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REVIEW ARTICLE

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# Update on temporal lobe-dependent information processing, in health and disease

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**Abstract**

The past decade has been characterized by a lot of remodeling in the field of learning and memory. Both of them, often associated with neuronal oscillations, an emergent property of brain networks, are governed by temporal lobe (TL) functional connectivity. An impairment of oscillatory mechanisms indeed often leads to TL-dependent cognitive deficits. While the classical view assigned the TL a major role in spatial information processing, new theories rather confer to the TL a more general function in cognitive processes beyond space representation. The present review covers, both in humans and in animal models, (a) the updated role of the TL in cognitive processes, addressing current debates in the field and proposing a scenario on how TL structures cooperate in order to bind an integrated representation of afferent information, (b) the oscillatory mechanisms underlying these TL-dependent cognitive functions (theta, gamma, sharp wave ripples) and (c) how TL-dependent cognition is altered during temporal lobe epilepsy, proposing a scenario on how reorganized TL networks in TLE leads to rhythmopathies and cognitive deficits. Temporal lobe epilepsy (TLE) is a well-studied neurological disease. Patients do not only suffer from epileptic seizures but also from cognitive and behavioral deficits between their seizures called comorbidities. TLE animal models are therefore used to understand how and when these comorbidities arise and what their underlying mechanisms are.

**KEYWORDS**

cognitive processes, episodic memory, oscillations, rhythmopathies, temporal lobe epilepsy

## 1 | INTRODUCTION

The temporal lobe (TL, cf. Figure 1 and Table 1) is very much involved in cognitive processes, in particular learning and memory, involving fast and flexible dynamic coordination, gating and routing of information. The hippocampus (HPC), a structure of the TL extensively described in spatial cognition, was long-assumed to be exclusively involved in the way we represent our current location in space, both in humans and in animals, especially in rodents (O'Keefe & Nadel, 1978). This traditional view aligned with the idea of a Cognitive Map which was first introduced by Tolman in 1948 and was then described as being specifically located in the HPC by O'Keefe and Nadel in the early 1980s in their seminal publication *The Hippocampus as a Cognitive Map* (O'Keefe & Nadel, 1978). This theory gained further support and was pretty much admitted in the field. Place cells and grid cells have been thoroughly described as coding space in the HPC and the entorhinal cortex (EC), respectively, the latter providing, together with the *reuniens* nucleus of the thalamus, the main input to the HPC and also implicated in spatial processes (Figure 1). In addition to place and grid cells, time cells have also been studied, both in rodents and in monkeys, defining time-lapse, for example,

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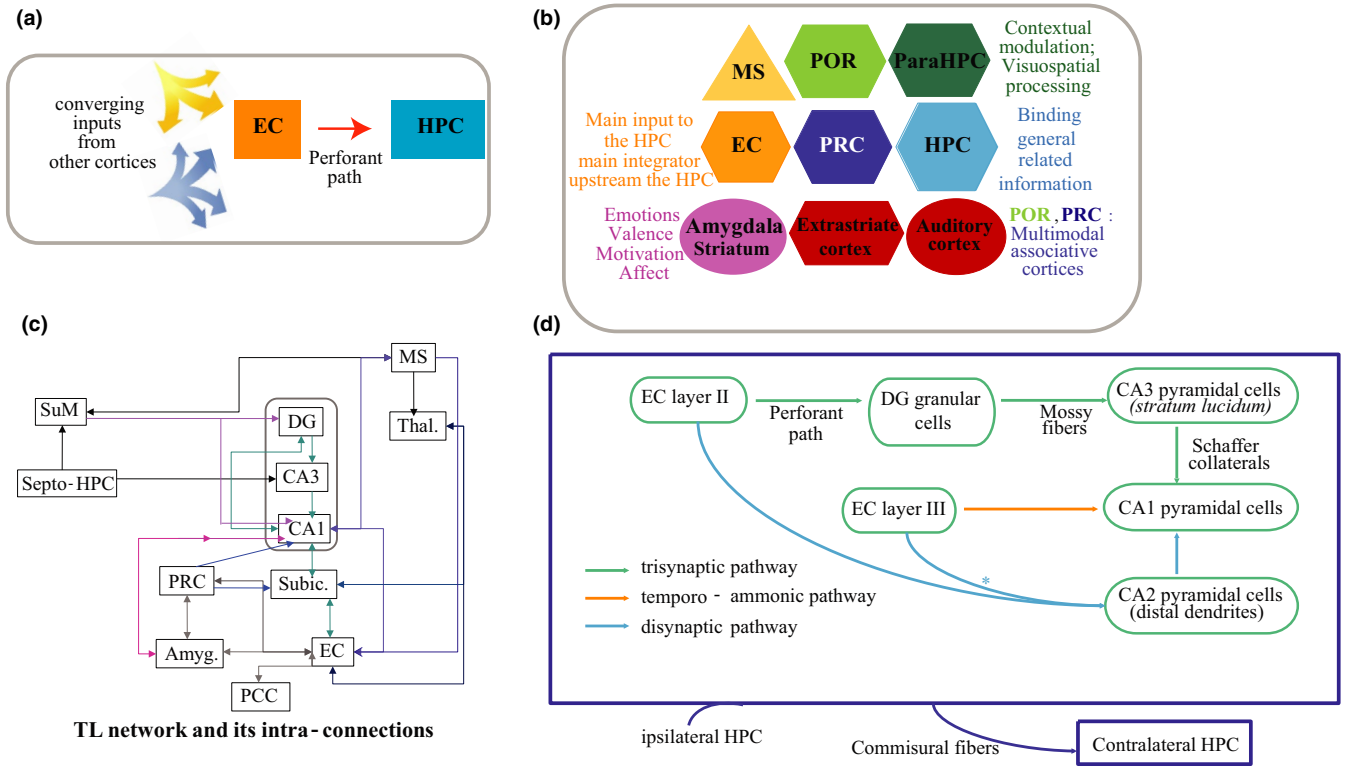


**FIGURE 1** Temporal lobe structures, intra-connections and main functions. (a) Converging inputs from different cortices arrive at the EC and get transmitted to the HPC via the perforant path. (b) The main TL structures and their main functions. The auditory and extrastriate cortices do not belong to the TL lobe but dorsally border the PRC (ventrally bordered by the EC). (c) TL network and its intra-connections. *Thal.*: Thalamus; *PCC*: Posterior Cingulate Cortex; *Subic.*: Subiculum; *DG*: Dentate gyrus; *EC*: Entorhinal cortex; *VMT*: Ventral midline Thalamus; *PRC*: Perirhinal cortex; *POR*: Postrhinal cortex; *MS*: Median septum; *SuM*: Supramammillary nucleus; *Septo-HPC*: Septo-Hippocampal Nucleus. CA1, CA3, CA2 and DG areas constitute the HPC. (d) Trisynaptic pathway and other connecting TL pathways. (*): It remains controversial whether EC layer III inputs synapse onto CA2 pyramidal cells (Kohara et al., 2014)

during the delay of a memory task when the subject has to hold information in order to complete the task (Salz et al., 2016). Both time and space are indicators of context into which information gets encoded as a unique episode, thus constituting hallmarks of episodic memory, the memory by which we remember past experiences defining the self. We will focus particularly on this aspect of memory. However, the past decade has been characterized by a lot of remodeling in the field of learning and memory: While the traditional view assigned the HPC an exclusive role in spatial navigation and memory, new theories rather confer the HPC a more general function in cognitive processes beyond space representation. The debate between the classical view and its updated version—which is attributing the HPC a global role in various cognitive functions—was recently covering much of the field, conferring to this region a standardized role in building memories, especially episodic memories. In this review, we will discuss evidence supporting the recent shift.

In the first part of this review (sections 2–4), we will address the updated role of TL brain networks and oscillatory processes in cognitive functions, in particular episodic memory, in healthy brains. We will highlight the dynamic paradigm shifts in TL cognition and discuss their underlying mechanisms. In the second part (section 5), we will review how cognitive processes are altered when the communication between distributed TL neuronal networks is modified, as it is the case in temporal lobe epilepsy (TLE). We will show how oscillatory processes, emergent properties of brain networks and key mechanism in cognitive functions, are modified by as well as consequently affect information processing. In both normal and pathological conditions, we will address these timely issues in both humans and animal models and propose a scenario on how TL brain networks underlie normal and altered episodic memory in healthy and TLE conditions, respectively, based on recent evidence.

## 2 | UPDATED ROLE OF THE TL NETWORK IN COGNITION

### 2.1 | Role in general cognition

Cognitive processes depend on the integrity of TL brain networks and on the dynamic interplay between them. Especially memory processes, as it requires the integration of information from various neural systems (i.e., episodic memory).

**TABLE 1** HPC pathways and TL intra- and inter-connectivity

**A. HPC pathways**

| | From | To | Via |
|---|---|---|---|
| Trisynaptic pathway | EC layer II | DG granular cells | Perforant Path |
| | DG granular cells | *stratum lucidum* of CA3 | Mossy Fibers |
| | CA3 PC | CA1 PC | Schaffer Collaterals |
| Temporoammonic pathway | EC layer III | CA1 and subiculum | |
| Disynaptic pathway | EC layer II and III[a] | CA2 distal dendrites, then to CA1 deep layers | Perforant Path |
| | Ipsi- HPC | Contralateral HPC | Commissural Fibers |

**B. Extra-HPC structural connectivity**

| INPUTS from → | to | from | → OUTPUT to | References[b] |
|---|---|---|---|---|
| Subiculum | HPC | CA1 | Subiculum | Cassel and Pereira de Vasconcelos (2015), Cholvin, Hok, Giorgi, Chaillan, and Poucet (2018), Freund and Antal (1988), Freund and Buzsáki (1996), Griffin (2015), Hallock, Wang, and Griffin (2016), Maglóczky, Acsády, and Freund (1994), Pitkänen, Pikkarainen, Nurminen, and Ylinen (2000), Witter, Hoesen, and Amaral (1989), Witter, Griffioen, Jorritsma-Byham, and Krijnen (1988), Wouterlood, Saldana, and Witter (1990) |
| Septo-HPC nucleus | | | Amygdala | |
| MS | | | MS (*via fimbria-fornix pathway*) | |
| VMT | | | EC | |
| SuM | | | VMT | |
| PCC | | | Mammillary bodies (including the SuM) | |
| PRC | | CA2 | MEC layer II (*monosynaptic connection*) | Rowland et al. (2013) |
| Amygdala | | | mPFC | Griffin (2015) |
| PCC | Subiculum | | CA1, CA2<br>EC<br>pre- and parasubiculum<br>mammillary bodies, thalamic nuclei, amygdala, septum, accumbens nucleus, and PFC (via fornix) | Groenewegen, Zee, Kortschot, and Witter (1987), O'Mara (2005), Swanson and Cowan (1977), Tamamaki, Watanabe, and Nojyo (1984) |
| VMT, PCC, PRC, Subiculum, Amygdala | EC | | PCC | Amaral and Witter (1995), Burwell and Amaral (1998), Insausti, Herrero, and Witter (1997); Suzuki and Amaral (1994) |
| cortical inputs (project to the HPC) | EC superficial layers | | all HPC regions<br>EC deep layers | Segal and Landis (1974), Steward (1976) |
| HPC inputs (also project to the neocortex) | EC deep layers V and VI | | CA1 and Subiculum<br>PRC and mPFC | Chrobak, Lörincz, and Buzsaki (2000) |
| Frontal, insular and piriform cortices | PRC | | EC | Burwell and Amaral (1998), Deacon, Eichenbaum, Rosenberg, and Eckmann (1983), Furtak et al. (2007), Jones and Powell (1970), Turner and Zimmer (1984); Van Hoesen and Pandya (1975) |
| Temporal and occipital cortices | | | Subiculum, Ventral Subiculum, HPC formation | Burwell and Amaral (1998), Kloosterman, Haeften, Witter, and Lopes da Silva (2003), Van Hoesen and Pandya (1975) |
| Ventral HPC | | | Amygdala | |
| Amygdala | | | CA1 (*controversial)* | Canning and Leung (1997), Furtak et al. (2007), Liu and Bilkey (1996), Suzuki and Amaral (1994), Witter et al. (1989), Witter et al. (1988) |

(Continues)

**TABLE 1** (Continued)

| B. Extra-HPC structural connectivity | | | | |
|---|---|---|---|---|
| **INPUTS from →** | **to** | **from** | **→ OUTPUT to** | **References[b]** |
| Dorsal HPC | POR | | EC | Agster and Burwell (2013), Burwell and Amaral (1998) |
| Ventral temporal cortex | | | Dorsal CA1 | Broussard, Sarter, and Givens (2006), Kloosterman et al. (2003), Majak and Pitkänen (2003), Naber, Caballero-Bleda, Jorritsma-Byham, and Witter (1997), Pitkänen et al. (2000), Posner and Petersen (1990), Shi and Cassell (1997), Vaudano, Legg, and Glickstein (1991) |
| Posterior parietal cortex | | | Subiculum | |
| Dorsal retrosplenial cortex | | | Lateral posterior nucleus of the thalamus | |
| Amygdala | | | Amygdala | |
| EC<br>CA1<br>PRC<br>Thalamus<br>Subiculum | Amygdala | | EC (mainly layer III and layer V)<br>CA3 region<br>PRC<br>Subiculum | Pitkänen et al. (2000) |
| CA1<br>CA3<br>Subiculum<br>SuM | Septum (LS) | Septum | Thalamus<br>SuM<br>MS<br>HPC (via the fimbria-fornix pathway)<br>HPC through amygdala (ventral pathway) | Amaral and Witter (1989), Amaral and Witter 1995), Borhegyi, Maglóczky, Acsády, and Freund (1998), Borhegyi and Freund (1998), Kiss, Csáki, Bokor, Shanabrough, and Leranth (2000), Leranth and Frotscher (1987), Leranth and Kiss (1996), Risold and Swanson (1996), Vertes (1992), Vertes and Martin (1988) |
| | | MS | EC | Viney et al. (2018) |
| Septo-HPC | SuM | | HPC (mainly DG)<br>MS<br>dHPC | Haglund, Swanson, and Köhler (1984), Maglóczky et al. (1994), Vertes (1992), Vertes and Martin (1988) |
| | medial SuM | | DG (the inner molecular layer of its ventral part)<br>and the CA2-CA3a HPC pyramidal layer | Soussi, Zhang, Tahtakran, Houser, and Esclapez (2010) |
| | lateral SuM | | supragranular layer of the DG, mainly its dorsal part | Soussi et al. (2010) |
| | Thalamus | | EC layers I, III and V<br>Subiculum | Wouterlood et al. (1990) |
| MS and Subiculum | VMT/ RE | | HPC, paraHPC regions and PFC<br>basolateral amygdala | Griffin (2015) |
| EC | PCC | | EC<br>CA1, CA3, DG and subiculum | Burwell and Amaral (1998), Insausti et al. (1997), Jones and Witter (2007), Suzuki and Amaral (1994) |

[a]Controversial.
[b]See reference list in the manuscript.

