

The role of REM theta activity in emotional memory

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In review

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12 Abstract

13 While NREM sleep has been strongly implicated in the reactivation and consolidation of memory
14 traces, the role of REM sleep remains unclear. A growing body of research on humans and animals
15 provide behavioral evidence for a role of REM sleep in the strengthening and modulation of
16 emotional memories. Theta activity – which describes low frequency oscillations in the local field
17 potential within the hippocampus, amygdala and neocortex – is a prominent feature of both wake and
18 REM sleep in humans and rodents. Theta coherence between the hippocampus and amygdala drives
19 large-scale PGO waves, the density of which predicts increases in plasticity-related gene expression.
20 This could potentially facilitate the processing of emotional memory traces within the hippocampus
21 during REM sleep. Further, the timing of hippocampal activity in relation to theta phase is vital in
22 determining subsequent potentiation of neuronal activity. This could allow the emotionally
23 modulated strengthening of novel and the gradual weakening of consolidated hippocampal memory
24 traces observed in both wake and REM sleep. Hippocampal theta activity is also correlated with
25 REM sleep acetylcholine levels – which are thought to reduce hippocampal afferent inputs in the
26 neocortex. The additional low levels of noradrenaline during REM sleep, which facilitate recurrent
27 activation within the neocortex, could allow the integration of novel memory traces previously
28 consolidated during NREM sleep. We therefore propose that REM sleep mediates the prioritized
29 processing of emotional memories within the hippocampus, the integration of previously
30 consolidated memory traces within the neocortex, as well as the disengagement of consolidated
31 neocortical memory traces from the hippocampus.

32 1. Introduction

33 Though the body may seem inert during sleep, the brain most definitely isn't. Mammalian sleep
34 cycles through multiple electrophysiologically and neurochemically distinct sleep stages. These
35 stages are generally split into two categories, based on the occurrence of rapid-eye movements
36 (REMs), i.e. REM and non-REM (NREM) sleep. While evidence strongly supports a pivotal role of
37 NREM sleep in memory consolidation, the function of REM sleep remains elusive.

38 In this review, we propose that REM sleep represents a unique brain state that allows the emotionally
 39 modulated integration and recombination of neocortical memory traces previously consolidated
 40 during NREM sleep. In addition, we suggest that REM sleep is involved in the gradual
 41 disengagement of successfully consolidated memory traces from the hippocampus – thus mediating
 42 the decontextualization of novel memories, allowing generalization, abstraction, etc. To support this,
 43 we initially review behavioral evidence linking REM sleep and emotional memory processing in both
 44 rodents and humans. We then discuss how this relationship may be mediated by electrophysiological
 45 (in particular theta) activity within the hippocampus, amygdala and neocortex during REM sleep.

46 **2. REM vs NREM physiology in humans and rodents**

47 REM and NREM sleep differ remarkably in several ways: while NREM sleep is characterized by
 48 high amplitude, low frequency (0.3-4 Hz) electroencephalographic (EEG) activity reflecting
 49 synchronization across large neuronal populations, the low-amplitude, mixed frequency EEG activity
 50 observed during REM sleep more closely resembles that of quiet wake (Llinas & Ribary, 1993;
 51 Steriade et al., 1996). Neuromodulator levels also differ between these two brain states: during
 52 NREM sleep, acetylcholine levels in the brain stem, forebrain and hippocampus are at a
 53 physiological nadir (Hobson et al., 1975; Marrosu et al., 1995), while cholinergic modulation during
 54 REM sleep increases to levels just below that of wake in the neocortex and even exceeds wake levels
 55 in the hippocampus (Hasselmo, 1999). In contrast, while aminergic (i.e. serotonergic and
 56 noradrenergic) neurons fire at reduced rates during NREM sleep compared to wake (Aston-Jones &
 57 Bloom, 1981), they are almost completely silenced during REM sleep (Pace-Schott & Hobson,
 58 2002). Besides the occurrence of rapid-eye movements, REM sleep is also identified by a significant
 59 reduction in muscular tone. This atonia of the skeletal musculature is a vital characteristic of REM
 60 sleep, the loss of which results in dream enactment (McCarter et al., 2012). Furthermore, while
 61 dreams can occur during all sleep stages, those of REM sleep tend to have a comparatively bizarre,
 62 emotional, and vivid quality (Suzuki et al., 2004).

63 In humans, NREM sleep is divided into light sleep and slow-wave (or deep) sleep (Iber et al., 2007),
 64 while in rodents all NREM sleep stages are collectively referred to as NREM or slow-wave sleep
 65 (Genzel, Kroes, Dresler, & Battaglia, 2014; Oyanedel et al., 2014; van Twyver, 1969), with only few
 66 studies differentiating between light and deep NREM sleep (e.g. Benedetto et al., 2013), and in some
 67 cases including a spindle-rich transition to REM sleep (TR) phase (e.g. Watts, Gritton, Sweigart, &
 68 Poe, 2012) which is not reported in the human literature. In rodents and humans, the proportion of
 69 slow-wave sleep (SWS) in a given sleep cycle decreases with diminishing sleep pressure (Borbély &
 70 Achermann, 1999; Yasenkov & Deboer, 2012). In human nocturnal sleep, SWS predominates during
 71 the first half of the night while REM sleep – regulated by circadian factors - displays an inverse
 72 relationship with SWS, becoming increasingly prevalent towards the morning (Wurts & Edgar,
 73 2000). In rodents, REM sleep does not appear to follow a circadian rhythm (Yasenkov & Deboer,
 74 2012) and takes up a higher proportion of overall sleep compared to humans (Mendelson &
 75 Bergmann, 1999).

76 **3. NREM sleep and memory consolidation**

77 The idea that sleep is important in the consolidation and processing of both recent and remote
 78 memories is well established (for an extensive review, see Rasch & Born, 2013). Based on early
 79 rodent work this memory function of sleep was primarily ascribed to REM sleep. However, more
 80 recent work in both rodents and humans strongly supports a role of NREM sleep in memory
 81 reactivation and consolidation (Diekelmann & Born, 2010; Rasch & Born, 2013; Stickgold, 2005;

