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THEORETICAL REVIEW

Consolidative mechanisms of emotional processing in REM sleep and PTSD

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SUMMARY

Research suggests sleep plays a role in the consolidation of recently acquired memories for long-term storage. rapid eye movement (REM) sleep has been shown to play a complex role in emotional-memory processing, and may be involved in subsequent waking-day emotional reactivity and amygdala responsivity. Interaction of the hippocampus and basolateral amygdala with the medial-prefrontal cortex is associated with sleep-dependent learning and emotional memory processing. REM is also implicated in post-traumatic stress disorder (PTSD), which is characterized by sleep disturbance, heightened reactivity to fearful stimuli, and nightmares. Many suffers of PTSD also exhibit dampened medial-prefrontal cortex activity. However, the effects of PTSD-related brain changes on REM-dependent consolidation or the notion of 'over-consolidation' (strengthening of memory traces to such a degree that they become resistant to extinction) have been minimally explored. Here, we posit that (in addition to sleep architecture changes) the memory functions of REM must also be altered in PTSD. We propose a model of REM-dependent consolidation of learned fear in PTSD and examine how PTSD-related brain changes might interact with fear learning. We argue that reduced efficacy of inhibitory medial-prefrontal pathways may lead to maladaptive processing of traumatic memories in the early stages of consolidation after trauma.

Overview & purpose

Fear-learning plays an important role in the formation of newly acquired traumatic memories, and an understanding of the role of sleep in fear-learning may inform the development of new interventions for fear-based disorders. In this paper we propose a model of REM (rapid-Eye-Movement) sleep-dependent consolidation of learned fear in post-traumatic stress disorder (PTSD). Like all memories, memories of trauma must undergo encoding via synaptic plasticity post-experience. These memories are then consolidated (strengthened over time) for long-term storage. Sleep is thought to play a role in this process [1], and REM sleep is more specifically implicated in the consolidation of recently acquired emotional memories, and also plays a more complex role in subsequent waking-day reactivity to emotional stimuli [2]. REM sleep has also been implicated in several emotion-related disorders, such as anxiety, major depressive disorder [3–8], post-traumatic stress disorder [9], and nightmares. PTSD is characterized by hyper-reactivity to emotional stimuli and an inability to extinguish memories of trauma, whose onset is triggered by exposure to actual or threatened death, serious injury, or sexual violation [10]. PTSD is also often accompanied by sleep disturbances and treatment-resistant nightmares, highlighting that sleep may play a significant role in the disorder. Thus, the interaction of REM-dependent learning and PTSD is of great interest.

Our main argument is that although some authors suggest restoring normal REM may benefit extinction learning in PTSD [11], REM may also have the opposite effect on subsequent expression of learned fear during the early stages of memory consolidation post-trauma. Thus, during initial formation of traumatic memories it is possible that REM suppression could exert a therapeutic effect on learned fear in the early stages of memory consolidation while exerting a deleterious effect if applied at later stages of the disorder (during extinction learning). In addition we also suggest that medial-prefrontal inhibitory pathways that mediate fear-circuits in the amygdala likely play a key role in this effect, but also that it is possible this pathway could be disrupted without affecting either

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Abbreviation

ACC	anterior cingulate cortex
BLA	basolateral nucleus of the amygdala
CA1	cornus ammonus region 1 of the hippocampus
CeA	central nucleus of the amygdala
CeL	lateral nucleus of the CeA
CeM	medial nucleus of the CeA
CRF	Corticotropin-releasing factor
dDG	Dorsal dentate gyrus
dLGN	dorsolateral geniculate nucleus of the thalamus
dPFC	Dorsal prefrontal cortex
DRN	dorsal raphe nucleus
GABA	gamma-aminobutyric acid
HPA-Axis	Hypothalamic-pituitary adrenal axis
IL	Infralimbic Cortex
ITC	intercalated cells
LA	lateral nucleus of the amygdala
LTP	long-term potentiation
mPFC	medial prefrontal cortex
NMDA	N-methyl-D-aspartate
NMDAR	NMDA Receptor
NREM	non-REM sleep
OFA	Orbitofrontal area
PGO	wave Ponto-geniculo-occipital wave
PIA	Pontine inhibitory area
PL	Prelimbic Cortex
REM	rapid eye movement sleep
SLD	sub-lateral dorsal tegmental nucleus
SUML	supramammillary nucleus
SWS	slow-wave sleep
vDG	Ventral dentate gyrus
vlPAG	ventrolateral periaqueductal grey
vmPFC	Ventromedial prefrontal cortex
VTA	Ventral tegmental area

prefrontal or limbic sites directly. This may in part explain why not all individuals with PTSD exhibit decreased medial prefrontal cortex (mPFC) activity [12] and why PTSD-like symptoms can be replicated by physical head trauma without any conscious recognition of exposure to psychological trauma [13].

In the subsequent sections of this paper, we will discuss the underlying neural circuitry of sleep-dependent processing of emotional memories during REM sleep. First, we review REM's involvement in fear-learning and develop a model of the neural circuits that likely support processing of fear-memory during REM (illustrated as a model of the rodent brain). We then consider how PTSD-related brain changes might alter signalling of these circuits to produce maladaptive memory processing during REM in humans.

REM & emotional memory processing

Consolidation

There is some evidence to suggest sleep may play a role in memory consolidation [14], although the precise role of each stage remains unknown. For example, slow wave sleep (SWS) has been shown to be associated with declarative and spatial memories in some studies [15,16]. Presentation of odour cues during SWS for odours that accompanied encoding of memories during wakefulness improves retention of hippocampus-dependent declarative memories, but not hippocampus-independent procedural memories [17]. There is large body of literature that suggests dreams (most often associated with REM sleep) might also reflect waking-day learning [18–27] (although there is little evidence that dreams play an active role in the learning process). Of importance to PTSD and sleep is the mounting evidence that REM preferentially supports the consolidation of amygdala-dependent emotional-memory [28].

Consolidation refers to the process that underlies strengthening of formed memories over time after encoding/acquisition [29], and consolidation of emotional learning necessitates involvement of the basolateral amygdala (BLA) and infralimbic mPFC [30,31]. Both pre- and post-training REM deprivation yield significant learning and memory deficits on fear or aversion related tasks in rodent models [32,33] and some evidence suggests there may be an overnight selective enhancement of memory for emotionally arousing stimuli in humans [34]. Sleep-dependent facilitation of emotional-memory is also significantly correlated with REM percentage of total sleep time and prefrontal theta power during REM [35], and sleep preferentially enhances emotional stimulus recognition in children [36]. At the cellular level, REM also plays a role in selective pruning and maintenance of newly formed dendritic spines, which is critical for incorporation of new learning [37].