The HPC, hypothesized to be a convergence zone between TL networks, may allow the formation of such memory by expressing an integrated representation of multifaceted and multimodal information. We will see in the following sections how TL structures work in cooperation with the HPC to form this integrated representation, as well as how they code and process cognitive information in general, beyond spatial memory.

### 2.1.1 | Functional hippocampal-entorhinal processes in declarative memory

In humans, HPC and EC play a crucial role in declarative memory (Fell et al., 2006), the memory which involves, on a daily basis, specific conscious information, from general facts to detailed events, that is, from general knowledge to past experiences regarding our life (Hasselmo & McClelland,

1999). Declarative memory gathers episodic memory (contextual) and semantic memory (non-contextual) (Buzsáki, 2005). Examples are, what did you do during your last holidays and what is the capital of New Zealand, respectively. While the former would be retrieved with a context associated with it (e.g., who you were with, how was the weather), the latter does not need any contextual information to be recalled (the answer is simply *Wellington*).

Successful memory formation is accompanied with an initial increase of synchronization of the HPC-EC pathway, reflecting a fast coupling (coordination) between these two regions, followed by a desynchronization (HPC-EC decoupling). This suggests that effective declarative memory is accompanied by a direct but temporally limited cooperation between structures of the TL, especially of the medial TL (Fell, Klaver, et al., 2003; Fell, Klaver, Elger, & Fernández, 2002; Fell et al., 2001; Fell, Staedtgen, et al., 2003). Nevertheless, further development has been made regarding the implication of coupling/decoupling in declarative memory, associated with high-frequency band synchronization (coupling) versus low-frequency band desynchronization (decoupling). The former is established in the HPC between theta and gamma bands while the latter occurs in the neocortex between alpha and beta bands (for review, see Hanslmayr, Staresina, & Bowman, 2016). Such hippocampal–neocortical dichotomy of coding an episode may be complementary to ensure the successful encoding of a memory. The HPC synchronization (e.g., the power increase of theta or gamma oscillations) may permit the binding of the episode from its constituents as a conjunctive representation; the neocortical desynchronization (e.g., power decrease of alpha/beta oscillations) may associate such episode to a given/appropriate context (contextual representation). For example, 20–40 Hz coordination of inputs between distinct neuronal ensembles from both lateral EC and distal CA1 (*Corne d'Ammon 1*), the first and main region of the HPC (Figure 1c-d), has been recently described during associative learning in rodents (Igarashi, Lu, Colgin, Moser, & Moser, 2014).

HPC-EC connectivity is therefore a key factor in the formation of general cognitive processes (Aronov, Nevers, & Tank, 2017); for review see (Buzsáki & Moser, 2013). In an elegant study using transgenic mice whose EC layer III inputs to the HPC have been inactivated, authors indeed showed that these mice presented spatial working memory deficits in a trace-fear conditioning task (Suh, Rivest, Nakashiba, Tominaga, & Tonegawa, 2011). These results confirmed a critical involvement of this HPC-EC pathway in temporal association memory. Other recent studies have shown common coding (phase-coded) mechanisms for spatial and episodic memory in the HPC and the EC (Deuker, Bellmund, Navarro Schröder, & Doeller, 2016, but see, Tanaka et al., 2018), with a role in social aspects of cognition being also reported (Tavares et al., 2015). These findings highlighted that the HPC-EC system encompasses a role beyond spatial navigation.

In their review, Buzsaki and Moser (2013) stated that in order to support efficient memory, "a neural system evolved for navigation must meet two more requirements. It must have the capacity to store large quantities of seemingly unrelated, or orthogonal, representations, and it must be able to self-generate temporally evolving cell assembly sequences," justifying that the HPC-EC network would be suited to meet such requirements. Nevertheless, a debate about whether stored memories, especially semantic information, still depend on the HPC once they have been consolidated or simply become HPC-independent is still ongoing (Moscovitch, Cabeza, Winocur, & Nadel, 2016).

### 2.1.2 | Beyond a role of the hippocampus in pure spatial navigation

The traditional view confers the HPC an exclusive role in spatial memory. Spatial memory corresponds to the ability to find our way in a given environment based on spatial information previously encoded. Place cells, which fire when the animal is at a particular location, thus defining specific spatial firing (receptive) fields (O'Keefe, 1976; O'Keefe & Dostrovsky, 1971), have been described to remap not only in new environments (global remapping; Fyhn, Hafting, Treves, Moser, & Moser, 2007; Leutgeb, Leutgeb, Moser, & Moser, 2007) but also with new goal-oriented behaviors despite familiar environments (Dupret, O'Neill, Pleydell-Bouverie, & Csicsvari, 2010), for a review see (Hasselmo & Stern, 2015).

The implication of the HPC in cognitive processing is thus dual: While some authors still refer to the Cognitive Map Theory (O'Keefe & Nadel, 1978) whereby the HPC would exclusively code spatial processing necessary for navigation, with non-spatial constituents (e.g., time and item) only coming into play if they require spatial processing, the literature goes more and more into the direction of assuming that the HPC has a main general role in binding information, comparing it with previously stored knowledge and producing a signal depending on this comparison (Olsen, Rondina, Riggs, Meltzer, & Ryan, 2013; Yonelinas, 2013). We support this latter updated view in our review.

The key debates thus lie in the challenged view of the HPC beyond its sole role in spatial navigation, exploration and memory. We will now start discussing its updated role in encoding and retrieval processes, then later on its proposed role as a "convergence zone."

### 2.1.3 | Updated role of the hippocampus in encoding and retrieval processes

Lately, the HPC has been hypothesized to bind elements of the same episode into a coherent representation of this episode

(Backus, Bosch, Ekman, Grabovetsky, & Doeller, 2016). These encoded episodes will form lasting memory representations which are later available for pertinent recall. Indeed, more important than the encoding of information is the retrieval of information which remains a matter of debate (see Ben-Yakov, Rubinson, & Dudai, 2014). Retrieval of information implies one or two phases. First, a rapid and unconscious HPC-dependent reactivation occurs through the priming of relational features, as episodic memory is compositional: Each element of that memory can be retrieved individually or in relation to each other. Then, an explicit (conscious) recollection of the whole episode (mental representation) is governed by HPC and parietal/prefrontal regions, if we consider explicit memory requiring selective attention (Henke, 2010).

A current debate in human research still investigates whether the same HPC subregions—anterior HPC (aHPC) versus posterior HPC (pHPC)—and the same HPC cells are involved in both the encoding and the retrieval of memory information or whether the aHPC preferentially codes for memory encoding while the pHPC codes for the retrieval of information. A recent study has shown that the encoding and the retrieval of activity patterns do not follow a topological gradient along the longitudinal HPC axis but a dorsoventral gradient (Nakamura & Sauvage, 2016). The authors found that the encoding and retrieval of afferent input activity patterns taking place in the rat dorsal HPC (pHPC in humans) were able to predict successful completion of the memory task by the animals; however, such prediction was not visible in the ventral HPC (aHPC in humans). These results reconciled views by showing that while encoding and retrieval processes per se are not segregated along the HPC long axis, the predictive activity of memory performance occurs specifically in the dorsal HPC in rodents (pHPC in humans). Encoding and retrieval had moreover been found to be promoted by the activation (encoding) or reactivation (retrieval) processes of the same cells. Memory processes thus occurred in the same cells located in the dorsal HPC in rats, which can be translated to the pHPC in humans, as the task authors used in their study was selected for its translational feature to be further applied in humans (Nakamura & Sauvage, 2016).

Another question is whether retrieval implies recurrent retrieval or re-encoding processes. Several mechanisms have been proposed, usually involving sharp wave ripples (for a review see (Buzsáki, 2015); cf. section 3.3). The basic idea is that the recall of specific features of an event—consciously or unconsciously—will reinstate the entire memorized episode by reactivating the appropriate oscillatory cycles and associated representations (Moscovitch et al., 2016) (Figures 2 and 3).

Lastly, how HPC integration can segregate neuronal representations of similar events in order to avoid interference (i.e., memory overlap) during retrieval of such events (Favila, Chanales, & Kuhl, 2016; Rolls, 2016) requires further attention. One mechanism hypothesized to play a role in disambiguating similar features of an event or similar events is pattern separation, or orthogonalization, of activities within the Dentate Gyrus (DG)—CA3 (*Corne d'Ammon 3*) network (Chadwick, Bonnici, & Maguire, 2014; Kassab & Alexandre, 2018; Lacy, Yassa, Stark, Muftuler, & Stark, 2010; Leutgeb et al., 2007), the two other main regions of the HPC (Figure 1c-d); for review see (Buzsáki & Moser, 2013). A more radical hypothesis involves a differentiation described as "push[ing] representations past the point of orthogonalization" (Favila et al., 2016) or even "repulsion of hippocampal representations" by other authors studying the question in humans using neuroimaging (fMRI; Chanales, Oza, Favila, & Kuhl, 2017). According to these authors, "repulsion necessarily requires that an event's representation is directly shaped by a similar (competing) event's representation." During encoding, two potential networks have been suggested to have a role in preventing interferences between familiar and novel environmental representations: The ventro-medial thalamic nucleus (VMT), and the perirhinal cortex (PRC), a cortical region located in the medial TL (Figure 1b-c), together with the HPC, maybe constituting all together a cooperative "anti-interferences" network.

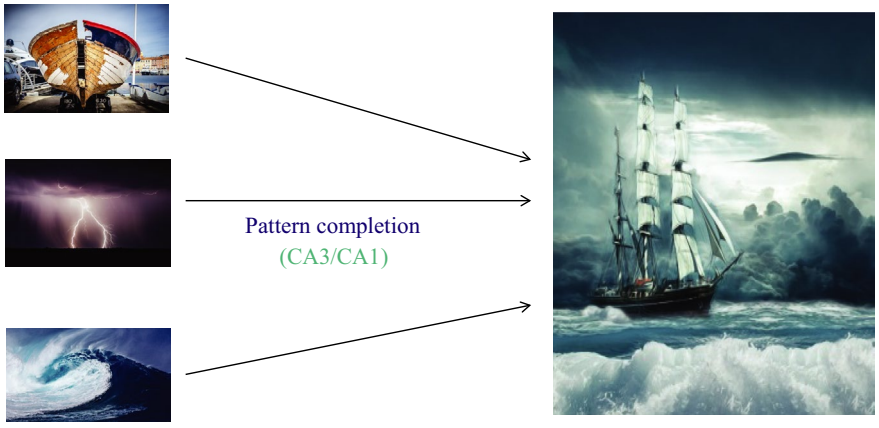


**FIGURE 2** Pattern completion. Retrieval of a whole episode (displayed in details in Figure 3) via the recall of a single cue (either from the top cue or from the middle and bottom cues) via CA3 and/or CA1 pattern completion mechanisms

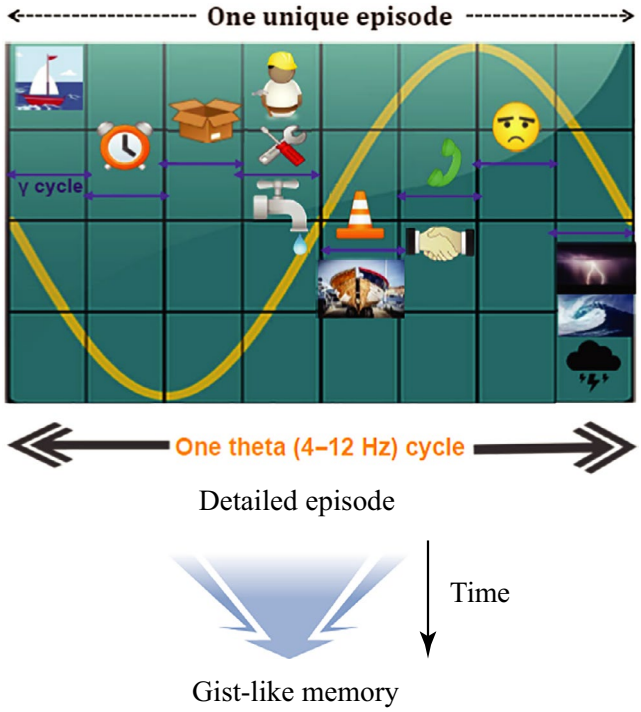


**FIGURE 3** Encoding of multi-featured input patterns into a unique episode within a single theta (assembly sequence) cycle. Encoding of a unique episode represented by multifaceted input patterns constituting the event. Each feature is implemented within a gamma assembly sequence (~10–30 ms) nested in a theta oscillatory (4–12 Hz) cycle (~100 ms). This detailed representation of the episode will develop over time to be coded as a gist-like memory, where details about the episode will slowly fade out and switch to a semantic-like representation of the event

More recently, Kassab and Alexandre implemented a new computational model of pattern separation and suggested that distinct circuits within the DG-CA3 network would be selected according to several criteria (Kassab & Alexandre, 2018). Such criteria would be determined by the necessary amount of pattern separation and by network resources. According to the authors, the necessary amount of pattern separation would be defined by the DG hilar region. The latter is a convergence zone for external and intrinsic HPC signals, according to bottom-up (e.g., degree of similarity between two spatiotemporal input patterns) and top-down factors (e.g., emotional and motivational affect) which would modulate pattern separation processes. Each specific circuit of pattern separation would underlie a particular mechanism, identified by the model: sparsification, inhibition and orthogonalization. Further experimental evidence is however required to validate this newly proposed model.

