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ABSTRACT

The consolidation of declarative memories is believed to occur mostly during sleep and involves a dialogue Episodic memory between two brain regions, the hippocampus and the medial prefrontal cortex. The information encoded during experience by neuronal assemblies is replayed during sleep leading to the progressive strengthening and integration of the memory trace in the prefrontal cortex. The gradual transfer of information from the hippocampus to the medial prefrontal cortex for long-term storage requires the synchronization of cortico-hippocampal networks by different oscillations, like ripples, spindles, and slow oscillations. Recent studies suggest the involvement of a third partner, the nucleus reuniens, in memory consolidation. Its bidirectional connections with the hippocampus and medial prefrontal cortex place the reuniens in a key position to relay information between the two structures. Indeed, many topical works reveal the original role that the nucleus reuniens occupies in different recent and remote memories consolidation. This review aimed to examine these contributions, as well as its functional embedment in this complex memory network, and provide some insights on the possible mechanisms.

Keywords: *Nucleus reuniens; Hippocampus; Prefrontal cortex; Oscillation; Cortico-hippocampal dialogue; Cell assemblies; System-level consolidation*

Abbreviations: ACC, anterior cingulate cortex; AGm, medial agranular cortex; AMY, amygdala; CA1, region CA1 of the hippocampus; CA3, region CA3 of the hippocampus; DG, dentate gyrus; EC, entorhinal cortex; fMRI, functional magnetic resonance imaging; HPC, hippocampus; IEG, immediate early gene; IL, infralimbic cortex; LFP, local field potential; LTD, long-term depression; LTP, long-term potentiation; mPFC, medial prefrontal cortex; MRI, magnetic resonance imaging; NMDA, N-methyl-D-aspartate; NR, nucleus reuniens; PL, prelimbic cortex; Rh, rhomboid nucleus; SO, slow oscillations; SWS, slow-wave sleep; TRN, thalamic reticular nucleus; vHPC, ventral hippocampus.

1. Introduction

All living organisms can store information or memories after interacting with their environment. Such memories can take multiple forms, including phosphorylation processes, epigenetic modifications, and synaptic modifications, at the DNA, molecular, and circuit levels. Memories are essential for survival and define the identity of any uni- and multi-cellular organism. Understanding how information is stored and retained over time is a central question. Following early experimental psychology and neurology works (Ebbinghaus, 1885; Lashley, 1921, 1950; Müller and Pilzecker, 1900; Scoville and Milner, 1957), memory functions have been divided into three major processes: encoding, consolidation, and retrieval. Yet, different memory types and systems can be distinguished. How, when, and where memory processing occurs remains unclear. The conceptual framework commonly used is that the encoding of novel information corresponds to the formation of a representation, which is translated into a new memory trace. The perception of a stimulus would be stored into a neuronal representation, called "engram" (Semon, 1904). This initial engram is assumed to be fragile and prone to decay. Memory consolidation would transform the labile memory trace into a more stable and long-lasting representation (Müller and Pilzecker, 1900). Then, in an appropriate environmental context, the memory trace would be accessed and reactivated, which is the retrieval of the information. The focus of this review is on memory consolidation. Although this process relies on a critical dialogue between the hippocampus (HPC) and the medial prefrontal cortex (mPFC) (Frankland and Bontempi, 2005), recent evidence indicates that the nonspecific thalamus is a key partner.

In particular, the nucleus reuniens (NR) is bidirectionally connected to the hippocampus and medial prefrontal cortex and, as such, holds a key position to regulate cortico-hippocampal interactions (Cassel et al., 2013; Cassel et al.,

2020; Dolleman-van der Weel et al., 2019). We will first introduce the main theories on memory consolidation and the structures involved in this process, with an emphasis on episodic memory, where the hippocampus and medial prefrontal cortex have well-established roles in recent (few hours to few days) and remote (several days to weeks and months in laboratory animal models, and years and decades in humans) memory. The functional basis of their dialogue will be described to better understand how episodic memories are consolidated over time. In a second part, we will highlight the privileged position of the NR as an anatomical and functional relay between the HPC and mPFC and place its role in perspective as part of a larger network. We will examine NR participation in different types of recent and remote memory processing and finally report what has been shown, so far, regarding how the NR regulates cortico-hippocampal interactions.

2. About system-level consolidation

2.1. Generalities

The consolidation of memories, a term first adopted by Müller and Pilzecker to describe post-experience processes of memory stabilization, refers to the initially encoded information which is labile and must be transformed into a more permanent, stable, and long-lasting form (Lechner et al., 1999; Müller and Pilzecker, 1900). This memory trace, called the engram by Semon (1904), corresponds to all the necessary biophysical and biochemical modifications allowing the persistence of the information. Consolidation is generally described at two levels: (i) the cellular/synaptic level, which is the post-encoding transformation of information into a long-term form at local synaptic and cellular nodes in the network encoding the memory, and (ii) the system level, which is the post-encoding gradual reorganization of the distributed brain circuits supporting the memory.

We will refer here to the consolidation of events associated with a specific spatial and temporal context, i.e. the consolidation of episodic memories.

Historically, the system-level consolidation involves an interplay between the HPC and the cortex. It was initially defined as the process by which memory becomes independent of the HPC (Dash et al., 2004), but both human and animal data led to the emergence of different theories of consolidation. First, the ***standard two-stage model*** of consolidation has been proposed by Marr (1971) and assumes that memories are initially stored in the HPC and then gradually transferred to the neocortex for long-term storage. This reorganization process depends on repeated reactivations of waking patterns of neuronal activity during "off-line" periods like sleep. The information initially encoded in the HPC and other specialized cortical areas is replayed, leading to the strengthening of cortical circuits and the integration of the new memory in the cortex. According to this model, the new memory trace becomes independent of the HPC. The HPC is considered as a "temporary" memory system (Klinzing et al., 2019; Squire, 1992; Squire and Alvarez, 1995). This standard model of consolidation commonly applies to declarative memory, which includes the memory of events (episodic memory) associated with a spatiotemporal context and the memory of facts and overall knowledge (semantic memory). Second, the ***multiple-trace theory*** states that semantic information is stored independently of its context, respectively, in the cortex and HPC. Each reactivation of a memory generates an additional trace in the HPC and facilitates the neocortical extraction of abstract, factual information. The retrieval of a rich episodic memory will always require the HPC (Moscovitch et al., 2016; Nadel and Moscovitch, 1997). The ***transformation theory*** claims that the two aforementioned types of memory traces co-exist and dynamically interact for the recall (Dudai et al., 2015). The circumstances of the retrieval will determine which of these memories is evoked (Winocur et al., 2010).

While the transient role of the HPC is debated, these theories agree that cortical plasticity is essential for long-term storage and depends on ***cortico-hippocampal interactions*** (Frankland and Bontempi, 2005). It is also sensible to expect that such interaction might vary in time, intensity, or nature according to the type of information considered (like its salience or its spatial, emotional nature), and at which stage (recent *vs.* remote) the memory is tested. These features also seem sufficient to support the existence of different consolidation theories.

Among the cortical regions, the mPFC has been shown in humans and animal models as a key partner of the HPC in memory function (see Eichenbaum (2017) for review). The hippocampal-prefrontal pathway is therefore considered as a privileged route to transfer the information from the HPC to mPFC for its long-term storage. *2.2. From the hippocampus to the medial prefrontal cortex*

2.2.1. The hippocampal-prefrontal pathway

Studies in humans and animal models have long shown that hippocampal-prefrontal circuits support episodic memories over time. The hippocampal-prefrontal pathway, which is functional as soon as the first postnatal week (Brockmann et al., 2011; Cassel et al., 2020), is believed to be an essential component of a unique memory system allowing, notably, cortico-hippocampal interaction for long-term storage (Eichenbaum, 2017).

In humans, the HPC extends through a posterior-anterior axis corresponding to a dorso-ventral axis in rodents (Strange et al., 2014). The dorsal, ventral, and intermediate parts of the HPC have been distinguished and associated with specific connectivity patterns (Fanselow and Dong, 2010). However, such differences appear to be more gradual than absolute (Strange et al., 2014). The ventral hippocampal CA1 region strongly projects to the mPFC, whereas the intermediate and the dorsal parts only send moderate and no projections, respectively (Cenquizca and Swanson, 2007; Jay and Witter, 1991; Swanson, 1981). In rodents, the mPFC is commonly divided into four parts along the dorso-ventral axis: the medial agranular cortex (AGm), the anterior cingulate cortex (ACC), the prelimbic cortex (PL), and the infralimbic cortex (IL). The dorsal mPFC (AGm and ACC) mainly receives inputs from sensorimotor areas, whereas limbic structures predominantly target the ventral mPFC (IL and PL) (Heidbreder and Groenewegen, 2003; Hoover and Vertes, 2007). Thus, each of these regions receives a unique combination of inputs (See Cassel et al. (2020) Fig. 1 in this special issue).

Several studies report that the ventral HPC (vHPC, from CA1/subiculum) massively projects to the mPFC but with a higher density in IL and PL cortices (Hoover and Vertes, 2007; Jay and Witter, 1991; Swanson, 1981). This connection constitutes the most direct communication path from the HPC to the mPFC. Hippocampal fibers form asymmetric synapses on mPFC pyramidal neurons (Carr and Sesack, 1996) but also project on interneurons (Gabbott et al., 2002). The vHPC inputs innervate cells in both superficial and deep layers of IL, but only the deep layers of PL (Liu and Carter, 2018). Interestingly, these inputs appear to recruit distinct prefrontal neuronal populations, preferentially engaging and driving the activity of IL cortico-cortical neurons, which supports the idea that this pathway preferentially allows the activation of the intra-telencephalic network. Moreover, such a direct pathway can induce long-term potentiation (LTP) (Jay et al., 1995; Laroche et al., 1990). This altogether provides further support for a possible direct transfer of memories (and/or local re-creation of the memory trace) from the HPC to the mPFC and possibly other cortical modules. Surprisingly, whereas the mPFC receives strong monosynaptic inputs from the vHPC, there are no direct projections from the mPFC to the vHPC (Hoover and Vertes, 2007; Jay et al., 1989; Jay and Witter, 1991). Only two cortical pathways involving a single node connect the mPFC back to the HPC: the cortical pathway via the perirhinal cortex and the entorhinal cortex (EC) (Agster and Burwell, 2009; Apergis-Schoute et al., 2006; Burwell and Amaral, 1998; Witter et al., 2000). Moreover, Rajasethupathy et al. (2015) report a monosynaptic connection between the ACC and dorsal HPC CA1 and CA3 fields, providing another route to connect the mPFC to vHPC.