Post-sleep memory improvements are significantly more pronounced for emotional texts following REM in the second half of the night [28]. It remains unclear whether the effect is inherent to late night REM, or simply an artefact of the increased REM density in the latter half of the night. The same effect on emotional-memory may be observed using a napping paradigm, and improvements correlate with REM percentage of total sleep time [24]. This suggests early-night REM may play a role in emotional-memory processing as well, and also that increased REM density in the latter half of the night may explain the late-night REM bias.

Some research has found that sleep leads to increased memory for negative emotional stimuli and decreased memory for non-emotional stimuli (sleep enhances memory for emotional components of episodic memories in an emotional trade-off paradigm; [38]). Further investigation by Payne et al. revealed that sleep more specifically enhanced memory for emotion-related objects in the paradigm, while having the opposite effect on memory for backgrounds as well as neutral scenes and objects [39,40] – although this is not always observed with other paradigms involving both negative and neutral stimuli [41–45]. Behavioural strategies and learning patterns adopted following avoidance learning are also associated with different patterns of REM changes in rodents [46–48]. It is possible that REM preferentially consolidates memory for emotionally salient stimuli in an adaptive fashion to prioritize memories that aid in survivability under some circumstances.

A similar mechanism might be responsible for the effects on emotional-memory following late-night REM [49], and diurnal rhythms of cortisol (a stress-related glucocorticoid hormone) might explain both the heightened memory for emotional components of episodic memories following sleep as well as the apparent bias of late- versus early-night REM for emotional-memory consolidation [49]. Evidence suggests that nocturnal secretion of cortisol is low during the SWS-rich first half of the night, and is enhanced during the REM-dense latter half of the night [50]. When administered shortly after training, glucocorticoid hormones enhance memory for inhibitory-avoidance in animal models [51]. Elevated cortisol levels during encoding also produce enhanced long-term recall

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performance for emotional stimuli in humans [52]. Additionally, administration of hydrocortisone following encoding and during sleep selectively enhance memory for emotional stimuli, while also resulting in reduced amygdala reactivity on subsequent testing trials [53]. This suggests cortisol secretion might mediate REM-dependent selective enhancement of memory for emotional stimuli at the expense of memory for neutral stimuli, while also reducing reactivity to emotional stimuli.

Extinction

Extinction is the process by which new learning inhibits the expression of older memory [54–56]. Thus, much like the initial fear-learning, extinction memory must be encoded, consolidated, and retrieved. Acquisition of extinction-learning induces BLA plasticity [30], and activation of the infralimbic PFC (IL) is also necessary for consolidation of emotional extinction memory in rodents [54,57]. Animal models suggest that REM deprivation leads to deficits in the extinction of cued fear responses [58,59], and the negative effects of REM deprivation are at least partially reversed by NMDA receptor (NMDAR) agonists [59]. Since NMDAR activation at BLA and IL is necessary for acquisition and consolidation/retrieval of extinction memory [30,60], respectively, this suggests that REM deprivation may affect extinction of fear-learning via attenuating NMDA or NMDARs (hence the effect is reversed by an NMDAR agonist). Administration of metyrapone (a corticosterone inhibitor) also failed to reverse the effects of REM deprivation on recall in one study, suggesting that glucocorticoids likely do not mediate the effects of REM deprivation on memory [61].

REM is also involved in hippocampus-dependent extinction learning. While REM deprivation selectively impairs recall of fear-extinction in hippocampus independent tasks in rodents [62], it may also lead to significant deficits in long-term potentiation (LTP) in the hippocampus [63–67]. REM deprivation also impairs consolidation of hippocampus-dependent contextual fear-learning [67]. Other studies have also confirmed REM deprivation leads to impaired hippocampal LTP, and showed that REM-rebound does not reverse REM-deprivation induced LTP impairment [68] – although other evidence suggests REM-sleep rebound can restore contextual fear-learning consolidation and LTP [67]. Further research is necessary in this regard in order to clarify the role of REM sleep rebound on LTP and fear-learning.

Emotional reactivity

Interestingly, PTSD is characterized by hyper-reactivity to emotional stimuli – and in addition to its role in consolidation and extinction, REM is also involved in subsequent fear expression and emotional reactivity post-conditioning. Selective REM deprivation leads to enhanced emotional reactivity on subsequent waking-day tasks, while non-REM sleep (NREM) interruption has no such effect [69]. This suggests that although REM enhances memory for emotional stimuli, it may also decrease emotional reactivity to those stimuli. Van der Helm et al. [2] also demonstrated with a combination of EEG and functional imaging that sleep dampens amygdala reactivity to previous emotional experiences, supporting a role for REM in the suppression of emotional reactivity. Gujar et al. [70] further showed that reactivity to negative stimuli is dampened following REM-containing sleep.

Conversely, some research suggests that although REM enhances emotional-memory, it preserves emotional reactivity [71]. One study showed no differences in terms of emotional reactivity between REM or NREM deprived participants despite finding enhanced memory for emotional stimuli following REM [72], while another demonstrated no effect of REM on ratings of emotional valence or reactivity despite yielding significant increases in emotional picture recognition [73].

Our current understanding of the relationship between REM and emotional reactivity is incomplete. While there seems to be sufficient evidence to suggest a role for REM in dampening subsequent emotional reactivity under some circumstances, it is also clear that REM does not affect all emotional memories equally. For example, partial and total sleep deprivation have opposite effects on reactivity to positively versus negatively valenced stimuli [74]. Increased anterior frontal lobe theta is also positively correlated with negative valence in REM dreams, suggesting that frontal theta during REM may be more specifically associated with processing of negatively valenced memories [75]. REM also enhanced electrodermal responses to emotional stimuli in one study [76]. The same study suggests that stimulus intensity may mediate the effects of REM on subsequent emotional reactivity.

Importantly, administration of hydrocortisone during sleep reduces subsequent amygdala reactivity related to recall of negative stimuli [53]. This suggests glucocorticoid mediation may play a role in REM's effects on emotional reactivity. Given that hydrocortisone administration during waking-day encoding yields increases in memory for emotional stimuli, it is possible that glucocorticoid mediation directs subsequent REM-dependent memory processing. While it is clear that REM reduces amygdala reactivity under some circumstances, it is also clear that this is only sometimes the case. Since glucocorticoid secretion at encoding influences sleep-dependent consolidation of emotional memories [53], biomarkers of stress (e.g. CRF, cortisol) may be a good predictor of how memories and amygdala reactivity will be later affected by REM sleep.