As a summary, these findings challenge (a) the segregation of encoding and retrieval processes along the HPC long axis but reveal a dorsoventral gradient and confirm that the same HPC region (dorsal HPC in rodents/ pHPC in humans) support both processes, (b) the classical view according to which specific HPC structures are involved either in pattern completion or in pattern separation, both key mechanisms for the specific retrieval and encoding of information, respectively.

### 2.1.4 | Associated mechanisms

Based on Hebb seminal postulate, according to which memories are stored in the brain as modifications of synaptic connection strength between neurons, the synchronization of oscillatory activities between brain regions appear to be a good candidate for memory encoding (Buzsáki, 2010; Fell & Axmacher, 2011). However, a real conundrum in episodic memory lies in the fact that both synchronization and desynchronization occur during memory encoding. As synchronization processes have been mostly described within the medial TL while desynchronization has been mostly described in the neocortex, how a synchronized HPC and a desynchronized neocortex code memories is the question that Parish, Hanslmayr, and Bowman (2018) tried to answer with their recently published "Sync/deSync" model. The authors found that both neocortical desynchronization and HPC synchronization were associated with successful encoding and retrieval (Buzsáki, 2010; Fell & Axmacher, 2011; Hanslmayr & Staudigl, 2014; Hanslmayr, Staudigl, & Fellner, 2012; Parish et al., 2018). This may apply in the context of physical spatial navigation, mental travel (imagination, future thinking) and navigation (virtual-reality tasks), problem-solving and decision-making tasks, perceptual discrimination and working memory tasks.

Hippocampal–entorhinal functional connectivity has also been associated with the coupled activity of time-dependent oscillatory processes, that is, theta and gamma oscillations (cf. section 3), which selectively modifies both feedforward (mossy fibers and synapses of the perforant path, cf. Figure 1d) and feedback connections (CA3 recurrent collaterals) via different mechanisms. Excellent reviews emphasized the role of theta-gamma coupling as a crucial neural code for mnemonic processes within the HPC-EC network (e.g., Colgin, 2015; Lisman & Jensen, 2013; but see also Aru et al., 2015).

Finally, as encoding requires NMDA (*N-methyl-D-aspartate)* receptors whereas recall recruits AMPA (*α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid*) receptors, distinct underlying mechanisms may be at play (for review see (Rolls, 2017).

## 2.2 | Anterior/posterior human hippocampus functional dichotomy

The functional dissociation between posterior and anterior HPC in humans shapes the debate presented here. This distinction along the HPC longitudinal axis was first introduced by Ramon and Cajal (1901–1902), followed by (Lorente de Nò, 1934). The functional association of such

HPC dichotomy is still under debate. The traditional view attributes a role to the pHPC in humans, also called the septal pole, in mnemonic processes, in particular in spatial memory processes, and a role to the aHPC in humans, also called the temporal pole, in behavioral aspects, especially the ones related to stress and emotions. Corroborating these data, gene expression studies revealed a correlation of the pHPC in humans (dorsal HPC in rodents) with cortical brain areas and of aHPC in humans (ventral HPC in rodents) with brain areas involved in emotional- and anxiety-related behaviors, as amygdala and hypothalamic nuclei (Dong, Swanson, Chen, Fanselow, & Toga, 2009; Thompson et al., 2008; both from adult mouse brain); for a review, see (Fanselow & Dong, 2010). Later anatomical and functional connectivity studies revealed connections of the pHPC with posterior neocortical regions involved in perception, and of the aHPC with anterior regions such as the ventro-median prefrontal cortex and the lateral temporal cortex (Aggleton, Wright, Vann, & Saunders, 2012) involved in schematics and semantic information (e.g., what is usually in a kitchen or how a balloon must stand in the air (Figure 4) (Bonner & Price, 2013) for a review see (Ranganath & Ritchey, 2012; Strange, Witter, Lein, & Moser, 2014). A new picture then arises: aHPC connected to areas involved in semantic memory and emotions may be involved in general knowledge or locations where episodes occur, thus coding for "coarse map-like representations" whereas the pHPC would be coded for perception and precise locations, associated with finer-grained map-like representations of events (for review see Morton, Sherrill, & Preston, 2017; Moscovitch et al., 2016; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013). aHPC has also been proposed to encode novel items and code for the conceptual aspects of an event whereas the pHPC may encode familiar and repeated items and code for the perceptual nature of an event (Poppenk et al., 2013). The HPC may thus discriminate the processing of semantic versus episodic information along its anterior/posterior longitudinal axis in humans.

In rodents, ventral HPC place cells have been identified with larger spatial receptive fields (i.e., place fields) than place cells in the dorsal HPC (Strange et al., 2014). This gradient of place fields' size along the rodent HPC dorsoventral axis, if homologous to the anterior–posterior axis in primates, may impact the scale on which memories get integrated. For example, larger place fields (aHPC) may represent experiences occurring at distinct locations within the same context/environment (Keinath et al., 2014). Temporal coding may also vary according to the same scheme (Dandolo & Schwabe, 2018; Long, Bunce, & Chrobak, 2015; Morton et al., 2017; Schlichting, Mumford, & Preston, 2015). Similarly, the medial prefrontal cortex (PFC), with its anterior and posterior subregions, has also been shown to exhibit distinct integration patterns mimicking the functional dichotomy of aHPC versus pHPC (Schlichting et al., 2015), though more work is

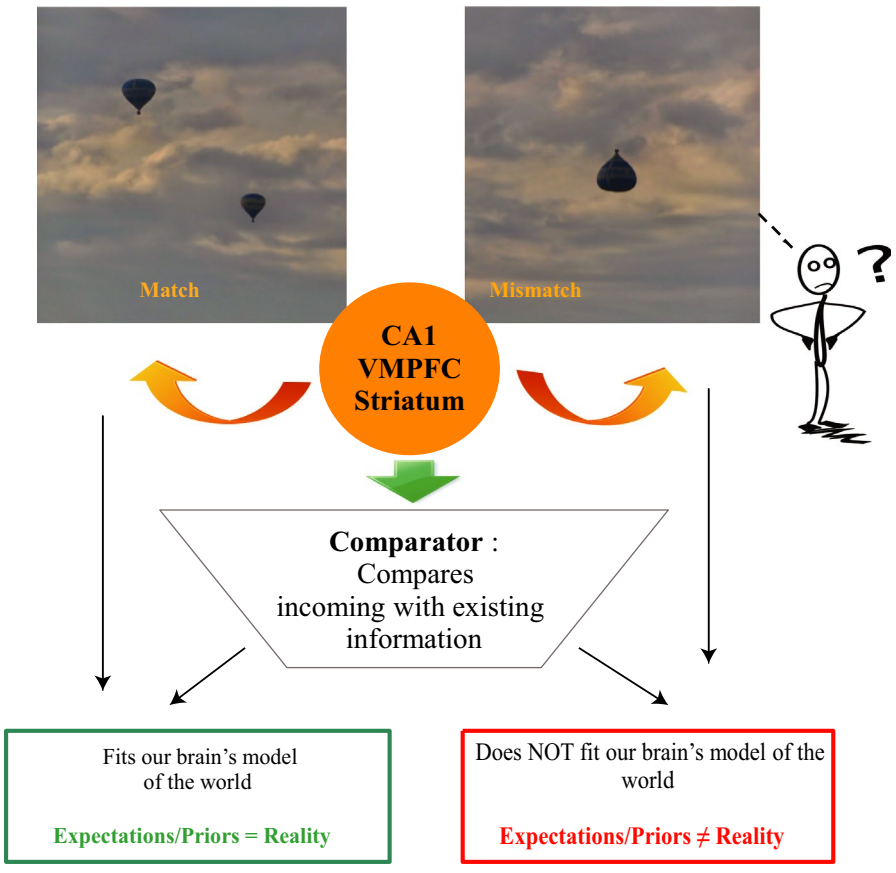


**FIGURE 4** Match–mismatch detector. If the information we process fits the model our brain created about the world, that is, our prior experience and expectations about how the world works, it is a match; otherwise, a mismatch. In the example, our brain learned in which direction an airballoon is supposed to fly, generating a match or a mismatch, immediately calling our attention accordingly. Match–mismatch detection occurs by comparison between incoming information from the world and intrinsic existing knowledge our brain has previously stored. The comparator network is mainly constituted of CA1-ventro-median PFC-striatum network. *VMPFC*: ventro-median PFC

needed to confirm a similar functional distinction between human medial PFC subregions. Finally, we will see how HPC is newly defined as a *convergence zone*.

## 2.3 | The hippocampus as a "convergence zone"

Mnemonic convergence is defined by the integration of distributed information which is processed by different brain networks and bound into a unique episodic memory. HPC has been hypothesized to be a *convergence zone*, processing and integrating incoming information from the PRC (objects, i.e., non-spatial) and the paraHPC (scenes, i.e., spatial) cortices (Backus, Bosch, et al., 2016; Staresina & Davachi, 2009; Staresina, Duncan, & Davachi, 2011), probably also from higher brain regions, especially the medial PFC, to integrate memory (Backus, Schoffelen, Schoffelen, Szebényi, Hanslmayr, & Doeller, 2016; Sekeres, Winocur, & Moscovitch, 2018). Moreover, while the HPC long axis has been reported to carry a temporal reorganization of stored information from detailed episodic memories to schematics (semantic-like or gist-like) representations, from the pHPC to the aHPC and medial PFC, respectively (Dandolo & Schwabe, 2018), see review of (Sekeres et al., 2018), we are more in favor of a gradual (temporal) evolution of stored information from unstructured to structured knowledge which can then be retrieved to not only recall the entire episode as reminiscence (the subjective experience of remembering, also called autonoetic consciousness by Tulving) but also to extract useful information learned over past experiences and address it into a new context which can be useful for current decision-making process, future planning and action selection (Tompary & Davachi, 2017). When indeed faced with a new decision to take or a new problem to solve, we tend to reflect on the content of previous experiences stored as past memories to drive our choices and/or actions. This is achieved via the PFC. Specific elements of past experiences can be reactivated within the HPC (especially CA1) and PRC regions, while using these elements to make further choices (Mack & Preston, 2016). The newly mnemonic convergence function of the HPC binding discontiguous elements received from distributed regions into a coherent episodic representation has been hypothesized to imply the overlap of conjunctive coding and hub-like, highly interconnected networks, though the mechanisms remain to be defined. In that case, HPC would serve for binding, and higher attentional PFC networks together with the VMT sending information back to the HPC may constitute such a hub. Conjunctive coding may apply via HPC (theta/gamma) synchronization and/or via neocortical (alpha/beta) desynchronization. We will now tackle another update in the field of TL functions in cognitive processes, addressing the debate about recollection and familiarity.

## 2.4 | Recollection versus familiarity: a brief update on where we are/Is familiarity a "binding failure"?

Debates are still animated about which TL structures are involved in recollection versus familiarity. However, we will not go through the details as this topic has already been addressed in several good reviews (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Lech & Suchan, 2014; Ranganath et al., 2004) but only touch on the main points of the debate with key references.

The debated aspect is the role of the paraHPC in familiarity-judgments, in particular the lateral EC and PRC cortices, and whether this role is governed by the HPC, the same region as for recollection. Conflicting results have recently emerged regarding the role of HPC in familiarity processes (Atucha, Karew, Kitsukawa, & Sauvage, 2017). One reason for this is the distinct contribution of CA1 and CA3 HPC subfields in familiarity processes. Authors have found that compared to CA1 and CA3, the lateral EC, especially its deep layers, is recruited in familiarity-judgments. This study showed the first evidence that familiarity and recollection do not share the same cerebral substrates (Atucha et al., 2017).

To reconcile views, the use of different experimental paradigms instead of generalizing cognitive mechanisms or thinking in terms of representations instead of cognitive processes has been suggested (Lech & Suchan, 2014). In his last paper, Eichenbaum wrote, "In my view, the demand for hippocampal function in 'recollection' depends on the extent to which performance normally benefits by memory of items in the context of the study experience." (Eichenbaum, 2018). We could also hypothesize that familiarity may be the result of a binding failure where context has not been bound to its related event.

## 2.5 | Is the "what and where" entorhinal cortex dual stream hypothesis still applicable?

The debate presented here stands in the controversy about the functional dichotomy of the medial (MEC) and lateral part (LEC) of the EC. The question is whether this functional dichotomy still applies to the traditional "*what* versus *where*" dual stream hypothesis.

A clear dichotomy between MEC and LEC has yet to be established (Kerr, Agster, Furtak, & Burwell, 2007; Sewards & Sewards, 2003). This dichotomy within the EC is part of a general theory of two distinct processing pathways, with the MEC belonging to the dorsal pathway (i.e., the "where" stream, consisting of spatial processing) and the LEC to the ventral pathway (i.e., the "what" stream, consisting of non-spatial processing (Mishkin, Ungerleider, & Macko, 1983). These two streams converge to the HPC which will link both

spatial and non-spatial information within a single episodic representation (Save & Sargolini, 2017). In accordance with this "dual-stream hypothesis," a study found that the LEC (and the PRC) processed information about items ("what" stream) whereas the MEC (together with the postrhinal cortex) processed information about spatial locations ("where" stream), with both types of information integrated within the HPC (Beer, Chwiesko, Kitsukawa, & Sauvage, 2013). However, recent findings, especially MEC/LEC lesion studies, have challenged the dual stream hypothesis. A study showed that MEC could carry distinct information types, as position, time, object location and context (Keene et al., 2016), attributing to the MEC more complex functions for memory encoding than previously found (Hardcastle, Maheswaranathan, Ganguli, & Giocomo, 2017; Lisman et al., 2017). MEC and LEC functions can thus be segregated depending on behavioral and cognitive demands rather than on the nature of the information (spatial vs. non-spatial, but see Lech & Suchan, 2014). For example, it has been reported that there is a differential involvement of MEC and LEC in goal-directed navigation versus exploration while both regions were activated during high-cognitive demand, that is, when a large amount of information had to be processed and complex relationships between afferent input patterns had to be made. From this view, the separated "what" and "where" information integrated by the dual EC inputs into a conjunctive representation is conveyed to the HPC to be further bound as an episodic memory. Super high-resolution fMRI could be a way to resolve this dual-input dichotomy in humans (Lisman et al., 2017). Another suggestion has been made regarding the functional MEC/LEC dichotomy, with a role of MEC in "properties of self" and of LEC in "properties of the external world" (Lisman et al., 2017), echoing the pHPC/aHPC dichotomy (cf. section 2.2).