2.2.2. Functional evidence

2.2.2.1. Activity-related reorganization.

The first indications that the HPC is a key node for episodic memory formation came from clinical studies. In the patient Henry Molaison, also known as H.M, the extensive removal of the medial temporal lobe (including bilateral hippocampi, in order to treat a severe refractory epilepsy) induced anterograde amnesia (Scoville and Milner, 1957). He was unable to memorize new facts or events. However, his ability to form non-declarative memories was intact. Even though there have been contradictory results concerning the role of the HPC in all forms of declarative memory (Bayley and Squire, 2005; Tulving and Markowitsch, 1998; Vargha-Khadem et al., 1997), both human and animal studies established that the HPC is crucial for the formation of spatial memory (Burgess et al., 2002; Morris et al., 1982). More importantly, this anterograde amnesia was associated with a temporally graded retrograde amnesia. Indeed, after the surgery, H.M lost his memories over the last 11 years but could remember older memories (Scoville and Milner, 1957), suggesting a time-limited role of the HPC on memory storage and recall. Other lesion-based studies in rodents and humans revealed a similar gradient according to the extent of the lesion, indicating that long-term storage may involve different regions (Anagnostaras et al., 1999; Kirwan et al., 2008; Reed and Squire, 1998; Winocur et al., 2001). Multiple approaches have been used to identify brain regions and circuits supporting the memory trace over time. In an early imaging study, Bontempi et al. (1999) used a spatial discrimination task and observed that hippocampal activity was higher during recent memory retrieval (5 days) than during the remote one (25 days). In contrast, the recruitment of different cortical areas including the ACC was enhanced 25 days after training. Similar results were reported later in the human literature using functional magnetic resonance imaging (fMRI). The mPFC showed an increase of activity correlated with the duration of the retention interval over three months in a recognition memory test, whereas the hippocampal activity decreased over time (Takashima et al., 2006). These results agree with the standard consolidation theory, which suggests a time-dependent spatial reorganization of the memory trace for long-term storage. The mPFC, especially, has been shown to play a crucial role in the retrieval of remote memories. Other studies explored the expression of immediate early genes (IEGs), which are markers of neuronal activation, to identify brain areas supporting long-lasting memories. They observed a significant increase of *c-fos* and *zif268* expression (IEGs) in mPFC during retrieval one month after training, as compared to one day, in a water- and five-arm mazes, which assess spatial memory (Maviel et al., 2004; Teixeira et al., 2006). Consistent with the data provided by the early gene expression, the inactivation of the mPFC right before the memory test blocked the expression of remote (30 day old) spatial memory but not of the recent one (1 day old). In contrast, the recruitment of the HPC during recall appears to be more controversial. While Maviel et al. (2004) observed a significant decrease of *Zif268* expression in the HPC during remote memory testing, Teixeira et al. (2006) reported similar levels of *c-fos* expression during both recent and remote probe tests. Inactivation of the

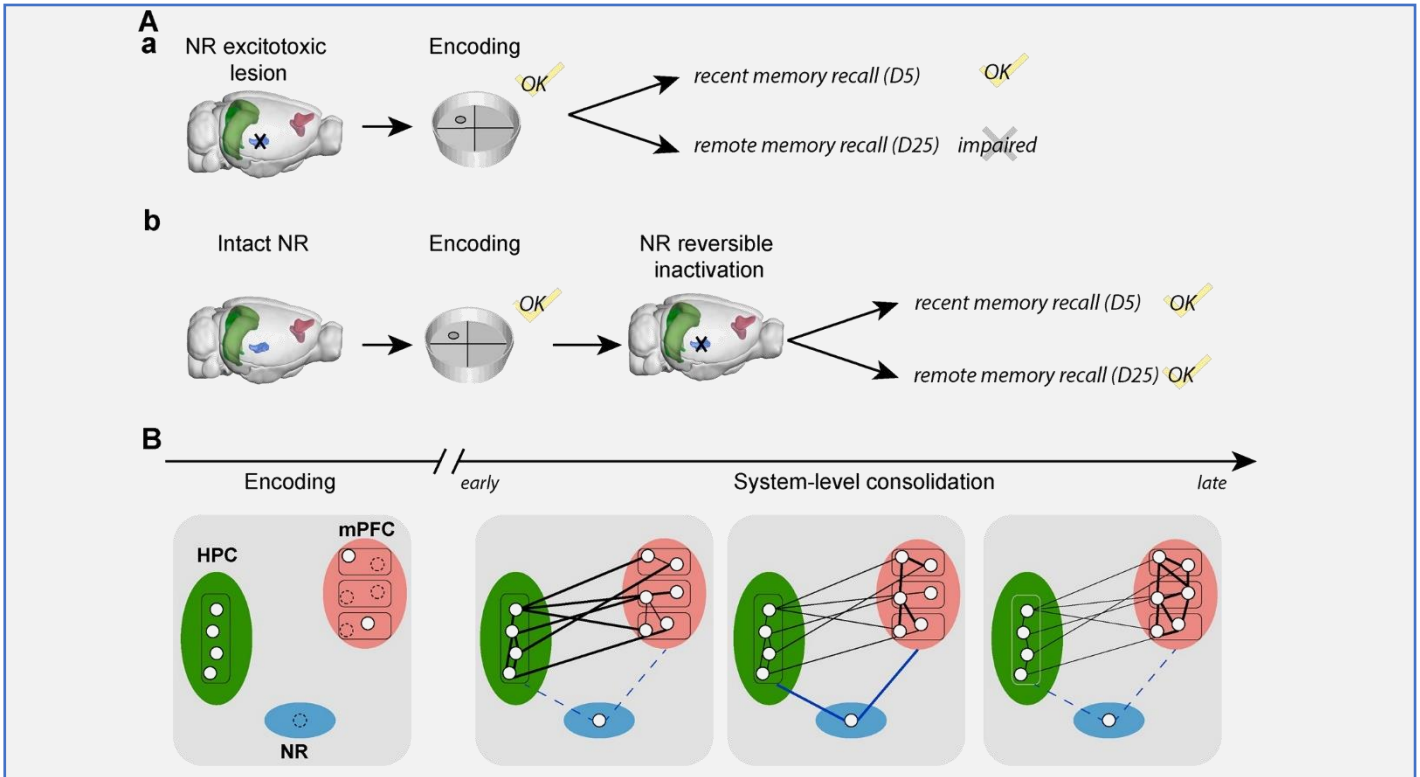

Fig. 1. NR contribution in HPC-mPFC dependent long-term memory consolidation.

A. Graphical abstract depicting how the NR contributes to the system-level consolidation of spatial memory (as shown in Loureiro et al. (2012)).

a. Rats subjected to NR (and Rh) excitotoxic lesions successfully acquired the water-maze task and remembered the location of the hidden platform 5 days later (D5) but showed no evidence of memory retrieval 25 days after learning (D25).

b. Following the drug-free acquisition of the task, reversal NR inactivation right before the memory test did not alter rat memory performance at both post-acquisition delays. These results suggest an involvement of the NR in the long-term consolidation process, and not in the recall of a spatial memory. (The rat brain representations only include IL and PL portions of the mPFC and are adapted from the Allen Institute Atlas).

B. Representation of the putative functional connectivity between HPC, mPFC, and NR from the encoding of spatial information to its long-term imprinting in these networks (modified from Frankland and Bontempi (2005)). Initially, during encoding, cell assemblies are recruited in HPC and mPFC (white circles) but few or none in the NR (dashed circles). With time, the HPC-mPFC dialogue will reinforce the information-relevant cell assemblies, an NR-dependent process. NR would be dynamically engaged until the information is eventually reconstructed in the cortical modules for long-term storage (Klein et al., 2019; Loureiro et al., 2012). The HPC representation of the information might subsist in time (Klein et al., 2019).

HPC disrupted either the recent (Maviel et al., 2004) or both memory performances (Teixeira et al., 2006). Lopez et al. (2012) notably proposed that HPC recruitment during remote memory recall is influenced by the richness and saliency of environmental cues, in line with the multiple-trace theory (Moscovitch et al., 2016; Nadel and Moscovitch, 1997), postulating that the HPC will always be needed to retrieve a rich contextualized memory regardless of the delay.

In contextual fear memory, several studies reported a similar high profile of IEG expression in mPFC during remote memory test while contradictory results were observed in the HPC (Frankland et al., 2004; Graff et al., 2014; Khalaf et al., 2018; Kitamura et al., 2017; Tayler et al., 2013; Wheeler et al., 2013). Interestingly, Silva et al. (2019) reported a differential recruitment of the dorsal *vs*. ventral HPC during fear memory recall at 30 days, as the ventral pole displayed increased *c-fos* levels, but not the dorsal one. Therefore, the role of the HPC in the retrieval of remote memories, as assessed by the expression of early genes, remains debated. The difference in the nature of the memory (spatial *vs*. contextual fear memory) can be a tangible explanation for the discrepancies observed in the HPC involvement at remote time points and would therefore advocate for the different theories of consolidation. In recent work, Tonegawa's group performed brain-wide identification of *c-fos* positive regions holding engrams after a contextual fear memory recall at 1 day (Roy et al., 2019). They elegantly showed that HPC and mPFC, together with a dozen of other regions distributed across the brain, were robustly activated by encoding. Their chemogenetic reactivation could achieve to reproduce partial freezing in mice, hence mimicking the natural memory recall. Many of these engram-holding regions were functionally connected to HPC and/or amygdala (AMY). The authors showed that when multiple regions were reactivated together, the memory recall was greater as compared to single-region reactivation. Such results support the idea of distributed memory traces over the brain, as proposed by the multiple-trace theory of system consolidation (Dudai et al., 2015; Moscovitch et al., 2016; Nadel and Moscovitch, 1997), and open the way to consider even larger networks.