82 Girardeau et al., 2009; Ego-Stengel & Wilson, 2010). The high frequency thalamocortical spindles
83 and associated hippocampal sharp-wave ripples, which occur during both stage 2 NREM and SWS
84 (Genzel et al., 2014), are thought to reflect processes underlying synaptic plasticity (Sejnowski &
85 Destexhe, 2000; Steriade, 1999). The low levels of acetylcholine during NREM sleep disinhibit
86 communication between the hippocampus and neocortex (Hasselmo, 1999). This, in conjunction with
87 the high amplitude slow waves of SWS is thought to drive the transfer of declarative memory traces
88 from the hippocampus to the neocortex (Rasch & Born, 2013) by providing windows of wide-spread
89 depolarization during which higher frequency activity (including spindles) is synchronized across
90 various brain regions (Compte et al., 2008; Mölle & Born, 2011, 2009; Battaglia et al., 2014). In
91 support of this, overnight improvement in memory performance is predicted by the amplitude of slow
92 waves in both rats and humans (Heib et al., 2013; Marshall et al., 2004; Binder et al., 2014), as well
93 as the occurrence of spindle activity during the up-phases of slow oscillations in humans (Ngo et al.,
94 2013; Mölle et al., 2011; Cox et al., 2012). Similarly, the duration of stage 2 NREM sleep predicts
95 overnight consolidation of both declarative and motor memories (Walker et al., 2002; Fogel & Smith,
96 2006; Ruch et al., 2012). Studies investigating the function of REM sleep have been comparatively
97 unfruitful – often yielding conflicting results, thus leading to an overall neglect of this sleep stage.
98 There is however considerable evidence linking REM sleep with the processing of emotional
99 memories, discussed in the following section. A separate line of research implicates REM sleep in
100 the consolidation of procedural skills, the mechanism of which deserves consideration; however this
101 exceeds the scope of this review.

102 4. REM Sleep and Emotional Memory

103 Events that elicit an emotional response tend to be remembered more reliably and for longer term
104 than comparatively unemotional events (LaBar & Cabeza, 2006). Emotional responses are most
105 commonly elicited by situations relevant to survival. Although emotions are undoubtedly important
106 in guiding immediate behavior - whether by triggering a fight or flight response, driving reproduction
107 or seeking nourishment - retaining memory of the experience that elicited the emotion carries the
108 additional benefit of guiding future behavior in similar situations, and thus would improve chances of
109 survival in the long-term (Hamann, 2001). The neural mechanism underlying the influence of
110 emotion on long-term memory retention involves co-activation of the hippocampus and the amygdala
111 – the emotional center of the brain. The amygdala appears to modulate hippocampal activity, thus
112 facilitating the preferential encoding of emotional memories and potentially their tagging for future
113 consolidation.

114 Several studies support the central role of the amygdala in mediating the prioritized consolidation of
115 emotional vs. neutral memories. Bilateral amygdala damage selectively impairs emotional memory
116 (Adolphs et al., 1997). In a separate study, the degree of left hippocampal damage was found to
117 predict emotional memory performance (Richardson et al., 2004). More strikingly, amygdala activity
118 during memory encoding predicted later recall of negative (Cahill et al., 1996) and positive (though
119 not neutral) memories (Hamann et al., 1999). Furthermore, using event-related fMRI, Dolcos et al.
120 (2004) showed that the interaction of activity in the amygdala and hippocampus predicted recall of
121 emotional vs. neutral memories.

122 In rodents, memory tasks tend to be inherently emotional. Often the emotional response represents
123 the actual memory (e.g. in fear conditioning or extinction), or else it is used as an incentive to
124 perform a memory task (e.g. a food reward or the avoidance of pain). Similarly to the work in
125 humans, there is a large body of evidence supporting a role of amygdala activity in emotional
126 memory (i.e. fear conditioning) in rodents (for a review, see LeDoux, 2003). Though - due to the lack

127 of an adequate non-emotional control – the role of the amygdala in more indirect forms of emotional
128 memory in rodents is not as well characterized.

129 Sleep appears to facilitate the preferential consolidation of emotional memories. Though there is
130 evidence supporting a role of SWS in this process (Cairney et al., 2014; Groch et al., 2011), a larger
131 body of research implicates REM sleep in both the selective strengthening of emotional memories as
132 well as the modulation of the emotional response associated with specific stimuli. This dual-process
133 is described in the “sleep to forget sleep to remember” (SFSR) hypothesis proposed by Walker
134 (2009). Evidence for the role of REM sleep in emotional memory processing is summarized in the
135 following two sections.

136 **3.1 Behavioral Evidence**

137 Early studies on REM sleep examined the effects of REM sleep deprivation (REMSD) on memory
138 consolidation and encoding in rodents. Post-training REMSD was consistently found to impair
139 avoidance learning (Fishbein, 1971; Leconte & Bloch, 1970; Pearlman, 1969, Smith & Kelly, 1988),
140 avoidance conditioning (Leconte & Bloch, 1970) and fear conditioning (Menz et al., 2013).
141 Conversely, REMSD preceding training impeded the efficiency of fear conditioning (Bueno et al.,
142 1994; Smith, 1985; McGrath & Cohen, 1978) and avoidance learning (Hartmann & Stern, 1972;
143 Danguir & Nicolaidis, 1976; Sagales & Domino, 1973). Fear extinction was also impaired following
144 REMSD compared to uninhibited sleep in rats (Fu et al., 2007; Silvestri, 2005). However, it appears
145 the effects of REMSD are only short-lived, not persisting beyond recovery sleep (Fishbein, 1971).
146 Furthermore, it has been suggested that the deleterious effects of REMSD are explained by the
147 extreme stress resulting from the so-called flowerpot method used to prevent REM sleep (Horne &
148 McGrath, 1984). This method typically involves placing the animal on a small platform above water
149 so that when REM sleep associated muscle atonia sets in, the animal slips into the water and
150 awakens.

151 A recent study using REMSD provides more striking evidence for a role of REM sleep in emotional
152 memory processing: Ravassard et al. (2015) trained rats in contextual fear conditioning followed by
153 short-term and non-stressful REM sleep deprivation (REMSD). They found that 4 hours of REMSD
154 impaired both the consolidation of contextual fear conditioning and long-term potentiation (LTP)
155 within the CA1 region of the hippocampus. Conversely, rodents that obtained a comparably higher
156 amount of REM sleep following contextual fear conditioning displayed stronger consolidation, as
157 well as greater hippocampal LTP. Furthermore, both measures were positively correlated with REM
158 sleep amount. This fits with further evidence showing that increasing REM sleep duration in rats –
159 through either carbachol (an acetylcholine agonist) or through REMSD-induced REM sleep rebound
160 – led to enhanced memory retention of a reward-memory based Y-maze task across sleep (Wetzel et
161 al., 2003) – suggesting REM sleep may also benefit positive emotional memory processing.