Further debate arises with studies on grid cells suggesting a weak role of MEC in spatial processing when other studies found the opposite result, hence the controversy. MEC inactivation leads to CA1 time cell impairments and memory deficits (Robinson et al., 2017) whereas spatial and object representations remain unaffected (Igarashi et al., 2014; Sasaki, Leutgeb, & Leutgeb, 2015); for review see (Igarashi, 2016; Save & Sargolini, 2017).

In conclusion, the "what and where" dual stream hypothesis does not seem up-to-date. By contrast, a role of MEC and LEC beyond spatial and non-spatial processes, respectively, has gained support, with an involvement in various types of information processing and a dependence on task demands.

## 2.6 | Functional dichotomy along hippocampal brain regions: CA1 versus CA3

The functional roles carried by the two main HPC subfields, CA1 and CA3, remain a matter of debate. Recent studies have found that proximal CA3 and distal CA1 were involved in non-spatial processes whereas distal CA3 and proximal CA1 preferentially coded for spatial information (Flasbeck, Atucha, Nakamura, Yoshida, & Sauvage, 2018). Similarly, dorsal CA3 was shown to be tuned to spatial demand of the task whereas dorsal CA1 was comparably involved in both spatial and non-spatial processes (Beer, Chwiesko, & Sauvage, 2014); however, the ventral parts of both CA1 and CA3 were involved in both spatial and non-spatial processes with a preferential tuning toward spatial processes (Beer et al., 2014). A more recent study identified a greater proportion of cells involved in cognitive processes within the dorsal HPC compared to the ventral HPC for all HPC subregions (CA1, CA3 and DG, Chawla, Sutherland, Olson, McNaughton, & Barnes, 2018).

Regarding the retrieval of information, the admitted role of CA3 in recalling information through pattern completion also remains debated (Brun, 2002; Florian & Roullet, 2004; but see Rolls, 2017). A recent study revealed that CA1 and CA3 differentially support the retrieval of item features within episodes using a virtual-reality paradigm in human subjects. While CA1 was coding for items belonging to the same or similar related context, CA2-CA3-DG were discriminating between items within the same context (Dimsdale-Zucker, Ritchey, Ekstrom, Yonelinas, & Ranganath, 2018). This dichotomy within HPC subfields for episodic retrieval reflects how we are able to recollect specific information of our memories with accurate details. However, for very remote memories, CA3 does not seem to be needed, as compared to CA1. The paraHPC region, on the other hand, has been found to be fully activated during such processes (Lux, Atucha, Kitsukawa, & Sauvage, 2016). As the authors suggested, these findings open the way to the contribution of the temporoammonic pathway taking over the trisynaptic pathway for remote retrieval processes (Lux et al., 2016). Computational studies stated that CA1 coding has also been associated, compared to CA3, with the features extraction within the environment and their relatedness among episodes (Bahar & Shapiro, 2012). Human and rodent data have supported such findings (Hoge & Kesner, 2007; Johnson & Rugg, 2007), attributing CA1 a favoring role in memory integration. This is in line with CA1 integration of both spatial features coming from the EC and context-dependent features coming from CA3 via active dendritic mechanisms (Bittner et al., 2015). CA1 connectivity could indeed be a candidate underlying its privileged function. In humans, CA3 size has been correlated with neural interference between CA3 episodic memories, thus with the confusion of past memories retrieval (Chadwick et al., 2014). In contrast, CA1 has been described as a match–mismatch detector, detecting whether bottom-up extrinsic information coming from the outer world match our prior top-down expectations, that is, our model of the world, in cooperation with the ventro-median PFC and the striatum (Pine, Sadeh, Ben-Yakov, Dudai, & Mendelsohn, 2018) (cf. Figure 4).

In conclusion, these updated findings, aforementioned, specify the newly "integrated" role of the HPC in episodic memory. They highlighted (a) an intra-HPC CA1/CA3 "segregated" aspect of spatial versus non-spatial information processing, in addition to (b) an anterior-posterior HPC axis which segregates the processing of semantic versus episodic information and (c) a medio-lateral EC functional segregation of information processing (Figure 5). These results also highlight a dual segregation of spatial versus non-spatial information along the proximodistal and CA1-CA3 axes (Figure 5).

### 2.7 | Parahippocampal, perirhinal and postrhinal functions

A last ongoing debate about the function of TL structures in cognitive processes relies on the functional role of the paraHPC, perirhinal and postrhinal cortices.

PRC located at the top of the ventral visual "what" stream (object processing) has been described to be involved in the relational binding of perceptual and semantic features of items to facilitate their discrimination from other similar objects (Kivisaari, Tyler, Monsch, & Taylor, 2012). To support this view, the perirhinal and postrhinal cortices have been involved in carrying high processing and multimodal sensory information to the HPC via parallel pathways, one involving a direct projection and the other one a pathway through the EC (Furtak, Wei, Agster, & Burwell, 2007). This processing upstream the HPC into a coherent representation does not occur for simple features of visual processing as color or shape but really requires high-cognitive demand (Devlin & Price, 2007), as shown to be the case as well for the EC (Save & Sargolini, 2017). PRC function in visual processing corroborates studies across species with a broader functional repertoire (mnemonic, perceptual, linguistic). In humans, not fused (vs. fused) objects have been found in the left PRC (Rubin, Chesney, Cohen, & Gonsalves, 2013) which supports the perceptual binding of features coding for high-cognitive demand (i.e., highly integrated item representations) which needs to be fused upstream the HPC. Still in humans, functional connectivity between the right ventrolateral PFC, the posterior cingulate cortices and the PRC gets strengthened during recognition memory processing while during perceptual information processing, the fusiform regions shared reinforced functional connections with the PRC.

In summary, medial TL regions get distinctively involved in different information processing depending on their interactions with other cortical structures. This is in accordance with the recent shift in the implication of medial TL structures beyond long-term declarative memory, conquering cognitive domains as working memory, implicit memory and perceptual processing (O'Neil et al., 2012; Rubin et al., 2013).

In conclusion, we showed in this first part that the HPC and its associated extra-HPC TL structures play a role in processes beyond spatial navigation and object exploration, work in cooperation to form effective communication between functional networks, integrate multi-dimensional and multifaceted information into a unique memory (i.e., to create an integrated representation) and shape behavior in the context of general cognitive processes to drive our actions and build up our (episodic and semantic) memories. Next, we will review the mechanisms underlying TL-dependent cognitive processes, that is, oscillatory time-dependent processes, another emergent property of TL brain networks which plays a key role in the formation of such effective communication between distributed TL brain networks that underlie cognition.

## 3 | WHICH MECHANISMS UNDERLIE THOSE TL-DEPENDENT COGNITIVE PROCESSES?

Oscillations are ubiquitous emergent properties of E-I brain networks, in particular of TL brain networks, interconnected excitatory pyramidal cells and inhibitory GABAergic interneurons. Together they confer windows of opportunity to gate and route information within canonical brain circuits and complex neuronal networks. Brain oscillations are indeed a useful mechanism that provides convenient time frames and temporal structure to synchronize or coordinate distributed activity patterns between cell assemblies and neuronal ensembles in different brain areas or within layers to transmit a message. Within the TL, this message is often related to cognitive, and in particular, to memory processes, as we described in the previous sections. The interplay between E-I neurons within local or remote neuronal networks determine oscillation frequency. The latter infers the temporal structure within which a message can be transferred via synaptic gain increase to downstream targets. In the following sections, we will review how this temporal structure inferred by oscillatory processes underlies dynamic coordination between distributed TL networks to shape memory. We aim to provide an updated view, based on recent evidence, on how TL networks' function in cognition is intimately related with brain rhythms emanating from these networks. As comprehensive reviews already cover brain rhythms in rodents (Colgin, 2016; Colgin & Moser, 2010), we will focus on their role in shaping TL-dependent cognitive processes, especially memory, starting with the theta rhythm.

### 3.1 | Theta rhythm

#### 3.1.1 | Functional role of theta oscillations

Different functions of theta rhythm within the TL have been proposed, relative to the encoding and retrieval processes, for example, the facilitation of temporal interactions between

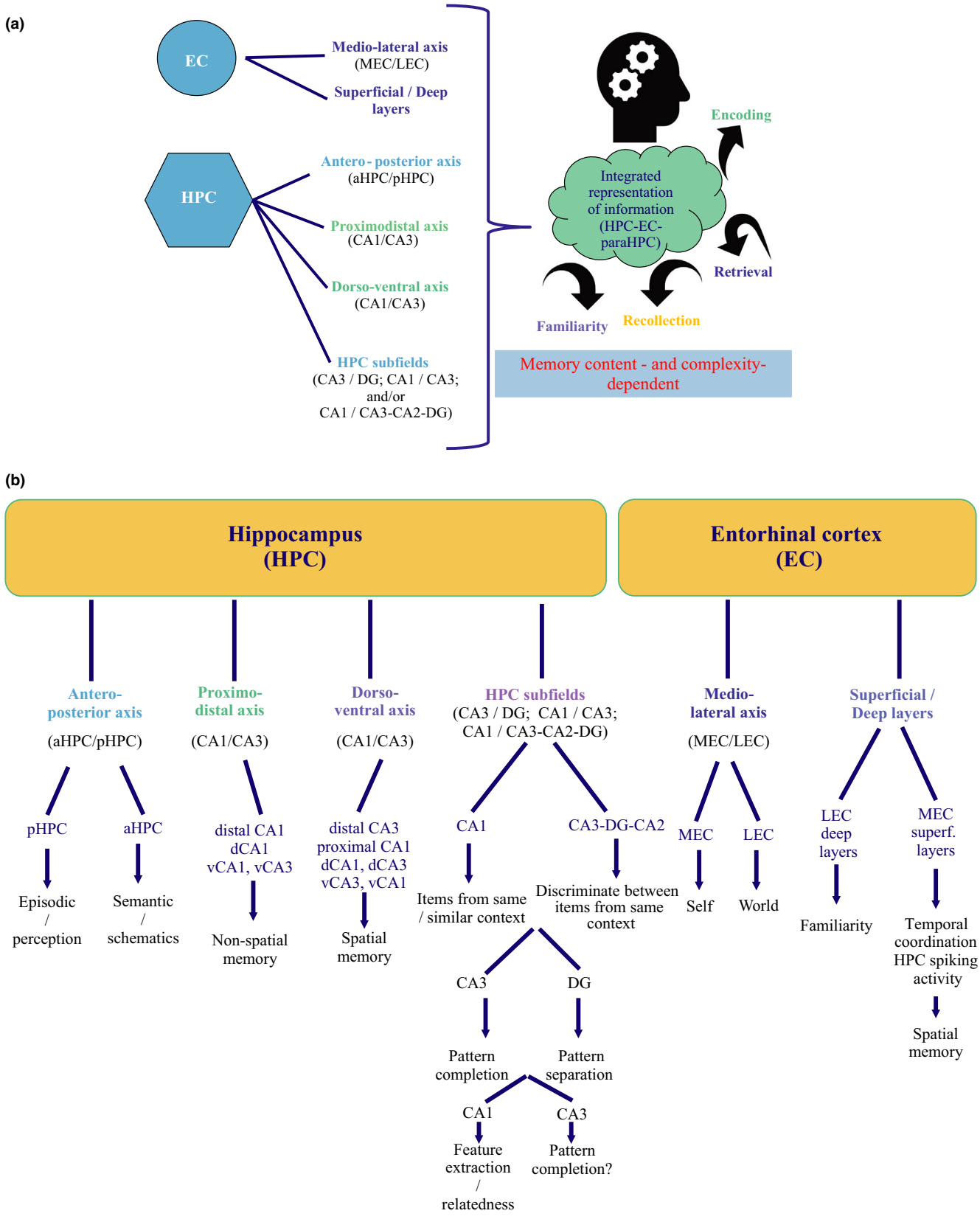


**FIGURE 5** (a) Summary of TL anatomical dichotomies covered in our review, reflecting functional segregations of information in order to shape a precise integrated representation of the whole episode, the latter containing all information within the HPC-EC-paraHPC network which, according to our view, may be dependent on memory content and complexity of information. (b) Detailed organizational chart specifying the functional dichotomies presented in (a) *aHPC*: anterior HPC; *pHPC*: posterior HPC; *dCA1*: dorsal CA1; *dCA3*: dorsal CA3; *vCA1*: ventral CA1; *vCA3*: ventral CA3; *superf.*: superficial

PFC and HPC (Benchenane et al., 2010; Hyman, Hasselmo, & Seamans, 2011; Hyman, Zilli, Paley, & Hasselmo, 2010; Kim, Delcasso, & Lee, 2011), the temporal distribution, or coordination, of AP output emitted by a selective portion of neuronal cell assemblies (e.g., place cells with overlapping place fields coding for the animal current, past and future position in its environment), the maintenance of neuronal cell assemblies decorrelated via inhibitory competitive mechanisms (e.g., place cells with non-overlapping place fields; Mizuseki & Buzsaki, 2014), all of these functions being key mechanisms in TL-dependent cognitive processes.