2.2.2.2. Structural reorganization.

The gradual imprint of the information in the neural networks is also accompanied by structural reorganizations, like sprouting and the formation of dendritic spines (Khalaf and Graff, 2016). Memory formation is therefore believed to rely on synaptic plasticity and has been associated with synaptic rearrangements rapidly achieved through an increase of spine density (Leuner et al., 2003; Restivo et al., 2006; Restivo et al., 2009; Vetere et al., 2011). Spatial learning in the water maze is followed by an increase of dendritic spines in the HPC (Moser et al., 1994; O'Malley et al., 2000). Restivo et al. (2009) described a sequential synaptic remodeling in the HPC and ACC during recent and remote memory retrieval, respectively. The authors observed a transient increase of hippocampal spine density when the mice were tested 24 h after contextual fear conditioning, followed by a significant increase in the ACC at a remote time point (36 days post-conditioning). This time-dependent spinogenesis is also observed without memory retrieval tests, implying that these structural changes are not triggered by the retrieval processes themselves, but may reflect consolidation mechanisms. More interestingly, a lesion of HPC directly after conditioning prevents the development of cortical spines and alters remote fear memory suggesting a leading role of the HPC in cortical plasticity. Additionally, Vetere et al. (2011) demonstrated that preventing post-training spinogenesis in the ACC disrupted fear memory consolidation. Altogether these results reveal a gradual reorganization at the spine level, from short- to long-term storage of memories, in a sequential recruitment of hippocampal-cortical circuits. The HPC is progressively disengaged in favor of the mPFC to support long-lasting memories.

However, other studies suggest that the HPC remains crucial for both recent and remote spatial memory retrievals, in line with the multiple- trace theory of system consolidation (Dudai et al., 2015). Indeed, Klein et al. (2019), while describing in rats a similar synaptic remodeling in the HPC and ACC at 5 days and 25 days post-acquisition in the water maze, reported that the increase of mushroom spines in CA1 persisted between the two time points. Interestingly, the HPC synaptic plasticity is associated with an increase of *c-fos* expression at both time points. Coherent with such findings, Lopez et al. (2012) showed that the spatial memory performance at these two post-acquisition times is impaired by the inactivation of the HPC. Kim et al. (2014) notably demonstrated that hippocampal synaptic plasticity is crucial for remote spatial memory recall in both water maze and contextual fear conditioning tasks.

Yet, it is important to note that the latest longitudinal imaging studies performed *in vivo* indicate a very fast turnover of spines in the cortex and HPC. In particular, in the *stratum oriens* of the HPC, where there is a spine turnover of 40 % within 4 days (Pfeiffer et al., 2018). Whether a larger turnover occurs on longer time scales is not known. These results consequently need to be considered in theories proposing that memory is stored in spines.

In conclusion, converging evidence coming from different levels of analysis identifies the HPC and mPFC as crucial regions supporting memories over time. Their interaction appears to be at the core of memory consolidation mechanisms. However, how such dialogue occurs and is regulated to allow time-dependent memory reorganization is still not fully understood.

2.2.3. Prefrontal-hippocampal coupling and memory consolidation

Neural oscillations refer to the rhythmic and/or repetitive electrical activity generated spontaneously and/or in response to stimuli by neural networks. Berger (1929) is generally credited with their discovery since he recorded the first electroencephalogram in humans. They are emergent properties of the neuronal networks (because they depend on network architecture) and are mainly composed of the temporal summation of synaptic currents converging in a volume of brain tissue (Buzsáki et al., 2012). They exist in different frequency bands, according to the brain state in which the individual is engaged (Buzsáki, 2006 ; Buzsáki and Draguhn, 2004). They are, therefore, often considered as a hallmark of network processes. Oscillatory activities within and across structures allow distant neuronal ensembles to interact and are believed to support an effective transfer and storage of information (Buzsáki, 2019). It is currently assumed that the consolidation of memories is mainly achieved through the hippocampal–neocortical interface at particular moments of the sleep-wake cycle, mainly during slow-wave sleep (SWS) (Born et al., 2006; Buzsáki, 1998 ; Diekelmann and Born, 2010; Gais et al., 2007; Langille, 2019; Maingret et al., 2016; Rothschild et al., 2016; Tononi and Cirelli, 2014). The various oscillatory activities interact at different timescales between the HPC and mPFC. They, therefore, provide windows of opportunity for a fine tuning of neuronal ensembles, allowing the reactivation of the cell assemblies (i.e., a group of neurons coactivated repeatedly for a given brain operation and thus representing a distinct entity embedded within neuronal networks) coding for the information to store (Buzsáki, 2019; Buzsáki, 2010 ; Hebb, 1949). Such an impact on neuronal ensembles in HPC and mPFC and interaction between the various oscillations is one of the hallmarks of the cortico-hippocampal dialogue.

During SWS, brain activity is dominated by slow oscillations (SO, 0.5– 4 Hz). SO provide an optimal time window to synchronize and recruit distant neuronal populations. They orchestrate faster cortical rhythms, such as spindles (10– 15 Hz) and ripples (80– 200 Hz), which have been linked to memory consolidation in both human and animal studies (Cowan et al., 2020; Gais et al., 2002; Girardeau et al., 2009; Maingret et al., 2016; Ngo et al., 2020; Tamminen et al., 2013). Hippocampal sharp-wave ripples (SPW-Rs) are considered as a key actor in memory consolidation. Several studies found that the disruption of SPW-Rs during sleep, after spatial training, impairs the subsequent performance in test conditions (Ego-Stengel and Wilson, 2010; Girardeau et al., 2009). More importantly, neuronal patterns activated during learning are replayed during sleep SPW-Rs (Buzsáki, 2015 ; Lee and Wilson, 2002; Nadasdy et al., 1999). The replay of entire sequences

of place cells activity during SPW-Rs has been demonstrated in numerous studies. These sequences are replayed at a faster timescale, with a 10– 20-fold factor as compared to their "on-line" activation (i.e., during behavior) (Buzsáki, 2015 ; Lee and Wilson, 2002; Nadasdy et al., 1999). These time-compressed sequences have been proposed to trigger synaptic plasticity mechanisms in target structures and thus to mediate information transfer. Dupret et al. (2010) designed a spatial memory task and observed that goal-related hippocampal activity is replayed during SPW-Rs. The more a goal location was reactivated during sleep SPW-Rs, the better the rat remembered it. Such a hippocampal replay of activity during sleep is assumed to drive memory consolidation processes through the reinstatement of neuronal activity patterns in cortical networks. This reactivation is thought to promote the gradual stabilization of the memory trace in the cortex. Replay of time-compressed sequences in the mPFC has been observed during sleep following behavior (Euston et al., 2007; Peyrache et al., 2009), and they have been hypothesized to reflect consolidation mechanisms both in animal models and human (Buzsáki, 2015; Liu et al., 2019; Zhang et al., 2018). The mPFC receives direct projections from the HPC (Hoover and Vertes, 2007; Jay et al., 1989; Swanson, 1981) and, as such, could be influenced by the strong hippocampal drive occurring during SPW-Rs. Wierzynski et al. (2009) demonstrated that some mPFC neurons consistently fire either ~10 or 100 ms after hippocampal SPW-Rs, a timescale relevant for synaptic plasticity mechanisms. To go further, Peyrache et al. (2009) trained rats on a Y maze and observed the reactivation of task-related firing patterns in the mPFC during sleep following the learning of a new rule. Most importantly, such replay closely followed hippocampal SPW-Rs with a ~ 40 ms delay, consistent with the idea that SPW-Rs led to the reactivation of neocortical assemblies during sleep. Furthermore, hippocampal SPW-Rs and thalamocortical spindles are modulated by SO and temporally coupled to each other (Amzica and Steriade, 1997; Maingret et al., 2016; Peyrache et al., 2011; Siapas and Wilson, 1998; Sirota et al., 2003; Varela and Wilson, 2020). Siapas and Wilson (1998) were the first to observe that SPW-Rs tend to precede spindles within a 1–2 second interval. Later, Maingret et al. (2016) reported that delta-spindle sequences tend to follow SPW-Rs with a ~ 140 ms delay. On a finer timescale, both human and rodents' studies, report the occurrence of SPW-Rs nested in spindle cycle (Clemens et al., 2011; Phillips et al., 2012; Sirota et al., 2003; Staresina et al., 2015). The role of such coupling in memory consolidation has been investigated in different studies (see Todorova and Zugaro (2018) for review). Maingret et al. (2016) have notably observed that cortico-hippocampal coupling is enhanced in sleep during memory consolidation. They developed a stimulation protocol to reinforce the endogenous coupling between SPW-Rs and delta spindle events. Rats were trained in a spatial memory task to be tested 24 h later for recall. The authors showed that following stimulation, rats exhibited a higher recall performance, suggesting that such fine temporal coupling promotes memory consolidation. Likewise, Novitskaya et al. (2016) disrupted ripple-spindle coupling through the high-frequency stimulation of the locus coeruleus at the time of SPW-Rs. Rats were trained on a radial maze, and stimulation was applied during rest after each daily training session, abolishing during 1 h the co-occurrence of SPW-Rs and spindles. The authors showed that such protocol resulted in a strong memory deficit. Similarly, Latchoumane et al. (2017) applied a closed-loop optogenetic stimulation in the thalamic reticular nucleus (TRN; see section 3.1.5 for more details on TRN) to induce spindles in mice during sleep after contextual fear conditioning. The stimulation was triggered by the online detection of the SO during either the UP or DOWN states. The authors demonstrated that the induction of spindle phase-locked to the slow oscillation UP states not only increased the triple coupling between SO, ripples, and spindles but also improved the memory performance of mice. It is also worth noting that the induction of spindles during the DOWN state had no behavioral effect suggesting that spindles *per se* do not influence memory consolidation.

Unfortunately, the functional cortico-hippocampal dialogue associated with memory consolidation has only been so far investigated for a recent memory (as 1-day old memory), and there is to date no dynamical description of such electrophysiological coupling for a remote memory. As described in section 2.2.2., the time-dependent involvement of the HPC and mPFC in recent *vs.* remote memory (and differential involvement of the HPC according to the nature of the information to be consolidated) brings many questions on a potential impact on the cortico-hippocampal dialogue in the time course of the consolidation of a memory at the systemic level. It appears, therefore, important to determine in the future whether this dialogue evolves or changes through the long process of consolidation.

