

## Review

# The nucleus reuniens of the thalamus sits at the nexus of a hippocampus and medial prefrontal cortex circuit enabling memory and behavior

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The nucleus reuniens of the thalamus (RE) is a key component of an extensive network of hippocampal and cortical structures and is a fundamental substrate for cognition. A common misconception is that RE is a simple relay structure. Instead, a better conceptualization is that RE is a critical component of a canonical higher-order cortico-thalamo-cortical circuit that supports communication between the medial prefrontal cortex (mPFC) and the hippocampus (HC). RE dysfunction is implicated in several clinical disorders including, but not limited to Alzheimer's disease, schizophrenia, and epilepsy. Here, we review key anatomical and physiological features of the RE based primarily on studies in rodents. We present a conceptual model of RE circuitry within the mPFC–RE–HC system and speculate on the computations RE enables. We review the rapidly growing literature demonstrating that RE is critical to, and its neurons represent, aspects of behavioral tasks that place demands on memory focusing on its role in navigation, spatial working memory, the temporal organization of memory, and executive functions.

## The importance of mPFC–HC interactions

Adaptive behavior and mental health require the integration of motivation, attention, memory, and the outcome of past actions as relevant circumstances change. Particularly in similar situations, goals are best achieved by adjusting actions according to expected outcomes that change with the current time and one's location (e.g., wanting coffee and remembering which shop is open and nearby). This cognitive flexibility necessitates incorporating the outcomes of many episodes, and requires interactions between the medial prefrontal cortex (mPFC) and hippocampus (HC). Bidirectional interactions between the two structures result in an intention-recollection cycle (Fuster 1995) that may reasonably describe how their complementary and distinct functions contribute to adaptive behavior. Beyond “what, where, and when,” the external facts that define episodes (Morris 2001), hippocampal representations include “why and how.” These internal features include outcome expectancies and abstract rules computed by the mPFC. Thus, mPFC signals relayed to HC can help guide both memory acquisition and retrieval. The HC signals relayed to mPFC allow remembered events to select associated goals, rules, and procedural representations. Importantly, mPFC–HC interactions depend heavily on the nucleus reuniens (RE), a thalamic region positioned at the center of a higher-order cortico-thalamo-cortical circuit bridging memory

and executive function. Not surprisingly, RE is emerging as a focus for research on the neurobiological substrates of learning and memory.

## Anatomy and physiology of RE

The anatomy and physiology of RE is essential for understanding its mechanistic contributions to the mPFC–HC system, and helps describe how RE is central to a wide array of cognitive and behavioral functions. RE has been the focus of anatomical and physiological studies in rodents for many years, and a homologous structure in humans has been described and associated with the interthalamic adhesion (e.g., Baydin et al. 2016) although it has received less attention, especially in functional studies (but see Reagh et al. 2017).

## Connections of RE with the limbic forebrain

RE lies ventrally on the midline, directly above the third ventricle, and extends longitudinally virtually throughout the thalamus. The largest of the midline thalamic nuclei, RE is notable for linking limbic subcortical to cortical structures (for review, see Vertes et al.

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2015). RE is generally subdivided into a central (or medial) portion and lateral segments that have been designated the lateral wings of RE, or the peri-reuniens nucleus (periRE). RE receives a diverse and widely distributed set of projections from limbic-related sites of the brainstem, hypothalamus, amygdala, basal forebrain, and limbic cortex (Vertes 2002, 2004; McKenna and Vertes 2004). However, unlike the widespread inputs to RE, the projections from RE are virtually restricted to “limbic” cortical sites; that is, to the orbital and medial PFC, the retrosplenial cortex, the parahippocampal region (perirhinal and entorhinal cortices) and the HC—including all parts of subicular cortices (Vertes 2006; Vertes et al. 2006).

RE projects substantially to the infralimbic (IL), prelimbic (PL), and anterior cingulate (AC) cortices of the mPFC with fibers terminating densely in layer 1 and layers 5/6 of these regions. RE projections to the mPFC predominantly (but not exclusively) originate from the periRE nucleus (Hoover and Vertes 2012; Varela et al. 2014). The mPFC is a pronounced source of return projections to RE, distributing throughout RE, indicating strong reciprocal connections between RE/periRE and the mPFC. The mPFC also innervates the thalamic reticular nucleus (TRN) which, in turn, exerts feedforward inhibitory actions on RE (Fig. 1; McKenna and Vertes 2004).

Within the HC, RE innervates selectively CA1 and the subiculum of the dorsal, intermediate and ventral HC. No RE axons project to the dentate gyrus or to CA2/CA3. RE fibers terminate in the stratum lacunosum-moleculare (slm) of CA1 and in the outer molecular layer of the subiculum (Wouterlood et al. 1990; Vertes et al. 2006). Although RE distributes to the dorsal HC (CA1), RE projections are approximately 10-fold stronger to ventral than to dorsal CA1 (Hoover and Vertes 2012; Varela et al. 2014). Recent examinations of the output of RE to its two main cortical targets, the mPFC and HC has shown that ~5%–10% of RE neurons distribute, via axon collaterals, to both structures (Hoover and Vertes 2012; Varela et al. 2014). The RE cells projecting to the HC or mPFC are somewhat segregated; that is, those distributing to HC tended to cluster at the rostral pole of RE, whereas those projecting to mPFC are predominantly located in periRE and in caudal RE (Hoover and Vertes 2012; Varela et al. 2014). This segregation suggests an anatomical, and perhaps functional, differentiation within RE wherein separate subpopulations of RE neurons may exert their primary

influence commonly on the HC (i.e., CA1 and subiculum) and mPFC, or perhaps selectively on either the HC (Dolleman-van der Weel and Witter 1996) or mPFC. As the mPFC strongly targets RE (Vertes 2002, 2004), there are equally dense projections from HC, or ventral subiculum, to RE (McKenna and Vertes 2004). In effect, RE is strongly reciprocally linked to HC and to mPFC.

Although the (intermediate/ventral) HC projects directly to mPFC (Jay and Witter 1991; Hoover and Vertes 2007), interestingly, there are no (direct) return projections from mPFC to HC (Laroche et al. 2000). Rather, RE appears to be the main link returning projections from the mPFC to the HC, thus completing a loop between these structures: HC → mPFC → RE → HC. Although the perirhinal (PRC) and entorhinal cortices (EC) comprise additional relays from the mPFC to the HC, it should be noted that RE also projects to both the PRC (via periRE) and EC, and therefore may also modulate information transferred from the mPFC to the HC, via PRC, and EC. Finally, although recent behavioral studies have focused on RE as a link between the mPFC and the HC, it is also the case (but often overlooked) that RE is an important (indirect) route from the HC to the mPFC—thus connecting these structures in the opposite direction: HC → RE → mPFC. This pathway may exert return hippocampal modulatory effects on the mPFC and/or may serve as a critical route for the actions of the dorsal HC (dorsal subiculum) on the mPFC, especially in light of very minor direct projections from the dorsal HC to the mPFC (Hoover and Vertes 2007; DeNardo et al. 2015; Ye et al. 2017).

## Neurochemistry and physiology of RE

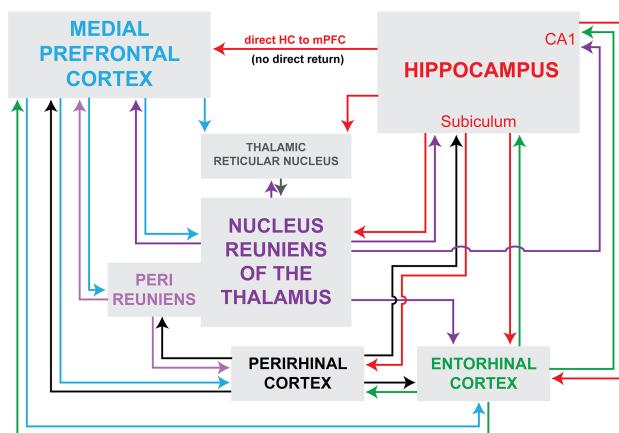
RE is thought to play a key role in cognitive and executive processes, likely by orchestrating the communication between mPFC and HC. Insight in the underlying mechanisms requires a detailed anatomical and electrophysiological knowledge of their interconnectivity. Data on the synaptic organization and physiology of RE remain sparse. For instance, RE target cells have been studied anatomically and/or electrophysiologically in HC and EC (Wouterlood et al. 1990; Wouterlood 1991; Dolleman-van der Weel et al. 1997, 2017; Dolleman-van der Weel and Witter 2000), but similar investigations are lacking for the RE → mPFC pathway (e.g., Cruikshank et al. 2012). To advance insight in the functioning of RE, we summarize the neurochemistry of RE neurons, review electrophysiological data regarding the projections between RE, CA1, EC, and mPFC, and finally discuss data on coupling of (rhythmic) neuronal activities in HC and mPFC through RE-mediated synchronization.