Developing a model of memory processing in REM and PTSD

Networks mediating REM-onset

In the following sections we begin to develop a “big picture” model of REM-dependent learning in the rodent brain (see Fig. 1a). REM is characterized by a variety of changes to both central states and the periphery. Disinhibition of glutamatergic REM-on neurons with ascending projections in the sublateral-dorsal tegmental nucleus (SLD) by GABAergic neurons of the ventrolateral periaqueductal grey (vlPAG) is believed to initiate the onset of REM sleep (mediated by inhibitory projections of the posterior hypothalamus and dorsal paragigantocellular reticular nucleus [DPGi] which inhibit vlPAG REM-off neurons), thus producing the electroencephalographic state throughout the cortex usually used to identify REM [77–79]. Although it has been suggested that indirect pathways of the SLD may induce cortical activation via the intralaminar thalamic nuclei, more recent evidence using retrograde tracing has observed that intralaminar thalamic nucleus neurons did not express FOS during REM hypersomnia [80]. Evidence instead suggests that activation of the anterior cingulate cortex (ACC), retrosplenial cortices, and dentate gyrus is produced by projections from the claustrum and supramammillary nucleus (SUML) [80]. Also, activation of the ventral dentate gyrus (vDG) is by glutamatergic and GABAergic SUML neurons while the dorsal dentate gyrus (dDG) is activated by medial entorhinal cortical neurons.

REM is also typically defined by an absence of muscle tone (atonia) – the characteristic muscle paralysis that accompanies the REM onset but not the onset of other sleep stages. REM atonia is believed to be produced by networks proximal to the pontine brainstem; early animal studies demonstrated that lesions to the locus coeruleus produced an absence of muscle atonia during REM [81] leading to expression of apparent complex behaviour during sleep. The condition resembles REM behaviour disorder (RBD), a

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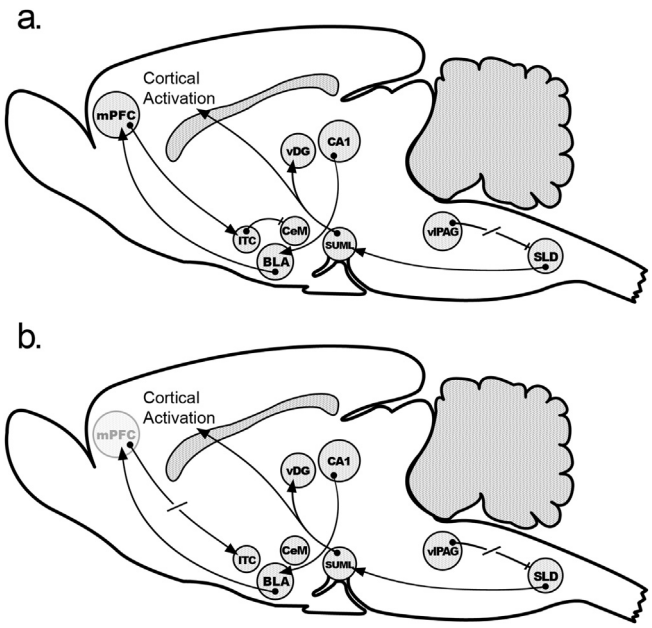

Fig. 1. a. During sleep, disinhibition of SLD REM-on neurons with ascending projections by GABAergic neuron populations of the vlPAG is associated with REM onset. Subsequent temporally sequenced neuronal reactivation and recapitulation of waking-day hippocampal theta (generated by an as-of-yet unknown mechanism possibly involving waking-day recruitment of the hippocampus and/or striatum during encoding) produces theta coupling with the BLA and mPFC. This activity correlates with sleep-dependent gains in memory for emotional stimuli. mPFC efferents subsequently inhibit CeM reactivity indirectly via ITC inhibitory projections. BLA: basolateral nucleus of the amygdala, CeM: medial nucleus of the central amygdala, CA1: CA1 region of the hippocampus, ITC: intercalated cells, vlPAG: ventrolateral periaqueductal grey, mPFC: medial prefrontal cortex, vDG: ventral dentate gyrus, SUML: supramammillary nucleus, SLD: sublateral dorsal tegmental nucleus. b. In PTSD, REM onset may be as normal. However, while Hi-BLA-mPFC theta coupling produces enhanced memory for emotional stimuli, reduced activity of ITC-projecting mPFC efferents prevents inhibition of CeM neurons. This results in both selective enhancement of emotional memories and a concurrent failure to depotentiate amygdala responsivity to those memories (leading to maintenance of waking-day reactivity to selectively enhanced emotional memories). REM: Rapid eye movement sleep, GABA: Gamma-aminobutyric acid.

human parasomnia which causes sufferers to act out their dreams [82]. RBD is associated with expression of violent or aggressive outbursts during REM [82], which is highly suggestive of intense emotional expression. More recently, it has been demonstrated that REM atonia is mediated by neurons of the pontine inhibitory area (PIA), and muscle atonia is produced following microinjection of NMDA receptor agonists to PIA [83]. RBD in humans is associated with neuronal cell loss in the pontine brainstem (for a review of RBD physiology, see Luppi et al. [84]). The fact that REM generation continues in patients with RBD suggests that REM muscle atonia and REM generation are controlled independently in humans [85,86].

Networks mediating learned fear during REM and the role of theta oscillations

Some structures implicated in waking-day fear conditioning and PTSD may also be active during sleep-dependent memory processing. Fear conditioning is largely dependent on neural circuitry of the amygdala, and interconnectedness between the amygdala, hippocampus, and medial prefrontal cortex [54]. There is also evidence that reward pathways become activated during REM sleep and in fear learning. Dopaminergic neurons of the ventral tegmental area (VTA) have altered (burst) firing patterns during REM sleep [87], and FOS expression of dopaminergic VTA neurons and GABAergic VTA/substantia nigra (SA) neurons is elevated during REM rebound [88].

The amygdala is composed of several nuclei. Among them, the lateral nucleus (LA) primarily receives inputs from sensory regions, acting as the point of convergence for sensory information from the periphery [89]. It has been suggested that the convergence of sensory inputs about stimuli at the LA might be responsible for transmission of information regarding conditioned stimuli and stimulus associations via indirect pathways to the central amygdalar nucleus (CeA), which projects to structures downstream that are principally responsible for behavioural expression of fear [90,91]. Fear learning also induces plasticity in areas of the cortex [92], suggesting interconnectedness of the amygdala and cortex plays a role in the formation of long-term fear-memories.

mPFC also exerts an inhibitory influence over CeA via an indirect mechanism, since mPFC sparsely projects to the central medial nucleus of the amygdala (CeM). mPFC projections may inhibit CeM neuronal activity by exciting GABAergic neurons (e.g. intercalated cell masses (ITC); [89]) which receive inputs from mPFC and project to CeM [93–95]. GABAergic intercalated cells also inhibit BLA principal neurons [96]. *In vivo* stimulation of the IL-amygdala pathway in rodents also enhances extinction, while optogenetic silencing impairs it [97]. Infralimbic inputs to BLA have been shown to potentiate ITC activity, and ITC efferents inhibit CeM [98]. ITC lesions also markedly reduce fear extinction in fear-conditioned rodents [99]. Although some frontal regions (e.g. middle frontal gyrus) are hypoactive during REM in humans, evidence suggests activity in some areas of mPFC is increased or comparable to wakefulness [100,101]. Decreased mPFC activity in PTSD may prevent the inhibition of brainstem-projecting CeM neurons, leading to excessive fear expression and reduced ability to extinguish traumatic memories.