3. The nucleus reuniens a key partner in memory consolidation

The NR belongs to the so-called nonspecific thalamus, which is distinguished from the sensory (and specific) thalamus on the basis of neuroanatomical arguments (Pereira de Vasconcelos and Cassel, 2015; Vertes et al., 2015). It is a midline thalamic nucleus that has received considerable attention over the last decade due to its reciprocal connections with the HPC and mPFC. A growing body of evidence points at the NR as a critical structure involved in various cognitive and memory processes (Cassel et al., 2013; Cassel et al., 2020; Dolleman-van der Weel et al., 2019). The NR appears to be one of the key structures underlying system-level memory consolidation (Ali et al., 2017; Klein et al., 2019; Loureiro et al., 2012; Quet et al., 2020b). Its central position at the interface between the HPC and mPFC makes it an ideal partner to regulate cortico-hippocampal interactions during memory consolidation (Frankland and Bontempi, 2005). Located just above the third ventricle, the NR is often associated with the rhomboid nucleus (Rh), which lies on top of it (see (Cassel et al., 2020) for more details information on Rh). NR has been intensively studied in rodents but has been identified in other species, including monkeys, cats, ferrets, and humans, even if thalamic nuclei delimitation is still a topic of debate (Amaral and Cowan, 1980; Aronson, 1934; DeVito, 1980; Herbert, 1963; Herkenham, 1978; Hirai and Jones, 1989; Insausti et al., 1987; Room and Groenewegen, 1986; Scheel et al., 2020; Toncray and Krieg, 1946; Yanagihara et al., 1985). Yet, human functional data about the NR are sparse and difficult to obtain (see Cassel et al. (2020) section 5 in this special issue). Its small size associated with methodological limitations makes the exploration of NR functions in humans particularly difficult. In this section, we will describe in rodents, the specific connectivity and physiological properties of this cortico-thalamo-hippocampal circuit to better understand how the NR may influence HPC and mPFC activity. Then, we will summarize data from the literature outlining the implication of the NR in the systemic consolidation of different types of memories and study how it orchestrates the dialogue between the HPC and mPFC.

3.1. The HPC-mPFC- NR circuit

3.1.1. Neurochemical and electrophysiological properties of NR neurons

Few studies have explored the NR's physiological and neurochemical properties. Walsh et al. (2017) were the first to characterize *in vitro* the intrinsic electrophysiological properties of NR neurons in mice. At rest, most of NR neurons spontaneously fire around 8 Hz (see Cassel et al. (2020) sections 3.1. and 5. in this special issue for more detailed information). The authors revealed that NR neurons exhibit highly atypical features for thalamic relay neurons. NR neurons, in contrast to other thalamic nuclei, do not seem to express HCN (hyperpolarization-activated cyclic nucleotide) channels which, in thalamocortical neurons, contribute to the membrane resting potential and are essential to the emergence of rhythmic activity (McCormick and Pape, 1990; Meuth et al., 2006; Pape, 1996). However, the authors noted that the presence of low-threshold T-type Ca^{2+} channels (CaV3) in the NR plays a role in the generation of high-frequency firing activity. Zimmerman and Grace (2018) report in anesthetized rats a mixed tonic and burst firing pattern of NR neurons, with >80 % of them burst firing. If the large majority of the neurons (>75 %) exhibit a firing rate at or below 3.0 Hz, the firing rates can reach 12 Hz in baseline condition.

From a neurochemical perspective, different neuronal populations have been identified based on the differential expression of calcium- binding proteins (Bokor et al., 2002). NR neurons do not express parvalbumin but only calbindin and/or calretinin proteins, which allow the distinction between "core" (parvalbumin-positive) and "matrix" (calbindin-positive) thalamic relay cells (Arai et al., 1994; Bokor et al., 2002; Jones, 1998; Winsky et al., 1992) (see Cassel et al. (2020) section 2.4, this issue). In the thalamus, matrix and core cells display different patterns of connectivity; the former widely project to superficial cortical layers while the latter project to the middle layers of more restricted areas (Jones, 2001). Therefore, the NR only contains thalamocortical matrix cells, which notably project in the first layer of the mPFC. Furthermore, Bokor et al. (2002) demonstrated the presence of aspartatergic/glutamatergic neurons in the NR projecting to the HPC. Nearly all of them appear to be calbindin-positive, and two-thirds of these projections also express calretinin. Similarly, Hur and Zaborszky (2005) used *in situ* hybridization techniques to reveal the location of Vlglut2 (vesicular glutamate transporter 2) neurons and identified glutamatergic projections from the NR to the mPFC. More recently, dopaminergic neurons were found in the NR (Ogundele et al., 2017). Using confocal imaging techniques, the authors showed in mice that most of these neurons were bipolar and characterized by an angulated cell body. While there is no evidence of the presence of inhibitory interneurons in the NR (Ottersen and Storm-Mathisen, 1984), it is noteworthy that the Blue Brain Cell Atlas reports 4153 ± 444 inhibitory NR (referred as the nucleus "reunions" in the atlas) neurons (https://bbp.epfl.ch/nexus/ce ll-atlas/; Ero et al. (2018)¨). This 3D mouse brain cell atlas was constructed based on Nissl microscopy dataset and genetic marker staining data from the Allen Institute for Brain Science. Yet, the GAD67 *in situ* hybridization experiments shared by the institute do not indicate any presence of inhibitory neurons in the NR (Lein et al. (2007), https://m ouse.brain-map.org/). Moreover, immunostaining for different neuropeptides (SOM, CCK, NPY, L-Enk, SP, CGRP, and VIP), which are often found in GABAergic neurons, was also performed and revealed no labeling in the NR (Bokor et al., 2002). Therefore, a further examination of the neurochemical content of NR neurons is mandatory to get a better grasp on NR function and to provide new targets for selective manipulation of its neurons.

3.1.2. NR – HPC functional connectivity

The NR constitutes the major source of thalamic inputs to the HPC. It selectively sends projections to CA1 in the *stratum lacunosum-moleculare*, as well as in the molecular layer of the subiculum, without targeting CA2, CA3, or the DG (Vertes et al., 2006). NR fibers form excitatory asymmetric synapses on both pyramidal cells (Wouterlood et al., 1990) and interneuron dendrites present in this layer (Dolleman-Van der Weel and Witter, 2000). Although NR projections extend through the entire dorso-ventral axis of the HPC, they preferentially project to the ventral part of CA1 and modulate CA1 excitability (Dolleman-Van der Weel et al., 1997; Hoover and Vertes, 2012). NR electrical stimulation results in a large negative deflection in the *stratum lacunosum-moleculare* associated to a positive one in the *stratum radiatum*, coherent with a (subthreshold) depolarization of pyramidal cell apical dendrites (Dolleman-Van der Weel et al., 1997). Interestingly, NR-evoked responses exhibit both monosynaptic and disynaptic latencies, according to the rostral or caudal stimulation of the NR, respectively. The authors hypothesized that the disynaptic response observed in CA1 reflects the intrinsic NR connectivity between its rostral and caudal poles. The authors confirmed the existence of a caudal neuronal population projecting to the rostral part of the NR and proposed it as the anatomical substrate underlying the disynaptic response. Most importantly, NR stimulation is unable to induce pyramidal cell discharge, whereas extracellular spikes are recorded in the *oriens/alveus* and *radiatum*, which likely indicates the activation of local interneurons. In contrast, Bertram and Zhang (1999) demonstrated that the NR exerts a strong excitatory action on CA1, able to evoke population spikes like those observed following CA3 stimulation. In some cases, it even induces a stronger effect than CA3 with the induction of LTP in CA1. Thus, this thalamic-hippocampal pathway can directly control the activity of the CA1 network. In return, the subiculum and vHPC (CA1) densely project to the NR (McKenna and Vertes, 2004).

3.1.3. NR – mPFC functional connectivity

The NR strongly innervates the mPFC, targeting predominantly its ventral part (IL, PL) rather than the dorsal one (AC, AGm) in layer 1 and 5/6 (Vertes, 2006). In accordance with this anatomical pathway, (Di Prisco and Vertes, 2006) demonstrated that NR stimulation elicits a large monosynaptic response in mPFC but with a larger amplitude in the IL and PL cortices. Similarly, paired-pulse stimulation produced a stronger facilitation effect in these two subregions, comparable to the one observed in HPC. Besides, Eleore et al. (2011) also showed that paired-pulse stimulation of the mPFC induces a potentiation in NR. Additionally, Cruikshank et al. (2012) used optogenetics to selectively activate matrix thalamocortical neurons, including NR cells, projecting to the first layer of the mPFC and showed that their activation drives a fast and robust postsynaptic response in layer 1 interneurons but also in pyramidal cells of layers 2/3, which extend their dendrites into the superficial layer. In some cases, such activation even triggered action potentials in postsynaptic neurons. More recently, Banks et al. (2020) reported that NR inputs to layers 2/3 and layer 5 prelimbic pyramidal neurons demonstrate a strong short-term depression in the theta band (5 or 10 Hz). Noteworthy is the fact that NR neurons spontaneously fire in this frequency range (Walsh et al., 2017). In return, the NR receives projections from layers 2/3, 5 and 6 prefrontal neurons (Jayachandran et al., 2019; Mathiasen et al., 2019; McKenna and Vertes, 2004; Vertes, 2002). Interestingly, Zimmerman and Grace (2018) used a chemogenetic approach to specifically inhibit IL terminals in the NR in anesthetized rats and observed a significant increase of NR neurons burst firing activity without changes in the number of spikes per burst, indicating a possible tonic control of NR activity by mPFC neurons.

3.1.4. The HPC-mPFC-NR network

Further anatomical data demonstrate that the architecture of the HPC-mPFC-NR pathway allows complex within-circuit communication. Vertes et al. (2007) demonstrated that mPFC fibers make excitatory synapses on NR neurons that project to the HPC. Similarly, a high proportion of prefrontal layer 5 pyramidal cells receive convergent inputs from the NR and HPC (Banks et al., 2020). The authors show that the action potential-threshold of prefrontal neurons receiving only HPC inputs is more hyperpolarized than those of neurons receiving either NR or NR/HPC inputs. These neurons also display a larger percentage of I_h-mediated sag current, which is a hyperpolarization-activated depolarizing current contributing to burst firing, as compared to the others and a lower input resistance than neurons receiving both NR and HPC inputs. The authors used a 5 Hz pairing stimulation protocol of both NR and HPC afferents to determine whether these inputs interact to induce synaptic plasticity. The results revealed that it induced an associative, NMDA receptor-dependent, long-term depression (LTD) in both inputs to mPFC. Interestingly, LTD was only produced when (1) HPC fibers stimulation precedes the NR one with a 10 ms lag (not with the reverse order) and (2) at – 50 mV and not at resting membrane potential (-70 mV). Therefore, these results suggest that the NR may control the salience of the HPC signal in a specific time window. Furthermore, a small proportion of NR neurons (3–9 %) send axonal collaterals to both HPC and mPFC (Hoover and Vertes, 2012; Varela et al., 2014). These neurons, as well as those strictly projecting on mPFC or HPC, while being present throughout the NR, are more concentrated in particular subregions. Prefrontal-projecting neurons are preferentially located in caudal NR and lateral wings, whereas the hippocampal-projecting ones are more rostral. In comparison, double projecting neurons are concentrated along the midline and in the lateral one-third of the NR. Therefore, the NR holds a key position to relay information between the HPC and mPFC. Its inactivation notably prevents the induction of LTP in the CA1-AC pathway (Sierra et al., 2017). More recently, Hauer et al. (2019) demonstrated that its chemogenetic inhibition

abolished the hippocampal response evoked by mPFC stimulation, indicating that the NR is a crucial node relaying information between these two structures.