## Neurochemical characteristics of RE

The primary neurotransmitter for RE is an excitatory amino acid, presumably aspartate and/or glutamate (e.g., Herkenham 1978; Bokor et al. 2002; Cruikshank et al. 2012). Accordingly, RE neurons form asymmetrical (i.e., excitatory) synapses on both pyramidal cells and interneurons in CA1, subiculum, and EC (Wouterlood et al. 1990; Wouterlood 1991; Dolleman-van der Weel and Witter 2000). Recently, dopamine-positive neurons were found in RE (Ogundele et al. 2017), which are suggested to be part of a hypothalamic neuroendocrine system. RE neurons are devoid of the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid (GABA), indicating the absence of inhibitory interneurons in RE (Ottersen and Storm-Mathisen 1984).

In addition, RE is devoid of the calcium-binding protein parvalbumin (PV) which is expressed in (subclasses of) GABAergic interneurons as well as in thalamic relay cells. Instead RE neurons contain the calcium-binding proteins calretinin (CR), calbindin (CB), and coexpress CR/CB (Frassoni et al. 1991; Arai et al. 1994; Montpied et al. 1995; Bokor et al. 2002; Drexel et al. 2011). The

## The mPFC-RE-HC System



**Figure 1.** Schematic representation of the connectivity in the mPFC–RE–HC system. The HC projects directly to the mPFC, but there are no direct return projections. RE (including periRE) thus serves as the main link completing an HC–mPFC loop as follows: HC → mPFC → RE → HC. Abbreviations: (HC) hippocampus, (mPFC) medial prefrontal cortex, (periRE) peri-reuniens nucleus, (RE) the nucleus reuniens of the thalamus.

absence of PV cells is important because CB- and PV-positivity (+) in thalamic neurons distinguish two classes of relay cells, namely CB<sup>+</sup> “matrix” cells with dense terminations in cortical layer 1, and PV<sup>+</sup> “core” cells projecting to the middle cortical layers 3/4 (Jones 1998). RE neurons are thus considered to be matrix cells, projecting predominantly to cortical layer 1, but also innervating layers 5/6 (Vertes et al. 2006), overlapping with hippocampal axons in mPFC (Jay and Witter 1991; Gabbott et al. 2002).

## Physiology of RE connections

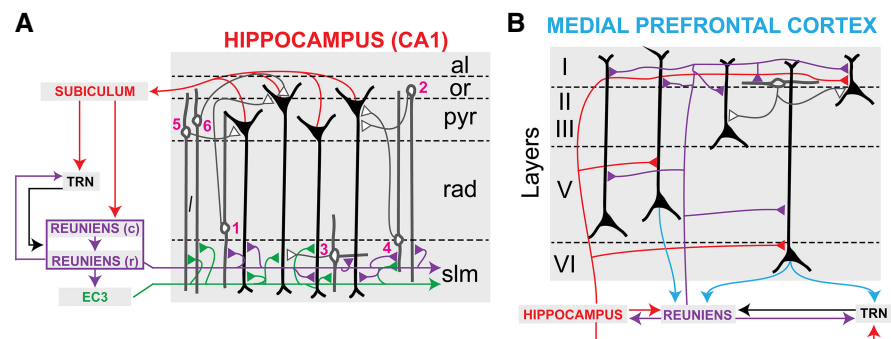
The neurochemical diversity of RE neurons is likely associated with their function (Walsh et al. 2017). For example, thalamic midline CR-negative (CR<sup>-</sup>) and CR-positive (i.e., CR<sup>+</sup> and CR<sup>+</sup>/CB<sup>+</sup>) neurons are differentially active during characteristic memory-related hippocampal network dynamics (Lara-Vásquez et al. 2016). These investigators showed that at theta frequencies (4–10 Hz) that are prominent during exploration and rapid eye movement (REM) sleep, CR<sup>-</sup> neurons display firing increases, whereas CR<sup>+</sup> neurons do not. In contrast, during sharp wave-ripples (SWR) that are prominent during quiet state  $\leq 1$  Hz slow oscillations and slow-wave sleep, the firing rate of the CR<sup>-</sup> neurons remains unaffected. However, CR<sup>+</sup> neurons are inhibited during a SWR event, but increase their firing just before and after (Lara-Vásquez et al. 2016). Thus CR<sup>+</sup> (including CR<sup>+</sup>/CB<sup>+</sup>) and single CB<sup>+</sup> RE projections to CA1, subiculum, and EC, may play different roles in, for instance, working memory (theta frequency-dependent) and memory consolidation (slow  $\leq 1$  Hz oscillations-dependent).

Surprisingly few electrophysiological studies have examined RE-elicited responses in HC and mPFC (Dolleman-van der Weel et al. 1997, 2017; Bertram and Zhang 1999; Zhang and Bertram 2002; Viana Di Prisco and Vertes 2006; Morales et al. 2007; Eleore et al. 2011; Cruikshank et al. 2012). In HC, Dolleman-van der Weel et al. (1997) used anesthetized rats to demonstrate that RE modulates the excitability of CA1 neurons through direct excitatory and indirect inhibitory mechanisms. RE axons in slm form asymmetrical (i.e., excitatory) synaptic contacts on the dendrites and synapses of CA1 pyramidal cells (Wouterlood et al. 1990) and on GABA-positive interneurons (Dolleman-van der Weel and Witter 2000). Dolleman-van der Weel et al. (1997) showed that electrical stimulation of the RE resulted in a local field potential (LFP) response indicative of an excitatory synaptic effect in slm. Paired pulse (0.1–10 Hz) stimulation elicited larger amplitude field excitatory postsynaptic potentials (fEPSPs) at 0.1–2 Hz stimulation than at theta frequencies (4–10 Hz). However, despite the strong RE-induced paired pulse facilitation (PPF), firing in principal cells was not observed. In contrast, low frequency (0.1–2 Hz) stimulation of RE resulted in driving radiatum interneurons, presumably Schaffer collateral-associated cells, and vertical oriens/alveus interneurons, both mediating feedforward inhibition of pyramidal cells. The inability of RE to generate

spiking in CA1 pyramidal cells in anesthetized rats was confirmed in later studies (Morales et al. 2007; Eleore et al. 2011; Dolleman-van der Weel et al. 2017). However, one study has reported that electrical stimulation of the thalamic midline region, including RE, evoked CA1 population spikes, similar to those evoked by contralateral CA3 stimulation (Bertram and Zhang 1999). This discrepancy with other reports may be due to the much larger thalamic region that was stimulated by the latter investigators. In addition to a clear monosynaptic RE input to CA1, there are indications for complex and presumably polysynaptic elicited field potentials in CA1 through a projection from caudal RE to rostral RE (Dolleman-van der Weel et al. 1997). This suggests a closed RE-HC loop between rRE  $\rightarrow$  CA1  $\rightarrow$  Sub  $\rightarrow$  cRE  $\rightarrow$  rRE (Fig. 2A), that may enable RE to modulate the activity level of CA1 cells depending on hippocampal output.

RE input to the EC has the potential to influence the mPFC–EC–HC flow of (spatial and nonspatial/sensory) information, presumably by modulating the excitability level of EC neurons (Fig. 2A). One study in anesthetized rats has reported excitatory responses in the EC following electrical stimulation of the thalamic midline region (Zhang and Bertram 2002).

A strong RE-mediated feedforward inhibition has been proposed to condition CA1 pyramidal neurons to discharge only under certain circumstances, namely, in the window when inhibition is diminished, and/or when the excitability level of the apical dendrites is further enhanced by other inputs, such as from EC (Dolleman-van der Weel et al. 1997, 2017). In a recent study, Dolleman-van der Weel et al. (2017), showed that low