During REM, theta oscillations are present in both the hippocampus and amygdala [102,103], and there is theta-rhythm coupling among CA1, LA, and mPFC during retrieval of conditioned fear in rodents (lending support to the notion that subcortical theta coupling may play a role in fear-learning; [104]). Theta is also increased during “REM-sleep windows” (RSWs; discrete post-training periods during REM sleep believed to play a role in memory consolidation) among rats that learned an avoidance task versus non-learners [105]. Further, recent evidence suggests that synchronized amygdalohippocampal and medial-prefrontal activity during REM sleep correlates with individual differences in consolidation efficacy, supporting a role for theta oscillations among limbic system structures in sleep-dependent consolidation processes in animal models [106]. Recently, it has been suggested that normal medial septum GABA-releasing neuron signalling (required for theta rhythm generation) is required for contextual memory consolidation, and optogenetic silencing of medial septum GABAergic neurons impairs contextual fear-learning in mice [107]. Additionally, the influence of hippocampal over BLA theta oscillations, and BLA over mPFC theta oscillations, is associated with increased consolidation efficacy [106]. Some evidence has also suggested asynchrony exists among sleep states in which hippocampal sleep states frequently transition to REM in advance of the cortex [108].

Lesting et al. [104] demonstrated that application of short trains of theta stimulation applied to LA and hippocampal region CA1 (intended to mimic LA–CA1 theta coupling) in the rat produced prolonged freezing during extinction learning, indicating that LA–CA1 coupling is associated with maintained fear responses, and BLA stimulation induces plasticity in the dentate gyrus [109]. Corsi-Cabrera et al. [110] recently demonstrated with *in vivo* recording that the amygdala does indeed become similarly activated during

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REM sleep in humans. However, due to electrode placement variability and sample size, it is not possible to draw further conclusions regarding how different amygdaloid nuclei become reactivated during REM in humans from this study. Prefrontal theta during human REM is also correlated with sleep-dependent gains in memory for emotional stimuli [35].

Recapitulation of theta oscillations and waking-day firing patterns have also been observed in the CA1 region of the hippocampus in rodents during REM following waking-day spatial learning [111], and similar patterns of neural trace reactivation have been observed in the human hippocampus with PET imaging during REM following waking-day learning [112]. In rodents, patterns of temporally sequenced neural activation of hippocampal place-cells during spatial learning are replayed during SWS [113]. Similarly, temporally sequenced neuronal firing which mimics patterns observed during waking-day learning has also been observed during REM in rodent models using *in vivo* recording [111]. Imaging studies have further demonstrated that a similar process may be present during REM in humans [112]. Although REM and NREM appear to be associated with different memory functions, the underlying mechanisms of consolidation may share some similarities. It appears that REM-dependent processing of some types of memory may be directed by mechanisms active during waking-day encoding, and it is possible that this applies to fear-learning as well. Together these findings suggest that coupled theta activity of the hippocampus, BLA, and mPFC during REM may significantly contribute to fear-learning.

Since control of both hippocampal over BLA theta activity and BLA over mPFC theta activity is associated with increased consolidation efficacy [106], learning-dependent recapitulation of waking-day theta activity in the hippocampus during REM and subsequent theta coupling among the hippocampus, BLA, and mPFC are strong candidates mechanisms for the consolidation of recently acquired emotional memories during REM. Some authors also suggest that stress-affected DG-CA3 circuits responsible for pattern separation may fail to accurately resolve precise differences among remote traumatic memories, leading to generalization (a core feature of PTSD in which sufferers' fear responses become generalized to other stimuli unrelated to the initial trauma) [114].

However, as discussed in a prior section, sleep also often appears to dampen reactivity to emotional stimuli [2,71,73]. This suggests that the involvement of CeM (the subnucleus of the CeA which projects to brainstem structures necessary for behavioural expressions of fear) at the time memories of emotional stimuli are recalled may be reduced following periods of REM sleep; conversely, studies that have reported an increase in reactivity to emotional stimuli following REM (e.g. Rosales-Lagarde et al. [69]) would imply enhanced or preserved involvement of CeM. A likely mechanism for this is inhibition of CeM by infralimbic mPFC efferents during REM-dependent memory processing (see Fig. 1a). Since few studies have specifically targeted the central amygdalar nucleus during REM, however, further investigation is required in order to clarify the role of the CeA and other nuclei of the amygdala during REM.

There is also evidence to suggest CeA activity may affect REM. The CeA contains reciprocal connections with REM-associated brainstem areas, and CeA stimulation increases the frequency of ponto-geniculo-occipital waves (PGO waves; an indicator of REM sleep onset) in the dorsolateral geniculate nucleus of the thalamus (dLGN) in animal models [115,116]. Microinjection of cholinergic agonist carbachol into CeA also produces long-term enhancement of REM sleep in cats [117]. Further, activation of REM-On neurons of the CeA (and thus their influence on dLGN activity) is mediated by serotonergic neurons of the dorsal raphe nucleus (DRN; [118]). Thus it is very likely that CeA hyper-responsivity during REM is associated with REM fragmentation.

Structures directing sleep-dependent consolidation during waking-day encoding

Although it appears that a mechanism during waking-day may direct subsequent sleep-dependent consolidation, there is a dearth of studies exploring how fear memories from waking-day are tagged for subsequent consolidation during REM. Competitive interaction between the hippocampus and striatum (caudate nucleus) as indicated by functional connectivity analyses during waking-day learning predicts subsequent sleep-dependent gains in motor learning task performance in humans [119]. Sleep-dependent gains in performance are also predicted by interaction of the caudate nucleus and mPFC. Albouy et al. [119] suggest that it is recruitment of the hippocampus which drives subsequent sleep-dependent consolidation, which is in agreement with *in vivo* recording studies in rodent models of sleep-dependent memory consolidation of learned fear [113].

Although findings regarding hippocampal recruitment during encoding are compelling, however, they are specific to motor sequence learning [119]. In rodents, there is some evidence to suggest that a similar process may be involved in reward-learning [120]. Whether or not the same structures are at play during waking-day encoding of fear memories for subsequent sleep-dependent consolidation is unknown. However, in order for waking-day fear memories to be “tagged” for later consolidation during sleep, a similar mechanism must exist. Further evidence is required to clarify how waking-day encoding directs sleep-dependent consolidation of fear-memory.

