REM sleep, depicted on the right, the network now additionally includes the amygdala and brainstem, which communicate via theta and PGO-waves respectively. In contrast to NREM during REM acetylcholine levels are high affecting hippocampal network activity (low output, high input instead of high output, low input during NREM) and cortisol is elevated, perhaps enabling or mediating possible effects. NREM = non-NREM, SWR = sharp wave ripples, SO = slow oscillation, PGO waves = ponto-geniculo-occipital waves, HPC = hippocampus, and mPFC = medial prefrontal cortex.

could show that the firing rates of pyramidal cells in the amygdala increase significantly during REM sleep compared to wakefulness and confirmed the previously observed strong coherence between amygdala and the hippocampus in the theta range during REM sleep. If this increase in firing rate is accompanied by some form of memory replay, remains unclear. While one study reported hippocampal replay during REM sleep (Louie Wilson, 2001), this has not been confirmed since. Interestingly by recording from head direction cells (cells which fire when the animal's head points in a specific direction), Peyrache, Lacroix, Petersen, and Buszaki (2014) could show that REM sleep shows more wakelike brain dynamics, while NREM sleep tends to be 10 times faster, which has been previously observed in all NREM-hippocampal replay studies. Further, it was shown that PGO waves, which occur during REM sleep, project to the hippocampus and amygdala and are important for the consolidation of emotionally laden tasks such as aversive learning (Datta, 2000; Datta, 2006; Datta, Li, Auerbach, 2008; Datta O'Malley, 2013; Datta, Siwek, Patterson, Cipolloni, 1998; Datta et al., 2004; Datta et al., 2005; Fogel et al., 2010; Mavanji Datta, 2003; Mavanji et al., 2004; Ulloor Datta, 2005).

These findings in animals, together with research on emotional and fear memory in humans, suggest that perhaps while the hippocampus and cortex have a bidirectional dialogue during NREM sleep via slow oscillations and sharp wave ripples consolidating neutral memory content, during REM sleep the amygdala is included in the network to consolidate and/or emotionally revaluate information (see Fig. 1). Additional evidence for valence processing can also be seen in the finding that the VTA – known for coding valence of e.g., novelty (Wang Morris, 2009) – switches to a prominent bursting pattern during REM sleep similar to activity seen during consumption of a food reward and inducing a large dopamine release (Dahan et al., 2007). The hippocampus also seems to have a different role during NREM and REM sleep, in relation with the cholinergic tone the hippocampus is in replay mode (high output, low input) during NREM, but in recording mode (low output, high input) during wake and REM sleep associated with theta (Schall Dickson, 2010) perhaps allowing for re-encoding or adaptation of the hippocampal memory engram under amygdala direction. Investigating intra-hippocampal connectivity during REM sleep, it was shown that phasic bursts of activity during REM sleep may provide windows of opportunity to synchronize the hippocampal trisynaptic loop and increase output to cortical targets (Montgomery, Sirota, and Buzsaki (2008). Furthermore, a recent study could show that during REM sleep theta seems to run "backwards" from the subiculum to CA3, instead of its usual progression through the tri-synaptic loop, which may provide the milieu for re-encoding of valence (Jackson et al., 2014). Of note, also evidence that REM sleep may also contribute to downscaling has been provided (Grosmark, Mizuseki, Pastalkova, Diba, and Buzsaki (2012).

10. Conclusions and future directions

Since the discovery of REM sleep in the 1950s, many functions have been attributed to this sleep stage, ranging from general memory consolidation to a more specific function in perceptual, procedural and fear memory consolidation, as well as a role in brain maturation or simulation of waking consciousness. Some of these topics have received more attention than others, leaving us with a confusing mixture of results and theories that are untested. For example, the potential role of REM sleep in brain maturation or simulation of waking consciousness has gained comparably little experimental attention so far.

In contrast, much more effort has gone into the connection between REM sleep and memory consolidation. Considering recent research in procedural and declarative memory consolidation, a dependence on REM sleep could be refuted with studies showing a benefit on performance in these tasks after a nap or night of sleep without REM sleep (Genzel et al., 2009; Genzel et al., 2012; Hornung et al., 2007; Saxvig et al., 2008); however, there does seem to be some relationship between REM sleep and amygdala-related memory processing. While there is no single obvious effect of REM sleep to be seen across all studies in humans and non-human animals, e.g., the strengthening of the actual memory or adjustment of emotional valence in a specific direction, an increasing number of studies demonstrates a role of REM sleep in the processing of tasks involving emotion and fear. Due to the methodology, claims about spatial memory based on mixed spatial/emotional learning tasks are difficult to interpret. Yet an increasing body of evidence is highlighting that particularly fear conditioning and extinction bear translational promise, due to remarkably similar neural circuitry across species and the possibility to use similar procedures, although more convergence is needed in the readouts (Erhardt Spoormaker, 2013). In contrast to animal research, where almost any study design involves some affective component to motivate the animal for the actual learning task, most human research has been done on either declarative or procedural memory tasks without decisive emotional aspects. And tasks aimed at inducing strong emotional valence in humans are not necessarily comparable in emotional strength across different labs as well as usually being much less stressful than tasks in other animals. Small difference in natural resistance or upbringing can change measured effects, as can even be seen in rats with seemingly the same rearing and similar genetic background (Fogel et al., 2011).

To sum up, in this review we propose that (1) NREM sleep is important for consolidation of cortical memory content and extraction of statistical overlap across different episodes via hippocampal led systems consolidation during the slow oscillation-sharp wave ripple–spindle complex involving a hippocampal-medial prefrontal cortical network (see also (Genzel et al., 2014) and Fig. 1) and in contrast (2) REM sleep supports memory processes that involve a wider network including the amygdala and brainstem and perhaps involve cortisol (see Fig. 1). Consolidation processes occurring during REM sleep most likely involve changing the strength of amygdala-related networks into whatever direction seems most adaptive to the organism, e.g., strengthening or weakening emotions and fear. Another argument in favor of this proposed theory is that both REM sleep and the amygdala have been conserved in evolution (or evolved twice independently) and are present in birds. In contrast, birds do not show memory reorganization across brain areas and also do not show NREM ripples and spindles (Rattenborg et al., 2011).

In conclusion, while research on the function of REM sleep has progressed less rapidly than for NREM, more evidence is accumulating pointing toward a connection between REM sleep and amygdala-related networks. However, for us to be able to gain true insight into the mechanisms and effects of REM sleep, more systematic and standardized approaches are needed. Special care has to be taken in controlling for and reporting any possible variables affecting the emotional component during the learning day. Further, more standardized and translational tasks are needed to be able to compare human with non-human animal work.

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