**Figure 2.** Schematic representation of RE inputs onto excitatory and inhibitory neurons in CA1 and mPFC. (A) Excitatory RE (purple lines) and EC (green lines) inputs in CA1, and a closed CA1  $\rightarrow$  subiculum  $\rightarrow$  RE  $\rightarrow$  CA1 circuit, including the thalamic reticular nucleus (TRN). The direct RE  $\rightarrow$  CA1 input in slm originates from the rostral part of RE; only a minor contribution arises from the caudal part. The output of CA1 (red lines) via the subiculum can be relayed back to caudal RE. In turn, caudal RE projects to rostral RE, which results in a di-synaptic (cRE  $\rightarrow$  rRE  $\rightarrow$  CA1) input in slm, thereby closing a loop. The direct EC  $\rightarrow$  CA1 pathway, arising from EC layer III cells, overlaps with the RE input in slm. RE  $\rightarrow$  EC input may have the ability to modulate the activity level of EC layer III cells. Electrophysiological data support the view that RE and EC inputs converge (at least partly) onto the same dendritic branch of a pyramidal cell in proximal slm. RE has been shown to drive presumed Schaffer collateral-associated cells (1) which are thought to inhibit pyramidal cells and other (unidentified) interneurons, and vertical oriens/alveus cells (2), mediating feedforward perisomatic inhibition of CA1 cells. EC is assumed to drive parvalbumin-positive basket cells (5) and chandelier or axo-axonic cells (6) providing feedforward somatic and axonal inhibition, respectively, of pyramidal cells; EC also drives neurogliaform cells in slm (3). RE and EC inputs are proposed to converge on slm-neurogliaform cells (3) providing feedforward inhibition of pyramidal cells and other interneurons in slm, and on a subclass of (presumed CCK/VIP) basket cells (4) located at the slm/radiatum border, providing (peri)somatic inhibition of CA1 cells. (B) mPFC layers 1 and 5/6 contain a high density of RE fibers onto mostly unidentified pyramidal cells and interneurons. They overlap with fibers from CA1/subiculum (red lines); it is not known whether RE and CA1/subiculum inputs convergence onto single neurons in mPFC. RE input drives presumed neurogliaform cells in layer 1, providing feedforward inhibition of pyramidal cells and interneurons. mPFC (light blue lines) provides direct excitatory input to RE as well as an indirect, presumed inhibitory input via the TRN (black arrow); RE reciprocates the TRN input (purple arrow). Abbreviations: (al) alveus, (c) caudal, (EC3) entorhinal cortex layer III, (or) stratum oriens, (pyr) pyramidal cell layer, (r) rostral, (rad) stratum radiatum, (slm) stratum lacunosum moleculare, (TRN) thalamic reticular nucleus.



frequency (0.1 Hz) paired pulse stimulation of either RE or lateral EC evoked CA1 fEPSPs (subthreshold) with strong homosynaptic PPF, whereas combined stimulation of RE and EC did not support heterosynaptic PPF. Coincident inputs induced a nonlinear enhancement of the elicited field potentials in slm but did not drive pyramidal cells. These data suggest that RE and EC synapses converge on the same dendritic branch of the pyramidal cells. The authors reasoned that the inability to induce CA1 cell firing could be due to persistent inhibitory influences, engaged by either route individually or by their coincidence. RE and EC inputs converge on neurogliaform cells in slm (Fig. 2A, cell 3), as well as on a subclass of cholecystokinin/vasoactive intestinal polypeptide-positive (CCK<sup>+</sup>/VIP<sup>+</sup>) basket cells located at the radiatum/slm border (Fig. 2A, cell 4) mediating additional perisomatic inhibition (Dolleman-van der Weel et al. 1997, 2017; Chittajallu et al. 2017). The coincident RE-EC induced perisomatic inhibition may modulate input-timing-dependent-plasticity (Dudman et al. 2007), among other inhibitory dynamics in CA1, gating computational activity.

Electrophysiological studies of RE input in the mPFC are limited. Extracellular recordings, reflecting RE-mediated glutamate release onto mPFC neurons (Pirot et al. 1994; Hur and Zaborsky 2005), indicate direct excitatory and indirect inhibitory components (Viana Di Prisco and Vertes 2006; Eleore et al. 2011; Cruikshank et al. 2012). It is assumed that, similar to the RE → CA1 pathway, both pyramidal cells and interneurons in mPFC receive RE input. Low frequency (0.1 Hz) paired-pulse stimulation of RE resulted in strong PPF in mPFC (PL/IL), similar to CA1 (Dolleman-van der Weel et al. 1997, 2017; Viana Di Prisco and Vertes 2006; Eleore et al. 2011). RE also appears unable to evoke action potentials in mPFC principal cells, with the strong caveat that these recordings have been performed in anesthetized animals. Using an optogenetic strategy, Cruikshank et al. (2012) found that activating matrix thalamo-cortical projection neurons, including RE cells, excited mPFC (PL) layer 1 inhibitory neurons, presumably neurogliaform cells (e.g., Overstreet-Wadiche and McBain 2015). In turn, this conveyed feedforward inhibition to pyramidal cells in layers 2/3 as well as other layer 1 interneurons (Fig. 2B). The thalamic-induced inhibition of the latter interneurons likely has a disinhibitory effect on postsynaptic targets. Speculatively, RE-induced feedforward inhibition may impose a narrow temporal window for exciting mPFC pyramidal cells via direct RE → mPFC, and RE → CA1, and/or CA1 → mPFC pathways, thereby facilitating the (timing of) communication between HC and mPFC.

Though the effects of mPFC inputs on RE neurons are not well known, a recent study investigated the influence of mPFC input on spontaneously active RE neurons in anesthetized rats (Zimmerman and Grace 2018) using extracellular single-unit recordings in RE and manipulated activity in the infralimbic prefrontal area (IL). The results showed that (1) following tetrodotoxin (TTX) inactivation of IL neurons RE burst firing was reduced, (2) following inhibition of the mPFC(IL) → RE pathway utilizing the projection-specific approach with DREADDs (designer receptors exclusively activated by designer drugs), a subset (40%) of the spontaneously active RE neurons showed an enhancement of burst firing without an increase in number of spikes, and (3) acute electrical (0.5 Hz) stimulation of mPFC (IL) resulted in complex responses in 75% of RE neurons. That is, while only eight RE neurons from three different rats were recorded, six of these cells initially stopped (tonic) firing, followed by rebound spiking (mostly bursting), and after 15–25 stimuli they stopped firing altogether. Thus, mPFC input to RE appeared to have shifted the firing mode from tonic to burst firing, followed by silence. Zimmerman and Grace (2018) hypothesized that the mPFC → RE input may entrain bursting in RE neurons, with silencing effects achieved via the mPFC → TRN → RE pathway (Fig. 2B). While direct mPFC–RE input is glutamatergic,

feedforward inhibition of RE occurs via GABAergic input from the TRN (Halassa and Acsády 2016). Muscimol inhibition of TRN, had no effects on the spontaneous firing rate, bursting or spike counts in RE cells, but it did reduce the number of spontaneously active cells (Zimmerman and Grace 2018). These results, although puzzling, indicate distinct roles of the TRN → RE, and mPFC (IL) → TRN → RE pathways.

## Role of RE in oscillations and synchronization

Several studies, not reviewed here, show that the interactions of the mPFC and HC are critical to cognition. It is commonly speculated that RE promotes these interactions, possibly through synchronization of slow, gamma, and/or theta frequency oscillations that facilitates communication.

The physiological properties of RE neurons (Jankowski et al. 2014, 2015; Lara-Vásquez et al. 2016; Walsh et al. 2017; Zimmerman and Grace 2018) appear supportive of a significant involvement of RE-CA1/subiculum and RE-EC projecting neurons in very slow oscillations (0.1–1 Hz). This is in line with electrophysiological results (Dolleman-van der Weel et al. 1997, 2017), showing that low ( $\leq 2$  Hz) frequency stimulation of RE yielded much larger amplitude CA1 fEPSPs than following stimulation at theta frequencies (4–10 Hz). Moreover, RE is thought to impose a slow oscillation on CA1 pyramidal cells through synapses on inhibitory neurons (Dolleman-van der Weel et al. 1997; Zhang et al. 2012; Duan et al. 2015). Xu and Südhof (2013) proposed that by facilitating the EC input during hippocampal slow oscillations, RE may contribute to the neocortical-hippocampal dialogue and subsequent memory consolidation, an idea that is supported by recent electrophysiological findings (Dolleman-van der Weel et al. 2017). Furthermore, behavioral studies have shown that RE is involved in (hippocampal-dependent) memory consolidation (e.g., Loureiro et al. 2012), a process dependent on slow (<1 Hz) synchronized oscillations in mPFC and HC (Huber et al. 2004; Mölle and Born 2011).

The long-range synchronization of gamma may enable communication between distant brain regions (e.g., Fries 2015). Ferraris et al. (2018) recently provided evidence that RE serves to synchronize bursts of gamma activity in CA1 and mPFC (PL). During slow oscillations synchronized gamma bursts (30–90 Hz) occur in the mPFC and HC in adult rats under anesthesia and natural sleep (Ferraris et al. 2018). Both CA1 and mPFC cells were entrained by the gamma oscillations, but they did not participate in the actual synchronization of CA1 and mPFC gamma bursts. Instead, RE neurons appeared related and increased their firing prior to the synchronized gamma burst onsets, while muscimol inactivation of RE disrupted synchronization of the CA1 and mPFC gamma bursts. The authors suggested that RE may actively promote/drive the mPFC–HC gamma burst coupling during slow oscillations, thereby providing a temporal window for information exchange/memory consolidation during slow wave sleep (Ferraris et al. 2018).

Synchronized prefrontal-hippocampal activity in the theta range (4–10 Hz) occurs predominantly during exploration and REM sleep and is related to several learning and memory processes (Boyce et al. 2016; Guise and Shapiro 2017). Whether RE plays an important role in driving hippocampal theta waves, and/or in the theta coupling between mPFC and HC is unclear from the available data. For example, during rat neonatal development the mPFC–RE connectivity is involved in theta band coupling of mPFC and HC, providing an early transthalamic feedback mechanism for mPFC control over CA1 activity (Hartung et al. 2016).