Pathophysiology of PTSD

PTSD is characterized by increased fear acquisition [121,122], suggesting amygdala hyper-responsivity may be characteristic of the disorder [123]. Indeed, amygdala hyper-responsivity has been observed in response to a wide variety of trauma-related stimuli in humans [124–128]. Collectively, data from imaging studies suggests that this activity also correlates with symptom severity [123]. There is also evidence to suggest there is decreased activation of mPFC in some individuals with PTSD, and differences in morphology of the frontal cortex in general. These include decreased volume of the ACC as well as a relationship between ACC volume and symptom severity [129–131]. Since mPFC pre-stimulation has been shown to drastically reduce firing of brainstem-projecting CeA neurons in rodents, it has been suggested that mPFC acts during waking day to inhibit fear expression [132]. Indeed, several animal studies suggest the presence of inhibitory control of amygdala nuclei by infralimbic projections [57,133]; infralimbic stimulation reduces expression of conditioned fear in rodents [134]. Microinjection of anisomycin (a protein synthesis inhibitor) into mPFC also inhibits extinction recall [31]. Finally, extinction training has also been shown to reduce the efficacy of mPFC excitatory projections to the BLA in animal models, while inhibitory projections from the mPFC are left unaffected [135]. Among humans with PTSD increased prefrontal theta is also associated with resilience [136], supporting a role for mPFC inhibitory control over amygdala reactivity in PTSD.

PTSD is also characterized by low levels of plasma cortisol despite elevated levels of corticotropin-releasing factor (CRF, a polypeptide hormone secreted by the hypothalamus as a part of stress-induced HPA-axis activity) [137–140]. CRF may play a role in consolidation of traumatic memories. In rodents, administration of a CRF_1 antagonist blocked the consolidation of stressor effects on startle magnitude in one study [141], suggesting a role for CRF in fear-learning. Also, since nocturnal administration of hydrocortisone reduced subsequent amygdala reactivity to negative stimuli in

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one study, it is possible that hypocortism in PTSD may play a role in preserving reactivity to emotional stimuli [53]. Noradrenaline is also implicated in PTSD and may exert effects on sleep. Some pontine REM-off neurons are noradrenergic in nature, and firing of those neurons is suppressed during REM [142–144]. Prazosin, an α-1 adrenoreceptor inverse agonist, has been shown to be efficacious at reducing PTSD nightmares [145,146].

PTSD-related sleep disturbances

Since REM is thought to play a significant role in emotional memory processing, disordered REM may be a significant contributor to pathophysiology of emotion-based disorders such as PTSD. A clear consensus regarding REM disturbances and the development of PTSD has not yet been reached, although sleep disturbances are a diagnostic criterion for the disorder. It has been suggested that poor extinction memory in PTSD may lead to heightened fear expression during waking-day, which in turn causes decreased REM sleep quality [11]. Findings from polysomnographic recording studies indicate that early development of PTSD is associated with shorter but more frequent REM cycles (i.e., REM fragmentation; [3]). Other findings have noted decreased REM density and sleep efficiency in PTSD [4] while studies on combat veterans with PTSD have indicated increased REM percentage of total sleep time [7,8]. However, caution should be taken in considering findings from veterans exposed to combat, since animal models suggest that mild traumatic brain injury (mTBI) from blast exposure can mimic the PTSD in the absence of any conscious awareness of trauma exposure [13]; studies of combat versus non-combat trauma exposure might therefore be an important target for future research. A meta-analysis also showed increased REM density and decreased SWS overall among studies of individuals with PTSD [147].

Interestingly, individual differences might account for the apparent discrepancy of trauma-related sleep disturbances. Chronic stress induces dichotomous changes in sleep architecture – with some animals demonstrating significantly enhanced REM, while others display significantly reduced REM [148]. In addition, research suggests REM theta synchronization decreases following cessation of stress paradigms [149]. Single prolonged stress (SPS; an animal model of PTSD) also causes alterations in theta and sigma band power suggesting that trauma exposure may result in altered cortical activity [150]. Furthermore, some evidence also suggests extinction-learning increases both SWS and REM; the same study demonstrated that rodents that retained extinction memory also exhibited an increase in pontine wave activity during post-training REM [151]. Avoidable and unavoidable shocks also produce different REM responses to aversive learning in rodents. Escapable shock produces enhanced REM while inescapable shock reduces it [47,48], suggesting that stressor predictability plays a significant role in fear-learning processes.

Interconnectedness of the amygdala and thalamic/brainstem regions associated with REM sleep activity suggests a reciprocal role of emotion regulation and REM onset, and waking-day exposure to emotional stimuli yields significant effects on subsequent REM. One study found that in rodents, fear conditioning enhanced PGO wave activity while also suppressing REM sleep [152]. Since CeA activity enhances PGO waves, learning-dependent amygdala activity likely also influences REM. Presentation of fear-related cues following fear conditioning also produces significant elevations of Fos expression in the amygdala and brainstem [153], while also leading to significant reductions in subsequent REM sleep. Further studies have also supported a reduction in REM following fear conditioning, with fear conditioning leading to decreased number of REM cycles and percentage of total sleep time [154]. As a result of the apparent reciprocal role of emotion regulation and REM, it has been hypothesized that PTSD-related amygdala hyper-responsivity may be a factor in PTSD-related sleep disturbances [9].

mPFC & amygdala dysfunction in REM

In this section, we synthesize some of the findings relating to pathophysiology of PTSD with what we know about memory-circuits active during REM in order to see how these circuits may interact with the PTSD-related brain changes to drive maladaptive processing of learned fear during the initial stages of consolidation (see Fig. 1b). Germain, Buysse, and Nofzinger [9] have proposed one of the few accounts specifically relating REM sleep to PTSD symptomology, suggesting that the REM-on/off cells of the pontine brainstem are affected by decreased mPFC activity in sufferers of PTSD resulting in both amygdala hyperactivity and disruption of the normal REM-on/off cycle (leading to REM fragmentation). This model addresses both the neurological traits of PTSD and PTSD nightmares (since the combination of REM fragmentation and amygdala hyperactivity during sleep is a strong candidate mechanism for PTSD nightmares), although they do not discuss the notion of 'over-consolidation' (the process by which rehearsed fear memories become sufficiently reinforced so as to become resistant to extinction) which has been theorized to play a significant role in PTSD symptomology [155]. The role of extinction memory in PTSD has been addressed in a separate review in which Pace-Schott et al. [11] suggest that stress effects and REM fragmentation following trauma may impair consolidation of extinction memory. Curiously, REM may enhance both consolidation of emotional memory [28] and consolidation of extinction learning [58,59,156] – thus blockade or fragmentation of REM might induce opposite effects on expression of learned fear following trauma depending on the circumstances (i.e., blockade of extinction consolidation may prevent inhibition – thus increasing expression – of older traumatic memories while blockade of consolidation for the original memory might diminish fear expression).