162 In humans, sleep in general has been shown to benefit fear extinction (Kleim et al., 2014; Pace-
163 Schott et al., 2009). The amount of REM sleep obtained following fear extinction was shown to
164 predict a decrease in autonomic arousal based on skin conductance (Spoormaker et al., 2010).
165 Conversely, disrupting sleep through repeated awakening only impaired extinction if awakenings
166 occurred during REM sleep, but not if they occurred during NREM sleep (Spoormaker et al., 2012).
167 In addition to supporting fear extinction, REM sleep was found to predict post-sleep recognition of
168 negative emotional pictures (Groch et al., 2013; Nishida et al., 2009), negative and positive
169 emotional faces (Wagner et al., 2007) as well as recall of emotional texts (Wagner et al., 2001)
170 compared to neutral controls. Administration of hydrocortisone during sleep following an emotional

171 memory task resulted in superior recognition for emotional vs. neutral images (van Marle et al.,
 172 2013). Although sleep was not recorded in this study, it is possible that the resulting increase in
 173 emotional memory was related to cortisol-mediated processes during REM sleep, as cortisol levels
 174 are naturally elevated during this stage compared to NREM sleep (Steiger, 2007).

175 **3.2 Physiological evidence**

176 Physiological evidence also supports a role of REM sleep in memory. Areas implicated in memory
 177 processing during wake, in particular limbic circuits within the medial temporal lobe, are highly
 178 active during REM sleep (Maquet et al., 1996; Braun, 1997; Nir & Tononi, 2010; Braun et al., 1998;
 179 Nofzinger et al., 1997). At a cellular level, Pavlides & Winson (1989) observed reactivations of
 180 hippocampal neurons active during prior wakefulness during subsequent REM sleep. Even at a
 181 molecular level - plasticity-related gene expression increases within the hippocampus during REM
 182 sleep (Ribeiro et al., 1999). A recent study from the same group compared mRNA levels of
 183 plasticity-related genes within the hippocampus following either exposure to a novel or familiar
 184 control environment (Calais et al., 2015). The rats were killed either after 30 minutes of stable wake,
 185 SWS or REM sleep. mRNA expression of several plasticity-related genes were significantly
 186 upregulated during REM sleep following exposure to a novel environment – though not during post-
 187 training SWS or wake. There was also no upregulation of plasticity-related gene expression in rats
 188 who had not been exposed to the novel environment. A further recent study also revealed that
 189 increasing REM sleep amount through REMSD-induced rebound up-regulated the expression of
 190 plasticity-related transcription factors within the hippocampus (Ravassard et al., 2015).

191 A distinct role for REM sleep in memory is also supported by the striking similarities and contrasts
 192 between neuromodulator states in REM sleep and wakefulness. The wake-like levels of acetylcholine
 193 in the limbic system suppress excitatory feedback potentials within the hippocampus and in the
 194 cortex (Hasselmo & Bower, 1993). During wake, this is thought to promote memory encoding by
 195 allowing the formation of new memory traces within the hippocampus without interference from
 196 previously stored memory traces (Hasselmo, 2006). Noradrenaline has been shown to suppress
 197 excitatory feedback transmission within the somatosensory and piriform cortex (Dodt, Pawelzik, &
 198 Zieglgänsberger, 1991; Hasselmo, Linster, Patil, Ma, & Cekic, 1997; Hasselmo, 1999), but not the
 199 hippocampus (Mueller et al., 1981). While wake is characterized by both high acetylcholine and
 200 noradrenaline levels, in REM sleep only acetylcholine is raised, as a consequence excitatory feedback
 201 within the neocortex would remain uninhibited (Hasselmo, 1999), while hippocampal afferent inputs
 202 would be suppressed (Marrosu et al., 1995).

203 Based on these neuromodulator states, it has been proposed that during REM sleep, memories within
 204 the neocortex – free from interference from the hippocampus – recombine and potentially integrate
 205 into existing memory networks between periods of NREM sleep-dependent consolidation (Hasselmo,
 206 1999; Sterpenich, Schmidt, & Albouy, 2014; Walker & Stickgold, 2010; Walker, 2009). It is
 207 important to stress that most of these observations are performed on cortical/hippocampal slices, thus
 208 the relationships inferred in terms of cortical-hippocampal interaction are very tentative.

209 **3.3 REM sleep, an emotional brain state?**

210 REM sleep possesses a unique physiology which appears particularly amenable to the processing of
 211 emotional memories (Hu, Stylos-Allan, & Walker, 2006; Paré, Collins, & Pelletier, 2002). Functional
 212 neuroimaging studies reveal significantly increased activation in the amygdala, striatum,
 213 hippocampus, medial prefrontal cortex and insula, which are areas strongly associated with emotional

214 processing in wake (Dang-Vu et al., 2010; Miyauchi et al., 2009; Nofzinger, 2005). The heightened
 215 activity within the limbic system in particular (Maquet et al., 1996; Wehrle et al., 2007; Miyauchi et
 216 al., 2009) alludes to the established link between limbic activation during emotional memory
 217 encoding and future recall (Cahill, 2000; McGaugh, 2004). Possibly as a consequence of its
 218 emotional physiology, REM sleep is unique for its comparably emotional dreams (Hobson et al.,
 219 2000) which often contain elements of the dreamer's recent memories (Nielsen & Powell, 1992; van
 220 Rijn et al., 2015).

221 **4 REM Sleep and Emotional Arousal**

222 In addition to a general role of REM sleep in emotional memory processing, a separate line of
 223 research has emerged concentrating on a more specific link between REM sleep and the modulation
 224 of emotional responses. Whether this role is part of the same mechanism, or relies on distinct
 225 processes is unclear and needs to be investigated more systematically. This section reviews evidence
 226 specifically linking emotional response modulation and REM sleep.

227 **4.1 The co-morbidity of REM sleep and mood disorders**

228 Though many psychological disorders are comorbid with sleep disorders, it is particularly of note
 229 that mood disorders tend to be associated with unusual REM sleep: in depression, REM sleep is
 230 pathologically increased (Armitage, 2007; Gottesmann and Gottesman, 2007; Tsuno et al., 2005). A
 231 hallmark of post-traumatic stress disorder (PTSD) is the occurrence of flashbacks during REM sleep
 232 – often resulting in dream enactment and distressing awakenings (Mellman et al., 2007). In patients
 233 suffering from anxiety, REM sleep percentage and rapid-eye movement density during REM sleep
 234 tend to be reduced (Fuller et al., 1997; Rosa et al., 1983). Thus it has been proposed that pathological
 235 REM sleep may underlie some of the symptoms of mood disorders (Walker & van der Helm, 2009).
 236 Even in mice models for depression (i.e. stress vulnerable or chronically stressed strains), REM sleep
 237 appears to be disinhibited (Kimura et al., 2014), suggesting that REM sleep is related to emotional
 238 processing in both humans and rodents.

239 **4.2 Experimental evidence for a role of REM sleep in emotional regulation**

240 Some evidence suggests a sleep-dependent decrease in both subjective emotional arousal and
 241 autonomic response in humans to negative stimuli compared to an equally long period of wake
 242 (Gujar et al., 2011; van der Helm et al., 2011). In line with this notion, sleep-dependent habituation
 243 was only observed across naps containing REM, not across naps consisting solely of NREM sleep
 244 (Gujar et al. 2011).