Theta rhythm can also be seen as a (convenient) selective mechanism whereby input activity patterns reaching the depolarizing peak of its oscillatory cycle will favor long-term potentiation (LTP) (Figure 6) whereas stimulation in the trough will induce (long-term) depression (LTD) (Huerta & Lisman, 1993), with LTP and LTD effectively shaping information processing. The same rule applies for beta and gamma oscillations (Wespatat, Tennigkeit, & Singer, 2004) in order, similarly, to shape cognitive behavior by selectively processing relevant (vs. irrelevant) information.

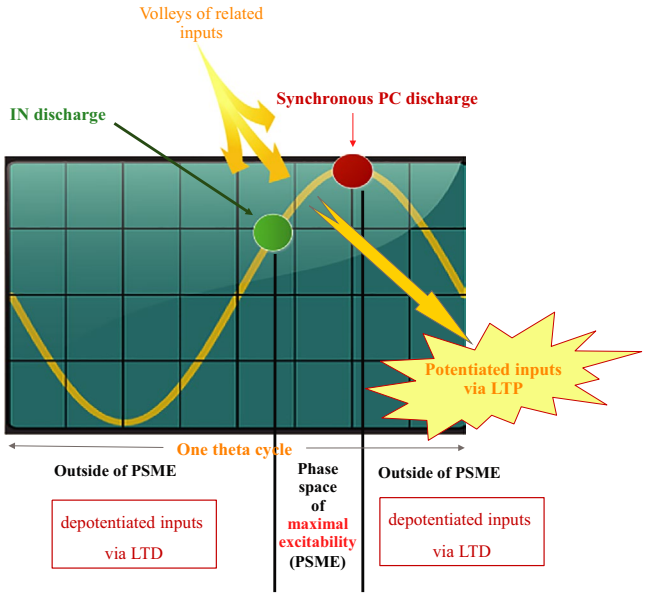


**FIGURE 6** General oscillatory mechanism. Schematics of how afferent related inputs, which need to be bound together, get potentiated when timely arriving around the depolarizing peak of the oscillatory cycle (theta in the example, likewise for gamma rhythm). The frequency of oscillations defines a window of opportunity (~ 100 ms for theta rhythm, ~ 10–30 ms for gamma rhythm) during which inputs can be either strengthened (in-phase) or weakened (if out-of-phase). Such time window corresponds to the phase during which postsynaptic neurons preferentially discharge as shunting inhibition is minimal. Such input potentiation, known as synaptic plasticity mechanism, is therefore time-dependent, relative to the temporal structure of ongoing oscillatory processes. For faster oscillations, as gamma rhythm, the window of opportunity is very short, compared to theta oscillations, thus providing a 10-fold more selective binding, gating and routing of information. *IN*: Interneuron; *PC*: Pyramidal cell; *PSME*: phase space of maximal excitability

An important point to note is that during theta-associated states, action potential outputs of the population of neurons firing together tend to fire less in synchrony but rather phase-distributed or phase-coordinated within the phase of theta cycles. Perisomatic inhibition is one mechanism which brings pyramidal cells firing closer together. Pairs of pyramidal cells thus become more correlated, hence more synchronized (i.e., tend to fire simultaneously) with other disinhibited pyramidal cells.

### 3.1.2 | Theta sequences and general cognitive processes

The admitted view of theta being critical in coordinating spiking activity during the processing of spatial information (e.g., during *phase precession*; Dragoi & Buzsáki, 2006; Foster & Wilson, 2006; but see; Lisman & Redish, 2009) has been reconsidered by recent studies which associate the emergence of place field generation in new environments with the absence or very low level of theta rhythm. One study was performed in bats, a species that exhibits low levels or no theta rhythmicity in their place cells firing activity despite successfully coding space via place cells (Yartsev & Ulanovsky, 2013). Another study was performed in septum-lesioned rats whose theta could not entrain spiking activity, although the rats could still encode space successfully through place fields' formation (Brandon, Koenig, Leutgeb, & Leutgeb, 2014). This suggests that theta could be a mechanism exclusively required to coordinate neurons within neuronal assemblies (Drieu, Todorova, & Zugaro, 2018; Mizuseki & Buzsaki, 2014) thus processing information at the neuronal ensemble level rather than at the single cell level (isolated place cells). This contrasted view opposes phase precession versus theta sequences (Feng, Silva, & Foster, 2015; Gupta, Meer, Touretzky, & Redish, 2012).

Indeed, theta sequences appear related to higher (more complex) demands requiring experience-dependency, learning (Feng et al., 2015), association with episodic memory (Wang, Romani, Lustig, Leonardo, & Pastalkova, 2015) and the coding of current goals (Wikenheiser & Redish, 2015), which appears in accordance with the updated view of the role of TL brain networks in cognitive functions highlighted in this review. This way, an entire and unique sequence of input patterns (e.g., spatiotemporal, feature-based, context-based) defining a unique episode could be recalled within a theta cycle (Colgin, 2015; Lisman & Jensen, 2013). As Colgin stated in her latest review, "theta rhythms link different cells together in functional ensembles that support memory operations by providing integrated representations of complex concepts and experiences." (Colgin, 2016). We support this view

which is congruent with our main hypothesis whereby any type of information (sensory, contextual, behavioral and mnemonic) gets processed, bound and integrated within the TL and its associated areas. Lastly, we will review how theta cycles underlie the newly updated role of TL brain networks in general cognitive processes.

### 3.1.3 | General role of theta oscillations in TL-dependent cognition

Recently, the notion that several distinct feature input patterns forming an entire episode are bound into a theta sequence that can be encoded and retrieved suggests that episodic memories are encoded as the sequential activation of functional neuronal ensembles by HPC (CA3 collaterals or CA3-CA1) connections. Indeed, related patterns of information would be stored in one theta cycle while unrelated information patterns would be discriminated into different theta cycles (Brandon, Bogaard, Schultheiss, & Hasselmo, 2013; Dupret, O'Neill, & Csicsvari, 2013; Jezek, Henriksen, Treves, Moser, & Moser, 2011); for detailed examples see the review of (Colgin, 2016). On these grounds, we may consider one theta cycle as one "bit" of information coding one sole episode, as a mechanism to link all detailed elements (multimodal and discontiguous input activity patterns) forming one (episodic) memory. This way, it becomes easy to understand how pattern completion may occur from the presentation of only one unimodal single element so that the whole episode bound with it gets quickly retrieved (cf. Figure 3).

Theta rhythm also has a prominent role in memory consolidation throughout its occurrence during REM sleep. However, we will not develop this point here, but refer the reader to the following reviews on the topic (Colgin, 2016; Watson & Buzsáki, 2015).

In summary, oscillatory processes in the theta frequency range underlie both spatial and non-spatial processes, supporting a key role of TL brain networks in general cognitive processes through theta cycles. Indeed, theta sequences, through their temporal structure, bridge effective communication between distributed TL networks (each structure processing distinct features of information) by sequentially and dynamically coordinating relevant patterns of information into their cycles, to integrate a mental representation of a unique episode gathering related multifaceted information, then allowing its fast and effective retrieval when necessary.

In conclusion, theta frequency appears to be a good candidate for coordinating both neuronal firing activity and the sampling of afferent sensory stimuli (Jutras, Fries, & Buffalo, 2013; VanRullen, 2016) in order to draw an integrative picture of the current environment (Colgin, 2016) (Figure 7), either directed toward immediate goals or in order to build episodic memories, then quickly retrieve them.

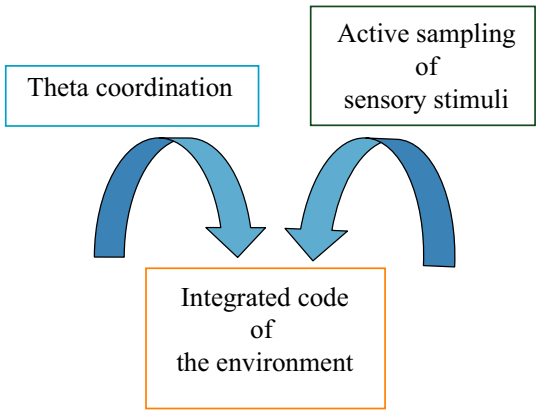


**FIGURE 7** Integration of the environment by theta oscillatory processes. Theta rhythm coordination coupled with the active sampling of sensory stimuli (perceptual rhythm at theta frequency) generates an integrated code of the environment

Next, we will review how gamma oscillations underlie TL-dependent cognitive processes.

## 3.2 | Gamma oscillations

Gamma oscillations and fast oscillations (>80Hz), in particular in the HPC, have been described to have a role in neuronal communication, for example, in the awake rat, where external inputs reach the HPC via the EC and gamma oscillations (Buzsáki, 1998). Synchronization of neuronal activity in the gamma frequency band allows the "binding" of neuronal representations (Gray & Singer, 1989; Singer, 1999a, 1999b) as well as the coupling of HPC and rhinal cortices activity during declarative memory formation (Fell et al., 2001). These oscillations have also been described as a physiological mechanism by which CA3-CA1 activity may be coordinated in order to retrieve previously encoded HPC-dependent information. For instance, during a working memory task where the power and coherence of CA3-CA1 gamma oscillations are increased at the decision point of the maze (Montgomery & Buzsaki, 2007). In other words, gamma activity allows the extraction of useful information from past experiences (e.g., trials) during which the rat learned which direction of the maze to go (left or right) in order to obtain reward. During working memory tasks, when several objects have to be kept in mind, one object is coded per gamma cycle nested in one theta cycle, as the window of opportunity of gamma cycle corresponds to cell assembly lifetime (10–30 ms; Buzsáki, 2006). It has also been shown that the activation of HPC gamma, through inhibition of the septal GABAergic transmission, improved cognitive performances (Ma & Leung, 2007).

Distinct types of gamma have been described. While slow gamma has been reported to be involved in the encoding of

bottom-up sensory inputs and in working memory, medial EC-driven fast gamma is key in memory retrieval and novelty detection (Bieri, Bobbitt, & Colgin, 2014; Zheng, Bieri, Hsiao, & Colgin, 2016; Zheng, Bieri, Trettel, & Colgin, 2015).

Gamma oscillations thus appear to represent a neuronal mechanism allowing relations between several activity patterns (distinct information types), binding them together, as a transient communication path, independently of any specific cognitive function, mostly in collusion with theta rhythm, as several gamma cycles appear nested in one theta cycle. This is in accordance with the updated view of an integrated representation of information bound via the HPC and described above. Through its cycles and as well as theta oscillations, gamma rhythms promote the encoding of separated but related patterns of activity necessary to complete the task at hand, extracting useful information from past experiences, encoding relevant information and processing general information.

Next, we will describe a third and last oscillatory mechanism which has been mostly described to underlie the retrieval of information, by comparison with theta and gamma oscillatory mechanisms which mainly occur during active sampling of the environment, the sharp wave ripple (SWR).

### 3.3 | Sharp wave ripples

One of the functional roles carried by sharp wave ripples (SWRs) is selective retrieval. Indeed during SWR, CA1 pyramidal cells, depolarized by sharp wave events, additionally receive shunting inhibition from ripples, which increases action potential threshold and prevents most cells from firing (Colgin, 2016).

There is a classical view and a new view concerning SWRs. The traditional view does not include SWR in the active sampling of afferent sensory inputs. SWR were rather attributed a functional role in offline processes as memory consolidation which mainly occurs during slow wave sleep (Chrobak & Buzsáki, 1996), leading to the creation of a lasting memory trace, or its erasure in case the pyramidal cells involved in SWR events were unable to overcome the shunting inhibition. During wakefulness, SWRs occur during quiet immobility and at the end of exploratory behaviors in a given environment (Axmacher, Mormann, Fernández, Elger, & Fell, 2006; Csicsvari, O'Neill, Allen, & Senior, 2007). In this case, the SWR is the mechanism during which the "reverse replay" of the spatial sequence previously encoded during exploration occurs (Foster & Wilson, 2006).

In contrast, the recent view confers SWR a role during online sampling of the environment. This occurs during transient periods when the animal stops between exploratory behaviors and may process future trajectories, for example, in decision-making or route-planning tasks. In spatial alternation tasks, successful trials corresponded to SWR coding the route that was subsequently followed. Another hypothesis is the involvement of SWR in intrinsically driven processes like path-integration-based type of mental navigation, episodic recall, future thinking and imagination (Colgin, 2016). Recently, an elegant study has shown that SWR appears to be the mechanism by which net synaptic depression during slow wave sleep occurs, down-regulating synapses carrying irrelevant information to allow the formation of relevant memories and the acquisition of subsequent new learning (Norimoto et al., 2018), but see (Kovács et al., 2016). This may explain why sleep deprivation confers a feeling of saturation of our ability to encode new memories, as synapses will be over-weighted therefore less neurally responsive to novel afferent information and/or less prone to potentiate the latter (Balduzzi & Tononi, 2013; Yoo, Hu, Gujar, Jolesz, & Walker, 2007).

In summary, ripples may be a selective mechanism whereby only pyramidal cells containing synapses which have been strengthened during encoding are worth escaping shunting inhibition. This way, information carried by these potentiated synapses can be sent to remote retrieval for long-term storage (memory consolidation). In addition to their admitted role in memory consolidation, SWRs appear to play a role while the subject samples the environment and prepares future moves (plans), in contrast to during passive exploration. This also grants support to the newly updated view of TL-dependent cognitive processes, where oscillatory processes underlie the encoding and retrieval of information beyond traditional aspects of spatial and non-spatial memory (e.g., goal-oriented behaviors).

Based on the aforementioned, we will now describe our proposed scenario on how TL structures process general information, encode and recall relevant memories, highlighting our hypothesis whereby complex information requires "*pre-binding"* upstream the HPC.