Due to the presence of dampened mPFC activity/volume and amygdala hyper-responsivity among those diagnosed with PTSD (regions that play a key role in the formation of long-term emotional memories), this leads us to posit as a natural extension of Germain et al.'s 2008 model [9] that in addition to the sleep changes highlighted therein, the memory functions of REM must also be altered in PTSD by the structural changes present among those with PTSD (and perhaps in a way which would exacerbate fear-expression). Normal healthy individuals are thought to undergo theta coupling of the Hippocampus, BLA, and mPFC during REM and recapitulation of waking-day activation patterns, leading to both increased memory for emotional stimuli and subsequent depotentiation of amygdala reactivity by mPFC inhibition of brainstem-projecting CeM neuron populations (See Fig. 1a; [2,106]).

In PTSD, however, dampened activity of inhibitory mPFC efferents would lead to a disruption of CeM inhibition. Importantly, disinhibition of CeM by mPFC (infralimbic-ITC projections) may cause a failure to depotentiate reactivity of brainstem-projecting CeM neurons, producing a maintenance (rather than dampening) of emotional reactivity to emotional stimuli over time (see Fig. 1b), while memory for emotional components of traumatic experiences are still enhanced by undisrupted recapitulation of waking-day activity (since there is no evidence to suggest inhibitory mPFC-CeM pathways affect recapitulation of waking-day CA1 activity).

Also, interruption of mPFC-CeM inhibition need not originate from mPFC itself. Rather, any disruption along the mPFC-CeM inhibitory pathway might be sufficient to produce symptoms.

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Indeed, some research indicates no abnormalities in prefrontal theta activity among some sufferers of PTSD [12]. Therefore it may be important to consider traumatic-stress disorders as having different points of origin among CeM-inhibiting pathways but a large degree of symptom overlap.

Since HPA-axis activation in waking-day is also associated with subsequent sleep-dependent consolidation [53], preserved reactivity to enhanced memories of traumatic experience in waking-day might very well lead to further strengthening of prior traumatic memories. PTSD is characterized by altered HPA-axis signalling including hypocortism and enhanced CRF [137–140]. Central CRF is believed to play a significant role in fear-learning [141,157–159] and administration of hydrocortisone following encoding and during sleep also reduced subsequent amygdala reactivity in one study [53]. Thus, enhanced CRF signalling but reduced cortisol may also play a role in both enhancement and preservation of traumatic memories. Frequent recall (rumination) of selectively enhanced traumatic memories may therefore produce the type of over-consolidation that has been theorized to play a significant role in PTSD [155].

In addition to the assertion that mPFC dysfunction and amygdala hyperactivity relate to REM fragmentation [9] (and may be associated with disinhibition of REM-On/Off-cell projecting CeA neurons [115,116,118,154]), we propose that dampened mPFC activity in PTSD should cause these specific fear-memory related effects throughout the brain: 1) failure to depotentiate amygdala reactivity to traumatic memories following fear-memory acquisition (specifically affecting inhibitory projections to CeA and thus brainstem projecting neuron populations associated with fear expression), 2) enhancement of memory for those traumatic experiences by normal REM-related Hi-BLA-mPFC neural trace reactivation, and 3) recall of those selectively enhanced traumatic memories may lead to reinforcement until they become over-consolidated and resistant to extinction. Finally, we would also suggest that 4) disruption of the mPFC-CeM inhibitory network may produce maladaptive memory processing if disrupted at any site along this pathway (not just if disruption originates directly from mPFC, since not all sufferers of PTSD display reduced mPFC activity). Therefore, PTSD-related brain changes may produce the same symptoms among individuals while affected brain regions along the same inhibitory pathway might differ.

With regards to the development of PTSD, this approach leaves open the question of whether traumatic experience causes PTSD-related brain changes (e.g., reduced mPFC volume) or if those changes exist as a predisposing factor. However, given the nature of this model, it also suggests that there are a wide variety of distinct issues that could lead to the development of PTSD-like symptoms and amygdala hyper-responsivity. While others highlight the role of mPFC [9], we would emphasize that *any* disruption of the mPFC-CeM inhibitory network could produce PTSD symptomology, since not all sufferers of PTSD exhibit mPFC dampening [12]. For example, ITC-CeM inhibitory projections could be implicated without affecting mPFC efferents – yet still yield a similar effect on CeA. Some hypothetical causes therefore might include (but are not limited to): 1) failure of the mPFC efferents to inhibit CeM via indirect inhibitory projections (e.g., due to reduced blood flow, congenital defects, reduced prefrontal volume, reduced glucose metabolism, demyelination, neuroplastic effects, etc.), 2) physical obstructions (lesions, stroke, etc.), 3) axon shearing due to head trauma/blast exposure reducing the effectiveness of the mPFC-CeM inhibitory network (this may explain why mTBI causes PTSD-like symptoms in the absence of any conscious awareness of trauma; see Elder et al. [13]), or 4) amygdala hyperactivity which is sufficient to overwhelm the inhibitory capacity of mPFC-CeM projections (due to overwhelming traumatic experience, neuroplastic effects, physiological factors, etc.). As a result, it is clear that one of the main challenges in elucidating the chronology of PTSD development may lie in the fact that the disorder might originate due to multiple different causative or predisposing factors (but all affecting the same end-point network of structures).

Much of what we know regarding the interconnectedness of mPFC and amygdala microcircuits comes from rodent studies (and, to a lesser degree, cats). With relevance to PTSD, though, it is important to consider how this model might apply to human brain anatomy. Unfortunately, evidence of human functional connectivity of the amygdala and prefrontal cortex is largely limited to imaging and electrophysiology studies, and many of the networks summarized in our rodent model are very poorly explored in humans – although some evidence from primate studies can give a clearer picture of how human pathophysiology of PTSD might look.

In rodents, the infralimbic cortex (analogous to human vmPFC) and prelimbic cortex (analogous to human dACC) are associated with fear learning and inhibitory control of central amygdala output. Evidence has suggested that the densest concentration of amygdala-projecting neurons in the Rhesus monkey is found at the posterior orbitofrontal cortex (OFC) [160]. However, amygdala-prefrontal connections display a high degree of complexity in primates (likely including humans), and all prefrontal regions appear to have some degree of interconnectedness with amygdala structures [160]. Similarly to rodents, vmPFC in primates contains excitatory projections to intercalated cells of the amygdala, which in turn exert inhibition over CeA [161]. Thus, vmPFC is thought to fulfil the role in humans that IL performs in rodents. However, while IL inhibits CeM via an indirect mechanism in rodents (and IL does not project directly to CeM [89]), vmPFC also contains excitatory projections directly to CeA in primates [162,163] allowing it to both inhibit and activate CeA. In addition, vmPFC projects directly to the hypothalamus in macaques and plays a role in mediating HPA-axis activity [164]. In humans, regional cerebral blood flow (rCBF) is also enhanced in the amygdala during REM [165], and – although mPFC activity is drastically reduced during SWS - medial prefrontal activation during REM is comparable to wakefulness [100]. Post-sleep reductions in amygdala reactivity are also associated with increased vmPFC activity [2].