3.1.5. Modulation of the HPC-mPFC-NR network

While assessing the function of the HPC-mPFC-NR network, one needs to keep in mind that other brain regions' activity might heavily contribute to the functioning of this network.

For instance, the NR projects to EC which also connect the HPC (Vertes et al., 2006; Witter et al., 1988) and interestingly, EC projections to CA1 are overlapping NR ones (Dolleman-Van Der Weel and Witter, 1996; Herkenham, 1978; Wouterlood et al., 1990). It has been shown that both NR and EC inputs modulate hippocampal excitability by targeting both principal cells and GABAergic neurons, and the combined activation induces facilitation in CA1 (Dolleman-van der Weel et al., 2017; Vu et al., 2020; Zhang and Bertram, 2002). It is thus imperative to determine if those inputs occur simultaneously, and if so, when does it happens. Dolleman-van der Weel et al. (2017) showed that coinciding low-frequency activation of the NR and EC inputs caused high excitation of the CA1 cell apical dendrites in *lacunosum moleculare*, which could occur during low-frequency oscillatory states such as SWS or immobility. A potential source for a simultaneous triggering of both EC and NR pathways to the HPC could be the mPFC, which is at one synapse away from both the EC and NR (Agster and Burwell, 2009; Apergis-Schoute et al., 2006; Burwell and Amaral, 1998; McKenna and Vertes, 2004; Vertes, 2006; Witter et al., 2000). The firing of mPFC, NR, and EC neurons being well entrained by SO (Clawson et al., 2019; Ferraris et al., 2018; Hauer et al., 2019; Isomura et al., 2006; Sirota and Buzsáki, 2005), such a network mechanism appears well suited to gate synchronized inputs to HPC during SWS-like states, in which consolidation is supposed to occur and shape the HPC-mPFC dialogue.

Another node to consider is the AMY, which is reciprocally connected to the NR, mPFC, and HPC (Gabbott et al., 2002; Herkenham, 1978; Hoover and Vertes, 2007; McKenna and Vertes, 2004; Petrovich et al., 2001; Pitkanen et al., 2006¨). Such a complex interaction might actively modulate the HPC-mPFC-NR network (Ali et al., 2017). AMY has already been shown to modify the storing of HPC-dependent memories (McIntyre et al., 2012; McIntyre et al., 2003). Here again, the nature of such control's dynamics remains to be determined.

Zimmerman and Grace (2018) report that mPFC and the TRN input can control the firing parameters of NR neurons in a complex manner. TRN provides a powerful feed-forward inhibition driven by the cortex (Crandall et al., 2015; Halassa et al., 2014) and also connects the NR (Cavdar et al., 2008; Kolmac and Mitrofanis, 1997; McKenna and Vertes, 2004). Pharmacological inhibition of the IL portion of the mPFC in anesthetized rats reduces the bursting of NR neurons without affecting their mean firing rate, and TRN inhibition reduces the number of spontaneously active neurons in NR. However, the chemogenetic inhibition of IL terminals in the NR produces an enhancement of burst firing in a subset of NR neurons. The electrical stimulation of IL instead reduces the tonic firing and promotes burst firing, and repeated stimulations completely silence 75 % of NR neurons. Such modulation of neuron firing could profoundly influence how NR impacts its target neurons, both in HPC and mPFC. It is interesting to note that the HPC connects the rostral part of the TRN that connects the NR (Cavdar et al., 2008). The TRN participates to the generation of SO; its inhibitory neurons evoke inhibitory post-synaptic potentials and rebound bursting in cells of the dorsal thalamus, which then entrain their postsynaptic targets in the neocortex (Amzica and Steriade, 1995; Contreras and Steriade, 1995; Neske, 2015; Steriade et al., 1993a; Steriade et al., 1993b; Steriade et al., 1993c; Timofeev and Steriade, 1996). This subnetwork represents, therefore, another way to moderate the cortico-thalamic-hippocampal dialogue, particularly during SWS-like states.

3.2. NR and spatial memory consolidation

The role of the NR in memory consolidation has been investigated in a few studies using different behavioral paradigms (reviewed in Cassel et al. (2013)). Loureiro et al. (2012) used the water maze to assess the role of the NR in spatial memory with different approaches combining permanent pharmacological lesions, reversible inactivation, and IEG expression. Naïve non-operated rats were trained for six days to learn the location of a platform and were then tested either 5 or 25 days after training. During the retrieval, control rats displayed a significant increase of *c-fos* activity in the NR (but also in the Rh) but only at a 25-day delay, suggesting a specific involvement of the NR in remote rather than recent spatial memory. A second experiment using excitotoxic NMDA lesions showed that while NR lesions did not impact the learning or recent memory recall (5 days post-acquisition), the memory performance was impaired 25 days after training. However, such a deficit could reflect an alteration of either long-term consolidation processes or retrieval mechanisms (Fig. 1Aa). To distinguish between the two possibilities, the authors inactivated (lidocaine injection) the NR just before the recent and remote memory tests. The reversible inactivation of the NR had no impact on memory performance independently of the delay (Fig. 1Ab). Thus, the NR seems to participate in the formation of long-lasting memories rather than in information retrieval. These results suggest that a lesion of the NR disrupts system-level consolidation processes, which allow the persistence of a recently acquired memory over time, probably by an alteration of the dialogue between the HPC and mPFC (Fig. 1B). This proposal is reinforced by recent data showing that NR lesions interfered with prefrontal-hippocampal synaptic connectivity (Klein et al., 2019). As described in section 2.2.2.2, spatial training in the water maze triggers in sham rats (1) a persistent increase of spine density in the HPC between 5 days and 25 days after learning (2) and a dramatic increase in the number of spines in the mPFC only at the remote time point. An excitotoxic lesion of the NR prevented not only the maintenance of hippocampal spines over time but also the cortical spinogenesis 25 days post-acquisition. Moreover, the activation (*c-fos* imaging) of the ACC at the remote time-point was reduced in lesioned rats. Altogether these findings support the idea that the NR is required to the formation of remote memories, as its integrity is necessary to the synaptic remodeling underlying system-level consolidation between the HPC and mPFC (Fig. 1B). Yet, this HPC-mPFC-NR circuit does not exist *per se*, i.e., as an independent entity in the brain. Even though the NR activity appears to be necessary for memory consolidation, this process probably involves interaction with other structures. Ali et al. (2017) notably demonstrated that NR lesion not only reduced prefrontal *c-fos* expression during remote memory retrieval but is also associated with a significant increase of *c-fos* expression in the AMY under baseline condition (no memory). The AMY shares reciprocal connections with the NR, mPFC, and HPC (Gabbott et al., 2002; Herkenham, 1978; Hoover and Vertes, 2007; McKenna and Vertes, 2004; Petrovich et al., 2001; Pitkanen et al., 2006¨). Therefore, it is plausible that its lesion-induced hyperactivity may also contribute to altering either directly or indirectly consolidation processes. In addition, the authors showed that NR-lesioned rats exposed to an enriched environment for 40 days before training were able to remember the location of the platform 25 days later. The restoration of this long-term memory capacity was accompanied by the reinstatement of the mPFC neuronal activity and by a significant attenuation of AMY hyperactivity during remote memory retrieval. We should also keep in mind that while the NR seems to be involved in system-level consolidation within a temporal window between 5 and 25 days after learning, similar memory deficits were observed following a lesion of the intralaminar thalamic nuclei (i.e., the paracentral, centrolateral, and centromedial nuclei) (Lopez et al., 2009). Intralaminar nuclei, as compared to the NR, only project to the mPFC, not to the HPC (Pereira de Vasconcelos and Cassel, 2015; Vertes et al., 2012; Vertes et al., 2015), suggesting that the lesion might have impacted preferentially mPFC-dependent remote memory processing. Yet, Ali et al. (2017) reported that neither a lesion of the NR or the housing condition (standard *vs*. enriched)

had an impact on the *c-fos* expression in these nuclei. These results suggest that the recovery of the long-term memory capacity in NR-lesioned rats housed in an enriched environment does not depend on a compensatory recruitment of intralaminar nuclei. Another important point to consider is that in all these studies, thalamic lesions encompassed both the NR and Rh (Ali et al., 2017; Klein et al., 2019; Loureiro et al., 2012). Given their size and proximity, it is very challenging to manipulate the activity of one nucleus without impacting the other. The authors defined "acceptable" lesions as those damaging at least 50 % and 25 % of the NR and Rh, respectively, but less than 10 % of other neighboring nuclei. Therefore, it is impossible to distinguish the respective contribution of the NR and Rh to system-level consolidation, especially considering the fact that both project to the HPC and mPFC (Cassel et al., 2013; Cassel et al., 2020).

Interestingly, even if converging studies tend to demonstrate that the disruption of NR activity has no impact on the acquisition of spatial information in the water maze (Ali et al., 2017; Dolleman-van der Weel et al., 2009; Klein et al., 2019; Loureiro et al., 2012), a recent study revealed that a lesion of the NR impaired the stability of CA1 place cells in a familiar environment (Cholvin et al., 2018). The authors showed in rats that repeated exposures to the environment progressively improved their stability to finally reach baseline level. Thereby, it is conceivable that the remote memory deficit observed in NR-lesioned rats 25 days after acquisition does not reflect an impaired memory consolidation but instead an initial defect in the encoding of the memory trace. The memory trace, being more labile and fragile, is retained for a short time while long-term memory consolidation processes are not sufficient to stabilize the trace at longer delays.

In contrast to these results, other studies suggested a preferential role of the NR in retrieval rather than in consolidation. Mei et al. (2018) trained rats in an elevated crossword-like maze to evaluate the effect of post-learning NR inactivation on spatial memory. Systematic inactivation of the NR after each learning session did not alter the acquisition of the task or remote memory performance 20 days later. However, retrieval deficits were observed when the NR was inactivated before the memory test at a short delay (2 days after training). The discrepancy with the previous work by Loureiro et al. (2012) might be explained by the short-lasting inactivation of the NR. Indeed, the authors have used an infusion of muscimol that is usually washed out in 2– 3 h (Allen et al., 2008), which might be too short for interfering completely with the early phase of the "off-line" consolidation. Hence, while the exact contribution of the NR to spatial memory processing remains to be determined, numerous studies converge to demonstrate that NR activity is required to allow memories to persist. As spatial memory consolidation is thought to mostly occur during SWS, it is reasonable to think that a lesion of the NR may interrupt off-line consolidation processes by disrupting information exchange between the HPC and mPFC. Thus, the NR appears to be a crucial subcortical node, controlling the transfer of spatial information to the mPFC for long-term storage (Fig. 1B).