Additionally, RE contains a small percentage of neurons with various spatial properties, i.e., head direction cells, “place cells”

with low levels of spatial information, and perimeter/border or boundary cells (Jankowski et al. 2014, 2015). In freely moving rats these cells display firing properties in the theta range, however coherence with hippocampal theta oscillations is low. RE cells display trajectory-dependent activity in a continuous alternation task, phase-locked to theta rhythm in CA1 (Ito et al. 2015). Recently, Ito et al. (2018) reported that firing of mPFC and RE neurons show enhanced coordination with the CA1 theta rhythm when rats approached the choice point in a T-maze. However, the temporal coordination in mPFC-RE-CA1 seemed dependent on the supramammillary nucleus (SUM) determined by optogenetic silencing.

In anesthetized rats, however, various reports have indicated that RE has little effect on hippocampal theta. For instance, RE is likely not involved in atropine-resistant theta (Vanderwolf et al. 1985), and RE spiking activity during spontaneous or tail-pinch induced hippocampal theta oscillations displayed only a very low coherence with hippocampal theta (Morales et al. 2007). In addition, low frequency (0.1–2 Hz) electrical stimulation of RE may disrupt spontaneously occurring hippocampal theta oscillations, even up to a point of near complete suppression (Dolleman-van der Weel, unpublished observations).

There are some contrasting results on theta coupling between mPFC and HC. On the one hand, lidocaine inactivation of RE resulted in a decreased coherence between 2–5 Hz delta oscillations in mPFC (PL) and HC, but had minimal effect on coupling at theta frequencies (Roy et al. 2017). On the other hand, an *N*-methyl-D-aspartate (NMDA) lesion of RE impaired the coherence of mPFC–HC (PL-CA1) theta (and beta) frequency oscillations (Kafetzopoulos et al. 2018). Interregional synchronization in the dorsal CA1-RE-mPFC direction was also observed. Using a spatial working memory (SWM)-dependent delayed alternation (DA) task Hallock et al. (2016) showed that RE inactivation robustly decreased the proportion of mPFC neurons that were phase-locked to hippocampal theta during delay periods of the SWM task.

In summary, electrophysiological data indicate that RE can modulate neuronal activities in mPFC and HC through a complex interplay of direct excitatory effects on principal cells and subclasses of local inhibitory interneurons. Thus, RE may exert a (state-dependent) influence on the excitation/inhibition balance and level of plasticity. In addition, through activation of interneurons RE may impose an oscillatory rhythm on pyramidal cell ensembles that facilitates the local and interregional flow of information. Whether the latter involves the collateralized RE projections to CA1 and mPFC is as yet an unresolved issue. Return projections to RE, i.e., the direct mPFC–RE and indirect mPFC–TRN–RE pathways, are tentatively proposed to have distinct effects on firing mode of RE neurons.

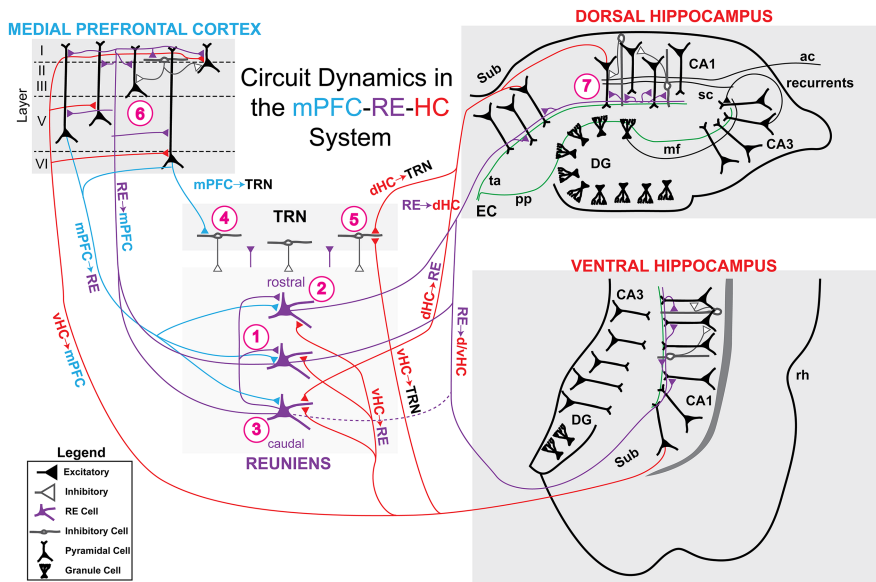
## Potential RE circuit dynamics

The anatomy and physiology of RE presents an emerging picture of an extensive network that includes the HC, EC, PRC, mPFC, and TRN involving a complex interplay of state-dependent excitatory/inhibitory effects on neuronal activity that occurs both locally and at the circuit/network level. Here we attempt to coalesce and simplify RE functions in a model based on the conceptualization of RE as a canonical, higher-order, cortico-thalamo-cortical circuit (Theyel et al. 2010; Sherman, 2017) situated at the nexus of the mPFC and HC. By modulating specific, temporally coherent patterns of neuronal activity, RE organizes interactions between an anatomically extended set of diencephalic, mPFC, and medial temporal lobe circuits—distributed *coalitions* that are required for the highest orders of cognition involving the integration of memory, motivation, and actions directed by expected outcomes. Though

the model incorporates several key anatomical and physiological features of RE circuitry, many details remain unknown, and our description is intended as a framework for further investigating RE circuit function. The model emphasizes integration and coordination functions of RE with respect to three levels of organization: anatomical connectivity, neuronal modulation, and computational process (depicted in Fig. 3). At a fundamental level RE neurons must act as integrators based on their massive inputs and limited outputs (see above anatomy). This input–output ratio likely implements a form of dimensionality reduction resolving appropriate features of information within the context of frontotemporal interactions, and influenced by the many inputs from regions associated with diverse behavioral and autonomic states. Likewise, the central location of RE positions it to coordinate activity throughout the mPFC–RE–HC system leading to the idea that RE serves a critical role in synchronization, gating, and inhibitory control.

In the conceptual model, we enumerate seven possible RE mechanisms: (1) RE could coordinate coherent interactions across mPFC–RE–HC through the 5%–10% of RE-CA1 projecting cells with collateralized axons to both mPFC and the HC (e.g., Hoover and Vertes 2012; Varela et al. 2014). As reviewed above, there are some indications for this role (e.g., Hallock et al. 2016; Roy et al. 2017), but direct evidence is lacking. Coordination could include delta and theta frequency bands, slow oscillations and/or coupling of these with higher frequency bands such as gamma. (2) RE cells could coordinate and integrate its vastly distributed afferents with specific inputs originating from mPFC, extract central features such as goal trajectory (Ito et al. 2015), and project this information onto the HC. This, in turn, might drive neuronal activation sequences related to situation appropriate memory acquisition or retrieval states in HC. (3) RE cells could coordinate and integrate its vast afferents with specific input originating in the HC, extract common features such as situation appropriate contextual representations (as opposed to detailed representations), and project this information onto mPFC. These inputs to mPFC might drive memory-based cognitive and behavioral control mechanisms. The latter two functions would be similar to other cortico-thalamo-cortical pathways where the thalamus has been shown to transfer information (e.g., Theyel et al. 2010). (4) RE cells could provide the mechanism for cortico-thalamic gating and/or, (5) subiculo-thalamic gating, via feedforward inhibitory inputs from the TRN neurons (Çavdar et al. 2008). Such TRN-based gating could enable RE cells to modulate the directional route of flow from mPFC → RE → HC or HC → RE → mPFC on fundamental neural integration and processing time scales (tens of milliseconds). Such a mechanism could allow for rapid informational loops updating increasingly advanced representations relevant to ongoing memory-guided behavior. Generally, this type of feedforward gating mechanism provides for rapid transitions between large cognitive networks via the thalamus. (6) RE → mPFC projections might drive both inhibitory and principal neurons providing computational control over cognitive states within the mPFC. (7) RE → HC projections could drive both inhibitory and principal neurons with its massive inputs to slm, but this excitatory input may not drive action potentials in pyramidal cells directly (Dolleman-van der Weel et al. 1997; Chittajallu et al. 2017). Instead, RE inputs might serve to alter the computational state of CA1, affecting encoding, consolidation and memory retrieval (e.g., Xu and Südhof 2013). For example, RE inputs may tune the magnitude and timing of network excitability reflected in local field potential oscillations. Such modulation would strongly affect synaptic integration, action potential generation, and plasticity mechanisms.