245 In contrast, Groch et al. (2013) found that subjective ratings of arousal to negative images was
 246 preserved over both SWS-rich early and REM sleep-rich late night sleep using a split-night design. In
 247 a further study, participants rated emotional stimuli as more negative across late sleep compared to
 248 early sleep (Wagner et al., 2002). Similarly, subjective emotional arousal went down across wake and
 249 was maintained across sleep (Baran et al., 2012). The degree of arousal maintenance was associated
 250 with greater time spent in REM sleep. REM sleep amount also predicted an increase in autonomic
 251 response in the form of skin conductance to emotional images shown before and after sleep (Baran et
 252 al., 2012). Furthermore, REMSD reduced arousal ratings to negative images presented before and
 253 after sleep (Lara-Carrasco et al., 2009). Thus it appears that REM sleep may modulate emotional
 254 arousal, however the direction of this change may depend on other yet to be determined factors, such
 255 as the nature of the emotional stimuli, the stress experienced during the task or possibly the
 256 involvement of memory (Genzel et al., 2015).

257 5. Theta activity

258 Theta activity describes synchronized oscillating local field potentials of neuronal populations within
 259 the range of 4-10 Hz initially observed in rodents (Siapas et al., 2005). It is considered a
 260 characteristic of hippocampal activity during both active exploratory behavior and REM sleep
 261 (Buzsáki, 2002; Kemp & Kaada, 1975; Winson, 1974). Rodents also display theta activity within the
 262 amygdala and ventromedial prefrontal cortex (Sörman et al., 2011; Brankačk et al., 2012) – areas
 263 strongly associated with cognitive and affective functions (Siapas et al., 2005; Sigurdsson et al.,
 264 2010). Furthermore, theta activity can be synchronized across disparate brain regions in wake
 265 (O'Neill et al., 2013) and REM sleep (Popa et al., 2010). Although humans also display a distinct 4-
 266 10Hz hippocampal activity during both active wake (Lega et al., 2012; Burgess & Gruzelier, 1997;
 267 Ekstrom et al., 2005) and during REM sleep (Cantero et al., 2003) which is also observed in the
 268 neocortex (Cape et al., 2000; Nishida et al., 2009), this activity does not appear to be synchronized
 269 between the hippocampus and neocortex (Axmacher et al., 2008, Cantero et al., 2003). Instead, a
 270 slower ~3Hz delta range activity – referred to as either rhythmic slow activity (RSA) or slow theta -
 271 has been proposed to be more physiologically analogous to rodent theta activity (Moroni et al., 2007;
 272 Lega et al., 2012). Similarly to the faster theta activity observed in rodents, human slow theta (hence
 273 forward referred to simply as theta activity) also occurs in the human hippocampus during both wake
 274 and REM sleep (Moroni et al., 2007; Lega et al., 2012). The possible explanation for humans having
 275 a slower version of theta activity is the comparatively large brain size which may require slower
 276 oscillations to travel greater distances between brain regions (Moroni et al., 2007). Accordingly, a
 277 slower hippocampal theta activity is also seen in dogs, cats and monkeys (Lega et al., 2012).

278 5.1 Theta generation and the role of acetylcholine in rats

279 Hippocampal theta activity appears to originate from nuclei within the brain stem which project via
 280 the hypothalamus to the septal complex comprising of the medial septum and a subregion of the
 281 Broca area (Pignatelli et al., 2012). The septal complex, in turn, projects to the hippocampus via the
 282 fimbria-fornix pathway. The medial septum contains pacemaker cells which fire at theta frequency
 283 (Dragoi et al., 1999). Some of these pacemaker cells release acetylcholine (Mesulam et al., 1983)
 284 and GABA (Freund, 1989). Inhibiting medial septum cell activity though targeted injection of
 285 lidocaine (Winson, 1978) or muscimol (Bland et al., 1996) leads to the complete suppression of
 286 hippocampal theta oscillations. Both acetylcholine and GABA jointly contribute to generating theta,
 287 as reductions of either leads to partial but not complete abolishment of theta power (Li et al., 2007;
 288 Yoder & Pang, 2005).

289 Given the strong link between acetylcholine and theta activity, the role of acetylcholine in memory
 290 processes within the hippocampus is highly indicative of the function of theta activity. It appears that
 291 high levels of acetylcholine enhance memory encoding during wakefulness, yet do not affect retrieval
 292 in a range of learning tasks in both rats and humans (for review, see Hasselmo, 2006). Early work in
 293 rats showed that blocking acetylcholine through muscarinic antagonists (such as scopolamine)
 294 disrupted memory encoding if the drug was administered prior to learning, as opposed to during the
 295 gap between learning and recall (Ghoneim & Mewaldt, 1975, 1977). In humans scopolamine also
 296 disrupted encoding of memories without affecting retrieval (Atri et al., 2004; Hasselmo &
 297 McGaughy, 2004). Thus it appears acetylcholine is only involved in the encoding though not the
 298 consolidation of novel hippocampal memory traces during wake.

299 This has enticing implications for investigating the function of REM sleep, during which
 300 hippocampal acetylcholine levels exceed those of wake. This would suggest encoding-related

301 processes occur during REM sleep – in stark contrast to the acetylcholine-independent memory
302 consolidation processes occurring during NREM sleep.

303 **5.2 The role of wake theta in memory**

304 Hippocampal theta activity during wake has been associated with memory formation and function in
305 a number of species (Dragoi & Buzsáki, 2006; Montgomery et al., 2008; Mizuseki et al., 2009). The
306 specific role of theta activity in this is thought to be the binding of disparate brain regions during
307 encoding and retrieval (Vertes, 2005).

308 Physiological evidence strongly supports a role of hippocampal theta activity in rats in the formation
309 of novel memories during wake. Thus seminal *in vitro* work by Huerta and Lisman (1995)
310 demonstrated that a priming pulse (4 pulses delivered at 100Hz) induces long-term potentiation
311 (LTP) in the hippocampal CA1 of a brain slice only if the pulse arrives at the peak of carbachol-
312 induced theta activity (defined by the authors as 5-12Hz). Conversely, pulses delivered at the
313 negative peak of theta activity resulted in long-term depression (Hölscher et al., 1997; Huerta &
314 Lisman, 1995) this effect from slice work has been subsequently confirmed in wake behaving
315 animals by stimulating at peaks/troughs of theta in the perforant path (Orr et al., 2001) and in CA1
316 (Hyman et al., 2003).