3.3. NR and aversive memory consolidation

Contextual fear memory has been shown to recruit both mPFC and HPC, but also more distributed regions in the brain, including the midline thalamic nuclei (Heroux et al., 2019; Roy et al., 2019; Vetere et al., 2017) (see also (Cassel et al. (2020) in this issue). Xu and Südhof (2013) were the first to assess the impact of a pre-conditioning NR inactivation on recent fear memory recall. The authors observed that the inactivation did not impact the retrieval of the information in the training context one day after acquisition. Yet, it induced an over-generalization of the memory, with a significant increase in freezing behavior in a novel environment one day later. Using optogenetic tools, the authors showed that the activity pattern of NR neurons during acquisition would either enhance or reduce fear generalization in the novel context without altering the retrieval in the original training chamber. Therefore, while NR activity appears to be necessary to determine the level of specificity of a memory trace, it does not seem essential to recall a recent and precise contextual fear memory one day after training. In accordance with such results, Quet et al. (2020b) performed a lesion of the NR(Rh) two weeks before training and observed no effect on recent (1 day post-acquisition) contextual fear memory assessed in the conditioning chamber. To investigate the role of the NR in memory consolidation, Troyner et al. (2018) used muscimol to inactivate the NR directly after conditioning. In line with previous reports, the results show no effect in the pairing context two days post-acquisition. Still, an increased amount of freezing is observed in another context at the same delay. Thus, these results suggest that NR activity is not only relevant during acquisition, as reported by Xu and Südhof (2013), but also during consolidation to modulate the content of contextual fear memories. Interestingly, no memory generalization was observed if NR inactivation occurred 6 h after conditioning, indicating that the NR modulates the specificity of the memory trace in a restrictive time window of memory consolidation following acquisition. On the other hand, contradictory results were reported by Ramanathan et al. (2018), who showed that rats conditioned after NR inactivation display a significant impairment of the recent memory recall two days after learning in the conditioning context, with a strong reduction of the freezing behavior. Such results suggest an NR-based influence on either acquisition or retrieval. Surprisingly, subsequent inactivation of the NR before the memory test can reverse the memory deficit induced by the pre-acquisition NR inactivation. Therefore, contextual fear memories acquired under NR inactivation can be recovered when NR activity is inhibited before retrieval. The authors demonstrated that the infusion of NMDA receptor antagonist in the dorsal HPC did not alter the recovery of these memories. Thus, it appears that in the absence of the NR activity, other brain regions are recruited to acquire contextual fear memory in a hippocampal-independent manner, revealing a system more complex than initially foreseen.

In their recent study, Quet et al. (2020b) also demonstrated that NR activity is crucial to allow such contextual memories to persist in time. Indeed, the authors evaluated the behavior of NR(Rh)-lesioned rats at both recent (1 day) and remote (25 days) time points after conditioning and observed a significant memory deficit at a 25-day delay. In another experiment in intact non-operated rats, the authors quantified the expression of the IEG *c-fos* 90 min after retrieval and found no significant changes in the NR at both post-acquisition delays, indicating that the NR (Rh) is not recruited during retrieval. Furthermore, chemogenetic inactivation of the NR(Rh) just before the memory tests did not alter the expression of contextual fear memory, whatever the delay, confirming that the NR does not participate in the retrieval of contextual fear memories *per se*. Altogether, this data points to a critical role of the NR (Rh) in contextual fear memory persistence, probably by mediating system-level consolidation processes, as observed in previous work regarding spatial memory (e.g., Loureiro et al. (2012)). Likewise, data from Troyner et al. (2018) also supports the implication of NR in long-term memory persistence. However, the authors reported that muscimol-induced inactivation of the NR directly after acquisition negatively modulated remote contextual fear memories specificity. Indeed, in the absence of NR activity, rats spent a significantly longer time freezing in the paired context as compared to control rats 21 days after conditioning. The freezing level was even higher than the one observed at the recent time point (1 day post-acquisition), suggesting a role of the NR in long-term fear memory maintenance and intensity during consolidation. Discrepancies between the two studies may results from the duration in NR silencing as Quet et al. (2020b), and Troyner et al. (2018) performed permanent excitotoxic NMDA lesion (few weeks) and transient muscimol-induced inactivation (few hours), respectively. Additionally, Troyner et al. (2018) looked at the expression of the *Arc* protein, known to regulate dendritic spine density and morphology, 90 min after either conditioning or NR inactivation. Contextual fear conditioning was accompanied by a significantly enhanced number of Arc-expressing neurons in the HPC and mPFC (IL), whereas no changes were observed in the NR. NR inactivation modulates this number and thus may influence cortico-hippocampal plasticity induced by contextual fear conditioning. One may assume that these overall changes in the plasticity of the HPC-mPFC-NR

circuit interferes with memory consolidation processes and thus confirm the role of NR in the persistence of contextual fear memories.

In contrast to Quet et al. (2020b) IEG expression data, Silva et al. (2019) observed that the recall of a one-month-old contextual fear memory recruits the NR but also a collection of different brain regions, including the HPC, mPFC, and AMY. Interestingly, the authors noted that the increased *c-fos* expression in the NR appears to be localized only in its posterior portion, suggesting a differential role of NR subdivisions in memory. These results are coherent with previous data obtained by Wheeler et al. (2013), which mapped *c-fos* expression over 84 brain regions to identify networks activated during contextual fear memory retrieval 1 day and 36 days after acquisition. The authors observed a distinct pattern of *c-fos* expression during recent and remote memory recall. Indeed, while the HPC was strongly recruited one day after training, remote memory recall recruited several brain regions, including the NR and mPFC. By computing the interregional correlation of *c-fos* expression, the authors observed that the mPFC exhibited a higher correlated activity with the thalamus and HPC at a 36-day retention delay than during recent memory recall. Using graph theory, the authors revealed that such a cortico-thalamic-hippocampal network engaged in remote memory retrieval had a small-world organization, in which the NR and mPFC, among other regions, were highly connected hub regions. To determine how this functional network participates in contextual fear memory consolidation, Vetere et al. (2017) used chemogenetics to (systematically) inactivate, in a series of independent experiments, a total of 21 regions after acquisition. The results showed that the inhibition of high degree nodes like the NR produces the largest memory deficit 10 days after conditioning. Overall, even if these two studies demonstrate that the NR is recruited during the retrieval of remote contextual fear memories, they do not establish whether the NR contributes to memory consolidation. Targeted recordings/manipulations of NR are needed to properly evaluate the dynamics of its involvement in contextual fear memory consolidation.

In contrast, the NR does not seem to participate in the processing of cue fear memory (Lin et al., 2020; Quet et al., 2020b; Ramanathan et al., 2018; Xu and Südhof, 2013). Different approaches using either pre-acquisition lesion/inactivation of the NR or direct NR inactivation prior to memory retrieval has no impact on recent or remote auditory fear memories. However, it is noteworthy that the authors used a no-delay fear conditioning protocol where the unconditioned stimulus (foot shock) directly followed or co-terminated with the conditioned stimulus (tone) and did not require the HPC, confirming that the NR is not involved in hippocampal-independent memory processing.

3.4. NR and the consolidation of other types of memory

Only one study has examined the role of the NR in passive avoidance memory (Davoodi et al., 2011). The authors used tetracaine to temporally inactivate the NR at different stages of passive avoidance memory processes. Rats were placed in an illuminated chamber connected to a dark compartment by a door. After spontaneously entering in the dark compartment, rats received a foot shock and were returned to their home cage 20 s later. Memory performance was evaluated by calculating the entrance latency to the dark compartment and the time spent inside. Inactivation of the NR 5 min before training did had no impact on the acquisition of the task but impaired the memory performance one day later. A similar memory deficit was observed 24 h after training, when the NR was inactivated 5 min after training but not at longer delays of 90- or 360-min post-acquisition, revealing a time-dependent role of the NR in memory consolidation. The NR appears to be specifically involved in the early phase of consolidation, especially considering the fact that in such protocol, tetracaine effects last ~ 20 min. Interestingly, infusion of tetracaine 5 min before the memory test also affected memory retrieval, suggesting that the NR might participate in both off-line and on-line stages of passive avoidance memory processing. Previous studies have already demonstrated that avoidance memory acquisition relies on a distributed network including the cingulate cortex, AMY, and HPC (Ambrogi Lorenzini et al., 1997; Blanco et al., 2009; Izquierdo et al., 1997; Lorenzini et al., 1996; Zhang et al., 2011). Being posed as a hub between these different structures, the NR inactivation might impair the whole network functional connectivity supporting this function.

More recently, the NR has been shown to be a key structure involved in associative recognition memory (Barker and Warburton, 2018). The authors used an object-in-place recognition task and demonstrated that the NR intervenes at different stages of memory processing. Interestingly, the authors showed that the persistence of an object-in-place memory (24 h post-acquisition) depended on NR protein synthesis. Indeed, the infusion of anisomycin or actinomycin D, two protein synthesis inhibitors, into the NR before acquisition altered the performance of the rat at a 24 h delay but not 3 h after training. Thus, the NR appears to be responsible for the stabilization and maintenance of the memory trace.

To further investigate the implication of the NR in memory processing, Quet et al. (2020a) used a social transmission of food preference task to study whether the NR contributes also to the system-level consolidation of social memories in rats. They used a typical olfaction-based task where a demonstrator rat eats a specific flavored food and then has social interaction with an observer rat who collects olfactory information. A food preference test was then conducted one day or 25 days after acquisition when the observer rat had access to one cup with the previous food eaten by the demonstrator and another one containing a novel flavored food. The authors performed fiber-sparing lesions of the NR(Rh) before training (as e.g., in Loureiro et al. (2012)) and observed that it influenced neither the acquisition nor the retrieval of the information, whatever the delay. These results are not in line with previous data showing that NR activity is necessary to consolidate both fear contextual and spatial memories in the long-term (25 days post-acquisition) (Ali et al., 2017; Klein et al., 2019; Loureiro et al., 2012; Quet et al., 2020b). Such variance might be explained since the role of the HPC in this type of task remains debated. Indeed, some data indicate that this task might be HPC-independent, and thus system-level consolidation might not rely on the NR.