While this conceptual model is neither exhaustive nor validated, it provides a simple framework for hypothesis-driven work on the role of the RE in cognitive neurobiology by considering circuit dynamics. The basic idea is that the mPFC and HC is an



**Figure 3.** Conceptual model of circuit dynamics in the mPFC–RE–HC system. Note that both the dorsal and ventral HC are depicted to emphasize these divisions. The model is focused on RE neurons (purple) with projections (dense, solid purple line; light, stippled purple line) to HC, mPFC, other RE neurons, and TRN. In turn, RE neurons receive input from HC (red), mPFC (blue), and TRN (dark gray). Throughout the model, inhibitory cells have a white soma and white triangle synapses; excitatory cells have black somas and colored triangle synapses. The model proposes seven potential circuit mechanisms: (1) mPFC–RE–HC synchronization might be achieved through the small subpopulation of RE neurons with collateralized axons to both mPFC and HC. (2) mPFC → RE → HC integration and propagation through RE neurons and (predominantly rostral) RE → HC projections. There is the potential for additional integration/modulation of rostral RE neurons via inputs from ventral subiculum and caudal RE neurons. (3) HC → RE → mPFC integration and propagation through a subpopulation of caudal RE neurons that receive (dorsal and ventral) subicular afferents, and project to mPFC. (4) Cortico-thalamic gating through mPFC → TRN projections, and (5) Subiculo-thalamic gating through d/v Subiculum → TRN projections, both providing feedforward inhibition on RE, or other thalamic nuclei. (6) RE → mPFC projections could modulate/drive the computational state of mPFC through excitatory inputs onto pyramidal cells, and on inhibitory interneurons in layer 1. (7) RE → HC projections could modulate/drive the computational state of CA1 through excitatory inputs onto pyramidal cells, and inhibitory interneurons, colocalized with EC layer III inputs in slm. Each of these circuit mechanisms could serve several functions in memory and behavior, but each needs to be tested in empirical studies using techniques able to isolate circuit-level mechanisms, such as optogenetics and DREADD based experiments in freely behaving animals. Abbreviations: (dHC) dorsal hippocampus, (CA1) cornu ammonis field 1, (DG) dentate gyrus, (HC) hippocampus, (mf) mossy fibers, (mPFC) medial prefrontal cortex, (pp) perforant path, (rh) rhinal sulcus, (RE) nucleus reuniens of the thalamus, (sc) Schaffer collateral, (slm) stratum lacunosum moleculare, (Sub) subiculum, (ta) temporoammonic pathway, (TRN) thalamic reticular nucleus, (vHC) ventral hippocampus.

instantiation of a canonical cortico-thalamo-cortical circuit in the brain capable of bridging the memory and executive systems.

## Behavioral functions of RE

In this section, we review the role of RE in navigation, spatial working memory, the temporal organization of memory, and executive functions. RE contributions to these tasks have been studied using lesions (e.g., electrolytic or NMDA), pharmacological inactivation (e.g., muscimol), circuit-specific approaches (e.g., optogenetics and DREADDs), and *in vivo* electrophysiological approaches (e.g., fine-wire tetrodes). Each approach has caveats for use in studying RE, the most obvious of which is that RE is difficult to target because it is deep and on the midline. Additionally, NMDA lesions may cause epileptic activity in CA1 (Hirayasu and Wada 1992), muscimol may spread to nearby thalamic regions and affect motor behaviors (e.g., Starr and Summerhayes 1983; Klockgether et al. 1985), and recordings in RE are difficult to localize *in vivo* due to a lack of an established electrophysiological signature. Regardless, careful application of these approaches has led to the overarching

conclusion that RE is critical to learning and memory, and involved in executive functioning.

## RE in spatial navigation

Spatial navigation is an essential ability for animals living in space. Although individual animal species appear to develop different navigation strategies, a key feature of rats (and humans) is their strategy based on internal maps in the brain (Tolman, 1948; O'Keefe and Nadel 1978). This map-based navigation eliminates the necessity to memorize sequences of individual movements toward goals. Instead, the extraction of geometric relationships between spatial landmarks allows animals to plan routes to various destinations flexibly. In support of this idea, studies have identified neurons that fire depending on the animal's position in space, such as place cells or grid cells (O'Keefe and Dostrovsky 1971; Hafting et al. 2005). However, it is still largely unknown how other cortical structures use such geometric relationships to plan a route, or action sequences, toward destinations.

The mPFC has been considered a key structure for navigation. For example, lesioning mPFC impaired flexible planning of route from different start positions to the goal (Granon and Poucet 1995). Furthermore, goal-directed navigation was impaired in a human patient with damage in the ventral mPFC (Ciaramelli 2008; Spiers 2008). Notably, the patient was able to navigate successfully if the goal location was repeated periodically, suggesting mPFC may play a role in goal representation and route planning during navigation. Consistent with this idea, studies have reported the temporal coordination of activity between mPFC and HC during navigation. When the animal makes a decision about the next route at a T-junction of a maze, the spectral coherence between mPFC and HC is modulated in the theta-frequency band (Benchenane et al. 2010). At the cellular level, mPFC spiking becomes phase-locked to theta oscillations in HC (Jones and Wilson 2005; Siapas et al. 2005; Ito et al. 2018). This behavior dependent spike-time coordination implies dynamic functional coupling between mPFC and HC during routing.

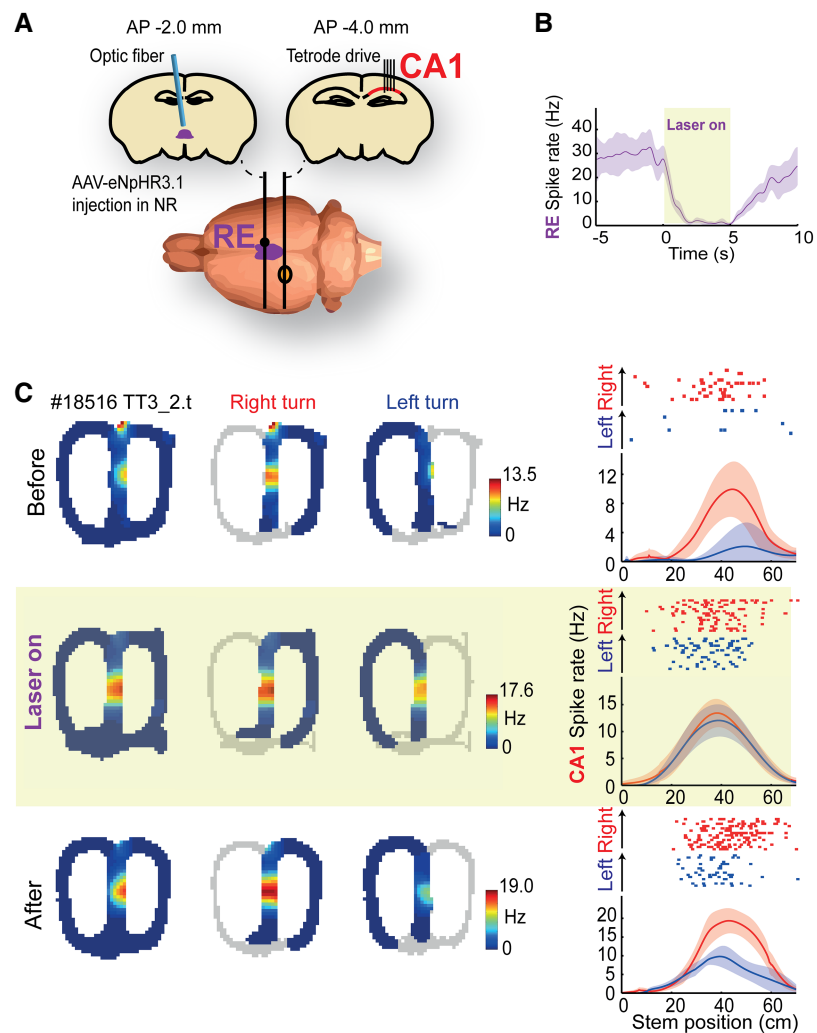
While previous studies indicate a key role for mPFC–HC interactions in navigation, the origin of the axonal projection in mPFC from HC is largely limited to its ventral and intermediate portion (Jay and Witter 1991; Hoover and Vertes 2007), in spite of a pivotal role of dorsal HC in fine-scale spatial representations and spatial learning (Nadel 1968; Moser et al. 1993; Sargolini et al. 2006). The absence of a direct projection from mPFC to HC leads to a question of how the mPFC–HC communicates in support of navigation. As reviewed above, RE may serve as the primary hub between mPFC and HC (Vertes et al. 2007), and thus navigational behavior may involve the mPFC–RE–HC system.



One line of evidence for a role of RE in mPFC–HC interactions in memory was provided by Xu and Südhof (2013). They demonstrated that the mPFC–RE–CA1 circuit plays a key role in balancing the specificity and generalization of contextual representations in a fear conditioning task. The results of this study suggest that a RE-mediated circuit may directly influence place cell firing in HC because similarities and differences between environments are thought to be represented by field locations and firing rates across a place cell population (Anderson and Jeffery 2003; Leutgeb et al. 2005; Colgin et al. 2008). Consistent with this notion, Cholvin et al. (2018) recently reported that RE lesions impaired the stability and firing-rate modulation of place cells, which may ultimately influence spatial cognition.