317 EEG current source density data has shown that subregions of the rat hippocampus are out of phase
318 with respect to theta activity (Buzsáki et al., 1986; Brankack et al., 1993). Specifically, theta activity
319 within the entorhinal cortex is 90° out of phase with that of CA3, and is in phase with that of CA1
320 cortex (Mizuseki et al., 2009). Taken together, this suggests both spatially and temporally differential
321 theta-driven plasticity within the hippocampus.

322 Behavioral evidence in rats also supports a role of hippocampal theta activity during wake in memory
323 encoding. Thus hippocampal theta power during encoding predicts the success of later recall (Berry
324 & Thompson, 1978; Seager et al., 2002; Nokia et al., 2008), while disrupting theta activity
325 pharmacologically - or through lesioning areas implicated in theta generation - significantly impairs
326 learning (Winson, 1978; Givens & Olton, 1990). It appears not only the presence, but also the timing
327 of learning with relation to theta is important in determining the success of encoding. Thus, the rate
328 of learning in rabbits is fastest when hippocampal theta power is at its peak (Berry & Thompson,
329 1978). Also in rabbits, the rate of conditioning to a stimulus is increased in both delay (Seager et al.,
330 2002) and trace conditioning (Griffin et al., 2004) when the stimulus is timed to appear during
331 bouts/periods of the theta rhythm.

332 Human studies are comparatively scarce, given that hippocampal theta activity can only be recorded
333 intracranially in epileptic patients. Whereas neocortical theta range (4-8Hz) activity reliably predicts
334 encoding, working memory and navigation (for review, see Kahana et al. 2001), the link between
335 hippocampal theta activity and memory appears to be more complex than that observed in rodents.
336 Lega et al. (2012) were the first to systematically analyze hippocampal electroencephalography in
337 humans during episodic memory encoding and retrieval. They reported peak activity around 3 Hz and
338 8 Hz within the hippocampus. While the power of 3 Hz activity increased during successful encoding
339 trials, 8 Hz activity displayed an inverse relationship. Furthermore, 3 Hz power was correlated with
340 hippocampal gamma power. From this, the authors concluded that delta range 3 Hz activity within
341 the hippocampus – similarly to the slower theta observed in humans during REM sleep - is the
342 human analogue to rodent hippocampal encoding-related theta activity. Both frequencies were
343 synchronized between the hippocampus and the temporal cortex, suggesting hippocampal-cortical

344 communication. Somewhat different results were reported by Rutishauser et al. (2010), who found
345 that performance in a visual recognition task was predicted by spike coherence with ongoing
346 hippocampal activity at an average of 5 Hz, though – similar to Lega et al. (2012) - this coherence
347 peaked at 3 Hz.

348 Taken together, there is strong evidence supporting a role of theta activity during wake in the
349 modulation of hippocampal plasticity which is clearly indicative of successful encoding/recall in
350 behaviour in both rodents and humans. The following section will highlight the similarities and
351 differences between wake and REM sleep theta activity.

352 **5.3 Wake vs. REM sleep theta**

353 Both wake and REM sleep theta share a similar frequency range and distribution throughout the brain
354 in rodents and humans. Theta activity in both states is associated with the burst-like discharge of
355 acetylcholine – which is strongly linked with plasticity – within the basal forebrain (Lee et al., 2005).
356 There is however some evidence that wake and REM theta differ in their generation and function.
357 Firstly, a genetic mutation in mice was found to slow down hippocampal theta frequency (defined as
358 5-9 Hz) in REM sleep, but not in wake (Tafti et al., 2003). A further study found that coupling
359 between theta and gamma activity within the parietal cortex of mice is greater in REM sleep
360 compared to wake (Scheffzük et al., 2011). This particularly applies to the coupling between theta
361 and fast gamma (120 – 160 Hz), which is 9-fold stronger in REM vs. wake. Taken together, this
362 suggests that – at least in rodents - wake and REM sleep theta differ in either their generation
363 mechanism or regulation and may serve distinct, though possibly related functions.

364 **5.4 REM sleep theta and gamma coupling**

365 REM sleep theta activity appears to also modulate higher frequency activity in the brain. Thus, theta-
366 gamma phase coupling during REM sleep within the hippocampal CA1 region in rats was found to
367 be distinct for slow, mid-frequency and fast gamma (Belluscio et al., 2012). Gamma amplitude
368 within these three bands was found to be modulated by theta phase. Phase-phase coupling was only
369 detected between theta and slow and mid-frequency gamma, though not between theta and fast
370 gamma. The authors interpreted this finding as suggesting an intricate multiple time-scale control of
371 neuronal spikes during REM sleep, supporting information transfer and spike timing-dependent
372 plasticity. Gamma oscillations nested within theta cycles have been proposed to allow the short term
373 working memory of 7 ± 2 items in a list, as this number corresponds to the number of sub-cycles of
374 gamma nested within one theta cycle (Lisman & Idiart, 1995). Therefore as different bands of gamma
375 are coupled differentially to the phases of theta between wake and REM; REM sleep could
376 effectively represent a reweighting of the items which are stored during wakefulness.

377 **5.5 Hippocampal temporal coding and sequential activity**

378 A prominent feature of the hippocampus is the presence of neurons which fire in particular locations,
379 with an ensemble forming a map of space when a rat navigates in the environment; these are termed
380 place cells (O'Keefe & Dostrovsky, 1971). These cells have been found across several species
381 including humans (Ekstrom et al., 2003). The spatial firing of these neurons is modulated by the
382 environmental geometry (O'Keefe & Burgess, 1999), context (Anderson & Jeffery, 2003), and
383 time/distance travelled (MacDonald et al., 2011; Pastalkova et al., 2008). This multi-faceted
384 representation has led to the suggestion that they encode episodes structured in space or episodic
385 memory on the single neuron level.

386 During wake, place cells are coordinated with the ongoing theta oscillation such that a place cell
387 spikes at subsequently earlier phases of theta as the rat travels through the firing field of the cell
388 (O'Keefe & Recce, 1993). Including and excluding spatially modulated cells, distinct classes of cells
389 within the hippocampal formation (i.e. pyramidal, interneurons and granule) fire on average at
390 particular phases of theta (Skaggs & McNaughton, 1996). Skaggs and McNaughton (1996) noted that
391 certain place cell firing within a theta cycle should reflect the order in which the cells' place fields
392 are arranged in space, thus giving rise the temporal encoding of traversed space over a theta cycle.
393 Furthermore individual cells in the hippocampus fire at different phases of theta in novel versus
394 familiar environments in wake (Lever et al., 2010) and in REM sleep (Poe et al., 2000). Hasselmo
395 (1999) proposed this phasic difference can act as a switch between encoding and retrieval memories
396 during wake. In REM sleep however, such a phase shift of cell firing could prioritize novel or
397 emotionally salient memories while offloading the hippocampus of memories with less novelty or
398 emotional valence. A possible indicator of such reorganization is provided in the work of Grosmark
399 et al. (2012) - where a change in excitability is seen in the form of greater synchrony and decreased
400 firing rate variability in the hippocampus in NREM sleep following REM sleep with high theta
401 power.