3.5. NR and cortico-hippocampal coupling

Since system-level consolidation of declarative memories is thought to occur during sleep and more precisely during SWS, it is reasonable to think that the NR influences consolidation processes by modulating cortico-hippocampal interactions during such brain state to promote information transfer between the two structures. Therefore, in order to better understand how NR activity may influence cortico-hippocampal functional connectivity, several studies used anesthesia, as a first step, to reproduce sleep-like brain states and dynamics to record this tripartite network (Fig. 2A). Recently, Ferraris et al. (2018) used a combination of urethane and xylazine/ketamine to obtain two stable brain states dominated by either SO or theta activity to mimic both SWS and paradoxical sleep, respectively. The authors used high-density multisite
silicon probes to collect both LFPs and single unit activity simultaneously in the NR, mPFC (PL, layer 5), and HPC (CA1, *stratum pyramidale*). They showed that some gamma oscillations in the mPFC and HPC are synchronized within a ~100 ms window, specifically during SO and not theta activity. These synchronized gamma bursts represented 40 % of the total recorded bursts; they entrain the local population, modulating the activity of both putative interneurons and pyramidal cells in the two regions. HPC gamma bursts generally preceded those of the mPFC with a ~100 ms delay. Interestingly NR neurons increased their activity just before the onset of synchronized gamma bursts in both structures, suggesting that NR activity may be instrumental in this coupling. In line with such a hypothesis, muscimol-induced inactivation of the NR disrupted such temporal coordination without affecting the occurrence of gamma bursts in both regions. Thus, altogether these results point to the NR as a functional hub able to finely coordinate hippocampal-prefrontal gamma bursts during slow oscillations. As gamma rhythms are believed to functionally couple distant regions to

facilitate inter-regional communication, one may assume that such NR-dependent hippocampal-prefrontal gamma synchronization allows information exchange between the HPC and mPFC during SWS to support memory consolidation (Fig. 2Bb). This hypothesis is reinforced by the fact that such HPC-mPFC gamma coupling was also observed during natural SWS (Ferraris et al., 2018). In the HPC, gamma oscillations in the *stratum pyramidale* of the CA1 area are known to result from the interaction of fast-spiking parvalbumin-expressing basket cells and pyramidal neurons (Bartos et al., 2007). These interneurons extend their dendrites to the *stratum lacunosum moleculare*, which is the only target zone of NR axonal projections in the HPC (Vertes et al., 2006). Although the type of interneurons targeted by the NR remains to be determined, it is conceivable that the NR influences the timing of hippocampal gamma bursts by interacting with the excitability of hippocampal parvalbumin-containing basket cells. A similar hypothesis can be proposed for mPFC gamma burst as parvalbumin basket cells have been shown to be present in layers 2–6 of the cortex (Tremblay et al., 2016). Nevertheless, it is important to stress that NR inactivation may just have impacted the activity of other regions responsible for the coupling, like the EC or AMY, in association or independently of the NR. Altogether, these data suggest that the HPC-mPFC gamma burst synchronization could correspond to another network mechanism offering specific temporal windows allowing the cortico-hippocampal dialogue that supports memory consolidation.

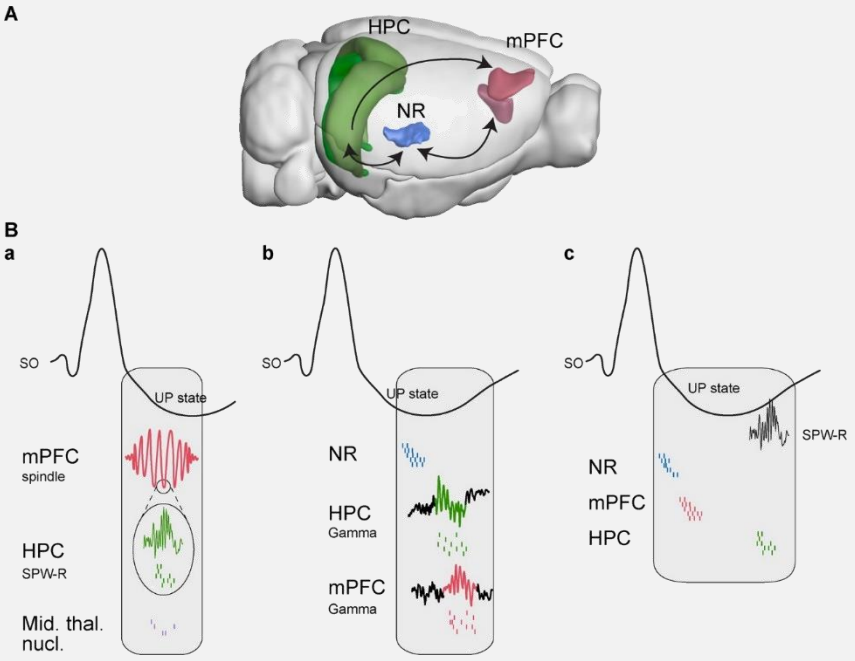

Fig. 2. Functional connectivity within the HPC-mPFC-NR network potentially supporting memory consolidation.
A. 3D view of the HPC, NR, and mPFC in a rat brain (adapted from Allen Institute Atlas; only the Il and PL portions of the mPFC are represented) and their interconnections (black arrows), showing a unilateral HPC → mPFC projection, whereas the NR shares bi-directional connections with both HPC and mPFC. The NR is, therefore, an anatomical hub between the HPC and mPFC ideally poised to participate/control to their functional interaction during memory consolidation processes. B. Models of functional interaction within the HPC-mPFC-NR network through different oscillatory activities during SO dominated states.
a. Model of SO/spindle/SPW-R organization of thalamic and CA1 spike dynamics (according to Varela and Wilson (2020)). The UP state organizes the occurrence of spindles (in the early UP state), in which HPC SPW-Rs are phase-locked and engage the replay of task-relevant HPC neurons (green spike raster) preferentially, coinciding with sparse co-activation of midline thalamic nuclei (Mid. Thal. Nucl.) neurons (purple spike raster). Such spindle-related organization associated with the sparse synchronicity in thalamic cell assemblies could favor HPC-driven plasticity in mPFC networks, in favor of a cortico-hippocampal dialogue supporting information consolidation. This model fits with the classical functional mechanism underlying memory consolidation through the coordination of SO, spindles, and SPW-Rs (Latchoumane et al., 2017; Maingret et al., 2016). Yet, the exact participation of actual NR neurons remains to be determined.
b. Cortico-hippocampal coordination through gamma burst synchronization (at the end of the UP state) driven by the early firing of NR neurons (blue spike raster) (Ferraris et al., 2018). Gamma bursts entrain the firing of HPC and mPFC neurons (green and pink spike rasters, respectively). Gamma bursts thus offer temporal windows allowing the transfer of information from HPC to mPFC and the recruitment of cell assemblies potentially carrying information. Such a model provides another functional mechanism underlying consolidation involving the coordination of SO and gamma oscillations.
c. Potential role of sequential NR firing (blue spike raster) in the recruitment of mPFC (pink spike raster) and HPC cell assemblies (green spike raster), at the UP state onset and during SPW-Rs (occurring later in the UP state), respectively (Angulo-Garcia et al., 2020). The NR acts as a functional hub through its sequentially organized cell assemblies and could influence the information packets transfer from the HPC to the mPFC.

Supporting results came from Hauer et al. (2019), which recently confirmed the crucial role of the NR in the coordination of prefrontal-hippocampal interaction during urethane-induced slow oscillation state. As noticed in different studies, the authors observed that NR neurons are modulated by SO (Angulo-Garcia et al., 2020; Ferraris et al., 2018; Varela and Wilson, 2020) and rhythmically discharge during this state. The authors demonstrated that chemogenetic inhibition of the NR did not reduce SO power in the HPC and mPFC but significantly impaired SO synchrony between the two structures. Therefore, the NR may constitute a key structure in "off-line" memory consolidation, able to synchronize SO in the prefrontal-hippocampal network. Indeed, numerous studies have provided evidence showing that SWS and SO themselves have been associated with consolidation processes. Marshall et al. (2006) used transcranial stimulation in humans to induce SO during early SWS sleep after learning and observed a significant enhancement of word-pairs retention on the following day. SO provide discrete processing time windows which organize, at different time scale, faster oscillatory activity within and between regions to coordinate inter-regional communication. Compatible with this idea, Ferraris et al. (2018) demonstrated that gamma oscillation bursts are modulated by SO and that NR inactivation not only disturbs HPC-mPFC gamma coupling but also induces a significant phase shift and decrease of modulation strength of gamma bursts in these two regions. Yet, the exact mechanisms by which the NR regulates both SO and gamma HPC-mPFC synchronization remain to be determined. It is worth mentioning that NR activity relates to its neuronal firing, not its oscillatory activities. Indeed, recorded oscillations in NR are not locally generated and therefore most likely volume-conducted from neighboring regions (see in Angulo-Garcia et al. (2020)), consistent with the fact that oscillations are emergent properties of networks bearing an adequate geometrical arrangement like the cortex or the HPC (Buzsáki et al., 2012 ; Herreras, 2016). Hauer et al. (2019) showed that mPFC stimulation evokes a response in CA1 with a maximal current sink in the *stratum lacunosum-moleculare,* which disappeared when the NR is inhibited. Interestingly, such reduction in sink amplitude is correlated to the drop of SO coherence (i.e. level of synchronization in a given frequency band) between the mPFC and HPC. Altogether, these data suggest that the NR mediates SO hippocampal-prefrontal coupling by relaying prefrontal activity to the HPC (Fig. 2Bb). Prefrontal inputs would rhythmically drive NR activity which in turn entrains the HPC. A similar assumption could be made regarding NR-dependent HPC-mPFC gamma coupling. Indeed, one possibility to consider is that NR increased activity before synchronized gamma bursts is triggered by the mPFC itself, initiating either (1) an mPFC → NR → HPC → mPFC loop or (2) an mPFC → NR → mPFC/HPC loop via the recruitment of the NR double-projecting neurons which would lead, in each case, to the precise coordination of hippocampal-prefrontal gamma bursts. As mPFC gamma oscillations quickly follow the HPC ones, the authors postulated that such coupling may allow the transfer of information from the HPC to the mPFC during memory consolidation. It is important to note that in both studies the NR is viewed as a "conductor" and not as a generator of either gamma or SO, able to coordinate prefrontal-hippocampal activity during SWS-like brain state. In this context, the mPFC would control the efficiency of the transfer through its direct afferents to the NR. The mPFC would act as a "checkpoint", ensuring the "quality" of the transfer during gamma oscillations. In any case, the contribution of the EC must be kept in mind as, like the NR, it projects to CA1 in the *stratum lacunosum moleculare* and also receives inputs from the mPFC (Agster and Burwell, 2009; Dolleman-Van Der Weel and Witter, 1996; Herkenham, 1978; Vertes et al., 2006; Witter et al., 1988; Wouterlood et al., 1990).