## 4 | PROPOSED SCENARIO

### 4.1 | Integrated view and "pre-binding" of complex information upstream the hippocampus

#### 4.1.1 | Integration of general information into a unique mental representation

To corroborate the new view presented in this review, namely that the HPC is involved in cognitive processes beyond spatial navigation and spatial memory, for example, in perceptual cognition, decision-making and planning, involving TL structures and the PFC cortex (Butler & Paulsen, 2015; Lisman et al., 2017; Schomburg et al., 2014; Shohamy & Turk-Browne, 2013), experience mapping may also occur when time or space variables are suppressed (Lisman et al.,

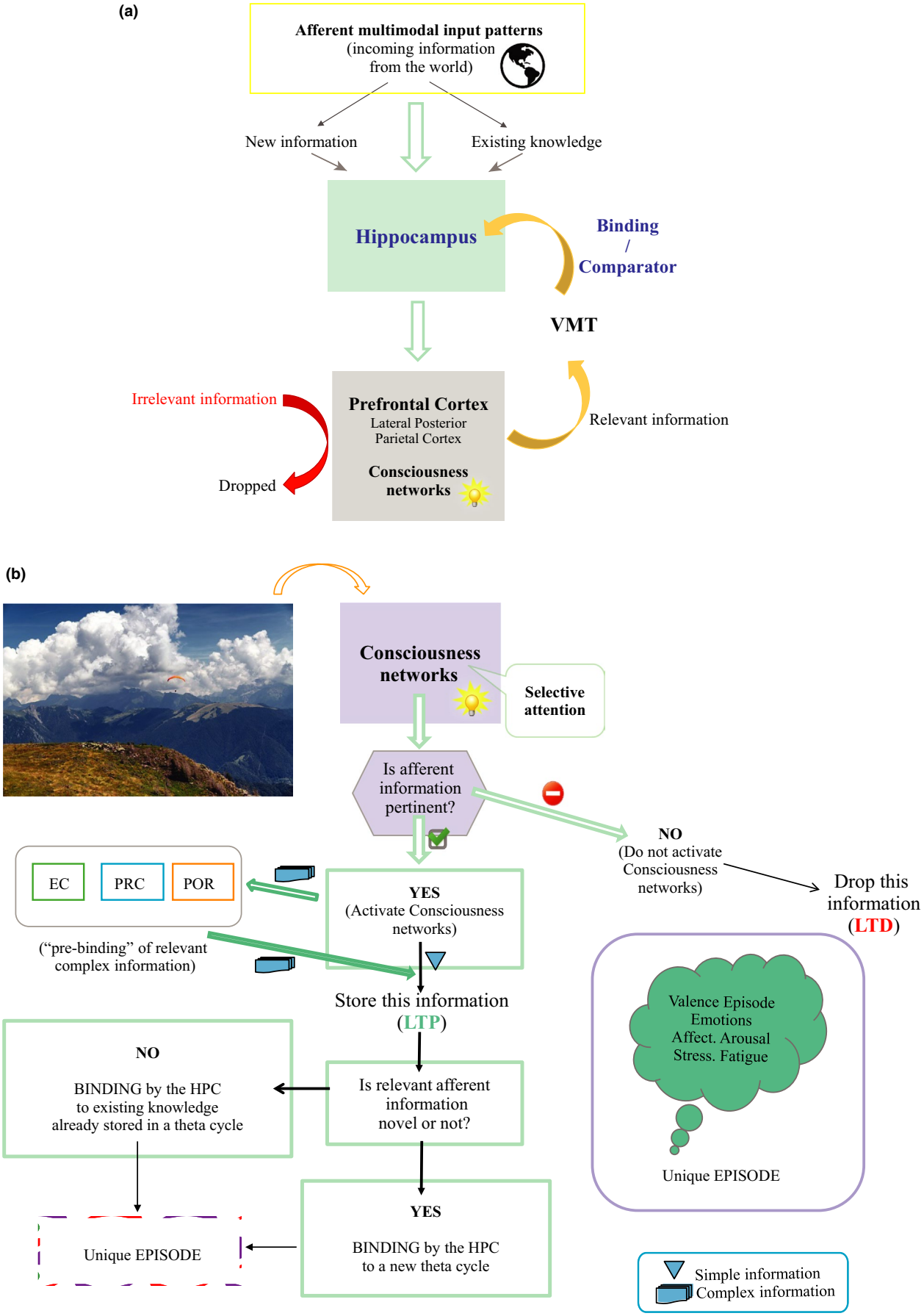
(a)
Afferent multimodal input patterns
(incoming information from the world)
New information
Existing knowledge
Hippocampus
Binding / Comparator
VMT
Irrelevant information
Dropped
Prefrontal Cortex
Lateral Posterior Parietal Cortex
Consciousness networks
Relevant information
(b)
Consciousness networks
Selective attention
Is afferent information pertinent?
NO
(Do not activate Consciousness networks)
Drop this information (LTD)
EC
PRC
POR
("pre-binding" of relevant complex information)
YES
(Activate Consciousness networks)
Store this information (LTP)
Valence Episode Emotions Affect. Arousal Stress. Fatigue
Unique EPISODE
NO
BINDING by the HPC to existing knowledge already stored in a theta cycle
Is relevant afferent information novel or not?
YES
BINDING by the HPC to a new theta cycle
Unique EPISODE
Simple information
Complex information

**FIGURE 8** Proposed scenario of how TL structures are involved in the encoding of information, especially of episodic information during explicit memory. (a) Ahead of the HPC, TL structures as EC, PRC, POR may integrate information and send it to the HPC. The HPC sends this information to higher networks to be validated as relevant or not by consciousness via selective attentional networks in parietal and prefrontal network areas. After such validation, the information is either dropped—if qualified as non-pertinent, thus LTD mechanisms may be at play to weaken, or de-potentiate, the input connections—or sent back to the HPC via the VMT nuclei if worth storing, that is, relevant. (b) In case of complex information (e.g., compound stimuli), we propose that "*pre-binding*" must operate by structures upstream the HPC (as PRC, postrhinal cortex (POR), EC). In this case, VMT may send this information directly to paraHPC regions to *pre-bind* it before sending it back to the HPC. The HPC then compares this information to previously stored knowledge: is it either new or similar to existing, stored activity patterns? In the former case, HPC would bind the information to a new theta cycle, where each feature of the episode may be stored in a nested gamma cycle; in the latter case, the piece of information may be bound to an existing theta cycle and added as an assembly sequence in a gamma nested theta cycle. Top-down information signaling intrinsic, self-generated information (e.g., emotions, affect) associated with the current episode may be added as contextual information and considered as a feature-event signal. Existing knowledge is hypothesized to be provided by CA3 while outer sensory information may be processed by the EC to the HPC (CA1). (In this case, we refer to explicit memory, by contrast to implicit learning which would not require the involvement of consciousness)

2017). In this case, these variables will be replaced by other pertinent variables as reflected in spiking activity and blood flow (Aronov et al., 2017; Deuker et al., 2016; Tavares et al., 2015). For example, sequence of time cells (MacDonald, Carrow, Place, & Eichenbaum, 2013; MacDonald, Lepage, Eden, & Eichenbaum, 2011; Modi, Dhawale, & Bhalla, 2014) could provide useful information about space when local cues are missing (Wang et al., 2015). This way, the HPC can integrate distinct dimensions beyond space and time and incorporate them into a cognitive map to form one unique episodic mental representation. We fully support this view, perceiving the HPC as an anatomical and major network hub receiving general information from several upstream structures through the EC (Backus, Schoffelen, et al., 2016; Lavenex & Amaral, 2000).

### 4.1.2 | "Pre-binding" of complex information upstream the hippocampus

We thus propose the following scenario (Figure 8): The HPC links related multifaceted and multimodal information together, brings them into context (i.e., associate them with related contextual information), and organizes them into unique sequences. To follow the metaphor of the late Eichenbaum in his most recent paper, the best way to picture the HPC in our proposed scenario is that the HPC is an orchestra master "whose role is to organize the performance of musicians who sit in different places and play in a distinct sequence" (Eichenbaum, 2018). To this view we propose that if the piece of music played is very complex, each subsection of musicians (feature modality) involved in the orchestra, segregated by the instrument they play, may have its own leader to synchronize the group right before the orchestra master takes over and leads the whole section in a harmonious sequence. In this example, the subsection leaders stand for the perirhinal, entorhinal and postrhinal cortices which will bind upstream the HPC (we call it "*pre-binding*") highly complex information required to be bound beforehand, that is, before the HPC binds all pieces of information to a single episode. It indeed appears easier to incorporate each aspect of information to the sequence if in its own subsection (dimension), where each aspect of information is already organized and bound to one unimodal invariant representation.

The nature of information assembled into memories may thus not be critical for HPC function; rather, it seems more appropriate and accurate to think in terms of memory content, namely simple versus complex information, the latter requiring prior processing (*pre-binding*) from upstream structures. As highly complex information, we define information beyond single and simple features. In our opinion, this phenomenon implies that the HPC may process any dimension of an episode in the same way, assigning it and binding it to a sequence representing one single mental representation.

### 4.1.3 | Integration of relevant dimension into the hippocampal cognitive map

The HPC may only encode behaviorally relevant variables for the task at hand or episode to remember, depending on the current context (Aronov et al., 2017). According to this study, space and time were assumed to be encoded right at the beginning of the task at hand (Eichenbaum, 2013; O'Keefe & Nadel, 1978; Ranganath & Hsieh, 2016) while sensory stimuli necessary to perform the task were encoded only after the animal had learned that they were relevant for the current context, that is, to complete the task (Aronov et al., 2017). An assumed hypothesis is that the HPC encodes a context according to an initial spatiotemporal code in order to determine what could be considered pertinent in this context (Eichenbaum, 2013; O'Keefe & Nadel, 1978; Ranganath & Hsieh, 2016). The selected dimensions considered relevant could be incorporated onto the HPC cognitive map coding the current episode. According to this view, interaction with the ventral parietal cortex, connected to the PFC, seems critical (van Kesteren, Ruiter, Fernández, & Henson, 2012; Preston & Eichenbaum, 2013; Zeithamova & Preston, 2010).

#### 4.1.4 | Selection, binding and comparison of relevant dimensions

The parietal–prefrontal network is involved in the consciousness and selective attention networks, encoding pertinent information (for review see Moscovitch et al., 2016). The thalamus has recently also been found to be involved in attentional control necessary in cognitive processes, especially goal-oriented (Halassa & Kastner, 2017). The HPC, via its interaction with the consciousness network, may segregate relevant from irrelevant information, depending on whether the information pertinence is high enough to activate the consciousness (selective attention) network (i.e., to be attended). In case of relevant information, the information dimension is submitted to another screening; however, if deemed irrelevant, the dimension of information coding is dropped. The next screening of relevant information consists in determining whether this information matches what the brain already "knows"—from existing knowledge (the storage pool)—or whether this is new information (van Kesteren et al., 2012; Preston & Eichenbaum, 2013; Zeithamova & Preston, 2010). To this aim, the HPC may look whether this information is related to some existing knowledge or past experiences in cooperation with the PRC and/or the VMT. The HPC may discriminate contextual information between experiences and when it goes beyond a certain threshold, a new context may be formed to which more experiences are linked (Fuhs & Touretzky, 2007; Lisman et al., 2017). After reaching the higher (parieto-prefrontal) networks (especially the ventro-median PFC), the information may be sent back to the HPC via the VMT nuclei (Ito, Zhang, Witter, Moser, & Moser, 2015).

We assume that what we just presented may stand only in the case of episodic (explicit) memory, in contrast to several implicit (therefore unconscious) processes of learning (e.g., when our brain unconsciously learns the usual distance between two stairs or how to grab a cup of coffee, namely semantic knowledge about the world). In case of explicit memory, the ventro-median PFC has been found to be a regulator of HPC encoding beyond spatiotemporal inputs (Gruber et al., 2018; Navawongse & Eichenbaum, 2013; Young & Shapiro, 2011). Extra-HPC regions can then be seen as "selectors" of dimensions beyond space and time pertinent to be coded by the HPC (Schedlbauer, Copara, Watrous, & Ekstrom, 2014; Zhang et al., 2013). We hypothesize that it is only once these representations have been qualified relevant by higher networks that they can be further sent back to paraHPC regions (perirhinal, entorhinal and postrhinal cortices). The latter will "*pre-bind*" relevant information ahead of the HPC in case of complex and high-dimensional afferent input patterns (e.g., compound stimuli beyond shape and color).

We think that this scenario is the only plausible possibility for the brain in terms of energy-cost, as otherwise complex information would need to be "pre-bound" ahead of its qualification as being relevant or irrelevant by high-level networks, which for us will cause energy loss in case of irrelevant information. Indeed, if the dimension would not be processed as being relevant, that is, does not activate the consciousness network (in case of explicit memory), then we argue that the brain would not spend energy to process (bind) it upstream if it is to be dropped afterward. Indeed, we suppose a higher energy-cost is necessary to bind and integrate complex (compound multifaceted) elements ahead of the HPC (*pre-binding*) compared to first-order information processing related to space or object features, as the former may require medial and lateral EC joint processing.

#### 4.1.5 | Hippocampus as a general integrator: summary and conclusion

The HPC could then be defined as a general integrator mapping all dimensions of an experience/episode, combining the classical view of its implication in spatial memory and the new perspective (Schiller et al., 2015). As mentioned above, space and time are important variables to give structure to any incoming information and to discriminate one episode from another (O'Keefe & Nadel, 1978). These primary spatiotemporal dimensions segregate our experiences into unique and/or related episodes defined as specific events (Eichenbaum, 2013; Ranganath & Hsieh, 2016). From this ground, any other dimension (e.g., contextual, perceptual, emotional) could be superimposed to the map (Eichenbaum & Cohen, 2014) if higher networks send a top-down or feedback message that the current dimension is indeed relevant to the given context (Lisman et al., 2017).

Lastly, it has recently been suggested that feature recognition may be supported by more than one unique strategy, with one HPC-dependent and one extra-HPC structures-dependent strategy, depending on task demands (Eichenbaum, 2018). We support this idea and hypothesize that HPC-dependent strategy would be used if cognitive (task) demand is low, in that case "pre-binding" by upstream extra-HPC regions will not (or less) be required, and HPC will keep its main function of binding elements together with their appropriate context (Bachevalier, Nemanic, & Alvarado, 2015; Butterly, Petroccione, & Smith, 2012; Eichenbaum, 2018).