402 A specific phenomenon - initially termed replay - identified the re-activation of place cell sequences
403 in a temporal order strikingly similar to that observed during previous experience (Foster & Wilson,
404 2007; Dragoi & Buzsáki, 2006; Gupta et al., 2012). This temporally coordinated firing of place cells
405 takes place at a rate 20 faster than experienced during traversal of the environment. These events
406 occur in both quiet wake (Foster & Wilson, 2006; Jackson et al., 2006; Diba & Buzsáki, 2007), as
407 well as during SWS - in both states these replay events are associated with the occurrence of
408 hippocampal sharp-wave-ripples (SWRs) (Wilson & McNaughton, 1994; Lee & Wilson, 2002;
409 Nadasdy et al., 1999; Skaggs & McNaughton, 1996).

410 Temporally coordinated activity of place cells preceding experience in a novel unexplored
411 environment (Dragoi & Tonegawa, 2011) has also been demonstrated, this phenomenon occurs
412 before experience of the environment and therefore could underlie prospective planning by
413 rehearsing and strengthening possible future trajectories.

414 Pertinent to our discussion, these sequences could also carry emotional valence as reactivations
415 leading to remembered goal (reward) locations appear to be preferentially activated during wake
416 SWRs (Pfeiffer & Foster, 2013). Such sequences are also active in prior SWS preferentially towards
417 rewarded yet unexplored goal locations (Olafsdottir et al., 2015).

418 Critically, coordinated sequential activity of hippocampal place cells also occurs during REM sleep
419 (Louie & Wilson, 2001) and thus in the presence of theta and absence of SWRs. Firstly the timescale
420 of reactivation resembled wake - unlike the ~20 fold increases seen in SWS. Secondly, REM sleep
421 does not reactivate sequences in a novel condition (a few rats ran in a track of the same geometry but
422 with different visual/odour cues) but instead reactivated representations in the familiar track,
423 although the sample sessions of REM analyzed were few (15 REM episodes); this could be due to
424 lower quality post-behavioral sleep following novelty or the inability to incorporate new mnemonic
425 information. Similarly recent evidence has shown coordinated sequential activity amongst head-
426 direction cells (another spatial cell which fires when the animal's head faces a particular allocentric
427 direction) during REM sleep following wake experience at similar timescale (Peyrache et al., 2015)
428 to awake as with the seminal study of Louie and Wilson. These pieces of evidence clearly implicate
429 the role of REM sleep in recapitulating wake experiences in terms of the sequential firing of
430 individual neurons.

431 Though there are no human studies investigating sequential reactivation of place cells during REM
 432 sleep, the phenomenon of cued-memory reactivation during sleep (both during SWS and REM sleep)
 433 supports the idea that memories are reactivated during both sleep stages. Thus, sound cues associated
 434 with Morse code presented during REM sleep resulted in improved performance following sleep,
 435 though only if cueing occurred during phasic – not tonic (the distinction is elaborated in 5.8)– REM
 436 sleep (Guerrien et al., 1989). In a separate study, participants were exposed to a loud ticking alarm
 437 clock while learning a set of complex rules (Smith & Weeden, 1990). Exposure to the same sound
 438 during following REM sleep led to a significant improvement in performance at a 1 week follow-up
 439 test compared to a non-cued group.

440 Sequential activations of cell assemblies representing experienced space are a clear candidate for
 441 stored memories. The fact that these occur during REM sleep in step with an ongoing theta
 442 oscillation and can be biased by affordances in the environment provides a strong case for REM sleep
 443 having a role in processing these memories.

444 **5.6 REM sleep theta and PGO waves**

445 REM sleep theta activity appears to share a common generation mechanism with other prominent
 446 REM sleep features. Thus, the generation of REM theta, rapid-eye movements, REM sleep atonia
 447 and pontine-geniculo-occipital (PGO) waves all depend on the ventral part of the oral pontine
 448 reticular nucleus (vRPO) (Reinoso-Suárez et al., 2001). PGO waves are large (250mV) field
 449 potentials which propagate from the pontine tegmentum, to the lateral geniculate nuclei of the
 450 thalamus and the occipital cortex (Callaway et al., 1987; Nelson et al., 1983). PGO waves during
 451 REM sleep in rodents have been repeatedly linked with emotional memory consolidation. While
 452 suppressing PGO wave generation in rats impaired avoidance memory retention across sleep
 453 (Mavanji et al., 2004), artificially enhancing PGO waves through injecting carbachol prevented
 454 deficits in avoidance memory across a period of REM sleep deprivation (Datta, Mavanji, Ulloor, &
 455 Patterson, 2004). It appears the quality of PGO wave activity is directly related to memory processes,
 456 thus a number of studies have reported an increase in PGO wave density following fear memory
 457 training in rats which predicted overnight strengthening of the memory (Datta & Saha, 2005; Datta,
 458 Li, & Auerbach, 2008; Datta, 2000; Ulloor & Datta, 2005). Additionally, the success of fear
 459 extinction was recently shown to be predicted by PGO wave quality during REM sleep (Datta &
 460 O'Malley, 2013). Furthermore, post-training PGO wave density was associated with increased
 461 activity of brain-derived neurotrophic factors and plasticity-related immediate early genes in the
 462 dorsal hippocampus (Datta et al., 2008; Ulloor & Datta, 2005). Selective elimination of PGO wave
 463 generating cells prevented these increases, while enhancing PGO waves through cholinergic
 464 activation of these cells augmented the increases. Thus, it has been proposed that PGO waves
 465 enhance synaptic plasticity in areas they pass through (Datta, O'Malley, & Patterson, 2011), which
 466 includes the hippocampus and amygdala (Datta et al., 1998).

467 Besides having an overlapping generation mechanism, PGO waves and REMs tend to be phase-
 468 locked to theta waves (Karashima et al., 2001; Karashima, Katayama, & Nakao, 2007; Karashima,
 469 Nakao, Honda, & Iwasaki, 2004). It appears both are driven by theta oscillations. Thus, eliciting theta
 470 in REM sleep through electrical stimulation applied to the medial septum in rats, entrains PGO waves
 471 and rapid-eye movements to theta (Reinoso-Suárez et al., 2001). Conversely, when PGO waves are
 472 elicited through audio stimulation, theta phase is not reset, though PGO waves eventually become
 473 phase locked with theta again (Karashima et al., 2002). In a further study, Karashima et al. (2004)
 474 reported a positive correlation between both peak frequency and amplitude of hippocampal theta
 475 oscillations with PGO wave and REM density in rats. The same group also found that in both cats

476 and rats, theta frequency accelerates several hundred milliseconds prior to the negative peak of PGO
 477 waves (Karashima et al., 2005). When PGO waves are inhibited by lesions to the subcoeruleus
 478 region, where PGO waves are generated, synchronization between regional theta waves is disrupted.
 479 Critically, PGO wave density also reflects theta synchronization between the hippocampus and
 480 amygdala during REM sleep in rats (Karashima et al., 2010).