As the neural memory trace is assumed to be represented by discrete neuronal cell assemblies whose reactivation during SWS promote the formation of long-lasting memories (Atherton et al., 2015; Euston et al., 2007; Lee and Wilson, 2002; Nadasdy et al., 1999; Pavlides and Winson, 1989; Peyrache et al., 2009; Skaggs and McNaughton, 1996; Wilson and McNaughton, 1994), one may ask whether NR activity has an impact on cortico-hippocampal assemblies. Angulo-Garcia et al. (2020) used multisite silicon probes to record during SWS-like state large neuronal populations in the HPC-mPFC-NR network and observed for the first time that NR activity is organized in spatio-temporal sequences at the beginning of the UP states. One hypothesis is that such coordinated firing may reflect the spatial information encoded during wakefulness. Indeed, the NR contains spatially tuned neurons, including place cells, head direction cells, trajectory-dependent cells, and border cells (Ito et al., 2015; Jankowski et al., 2014; Jankowski et al., 2015). Therefore, one may hypothesize that like in the HPC during SPW-Rs, these sequences correspond to internally generated cell assemblies as the ones coding for a memory representation which are reactivated during sleep to promote memory consolidation (Dragoi and Tonegawa, 2011; Euston et al., 2007; Giri et al., 2019; Ji and Wilson, 2007; Kudrimoti et al., 1999; Lee and Wilson, 2002; Pastalkova et al., 2008; Peyrache et al., 2009; Tatsuno et al., 2006; Wilson and McNaughton, 1994). Yet, these sequences displayed a dorso-ventral organization, raising the question about the ability of such rigid ordering to encode a new information. Besides, the origin of this topical organization remains to be elucidated as no anatomical or electrophysiological data can so far explain it. Interestingly, Angulo-Garcia et al. (2020) showed that NR sequences precede prefrontal sequences at the onset of the UP state, suggesting that NR activity may directly drive, or at least time them. Thus, it might constitute an alternative pathway to reinstate prefrontal activity, progressively leading to the reinforcement of cortico-cortical connections and the integration of the memory trace in the cortex. Still, what exactly these sequences represent remains to be determined and investigated in non-anesthetized animals involved in a consolidation process. Furthermore, Angulo-Garcia et al. (2020) reported that pharmacological inactivation of the NR disrupted the recruitment of neuronal assemblies in the mPFC during UP states and in the HPC during SPW-Rs, with less reliable sequences and recruiting significantly fewer neurons. Altogether these data suggest that NR activity may contribute to the stabilization and coordination of hippocampal-prefrontal sequences during SO and further support the role of NR as a functional key hub in memory networks (Fig. 2Bc).

To further investigate how the NR is recruited during SO, Lara-Vasquez et al. (2016) looked at NR activity, among other midline thalamic neurons, during SPW-Rs in anesthetized mice. Remarkably, the authors observed that NR neurons are differentially modulated by SPW-Rs, depending on the expression of the calcium-binding protein calretinin (CR). By regulating the intracellular Ca^{2+} homeostasis, they allow a fine control and timing of Ca^{2+}-related neuronal activity (Schwaller, 2010). Indeed, while calretinin-positive (CR+) NR neurons appeared to be inhibited during SPW-Rs, the discharge probability of calretinin-negative (CR-) ones remained unchanged. Conversely, only CR- neurons displayed an increased firing rate during anesthesia-induced theta oscillations. Therefore, distinct NR neuronal populations appear to be recruited during SPW-Rs and theta oscillation state and thus may participate in different phases of memory processing. Unfortunately, there is to date no available data on the precise nature of HPC and mPFC neuronal targets of CR + versus CR- neurons. The authors also noted that overall CR + neurons are more bursty but exhibit lower firing rates as compared to NR neurons lacking calretinin. These results appear similar to the ones in Angulo-Garcia et al. (2020), where NR inactivation does not affect the occurrence or properties of SPW-Rs, but the cell assemblies recruited. However, the inactivation was performed regardless of the neuronal classes present in the NR, and it is, therefore, difficult to make some mechanistic assumptions since it appears that different cell populations might display very different brain state-dependent activities (Lara-Vasquez et al., 2016).

In a recent study, Varela and Wilson (2020) investigated the temporal correlation between limbic thalamic neurons (including NR) firing and SWS oscillatory hallmarks (spindles, SPW-Rs, and delta waves) in freely-moving rats. Consistent with Lara-Vasquez et al. (2016) results, about half of the neurons of the limbic thalamus reduced their firing during SPW-Rs but tended to discharge in bursts. Even with a sparse firing, thalamic neurons tended to get co-activated during spindles and SPW-Rs. For instance, sparsely synchronous thalamic cells got co-activated within spindles, particularly at the descending phase of the spindle band-filtered mPFC LFP,

and showed a strong rebound of activity following delta waves. Since pairs of thalamic neurons were consistently phase-locked to the spindle trough, they suggest that individual spindle cycles would group and organize the recruitment of different thalamocortical ensembles. Moreover, SPW-Rs were nested to spindle troughs. The task-activated CA1 neurons were the ones preferentially reactivated during SPW-Rs, which were more correlated to spindles (locked to the trough) after exploratory behavior. However, if spindles seem to organize the reactivation of task-active HPC neurons during SPW-Rs, it appears that there is no selective selection of thalamic neurons by these reactivated HPC neurons, since each spindle cycle appears to recruit different thalamic cell assemblies. One possibility is that such spindle-related organization, together with the sparse synchronicity in thalamic cell assemblies, could favor HPC-driven plasticity in mPFC networks, supporting a cortico-hippocampal dialogue underlying information consolidation. Although what specifically belongs to NR activity proper remains to be determined, as this study mingles the activity of NR (~40 %), ventromedial nuclei (~30 %), and the rest from the mediodorsal, paratenial, Rh, and centromedial nuclei, it is difficult to extrapolate a clear network mechanistic view. The authors (eventually) propose that spindles would provide the temporal windows, where the recruitment of different groups of thalamic neurons promote incremental synaptic plasticity and facilitate the integration of information through HPC replay and its integration in cortical networks for long-term memory consolidation (Fig. 2Ba).

The coupling between SPW-Rs and spindles has been shown to promote memory consolidation at short-post acquisition delay, meaning during sleep following learning (Buzsáki, 2015 ; Latchoumane et al., 2017; Maingret et al., 2016), Yet, the NR seems to intervene in system-level consolidation between 5 and 25 days after training rather than in the early phase of episodic consolidation (Ali et al., 2017; Klein et al., 2019; Loureiro et al., 2012; Quet et al., 2020b) (Fig. 1). Thus, while NR neurons might facilitate ripple-spindle interactions, their activity might not be essential to the consolidation of recent memories, which might depend on the coordinated activity of different limbic thalamic nuclei (Varela and Wilson, 2020). On the other hand, NR neurons specifically, but not neighboring thalamic neurons, drive long-range gamma coupling between HPC and mPFC during SO. Overall, one theory is that, while the ripple-spindle coupling might be critical to the stabilization and storage of information in the short-term (hours to few days, i.e. recent memory), the NR-dependent HPC-mPFC gamma synchronization might be important during the formation of long-lasting remote memories (Ferraris et al., 2018). The NR would be progressively recruited after learning to become critical at longer post-acquisition delay. One can speculate that the initial involvement of NR neuronal populations is rather discreet, hence not visible using activity-dependent labeling of *c-fos* expression. Such a dynamic involvement could translate into a progressive recruitment of larger neuronal populations and/or an increased activity of NR neurons. This would be coherent with the data of Varela and Wilson (2020) showing a sparse firing of thalamic neurons around spindles in post-task sleep and those of Loureiro et al. (2012) showing a significant increase of *c-fos* expression in the NR after the remote memory test (25 days) but not the recent one (5 days).

4. Conclusion

System-level consolidation relies on more than a simple dialogue between the hippocampus and the cortex, whether it is theorized as a 2-step or a multi-trace process, or a mixture of both (Dudai et al., 2015; Frankland and Bontempi, 2005; Nadel and Moscovitch, 1997; Squire, 1992; Squire and Alvarez, 1995). The many new insights into the functional role of the nucleus reuniens in hippocampal-prefrontal interactions bring a new way of approaching the long-term imprinting of memories. Since the consolidation of declarative memories can occur during slow-wave sleep, the nucleus reuniens holds a key position to open temporal windows, enabling the exchange of information between the hippocampus and the prefrontal cortex. Future work is required to determine which type of information is exchanged and its temporal processing according to the nature of the particular memory to perpetuate. The current theory proposes that the information is supposed to be carried by engram neurons distributed over many brain areas (Kitamura et al., 2017; Roy et al., 2019; Semon, 1904; Tonegawa et al., 2018). It is therefore crucial to decipher the exact role of nucleus reuniens toward information-relevant cell assemblies, and determine its involvement in their modulation, coordination, recruitment, and/or if it also hosts engram neurons.

Future research is necessary to determine the distinct roles of the cell populations highlighted in nucleus reuniens (for instance, calretinin- positive neurons, double-projecting neurons, neurons firing in spatio- temporally organized cell assemblies, etc.), whether they target specific hippocampal and/or cortical neuronal types (principal versus which class of GABAergic neuron) in a brain state-dependent manner (as during SWS coupled to gamma oscillations or within a given memory- relevant behavioral task) and at specific phases of the memory consolidation process (as during encoding, early or late consolidation phases) in order to get a clearer picture on how NR is integrated into the large "memory network". However, one needs to keep in mind that nucleus reuniens, hippocampus, and prefrontal cortex are just three nodes in a vastly more complex network. So far, most of experimental approaches are reductionistic by construction, and the interpretations/discussions proposed rarely consider what happens in the rest of the brain. A nice illustration of this concept is provided by Xiao et al. (2017), who showed that the activity of a single thalamic neuron depended upon the activity of the whole cortex.

Altogether, the large body of evidence gathered in this review provides further indication that the nucleus reuniens is a functional hub tuning the hippocampal-prefrontal dialogue at both macroscopic (oscillations) and microscopic levels (cell assemblies). These two mechanisms being instrumental for memory consolidation, a combination of innovative tools, including genetics, behavior, electrophysiology, and imaging, are needed to extract meaningful information, challenge the functional place of nucleus reuniens, and provide the neuronal and network mechanisms supporting memory consolidation.

Declaration of Competing Interest

The authors have no conflict of interest to declare regarding the content of the current review.

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