Indeed, to create a context, several dimensions may be needed to shape a structure among continuous afferent sensory stimuli which need to be associated across time and space, that is, not just at a specific place but also at a particular time, adding another dimension to disentangle multiple associates to a particular dimension. Behavioral modulatory signals as emotions, affect, arousal, fatigue and stress may also add to the specific episodic context-dependent landscape (cf. Figure 8). This would apply with the use of oscillatory mechanisms, as theta oscillations coordinate both neuronal

activity and active sampling, that is to say, both sensory inputs and intrinsic functions (Colgin, 2016).

## 4.2 | Forgetting, remembering and encoding new memories

Our ability to remember is limited by the capacity to encode new memories. We propose studying whether heterosynaptic LTD would occur more often at CA3 synapses in rats who experienced rich environment with frequent novel afferent information to encode about their environment compared to rats in a stable and poor environment in which only rare new memories may need to be encoded by the HPC (i.e., only few representations would need to be newly formed). In the latter case, heterosynaptic depression will not be much at play compared to animals in which new memories would be frequently formed. LTD mechanisms would need to occur in order to erase some details of older memories (form structured/gist-like memories) and fit the network capacity for encoding and recalling (as part of learning) new information (Rolls, 2016, 2017). Therefore, if one wishes to create many new memories by frequently traveling all around the world, one may need to compile those memories in photograph books or albums as new memories will be formed at the cost of old detailed ones and overwrite them (St-Laurent, Moscovitch, & McAndrews, 2016). Pictures may then help recovering these faded memories whose details have been lost to create gist-like memories.

We will now describe the mechanisms associated with our proposed scenario.

## 4.3 | Associated mechanisms

### 4.3.1 | Dendritic plateau potentials as a general mechanism for binding

We hypothesize that one mechanism supporting the binding of distributed representations is dendritic plateau potentials, a NMDA-dependent regenerative event initially identified in CA1 cells which detects distinct separate inputs from CA3 and the EC and combines them as a coincidence detector while mice are running on a treadmill and coding space via CA1 place cells (Bittner et al., 2015; Sheffield & Dombeck, 2015). We propose these dendritic events as a general mechanism by which binding of information occurs (Figure 9). This rather long-lasting (few hundred milliseconds) dendritic

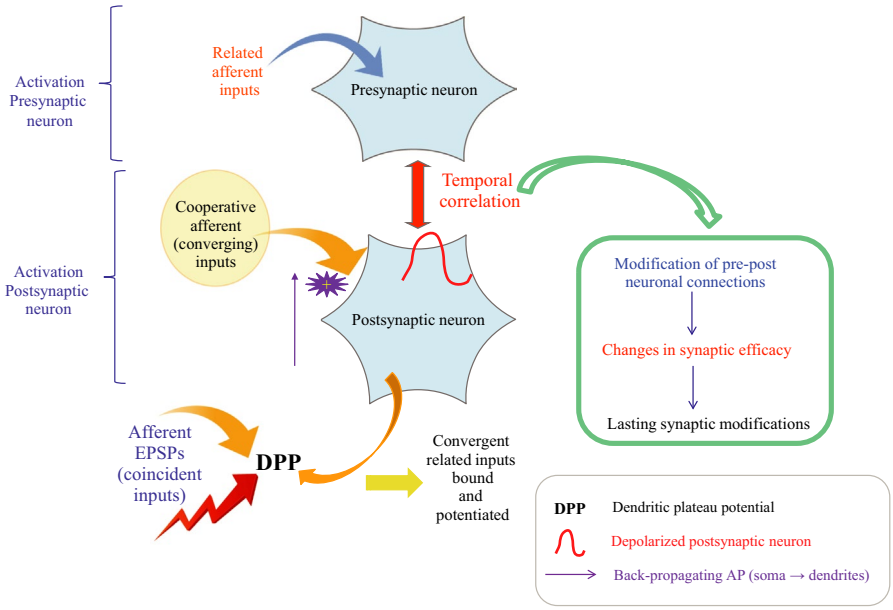


**FIGURE 9** Dendritic plateau potential as a general mechanism for binding related information. When related afferent inputs reach the presynaptic neuron concomitantly of the depolarization of the postsynaptic neuron, this promotes a change in the connection between these two (pre- and postsynaptic) neurons. Such change in functional connectivity impacts the efficacy between these synapses, modifying the synaptic gain which will be translated by a lasting change of synaptic connectivity or synaptic strength, influencing the dynamic gating and routing of relevant information. The depolarization of the postsynaptic neuron occurs when the neuron gets activated either by cooperative convergent afferent input patterns or via the back-propagation of action potential output from the soma to the dendrites when activity sums up and creates a dendritic depolarization. If the postsynaptic neuron is depolarized enough to generate a dendritic plateau potential (DPP; cf. section 4.3.1), afferent excitatory postsynaptic potentials (EPSPs) converging coincidently to this NMDA-dependent dendritic regenerative event (DPP) will be bound and potentiated. The higher the temporal coincidence will be, the higher the potentiation. This associative dendritic mechanism thus consists in a coincidence detector between the postsynaptic depolarization and the afferent EPSPs. We propose these dendritic events as a general mechanism by which binding of information occurs

mechanism may thus apply to bind related input activity patterns belonging to the same context/episode and coming from distributed processing pathways (TL and associated structures), for example, from the EC and PRC but also from higher networks, and converge to the HPC to be bound as one episodic mental representation.

#### 4.3.2 | Theta and gamma nested cell assemblies

Simple information may be easy to be bound within the HPC and then later easy to be read out as only one modality (feature) may be stored per gamma cycle nested in one theta cycle. Only 5 to 9 cell assemblies could indeed be active in a single theta cycle (Buzsáki, 2006) where a single episode is hypothesized to be coded (Colgin, 2016). One assembly (~ 10–30 ms lifetime) may code for one episodic feature stored in one gamma cycle (phase-coded representation of inputs, cf. Figure 3); therefore, all constituents of each modality, in case of complex information, would need to be bound as an invariant input pattern modality ahead of the HPC, standing for one feature. This would be achieved through the "pre-binding" phenomenon by structures like the perirhinal, postrhinal and entorhinal cortices.

Information may be received and processed by each brain structure upstream the HPC and assigned to a new local gamma rhythm in each brain region (Schomburg et al., 2014) which will be further assembled in one single theta cycle by the HPC (once the information would be validated as being relevant, therefore worth storing). The excitatory modulation provided at the population level is an increase in theta amplitude during encoding of new information and retrieval of previously encoded information (Copara et al., 2014; Horner, Bisby, Bush, Lin, & Burgess, 2015). These findings are consistent with the proposed scenario as the HPC may need to trigger the formation of new cell assembly sequences within a new theta cycle and increase the coupling between structures involved, in order to store novel information bound into a new episode (mental representation); and likewise for retrieving information as the latter probably has to be extracted from the assembly within the theta/gamma nested cycles, as declarative memories are compositional and flexible (Henke, 2010). Indeed, an increase in coupling strength, or synchronization, would require an increase in theta and/or gamma amplitude, thus potentiate input strength.

#### 4.3.3 | Medial temporal lobe theta-gamma coupling/neocortical alpha-beta decoupling

The binding of episodes may occur through HPC theta/gamma synchronization (coupling) while cortical alpha/beta desynchronization (decoupling) may be the mechanism by which the content of episodes may be coded (Hanslmayr et al., 2016). Theta/gamma coupling within the medial TL occurs whether gamma cycles are nested in the trough or at the peak of theta oscillations.

Neocortical mnemonic processing, in cooperation with the medial TL, generally processes semantic information, for example, items, and is associated with a decrease in alpha power in cortical (parieto-occipital) regions. Therefore, the HPC and the neocortex have been proposed to share complementary but distinct coding properties (for review see Hanslmayr et al., 2016; McKenzie et al., 2014). While the HPC formation structures and more generally the medial TL support a rather energy-efficient sparse coding of learned information patterns associated with fast online learning in "one shot/few shots" (Eichenbaum, 2017), the neocortex supports an already integrated representation formed over many repetitions therefore learned over training (several experiences, semantic information).

Both HPC and neocortical representations are complementary for the encoding—binding conjunctive representations according to items and context, respectively (BIC model, Diana, Yonelinas, & Ranganath, 2007)—and for the retrieval of information. The BIC ("Binding of Items and Context") model states that specific medial TL structures get activated according to the task at hand, behavioral demands and cognitive processes involved, that is, according to the nature of information processing. This model exhibits a rather exclusive representational view of the medial TL. Sitting at the end of the processing pathway (cf. our proposed scenario), the HPC can now bind pertinent-selected elements onto a unique episode. Such binding of conjunctive episodic representations may occur via the reinforcement of synapses undergoing LTP between constitutive neurons of the ensembles forming the assembly (Hanslmayr et al., 2016). The concept of convergence zones, with its core principles of conjunctive coding and high inter-connectivity with other brain regions (here within the TL and higher consciousness networks, cf. section 2.3), would therefore hold (Backus, Bosch, et al., 2016; Staresina et al., 2011); for a review in humans see (Lech & Suchan, 2014).

#### 4.3.4 | Learning selectivity via LTP/LTD mechanisms

Such LTP mechanism occurs for relevant information worth storing. If there is no input-specific drive from the neocortex, in particular from the ventro-median PFC, HPC firing would occur within the theta trough (toward the excitatory phase) and LTD will occur. However, relevant information would require the encoding of episodic information or imply repetitions of stimuli to acquire learning (in case of semantic or specific task-directed information). In the latter case, HPC firing occurring as a consequence of the repeated afferent activity input pattern would occur earlier and earlier within the theta cycle at each repetition (input stimulation), a well-known phenomenon called *phase precession*. Nevertheless,

only a selected population of HPC firing units driven by the afferent input pattern stimulation would phase precess at each theta cycle. This phenomenon is hypothesized to make learning selective (Hanslmayr et al., 2016; Hanslmayr & Staudigl, 2014), enabling only the relevant synapses to be selectively strengthened, that is, subject to LTP, when inputs arrive at the oscillatory phase space of maximal excitability (Figure 6). In contrast to theta/gamma synchronization (amplitude increase), alpha/beta power decreases during successful memory encoding of semantic and conceptual processes, maybe because semantic knowledge does not require to be bound to a particular context. We mentioned earlier that relevant synapses were strengthened as a way to promote selective learning. Indeed, information qualified as being irrelevant by higher networks could be immediately forgotten via LTD whereas pertinent information may be kept and stored by learning through LTP processes. LTP and LTD processes have been reported to occur sequentially, as a convenient mechanism occurring alternatively depending on which phase of the theta cycle the driven units arrive: If they arrive at the peak of the theta oscillation, which is the hyperpolarized phase where most HPC cells are inhibited, LTP occurs; otherwise, LTD would take over. SWRs also appear to contribute to the formation of memory engram and erasure of irrelevant information during slow wave sleep by increasing the synaptic net depression necessary to increase neuronal responsiveness (Norimoto et al., 2018). Indeed, engram neurons seem to be distinguished by repetitive burst firing at theta frequency (Balduzzi & Tononi, 2013; Tanaka et al., 2018).

#### 4.3.5 | Coordination of relevant information via theta rhythm

Theta mechanism has a dual function; first, the coordination of distributed cell assemblies firing into its cycle, second, their segregation according to its available phase space, depending on whether perisomatic inhibition is at play to narrow it down or not. This dual function plays a convenient role in temporally coordinating and/or synchronizing, with the involvement of inhibition, relevant input patterns of information, namely afferent external stimuli represented by bottom-up information and coding novel or related information and intrinsic cell assembly sequences coding existing knowledge, represented by top-down modulatory signals. The two types of assemblies may interact, depending on whether the HPC binds the new afferent input to already existing knowledge, in case of content- or context-related information, or creates a new episodic representation, therefore a new cell assembly sequence stored within a given theta cycle. The HPC indeed receives information about the current stimulus via afferent projections from the EC and about stored representations similar to the current stimulus from CA3. CA1 compares the representation from CA3 and EC and outputs a novelty signal when these representations do not match (Olsen et al., 2013). The internally generated cell assembly sequences may thus be of need to attribute a context- or content-related match with the incoming information and notify the HPC on the way to proceed after higher networks decided whether the afferent information was pertinent or not (information saliency).

In conclusion, all the mechanisms we described to underlie our proposed scenario imply the flexible and context-dependent relational binding of information, the fast selection of relevant information, the dynamic gating and routing of input patterns through largely distributed TL processing pathways, all occurring via effective neuronal coupling (synchronous synaptic gain) of large-scale neuronal networks and mainly implying temporal correlations in neural activity, key process in dynamic coordination within brain modalities. These processes play a crucial role in the dynamic, fast and flexible emergence of mental representations requiring the reciprocal coupling of excitatory-inhibitory (E-I) networks.

In the second part of our review, we wish to illustrate how a reorganization of these TL E-I networks in temporal lobe epilepsy leads to the impairment of oscillatory (rhythmopathies) and cognitive processes (cognitive deficits). Through this example, we aim at emphasizing the importance of the dynamic coordination between these variables (i.e., brain networks, oscillations and cognition) as well as the criticality of time-dependent processes in shaping cognition. We also aim at making the reader aware of the difficulty of addressing questions in diseases, as intertwined variables, together with the occurrence of compensatory mechanisms to re-establish brain homeostasis and treatment side effects sum up and add to the already existing complexity of studying diseases and their comorbidities.

## 5 | HOW IS TL-DEPENDENT COGNITION ALTERED IN TEMPORAL LOBE EPILEPSY?

We will start by giving the reader a brief introduction about temporal lobe epilepsy (TLE).

### 5.1 | Temporal lobe epilepsy

Epilepsy is one of the most frequent neurological disorders which affect approximately 1% of the population worldwide (Singh & Trevick, 2016). It is characterized by epileptic seizures, also called *ictal* activity, clinical manifestation of abnormally excessive or synchronous activity in the brain which translates into a brief and sudden episode of increased brain (often associated with body) activity.