481 Though readily detectable in rats and cats, scalp EEG does not suffice in revealing PGO activity in
 482 humans. However, based on fMRI evidence, the pontine tegmentum, thalamus, primary visual cortex,
 483 putamen and limbic areas activate in synchrony with the occurrence of rapid-eye movements, which
 484 strongly suggests a similar activity in humans (Miyachi et al., 2009; Wehrle et al., 2007). Due to the
 485 common generation mechanism of REMs and PGO waves, REM density is a commonly used
 486 measure for REM sleep intensity in humans. REM density has been observed to increase following
 487 stressful periods of learning – based on University students during an exam preparation (Smith &
 488 Lapp, 1991). This could reflect the enhanced processing of emotional memories (i.e. exam material
 489 paired with the fear of failing an exam) during REM sleep.

490 Taken together, it appears that in rodents, theta activity during REM sleep – and specifically the theta
 491 synchronization between the amygdala and hippocampus - drive large scale synchronized activation
 492 in the form of PGO waves, which in turn enhance synaptic plasticity within the hippocampus and
 493 amygdala. This, in combination with the evidence linking PGO wave density with emotional memory
 494 processing, strongly supports a specific role of REM sleep theta activity in the selective processing of
 495 emotional memories. It is possible that a similar relationship between theta coherence within the
 496 limbic system and PGO waves exists in humans, however evidence for this is lacking

497 **5.7 The role of REM theta in emotional memory**

498 In addition to evidence linking the occurrence of REM sleep with emotional memory consolidation,
 499 there is some evidence directly linking REM sleep theta with emotional memory processing.
 500 Following training in an avoidance task, compared to a preceding control night, rats displayed an
 501 increased amount of REM sleep periods 17-20h following training, as well as increased theta power
 502 during these REM sleep periods (Fogel et al., 2009). Interestingly, sleep spindle activity during SWS
 503 was also enhanced, supporting the notion that the two sleep stages serve complimentary roles in fear
 504 memory processing. In a study by Hegde et al. (2011) REM sleep duration in rats was also increased
 505 during the recovery period following several days of chronic stress immobilisation. The authors also
 506 found a decrease in theta coordination between the hippocampus and lateral amygdala which was
 507 negatively correlated with REM sleep duration.

508 A more compelling link between REM sleep theta and fear memory consolidation was shown in a
 509 study on rats by Popa et al. (2010), which showed that theta coherence between the hippocampus,
 510 medial prefrontal cortex and amygdala predicted bidirectional changes in fear memory across sleep.
 511 These same brain areas exhibit synchronized theta activity when a rat is presented with a conditioned
 512 stimulus in wake following Pavlovian fear learning (Seidenbecher et al., 2003). This is observed for
 513 long term conditioning (24h following fear conditioning), however not in the short term (within 2h)
 514 (Narayanan et al., 2007). This supports the notion that coherent theta activity within these areas
 515 during REM sleep is somehow involved in the long term consolidation of fear memories.

516 Due to the lack of an adequate non-emotional control task in rodent studies, we cannot exclude the
 517 possibility that non-emotional memory consolidation is equally dependent on REM sleep theta
 518 activity. Human studies allow a clear separation of emotional and non-emotional memories – though

519 human intracranial studies investigating the role of hippocampal theta activity during REM sleep on
 520 emotional memory processing are limited. However, given the coherence of theta activity between
 521 the hippocampus, amygdala and neocortex in rats both during wake (Lesting et al., 2013, 2011;
 522 Siapas et al., 2005) and REM sleep (Popa et al., 2010) it is possible that a similar coherence exists in
 523 humans. Theta activity recorded from the scalp during REM sleep using EEG may therefore be
 524 indicative of hippocampal theta activity. One such EEG based study in humans found that right
 525 prefrontal REM theta (4-7 Hz) power during an afternoon nap predicted superior post-nap
 526 recognition of emotionally negative vs. neutral images encoded before the nap (Nishida et al., 2009).
 527 In a wake control group, recognition of both image types did not exceed pre-nap baseline levels. In a
 528 separate study, Prehn-Kristensen et al. (2013) compared sleep-dependent emotional memory
 529 consolidation between adults, healthy children and children with ADHD. They discovered a stronger
 530 emotional benefit in healthy children compared to both other groups. Similarly to the previous study,
 531 frontal theta activity positively correlated with emotional memory performance in both adults and
 532 healthy children, however in children with ADHD, frontal theta activity negatively predicted
 533 emotional memory performance. Based on these two studies, it appears cortical theta activity during
 534 REM sleep represents some form of emotional memory processing in humans. However, intracortical
 535 evidence is needed to clarify the role of the hippocampus in this process.

536 **5.8 REM theta during tonic vs. phasic REM sleep**

537 REM sleep itself is not a homogenous state. It is often described as either phasic or tonic – with tonic
 538 REM sleep taking up approximately 95% of REM sleep in rats (Montgomery et al., 2008). During
 539 phasic REM sleep, rapid-eye movements, PGO waves and muscle twitches occur in bursts and are
 540 accompanied by an increase in vegetative activation as well as an increase in both frequency and
 541 amplitude of hippocampal theta activity (Brankačk et al., 2012). Tonic REM sleep in contrast is
 542 characterized by more evenly distributed PGO waves.

543 The existence of phasic REM sleep in humans is assumed based on a similar occurrence of phasic
 544 bursts of rapid-eye movements accompanied by muscle twitches and cardiorespiratory irregularities
 545 (Carskadon & Dement, 2005). Interestingly, unlike in rodents in which hippocampal theta activity
 546 occurs throughout REM sleep (Brankačk et al., 2012), Cantero et al. (2003) described phasic bursts
 547 of REM theta activity in humans - approximately 1s in duration - and a lack of theta activity during
 548 tonic REM sleep. A previous study had failed to detect significant REM theta activity during human
 549 REM sleep within the human hippocampus (Halgren et al., 1978; Bódizs et al., 2001), while a further
 550 study reported only a rare occurrence of theta in cortices surrounding the hippocampus (Uchida et
 551 al., 2003, 2001). Discrepancies between these studies were ascribed to differences in recording
 552 methods, specific brain areas recorded from, and the pathology of the respective subjects (e.g.
 553 epilepsy) (Bódizs, Sverteczki, Lázár, & Halász, 2005; Tamura et al., 2013).