What kind of information is represented in RE neurons? Jankowski and colleagues showed that a subpopulation of RE neurons exhibited a tuning to the animal's head direction or position (Jankowski et al. 2014, 2015), likely reflecting anatomical inputs from the subiculum and parahippocampal region to RE (McKenna and Vertes 2004). A key role of RE in navigation was investigated by Ito and colleagues (Fig. 4; Ito et al. 2015). They recorded the activity of neurons in mPFC, RE, and CA1 as rats performed a continuous alternation task in a T-maze. The study found that many neurons in RE or mPFC lack any notable tuning to the animal's position in space during navigation, which contrasts with neurons in HC. However, neurons in RE and mPFC change firing rates depending on the animal's next movement (either a right or left turn at the T-junction). This trajectory-dependent activity in RE neurons influenced the peak firing rates of place cells in the hippocampal CA1, which otherwise retained their spatially selective firing. While it has long been known that place cells change their activity depending on the animal's trajectory (Markus et al. 1995; Frank et al. 2000; Wood et al. 2000), such modulation is likely mediated by the mPFC→RE circuit. Consistent with this notion, the trajectory-dependent rate change of place cells was largely diminished by lesions or by optogenetic-silencing of RE (Ito et al. 2015).

The functional investigation of RE further elucidated a role for theta-rhythm spike-time coordination in mPFC–HC interactions. When the animal decides the next route at the T-junction, neurons in mPFC and RE enhance their spike-time coordination with the HC theta rhythm, resulting in efficient transfer of trajectory information from mPFC to HC (Ito et al. 2018). Interestingly, this spike-time coordination in the mPFC–RE–CA1 circuit was mediated by SUM in the hypothalamus that projects to mPFC, RE, and HC (Vertes 1992; Pan and McNaughton 2004), pointing also to subcortical structures as key nodes for controlling mPFC–HC interactions.



**Figure 4.** Trajectory-dependent coding in CA1 depends on RE activity. (A) Rats were implanted with an optical fiber targeting RE with RE cells expressing the enhanced halorhodopsin eNpHR3.1. Recordings were made from tetrodes implanted in dorsal CA1 while rats performed a continuous alternation task on a modified T-maze. (B) During “laser on” conditions RE neurons are temporarily silenced. (C) A sample CA1 neuron shown before, during, and after RE silencing. Under control (before and after) conditions, the CA1 neuron shows trajectory-dependent coding with more firing on the stem of the maze for right-bound runs. During RE inactivation trajectory-dependent coding is diminished. Abbreviations: (CA1) cornu ammonis field 1, (RE) nucleus reuniens of the thalamus. Reprinted from Ito et al. (2015) with permission.

While these studies indicate the role of RE in transferring information about the animal's next movement from mPFC to the HC, why is such information necessary in HC? The exact contribution of the RE-mediated information is unclear because lesions or inactivation of RE impairs the animal's performance in some navigation tasks (Cholvin et al. 2013; Mei et al. 2018), but not in others such as a simple alternation task or water-maze task (Dolleman-van der Weel et al. 2009; Ito et al. 2015). However, several hints are available. One study demonstrated that neurons in mPFC and RE represent the movement directions in a self-centered, or egocentric, perspective (Ito et al. 2015). However, during navigation, each intended movement must be evaluated based on the animal's position and head direction in the environment, information primarily represented in HC and parahippocampal structures (Moser et al. 2008, 2014). The mPFC–RE–CA1 circuit may therefore mediate the integration of egocentric action plans with a spatial map in the HC, providing a necessary

computational step to assess the next move based on its geometric relationships to the destination.

## RE in spatial working memory

Working memory is the maintenance of trial-specific information over a brief temporal delay. One example would be remembering the location of your parked car while walking into a store, or holding a phone number in mind before entering it into the contacts on your phone. Recent research into the neurobiological basis of SWM has focused on the mPFC–RE–HC system.

Most experimental SWM tasks involve alternations in a T-maze. As discussed above, the simplest variant is the continuous alternation (CA) task, in which the rodent runs from the left reward zone to the right reward zone in a figure-eight pattern without stopping (Wood et al. 2000; Lee et al. 2006; Ainge et al. 2007), with performance dependent on memory for the previous run in order to successfully alternate. In DA task versions, working memory demand is increased by having animals stop during a given time delay (seconds or minutes) before the next alternation can be made. Control tasks include all the same demands, but do not require the stimuli to be held in mind for successful performance. For example, the tactile-visual conditional discrimination (CD) task (Griffin et al. 2012) used different tactile floor inserts associated to different reward zones (i.e., the right or left side). CD depends on the integrity of the dorsal striatum but not dorsal HC, and the opposite is true for DA (Hallock et al. 2013a). Notably, CD tasks can be modified to make them SWM-dependent. Instead of covering the entire maze with the conditional cue, the cue is only presented at the beginning of the maze stem but absent at the T-junction. mPFC inactivation disrupts choice accuracy on the SWM version of the CD task, but not the SWM-independent version (Shaw et al. 2013).

SWM depends on mPFC–HC functional connectivity. For example, mPFC–HC oscillatory coupling in the 4–12 Hz (theta) range is prominent during SWM (Jones and Wilson 2005). Additionally, mPFC single neuron entrainment to the HC theta rhythm reflects accuracy on a delayed nonmatch to sample (DNMS) task performed in an operant chamber (Hyman et al. 2010). In agreement with these findings, Hallock et al. (2016) showed that mPFC–HC theta synchrony is strongest under situations in which SWM is required. Specifically, the authors found that theta coherence was significantly higher on DA compared to CD tasks as rats moved through the T-junction of the maze (Hallock et al. 2016). One important modulator of mPFC–dorsal HC theta synchrony is the ventral HC. For example, Spellman et al. (2015) optogenetically inhibited ventral HC terminals in mPFC during different phases of the delay nonmatch to place (DNMP) task in mice. Ventral HC terminal suppression during the sample, but not delay or choice phases, impaired accuracy and interfered with task coding in mPFC single-unit activity. This suggests that ventral HC inputs to mPFC are critical for encoding task-specific spatial information. Additionally, removal of ventral HC input to mPFC disrupted mPFC–dorsal HC synchrony, suggesting that the direct pathway from ventral HC → mPFC contributes to mPFC–dorsal HC functional coupling and SWM (O'Neill et al. 2013).

RE is ideally situated to modulate mPFC–HC interactions in SWM (Vertes et al. 2007). Consistent with this role, inactivation of RE with muscimol impaired performance on the SWM-dependent CD task, but leaves the SWM-independent variant unaffected (Fig. 5; Hallock et al. 2013b). Further as the delay length is increased, the deficits increase (Layfield et al. 2015). Recently, the temporal precision offered by optogenetic techniques was used to suppress RE during the sample, delay, and choice phase of a DNMP task (Maisson et al. 2018). Results showed that optogenetic

suppression of the RE during the sample phase, but not the delay or choice phases, impairs choice accuracy. Together with Spellman et al. (2015), these findings suggest that both RE and ventral HC input to mPFC are critical for encoding task-relevant information during SWM.

Another recent study answered a more mechanistic question of how RE might affect the mPFC–HC circuit (Hallock et al. 2016). In the study, RE inactivation was combined with dual-site LFP recordings in mPFC and dorsal HC. Rats were trained to asymptotic performance on the DA task. Before, during, and after RE inactivation with muscimol LFPs were recorded from mPFC and dorsal HC while DA trials were run. RE inactivation significantly impaired DA choice accuracy which was also accompanied by a reduction in mPFC–dorsal HC coherence.

Overall, these studies show that RE is critical for both SWM and mPFC–HC synchrony. However, many questions remain about how RE modulates SWM. For example, is the dependence on RE due solely to its role in synchronizing theta oscillations between mPFC and HC? What is the impact of RE inputs to mPFC, HC, and EC at different times during SWM? Exploring these, and other, circuit-level questions will be critical to understanding how and when RE contributes to SWM.