Similarly to rodents, the human amygdala, mPFC, and hippocampus are reciprocally connected [166–168] (for an overview of human and primate anatomical connections of the amygdala and PFC, see Salzman & Fusi [160]). In humans the hippocampus and amygdala are also both activated during recall of fearful stimuli [169]. However, whether coherent theta coupling of the amygdala, hippocampus, and mPFC during consolidation of fear memory is also seen in humans or primates is unknown – although *in vivo* recording has revealed similar activity in the human amygdala during REM sleep with a small sample [110]. Additionally, it is worth noting that hippocampal and neocortical theta may not be synchronized in humans similarly to rodents; instead, it has been suggested that rhythmic slow activity (or 'slow theta,' 3 Hz delta range) may play a similar role in humans to what theta fulfils in rodents (for a review of REM theta activity, see Hutchison & Rathore [170]).

While during REM in humans the amygdala becomes activated [100], it is also unclear whether CeA specifically is activated during REM – although evidence suggests amygdala reactivity to fearful stimuli may be reduced following sleep [2,70], which would suggest a dampening of CeA involvement post-REM. Since both vmPFC and the amygdala are active during REM [100,165] it is possible that vmPFC dampens CeA activity during REM while other areas (e.g., lateral and basal nuclei) associated with fear-learning and CS-US associations are activated (thus allowing CS-US associations and

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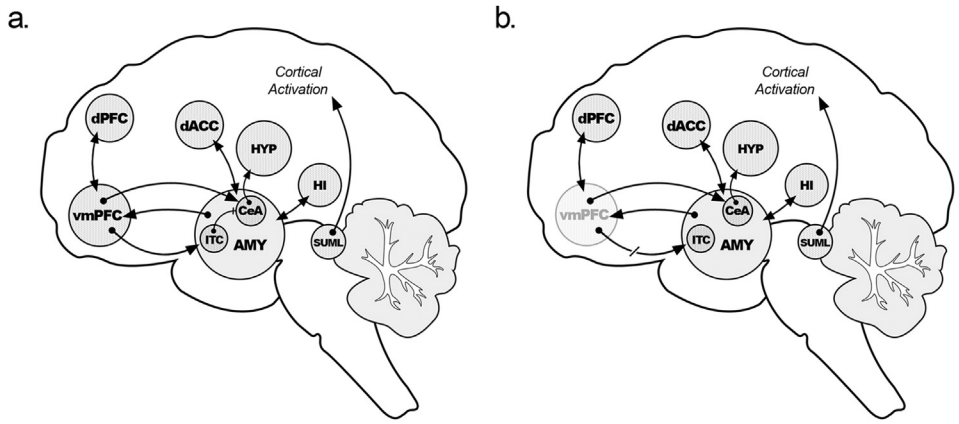

Fig. 2. a) Tentative model of networks involved in REM-dependent processing of emotional memories in humans. Unlike in rodents, primate vmPFC both inhibits (via indirect projections to inhibitory ITC neurons) and excites CeA (via direct projections to CeA). Similarly to rodents, the amygdala, hippocampus, and mPFC are reciprocally connected. b) In PTSD, one possibility is that vmPFC inhibitory control over CeA is reduced (leading to CeA over-excitation while memories of trauma are still enhanced by reciprocal connections among hippocampus, amygdala, and prefrontal regions). vmPFC: ventromedial prefrontal cortex, AMY: Amygdala, CeA: Central Amygdala, dPFC: Dorsal prefrontal cortex, HYP: Hypothalamus, HI: Hippocampus, dACC: dorsal anterior cingulate cortex, SUML: Supramammilary Nucleus, ITC: Intercalated cells.

fear-memories to be consolidated in the absence of fear-expression). However, there is unfortunately a dearth of studies in humans or primates exploring the differential roles of amygdala sub-nuclei during REM. Thus the specific pattern of amygdala nuclei activation during REM sleep remains unknown at this time. Interestingly, amygdala reactivity to emotional pictures was significantly greater following sleep deprivation in one study, and amygdala-mPFC connectivity was greater among those who had slept [171]. This suggests that top-down control of amygdala reactivity to fearful stimuli by mPFC inhibitory projections is at least partially sleep-dependent in humans.

With this in mind, we can construct a very preliminary model of the networks that might be involved in normal REM-dependent consolidation of fear learning (see Fig. 2a) wherein the role of the rodent IL is fulfilled by ventromedial prefrontal regions with different projections to amygdala structures. In keeping with this, if brainstem-projecting CeA neurons are inhibited by vmPFC during REM in humans, we can speculate that one might anticipate a reduction in vmPFC inhibitory control over CeA in PTSD (see Fig. 2b). There is some evidence to suggest this may be the case; for example, one study showed reduced OFC volume among suffers of PTSD [172]. However, another study showed increased rCBF among PTSD suffers during a script-guided task of traumatic imagery recall during wakefulness [173]. Importantly – unlike in rodents – vmPFC projects to both CeA and ITC in primates. Thus regional activation is difficult to interpret, since it may be associated with either inhibition or excitation of CeA. Therefore, similarly to our rodent model (see Fig. 1b), we would predict multiple possible causes for CeA over-excitation in PTSD. Since vmPFC both excites and inhibits the amygdala, two distinct possibilities arise in humans: 1) the inhibitory capacity of either vmPFC or ITC over CeA may be reduced, or 2) vmPFC may overexcite CeA. In either of these cases we would anticipate a similar cluster of arising symptoms, although the projections implicated in causation of the disorder differ. Curiously, since sleep deprivation causes a waking-day disconnect between mPFC and the amygdala in humans leading to increased amygdala reactivity (similarly to what our model suggests as the root cause of maladaptive memory processing in PTSD [171]), altered sleep patterns in PTSD may also be a contributing factor to amygdala reactivity in PTSD (i.e., both pathophysiology of fear-networks and sleep disturbance may each play a separate and independent role in the development of the disorder; in either case, the same end-point network of structures are implicated).