554 In rats, theta and gamma synchrony within the hippocampus are increased during phasic vs. tonic
 555 REM sleep (Montgomery et al., 2008). During tonic REM sleep, theta coherence is increased within
 556 the dentate gyrus (DG) and between the DG and CA3. Montgomery et al. (2008) suggest that the
 557 increase in DG synchrony accompanied by CA1/CA3 coherence reduction in the gamma range
 558 during tonic REM could mediate pattern separation for subsequent retrieval, which is thought to be a
 559 key function of the DG during wakefulness (Leutgeb et al., 2007; McHugh et al., 2007; Bakker et al.,
 560 2008). The heightened acetylcholine levels during REM sleep would facilitate this pattern separation
 561 by reducing interference of excitatory feedback within the hippocampus (Hasselmo, 1999), thus
 562 facilitating selective encoding.

563 In contrast, phasic REM sees an increase in theta and gamma coherence in DG together with an
 564 increase in gamma coherence in CA3/CA1, thus facilitating greater information exchange between
 565 the hippocampus and neocortex during REM sleep (Karashima et al., 2005; Datta et al., 2004;
 566 Montgomery et al., 2008), in which activity could be replayed to the cortex (Louie & Wilson, 2001).
 567 A separate study found greater theta synchrony within the prefrontal cortex of rats during phasic vs.
 568 tonic REM and an increased theta/gamma synchrony within the prefrontal cortex during tonic vs.
 569 phasic REM sleep (Brankačk et al., 2012). Though the significance of these findings in linking the
 570 two REM sleep states with memory is yet unclear, they support the notion that they serve separate
 571 functions.

572 6. Conclusion

573 Based on the evidence reviewed above, it appears that theta activity during REM sleep drives the
 574 emotionally modulated processing of novel memory traces within the hippocampus, possibly in
 575 preparation for consolidation during NREM sleep. This is supported by the observation that theta
 576 activity –in particular theta coherence between the hippocampus and amygdala - drives high-
 577 amplitude PGO waves, the density of which predicts the expression of plasticity-related genes within
 578 the hippocampus and amygdala. As amygdala-hippocampal coherence during wake predicts future
 579 recall of emotional events, it is possible that this coherence in REM sleep reflects the selective
 580 processing of emotional memory traces.

581 The timing of spike activity within the hippocampus with respect to theta phase is vital in
 582 determining whether long term potentiation (LTP) or depression (LTD) occurs. While hippocampal
 583 activity associated with a novel experience occurs at a similar phase during REM sleep compared to
 584 wake – thus promoting LTP - activity associated with a familiar experience occurs at a phase
 585 promoting LTD. In addition, evidence suggests theta activity during REM sleep increases unit
 586 synchrony and decreases firing rate variability. Taken together, this implies REM sleep in processes
 587 of separation and offloading of traces previously consolidated during NREM sleep, thus freeing
 588 capacity to encode and process novel memories.

589 In addition to emotionally modulated memory processing within the hippocampus, theta activity
 590 during REM sleep could also mediate the integration of novel memory traces within the neocortex.
 591 Acetylcholine – which reduces hippocampal interference in the neocortex – is raised during REM
 592 sleep and directly correlated with theta activity within the hippocampus. In addition to the rise in
 593 acetylcholine, noradrenaline levels are extremely low during REM sleep. As noradrenaline
 594 suppresses recurrent activation within the neocortex, this drop in noradrenaline during REM sleep
 595 could allow encoding-like processes of a more elaborate nature than wake, i.e. allowing
 596 recombination and integration of novel memory traces into pre-existing memory networks. This
 597 neocortical integration may give rise to the vivid dreaming experienced during REM sleep.

598 Those who refute a role of REM sleep in memory (Siegel, 2001; Vertes & Eastman, 2000) refer to
 599 the observation that many antidepressants markedly reduce REM sleep in humans without causing
 600 significant deficits in learning or memory consolidation (Vertes & Eastman, 2000). Instead, Vertes
 601 and Eastman (2000) suggest the primary function of REM sleep is to provide a period of wake-like
 602 endogenous stimulation, allowing the brain to maintain necessary levels of activity throughout sleep.
 603 By doing so, REM sleep supposedly promotes the recovery from SWS and thus prepares the brain for
 604 wakefulness. However, if this was the case, one would expect the amount of REM sleep in each sleep
 605 cycle to correlate with the respective amount of SWS. Instead, REM sleep displays an inverse
 606 relationship with SWS in humans (and remaining constant irrespective of SWS in rodents) across

607 sleep. This suggests that the function of REM sleep may not be merely a reversal of processes in
 608 SWS, but potentially an extension of SWS-dependent processes – such as the integration of novel
 609 neocortical representation within existing memory networks.

610 This emotionally modulated processing of memories within the hippocampus may prioritize the
 611 consolidation of emotional memories during NREM sleep. The following integration of these novel
 612 memories could allow emotional experiences to guide future behavior in similar situations. This is
 613 backed by behavioral evidence, which associates REM sleep with the selective strengthening of
 614 emotional memories and the modulation of emotional responses. The REM sleep dependent
 615 bidirectional changes in arousal reported in the literature could also be explained by integratory
 616 processes during REM sleep: if an emotional response associated with a given experience is of no
 617 direct use to the memory itself, this may be lost in this process. In contrast, an emotional response
 618 which is integral to the memory (e.g. avoidance of a deadly animal), the emotional response may be
 619 strengthened along with the memory. Thus the main function of REM sleep may be the emotionally
 620 modulated optimization of behavior.

621 This proposed function of REM sleep would explain why the suppression of REM sleep does not
 622 cause noticeable cognitive deficits in patients using REM-suppressing antidepressants. If not faced
 623 with emotionally trying experiences or significant changes to the environment - which would require
 624 rapid adaptation - the patients can rely on “outdated” behavioral responses to similar situations.
 625 Therefore, we hypothesize that REM sleep suppression during early childhood development would
 626 result in more striking behavioral deficits. In addition we hypothesize that parametrically varying
 627 emotional weight in the form of rewards/punishments in behavioural tasks should change the degree
 628 of theta synchronization between limbic structures, distribution of theta-phase firing of individual
 629 cells and also manifest itself as a differential number of sequence reactivations during REM sleep.
 630 Despite behavioral evidence predominantly pointing towards a role of REM sleep in predominantly
 631 emotional memory, it remains unclear whether non-emotional memories are processed independently
 632 of REM sleep – it is possible that they are also processed during REM sleep though with a lower
 633 priority. Further, it would be interesting to consider how the previously alluded to evidence linking
 634 REM sleep and procedural memory ties in with the proposed role of REM in emotional memory
 635 processing.

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In review