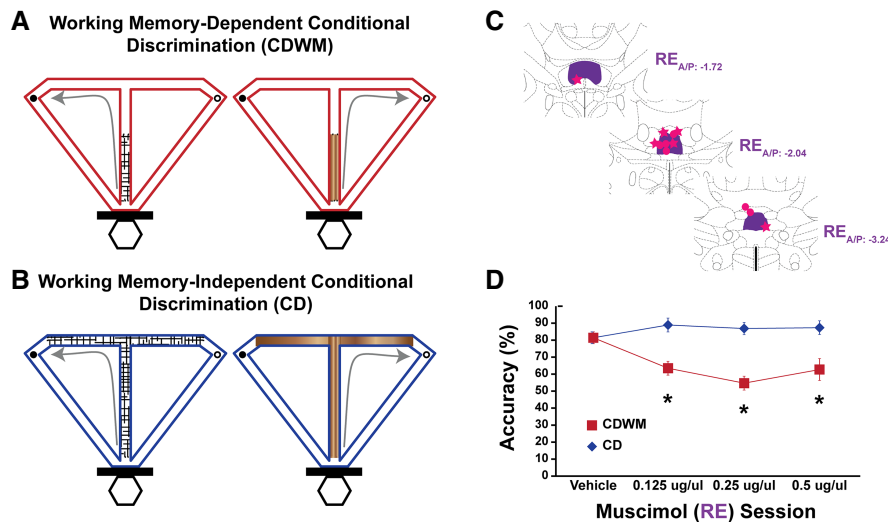
## RE in the temporal organization of memory

The temporal organization of memory has been studied in a wide array of tasks, and is generally thought to help assemble events into separate episodes (Clayton and Dickinson 1998; Tulving 2002; Kesner and Hunsaker 2010; Jacobs et al. 2013; Eichenbaum 2017). Although many of our experiences occur in the same places (e.g., our lab), with the same items (e.g., our computers), the temporal information is always distinct. That is, information about “when” an event occurred is stored in memory, in addition to “what” occurred and “where” it occurred (Allen and Fortin 2013).

A commonly studied form of the temporal organization of memory is the memory for sequences of events. Memory for sequences of events tasks are thought to model the fundamental flow-of-events aspect of episodic memory (Allen et al. 2014). That is, sequence memory provides a representation of the order of events as they occurred within an experience, and underlies our ability to “play back” experiences. Many studies have shown that memory for sequences of events is dependent on both mPFC and HC (Fortin et al. 2002; Kesner et al. 2002; Hannesson et al. 2004; Knierim et al. 2006; Barker et al. 2007; Ekstrom and Bookheimer 2007; Euston et al. 2007; DeVito and Eichenbaum 2011). Thus, if an essential role of RE is to support mPFC and HC functions, then RE should be critical for remembering sequences.

Although little is known about the role of RE in sequence memory, a recent report tested the hypothesis that RE is critical to remembering sequences of events in rats (Fig. 6; Jayachandran et al. 2018). In this study, rats were trained on an odor-based sequence memory task in which they had to identify odors as “in sequence” or “out of sequence” for water rewards. Notably, the sequence task explicitly controls for spatial variables by presenting all the odors within a sequence in the same nose port, thus extricating performance from a simple spatial interpretation. Importantly, a previous study has shown that the sequence task drives sequential representations in individual CA1 neurons, with spike timing that phase locks to the beta frequency band, and this activity corresponded with accurate memory performance (Allen et al. 2016). To test the role of RE in the task, Jayachandran et al. (2018) used a DREADD-based synaptic silencing approach (Stachniak et al. 2014) to suppress activity in the mPFC → RE projection prior to sequence memory testing in well-trained rats (memory was tested, not learning). Local infusions of clozapine





**Figure 5.** RE is critical for working memory in a T-maze. (A) A working memory-dependent conditional discrimination (CDWM) task was used in which a texture floor insert determined the availability of reward in the left or right reward zone (open/closed circles). However, the texture only covered the first half of the stem and was not present at the T-junction (the choice point) and thus successful performance required working memory. (B) A working memory-independent conditional discrimination (CD) task was used as a control in which all the same task demands were present, except working memory was not required because the floor insert covered the whole stem and T-junction. (C) Prior to testing, the GABA<sub>A</sub>-agonist muscimol was administered into the RE through a chronically implanted cannula. Cannula tip locations are depicted with pink circles for the CDWM task, and pink stars for the CD task. (D) Compared to vehicle infusion, RE inactivation with muscimol impaired performance on the CDWM task, but not the CD task, demonstrating a critical role for RE in working memory. Abbreviations: (RE) nucleus reuniens of the thalamus. Reprinted from Hallock et al. (2013b) with permission.

N-oxide (activating hM4Di receptors on presynaptic terminals from mPFC) were made directly into RE through cannulas. The results showed that silencing the mPFC → RE projection repeatedly and effectively abolished sequence memory in rats, but that silencing the mPFC → RE pathway did not affect running speed, odor sampling, reward retrieval, or nose poke times. An analysis of the distribution of nose poke times reinforced the conclusion that the effect of silencing the mPFC → RE projections is to reduce the accuracy of sequence memory decisions, rather than change the distribution of reaction times.

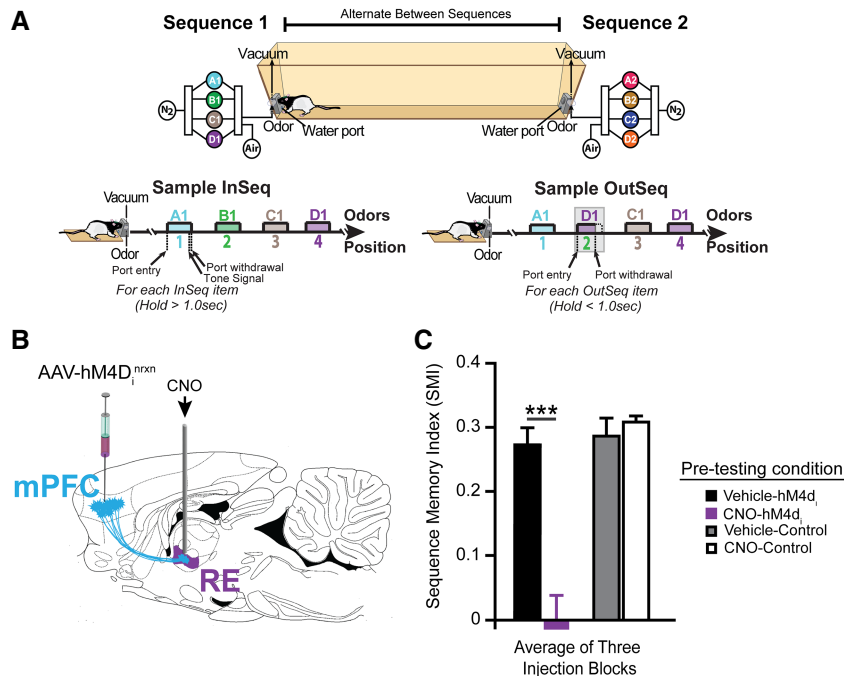
Through a detailed lag analysis, Jayachandran et al. (2018) revealed a pattern of deficits that resembled a reduction in a working memory retrieval strategy after silencing the mPFC → RE pathway, in contrast to a temporal context memory retrieval strategy, which was instead impaired by silencing mPFC → PRC. To clarify this issue, temporal context memory in the sequence task refers to the retrieval gradients that are observed in human studies of list learning (e.g., Howard and Kahana 2002; Kragel et al. 2015). When items are recalled from the list, people will tend to remember the nearby items (short lags), but they are less likely to recall distal items (longer lags). Because verbal recall cannot be performed by animals, the sequence task models list learning using a nonverbal response to probe memory (in and out of sequence decisions). Temporal context memory is demonstrated in this task with a lag analysis in which the retrieval of nearby items interferes with out of sequence decisions but distal items do not. In this same task, working memory is simultaneously tested on reverse lags because delay-match-to-sample strategies can contribute to successful performance. That is, in contrast to temporal context memory, working memory helps reject nearby items but does this less well for distal items (the opposite pattern). The mPFC → RE silencing effect on working memory retrieval during memory for sequences of events is gener-

ally consistent with the role of RE in SWM tasks (e.g., Hembrook et al. 2012; Cassel et al. 2013; Hallock et al. 2013b; Griffin 2015; Viena et al. 2018), and, from a retrieval standpoint, similar to the role of RE in hippocampal-dependent contextual fear memory (Ramanathan et al. 2018). Though more work needs to be done to test the role of RE in a variety of temporal tasks, these early findings suggest that the cognitive role of RE is not restricted to processing spatial variables, but rather RE influences multiple memory functions that likely contribute to episodic memory.