Future research

While a tentative model of how traumatic memories might be exacerbated by REM sleep (rather than suppressed) among those with reduced inhibitory control of CeA activity has been proposed herein, numerous questions remain. For example, Pace-Schott et al. [11] consider whether the effects of REM suppressants would be deleterious in PTSD. Here, we suggest that the effects of REM on subsequent expression may depend largely on the time-course following trauma. Without adequate inhibitory control of CeA by vmPFC, REM may exacerbate fear-learning and contribute to over-consolidation of traumatic memories during the initial stages of consolidation post-trauma. Thus in the immediate aftermath of trauma it is possible that REM suppressants would exert a therapeutic effect, serving to reduce consolidation of initial trauma memory. However, it is also clear that REM is necessary for consolidation of extinction memory. After consolidation of the initial trauma, REM deprivation or REM fragmentation may contribute to the failure to extinguish traumatic memories that is characteristic of the disorder. We therefore might expect opposite effects of REM deprivation or REM suppressing pharmacologic agents on long-term emotional reactivity or expression of learned fear depending whether it occurs immediately after trauma exposure (affecting consolidation of fear-conditioning) or later (affecting consolidation of extinction memory). Indeed, some research has suggested sleep deprivation yields reductions in fear-learning for pavlovian conditioning in humans and that sleep-dependent enhancement of fear-memory correlates with REM [174]. However, although REM deprivation (or pharmacologic REM suppression) post-trauma might reduce long-term recall of traumatic memories, total sleep deprivation would likely also cause a short-term spike in amygdala reactivity to frightening stimuli (as observed by Yoo et al. [171]).

The proposed model brings to light some testable predictions. First, if reduced vmPFC-CeA inhibition is a defining characteristic of maladaptive memory processing in the early stages of PTSD, severing the pathway between the IL and CeM (via lesioning or optogenetic silencing) in rodents could help to explore whether it is indeed a significant contributor to heightened emotional reactivity and fear expression in rodent models of PTSD without affecting either site directly. While infralimbic efferents projecting to the amygdala have been confirmed in mice [175], this would also elucidate whether multiple pathways are

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involved in inhibitory control of CeM-mediated fear expression in rodents.

Additionally, while much research has identified waking- and sleep-dependent mechanisms of consolidation, only recently has research addressed how waking-day learning directs sleep-dependent consolidation with functional imaging. Hippocampal/striatal interaction and hippocampal recruitment during waking-day learning predicts subsequent sleep-dependent consolidation of motor sequence learning [119]. However, these findings are specific to motor learning. Investigating how waking-day learning directs sleep-dependent processing of fear-memory is a necessary and important step for future research (since it is noted herein as a significant but as-of-yet unexplored mechanism).

Although not a primary focus of this paper, a combination of sleep fragmentation and amygdala disinhibition due to reduced vmPFC inhibitory control of CeA is a strong candidate mechanism for explaining PTSD nightmares (as others have suggested [9]) – although we would make the distinction that vmPFC may not be directly implicated in all cases (and that vmPFC-ITC and/or vmPFC-CeA projections might be affected differentially, or even without disruption of vmPFC as a whole). Interestingly, prefrontal theta is associated with negatively valenced dreaming during REM [75] but also with resiliency [136]. Thus we would suggest that REM dreams may reflect the processing of negatively valenced imagery while CeA responsivity is inhibited. If this is the case, dreamers may recall – *but not express* – fear during REM dreaming. In some cases, failure of vmPFC to appropriately dampen CeA may lead to fear expression during dreaming, leading to the phenomenological experience of a nightmare.

In future research, it would be of significant interest to address how PTSD nightmares might differ among individuals with varying degrees of vmPFC activation during REM. Although evidence suggests REM fragmentation should remain relatively similar, qualitative differences in nightmare content might emerge among individuals with a low versus high degree of vmPFC involvement in their condition. Further, although infralimbic/vmPFC efferents mediating inhibitory control of amygdala reactivity have been our central focus, it is important to note that a variety of neuromodulatory systems (e.g., systems of dopamine, histamine, orexin, acetylcholine, etc.) may also play a role in fear-learning and maladaptive processing of emotional consolidation.

Finally, a primary target for future research should be to clarify the role of REM in subsequent waking-day reactivity to emotional stimuli. While it seems apparent that sleep dampens amygdala reactivity under some circumstances, it is also clear that REM does not affect all memories equally. Also, since there is only sparse evidence of effects of nocturnal glucocorticoid secretion mediating REM's effects on memory processing, future research should elucidate how cortisol release during both encoding and REM influence subsequent waking-day reactivity to fearful stimuli.

Conclusion

In sum, the proposed model attempts to synthesize our current understanding of how REM-dependent memory processing and PTSD-related brain changes might interact to produce maladaptive consolidation of traumatic memories. In complement to previous models, we have focused primarily on the memory functions of REM (since encoding, consolidation, and reconsolidation of fear-memory likely play a key role in the formation of PTSD). In addition, we have highlighted a number of targets that may serve to guide future research into the pathophysiology of REM and PTSD which may yield valuable insight into novel avenues for treatment as well as our general understanding of the disorder.

Practice points

- Reduced efficacy of the mPFC-CeM inhibitory network may prevent REM-dependent amygdala depotentiation, resulting in maintenance of reactivity to trauma-related stimuli. Simultaneously, REM-dependent memory processing may enhance memory of those traumatic stimuli. Preserved reactivity to selectively enhanced fear-memories may thus contribute to waking-day symptoms of PTSD.
- Multiple routes of causation are also plausible, since any disruption of the vmPFC-amygdala inhibitory pathway would produce the same effects (even if vmPFC is not directly implicated). vmPFC also contains both excitatory and inhibitory projections to CeA in primates. Therefore it may be important to consider PTSD as traumatic-stress disorders with similar (but not necessarily identical) points of origin and a high degree of symptom overlap.
- In the immediate stages of consolidation post-trauma, it is possible that REM deprivation or REM suppressing pharmacologic interventions could exert a therapeutic effect.

Research agenda

- It is important that future research aims to clarify the role of REM sleep in subsequent reactivity to fearful stimuli; specifically, effects of HPA-axis activation during wakefulness at the time of original memory encoding on REM-dependent changes in reactivity should be investigated.
- Research should seek to identify the role of IL-CeM inhibitory pathways in mediating fear-learning, fear-expression, and sleep in rodents. Studies directed at severing this inhibitory pathway will elucidate whether multiple pathways play a role in CeM-mediated fear expression in animal models of PTSD.
- It will also be a necessary and important step to identify which brain regions act during waking-day learning to 'tag' fear-memories for subsequent processing during REM sleep in order to fully understand how waking-day learning directs subsequent sleep-dependent memory processing.

Conflicts of interest

None of the authors have any direct or indirect conflicts of interest of a financial or personal nature relevant to the present work.

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* The most important references are denoted by an asterisk.

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