## RE in executive functions

As discussed above, it is now fairly well established that RE directly participates in memory but considerably less attention has been paid to the role of RE in “executive functions,” such as attention, goal directed behavior, or behavioral flexibility. This is despite strong RE connections with the medial and orbital PFC, known to be critical for behavioral regulation (Bannerman et al. 2004; Dalley et al. 2004; Kehagia et al. 2010; Chudasama et al. 2012; Abela and Chudasama 2013; Abela et al. 2013). Regarding executive functions, Dolleman-van der Weel et al. (2009) initially reported that lesions of RE did not impair acquisition or retention

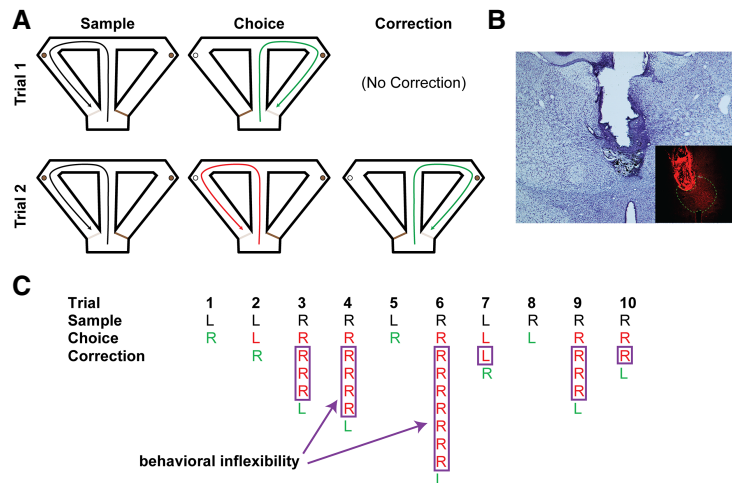
of spatial reference memory on a water maze task, but nonetheless led to a maladaptive search strategy which was deemed a PFC deficit. Specifically, on the probe test following acquisition, RE-lesioned rats swam directly to the correct quadrant of the pool but upon not finding the platform, immediately began to search the entire pool for the missing platform. This contrasted with sham-operated controls that persistently searched in the training quadrant of the pool. This very rapid switch in strategies of the RE-rats coupled with a failure to adopt a more efficient strategy was described as a deficiency in strategy shifting, typically seen with alterations of the orbital PFC (Amodeo et al. 2017; Izquierdo 2017). Consistent with this, Prasad et al. (2013) demonstrated that RE lesions produced premature responding on a 5-choice serial reaction time task (5-CSRTT), whereas other indices such as omitting responses (a measure of attention) were unaffected by the lesions. Premature responding is viewed as a deficit in impulse control and is produced with lesions of IL on the 5-CSRTT task (Chudasama et al. 2003). Cassel and colleagues (see Cholvin et al. 2013) further reported that following RE inactivation, rats were unable to successfully navigate a “double H” water maze which required a switch in strategy from response to place responding. Linley et al. (2016), using a seven-stage odor/texture discrimination task (Birrell and Brown 2000), found that rats with RE lesions were significantly impaired in reversal learning, indicating an inability to shift to new stimulus-reward contingencies—or behavioral inflexibility. Finally, Viena et al. (2018) recently reported that inactivation of RE with muscimol in rats produced deficits in SWM on a DNMS T-maze task, and additionally resulted in severe perseverative behavior (Fig. 7). Specifically, following incorrect choices on the T-maze, rats were given no-delay correction runs wherein they could immediately choose the correct arm of the maze to retrieve food. Unlike controls, rats infused with muscimol repeatedly



**Figure 6.** mPFC → RE projections are critical to memory for sequences of events. (A) Rats were tested on a linear track where two separate four-odor sequences are presented (one sequence on each side). Odor presentations were initiated by a nose-poke, and the rats had to correctly identify the odor as in sequence (hold for 1 sec) or out of sequence (withdraw prior to 1 sec). (B) Rats were injected with AAV-hM4D<sub>i</sub> (an inhibitory DREADD) in mPFC or a control virus, and a cannula targeted RE. (C) Well-trained rats were infused with CNO in RE (the DREADD agonist) or vehicle prior to testing. Silencing the mPFC → RE terminals (the CNO-hM4D<sub>i</sub> group) abolished sequence memory, demonstrating that the role for RE is not limited to spatial tasks. Abbreviations: (CNO) clozapine N-oxide, (mPFC) medial prefrontal cortex, (RE) nucleus reuniens of the thalamus. Reprinted from Jayachandran et al. (2018) with permission.

made incorrect choices on the maze in the absence of reward—or showed strong perseverative responding indicative of a lack of behavioral flexibility. Viena et al. (2018) concluded that RE not only serves a role in the SWM but “appears to be a core structure in an extended network mediating executive functioning.”

Regarding the network contributing to perseverative behavior (or the inability to switch strategies to changing environmental conditions), the HC and the orbital PFC appear to serve pivotal roles (for review, see Viena et al. 2018). For instance, Torres-Berrío et al. (2019) recently reported that ventral HC is critically involved in behavioral flexibility, as TTX-induced inactivation of the ventral HC significantly impaired the ability of rats to switch strategies on a plus maze. As there is limited direct communication between the HC and orbital PFC (Dollemann-van der Weel and Witter 1996; Reep et al. 1996; Vertes et al. 2006, 2007; Hoover and Vertes 2011, 2012), RE appears to be an important link between HC and orbital PFC as well, possibly serving a vital role in the adaptation to changing environment contingencies.



**Figure 7.** RE inactivation impairs behavioral flexibility. (A) Rats were trained to alternate in a T-maze after a delay, but this version of the task included error correction trials in order to test behavioral flexibility. During the sample phase, rats could choose either side for reward, but next had to choose the opposite side for reward following a delay (standard SWM test). If the rat made the correct choice (green arrow, trial 1) they would move onto the next trial. However, if the rat made a working memory error (red arrow, trial 2) they would be given an immediate opportunity to correct this choice with no delay (the correction phase; green arrow, trial 2). Rats were given repeated correction opportunities until they made the correct response. (B) Prior to testing, rats were infused with the GABA<sub>A</sub>-agonist muscimol into RE. (C) RE inactivation impaired SWM, but importantly, also resulted in severe spatial perseveration (repeatedly making the same wrong turn). An example performance following RE inactivation shows many repeated errors on correction runs (purple boxes), suggesting a role for RE in behavioral flexibility. Reprinted from Viena et al. (2018) with permission.

## Clinical relevance of RE dysfunction

Due, in part, to its key position in between the HC and mPFC, RE dysfunction may lead to major clinical problems, such as persistent working memory impairments and other types of cognitive dysfunction shared by many neuropsychiatric disorders (Meyer-Lindenberg et al. 2001, 2005; Lawrie et al. 2002; Bassett et al. 2012; Venkataraman et al. 2012; Argyelan et al. 2014). Although little is known about RE dysfunction, to date, RE has been suggested to be involved in Alzheimer's disease (Braak and Braak 1991; Moretti et al. 2011; Hardenacke et al. 2013), Korsakoff's syndrome (Visser et al. 1999), autism (Ray et al. 2005), stress and depression (Kafetzopoulos et al. 2018), epilepsy (Hirayasu and Wada 1992; Bertram et al. 2001; Graef et al. 2009; Sloan and Bertram 2009; Wang et al. 2009; Drexel et al. 2011), and schizophrenia (Cohen et al. 1998; Lambe et al. 2007; Lisman et al. 2010; Sigurdson et al. 2010; Lisman 2012; Zhang et al. 2012; Saalman 2014; Duan et al. 2015). In Alzheimer's disease, there is a highly specific pattern of neurofibrillary tangles in RE, a pattern that was consistently restricted to those patients with the most severe symptoms (Braak and Braak 1991). In schizophrenia, theta and delta frequency

abnormalities have been specifically attributed to RE dysfunction (Lisman et al. 2010; Lisman 2012; Duan et al. 2015), and the massa intermedia (or interthalamic adhesion) has been frequently reported as absent, or shorter/smaller in schizophrenic patients (e.g., Nopoulos et al. 2001; Ceyhan et al. 2008; Takahashi et al. 2008; Trzesniak et al. 2011, 2012; Landin-Romero et al. 2016). In epilepsy, the hyperexcitability critical for the generation and/or propagation of hippocampal seizure activity (Ang et al. 2006) has been suggested to be due, in part, to the loss of RE-induced feedforward inhibition targeting CA1 (Dolleman-van der Weel et al. 1997, 2017; Dolleman-van der Weel and Witter 2000). This would reflect a RE-HC circuit failure that facilitates a transition from a normal, to a hyperactive, HC-EC loop in limbic epilepsy (Stefan and Lopes da Silva 2013). Altogether these, and other studies, make it very clear that a detailed understanding of RE will importantly shed light on a variety of neurocognitive disorders and in particular why RE dysfunction can be such a detrimental pathological insult.

## Conclusions

The mPFC-RE-HC system, and its complex circuits, are central to memory and executive functions. HC function is needed for people to remember episodes, and selective CA1 lesions cause amnesia (Rempel-Clower et al. 1996). PFC damage does not cause amnesia, but impairs the flexible use of memory especially when recent episodes interfere with one another (Postle 2006). Integrating mPFC and HC requires RE. Although a rich body of anatomical, physiological, and behavioral work has been conducted on RE, the data on RE are far from complete. It has become increasingly clear that gating the flow of information through CA1 involves highly complex interactions between RE- and EC-mediated excitatory/inhibitory mechanisms, which require further testing. Additionally, the representations and functions of the HC → mPFC → RE → HC loop appear central to RE function, but few studies have been conducted observing part or all of the loop. Lastly, the role of RE in cognition and behavior likely depends on the activity of specific mPFC-RE-HC pathways and the RE subregion (e.g., rostral/caudal, RE/periRE) most involved. Thus, future studies on RE will benefit greatly from current advances in genetic and circuit manipulation tools (e.g., optogenetics and DREADDs) that are able to provide the level of specificity needed to rigorously examine detailed aspects of RE circuitry.

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