Sixty percent of epileptic patients had focal epilepsy. Among these focal epileptic patients, 66% had TLE (Semah et al., 1998); for a review on TLE epidemiology see

(Téllez-Zenteno & Hernández-Ronquillo, 2012). TLE is thus the most common form of partial epilepsy in adults. It represents about two thirds of intractable epileptic cases. Its origin is often symptomatic, its surgical outcome relatively promising, when feasible. Causes of TLE can be a traumatic brain injury, a stroke, dysplasia, meningitis or febrile seizures (Reddy & Kuruba, 2013); (Gorter, Vliet, & Aronica, 2015).

Two syndromes are currently admitted by the *International League Against Epilepsy* (1989) and its recent updates (Fisher et al., 2017; Scheffer et al., 2017): the mesial TLE and the lateral TLE, also called neocortical TLE (Bercovici, Kumar, & Mirsattari, 2012; Tatum, 2012); for review see (Ladino, Farzad, & Tellez-Zenteno, 2014). Neocortical TLE shows 10% occurrence, mesial type, 90%. Mesial TLE, associated with mesial TL sclerosis, is the most common type of partial TLE in adolescents and adults (Cendes, 2005). Mesial and lateral TLE are characterized and often accompanied by a frequent aura preceding epileptic seizures. This aura, specific of TLE, can be informative of TLE lateralization (for a comprehensive review on TLE semiology, see Blair, 2012). Most cases of mesial TLE are pharmacoresistant and surgery is not always a solution. TL is indeed not trivial to operate as it may result in profound memory loss.

## 5.2 | Rhythmopathies in TLE

In this section, we will review how reorganized TL brain networks together with the abnormal activities they generate affect oscillatory processes, that is, induce TLE rhythmopathies. The latter can emerge either from paroxystic (epileptic) activities occurring between seizures or during epileptogenesis, called *interictal* activity (IA) (Chauvière et al., 2012; de Curtis & Avanzini, 2001), spontaneous and recurrent seizures (SRSs; Klee, Brandt, Töllner, & Löscher, 2017) or from the epileptic reorganization resulting from reorganized TL structural connectivity. Post-SE TLE models will be the main model of choice when referring to animal models (Figure 10).

### 5.2.1 | Theta rhythmopathies

The integrity of HPC theta rhythm is associated with intact input from the medial septum (MS, Figure 1d and Table 1), a TL structure very much implicated in theta generation (Givens & Olton, 1990; McNaughton, Ruan, & Woodnorth, 2006) and from the MEC (Ormond & McNaughton, 2015; Schlesiger et al., 2015). Indeed, a 7.7 Hz stimulation of the MS increases performances at a spatial memory task in a pilocarpine rat TLE model (Lee et al., 2017). This stimulation reinstates comparable performances to control animals performing spatial learning and object recognition tasks. We suggest that this stimulation, by simulating septal input, may trigger temporal coordination of distributed firing covered by theta cycles usually brought about by septal input (for review see; Shuman, Amendolara, & Golshani, 2017).

While in normal conditions theta rhythm coordinates DG and EC activity, in epileptic mice EC theta has been found delayed compared to DG theta. The temporal structure shaping dynamic coordination between EC-DG networks (to potentiate inputs arriving from both structures) would thus be altered. This shift in HPC-EC theta coordination may thus impact cognitive processes relying on it.

In mesial TLE patients, the relative power of theta rhythm is decreased, compared to the one in non-epileptogenic areas

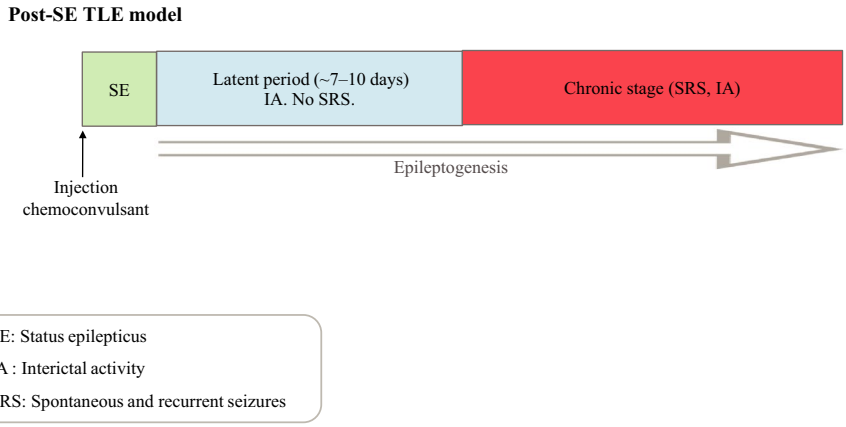


**FIGURE 10** Post-SE model of TLE. Post-SE models of TLE originate from an initial trigger (e.g., injection of a chemoconvulsant) which mimics the initial insult of human TLE (e.g., stroke, febrile seizures, dysplasia). This initial insult leads to a SE in most cases which will be followed by a latent period mostly characterized by the absence of SRS but already by the presence of EEG-pathological activity, IA, in the early stages of epileptogenesis. The latent period will end with the occurrence of SRS characterizing the chronic stage, that is, epilepsy per se. Epileptogenesis, characterizing the development of TLE, would then start at the beginning of the latent period and develop throughout the whole epileptic period

of the same patients (Bettus et al., 2009). This theta power decrease has been described to be due, at least in part, to IA. Studies in TLE animal models confirmed the decrease in theta power (Arabadzisz, Antal, Parpan, Emri, & Fritschy, 2005; Chauvière et al., 2009) and frequency (Chauvière et al., 2009; Kilias et al., 2018) and suggest potential explanations. An impairment of the theta generators, either by modification of the theta pacemaker structure or by aberrant connections (e.g., sprouting) between theta oscillators (Christenson, Leintz, Xamonthiene, Huang, & Krook-Magnuson, 2017; Dudek & Shao, 2004) was proposed, as well as a modification in the resonance features of neurons involved (Marcelin et al., 2009; Wolfart & Laker, 2015); for review see (Sharma et al., 2007). The authors also suggested that the evolution of TLE toward the chronic stage could affect even more strongly all these processes, consequently impairing theta frequency toward a more prominent and progressive decrease. However, the decrease in theta frequency we found in TLE rats was stable along epileptogenesis (Chauvière et al., 2009).

To complement our findings, where we showed a deficit in theta power and frequency correlating with spatial memory deficits in pilocarpine-treated rats (Chauvière et al., 2009), another study showed that theta power and phase-locking between CA1 and DG were altered in TLE rats (Inostroza, Brotons-Mas, Laurent, Cid, & Prida, 2013). While digging into the correlation between these theta variables and the task components to complete it, the authors found that theta power disruption was correlated to the spatial aspect of the task at hand (supporting our data) whereas theta coordination disruption was correlated with the temporal aspect of the task, showing a specific involvement of theta rhythm in completing episodic-like memory tasks and probably in encoding episodic information in general.

Kilias et al. (2018) found that "Theta frequency was decreased at all recording positions throughout the DG and in the MEC, irrespective of the extent of granule cell dispersion or the rate of severe epileptic events." Moreover, they found a theta frequency decrease during several behaviors (rest, exploration and running) within the MEC and along the DG septo-temporal axis, which nevertheless remained coherent across recorded regions as well as modulated by running speed, as in control mice. Thus, theta frequency decrease may not be a direct consequence of the local network remodeling during epileptogenesis but may emerge from global network alterations within the HPC formation. In an elegant study using a TLE model of KA-injected rats in the dorsal HPC, authors found that theta rhythm was completely abolished in the ventral HPC of these animals and that the firing frequency of the dendrite-targeted *oriens-lacunosum moleculare* (O-LM) interneurons, key players in theta rhythm generation, had been modified from theta to gamma frequency band due to an increase of the excitatory input strength (Dugladze et al., 2007). These findings showed that in this model, an impairment of the synaptic and intrinsic firing properties of O-LM interneurons induce HPC theta rhythmopathies.

Finally, some authors have looked at IA impact on theta phase stability, a measure of synchrony in addition to theta power in pilocarpine-treated rats (Ge et al., 2013). They found no correlation between theta power decrease and changes in theta phase stability and a time-dependent IA impact on theta rhythm. Supporting our findings (Chauvière et al., 2009), they highlighted a significant theta power decrease both during the latent and chronic periods. However, opposite changes of theta phase stability during these two periods occurred that the authors suggested were due to the evolution of neural network remodeling throughout epileptogenesis. The authors also showed that hypersynchrony of the networks involved in IA may persist for hours after IA burst, suggesting a negative impact of IA on mechanisms underlying theta rhythm generation which varies with epileptogenesis, especially between the latent period and the chronic stage. However, within the same model, we did not find any differences in theta-dependent functional deficits along these two periods (Chauvière et al., 2009).

### 5.2.2 | Theta rhythm as an anti-epileptic state

It is now well admitted that neuronal synchronization is increased in epileptic patients, during and between their epileptic seizures, especially in theta frequency bands (Clemens, Bessenyei, et al., 2007). In animal models, epileptiform discharges were largely reduced during spontaneous stimulus-induced (tail pinch) or chemically induced (carbachol) theta rhythm (Colom, García-Hernández, Castañeda, Perez-Cordova, & Garrido-Sanabria, 2006; Miller, Turner, & Gray, 1994). This suggests that induced-theta in the MS inhibits seizures and decreases IA between seizures, whereas a MS lesion completely abolishes HPC theta, thus decreasing the threshold of SRSs occurrence. In this study, theta rhythm appears as a functional state resistant to epileptic seizures, thus responsible for the decrease of their frequency, conferring theta an anti-epileptic role (Colom et al., 2006). We also observed that during REM (*Rapid Eye Movement*) sleep, a prominent theta state, almost no seizures occurred (Chauvière, 2010). The networks and mechanisms underlying HPC theta generation during REM (for review see Colgin, 2016; Watson & Buzsáki, 2015) may thus be more prone to induce this epileptic-resistant functional state. In that sense, theta rhythmopathies appear deleterious as it may prevent epileptic-resistant functional state from occurring in epileptic brains.

### 5.2.3 | Gamma rhythmopathies

Gamma rhythmopathies have been recently reported in TLE patients, compared to healthy subjects (Lega, Burke,

Jacobs, & Kahana, 2016; Lega, Dionisio, Bingaman, Najm, & Gonzalez-Martinez, 2015; Lopez-Pigozzi et al., 2016; Shirvalkar, Rapp, & Shapiro, 2010). In animal models, after the *status epilepticus* (SE) mimicking the initial brain injury in TLE patients (Figure 10), gamma oscillations are markers of seizure development. Occurring in the amygdala and the thalamocortical loop, their occurrence is the sign of a large depression and epileptiform activity.

A recent study identified the impairment of interneuronal parvalbumin basket cells poorly coordinated in theta cycle and associated with a decrease of gamma oscillations in TLE rats, probably related to lower input strength from the Schaffer collaterals and altered theta oscillations (Lopez-Pigozzi et al., 2016). This suggests that an alteration of the E-I networks will affect theta-gamma coupling which will be associated with episodic memory deficits. In addition, changes in spatiotemporal regularities of gamma cycles reflecting modifications in interneuronal synchronization dynamics are associated with focal ictogenesis (Sato et al., 2017). Local generation of gamma oscillations ahead of interictal epileptiform discharges (IA) reflects a role of these oscillations in pathological associated networks generating IA and may be used as useful association (gamma-IA) in clinics to map seizure-prone brain regions (Ren et al., 2015).

Synchronous GABAergic interneuronal activity implicated in gamma oscillations is the hallmark of interictal–ictal transition states when it becomes coherent with local field potential (LFP) population activity entrained at gamma frequency (Grasse, Karunakaran, & Moxon, 2013). In humans, regularity and synchrony provided by gamma rhythms are critical for interneuronal network synchronization (Bartos, Vida, & Jonas, 2007) within the seizure onset zone (Medvedev, Murro, & Meador, 2011). Gamma oscillation rhythmicity is thus a good index of inhibitory network synchronization, mostly GABAergic, reflecting inhibitory transmission coupling between TL brain regions, critical for the E-I balance between them and for dynamic coordination among local or remote distributed networks, both key elements in cognitive processes.

Lastly, as slow wave sleep has been hypothesized to participate in learning reinforcement, we will briefly introduce SWR during slow wave sleep as it may have its significance in the buildup of TL-dependent cognitive impairments.

#### 5.2.4 | Sharp wave ripples impairments during slow wave sleep

We saw previously that during slow wave sleep there is an increase of synaptic net depression to allow the formation of engram via SWR (Norimoto et al., 2018; Yoo et al., 2007). The local increase of slow wave sleep after learning was also associated with an improvement of cognitive performances after sleep (Huber, Felice Ghilardi, Massimini, & Tononi, 2004). Thus, a sustained focal pathological activity during sleep, as an epileptic seizure, may interfere with local slow wave sleep activity generated at the epileptic site and alter neuronal processes, and probably induce changes in local plasticity associated with learning and other cognitive functions (Tassinari & Rubboli, 2006). We argue that seizures during slow wave sleep might as well alter SWR occurrence, therefore prevent memory engrams from being formed and/or subsequent relevant information from being processed and stored.

In conclusion, TLE is associated with the impairment of oscillatory processes, especially theta and gamma rhythms. However, several questions remain unanswered. For example, how theta oscillation impairment, as well as its coupling with gamma oscillations, is causally related to cognitive impairments? Is it by modifying the gain of synaptic weight toward synaptic potentiation (synapses strengthening) or depression (synapses weakening)? Which mechanisms target strategies that intend to restore cognitive functions? Do these strategies re-establish interneuronal functions necessary to generate theta and gamma rhythms as well as their role in precisely coordinating action potential firing onto their cycles? Are these strategies rather targeting other mechanisms circumventing oscillatory processes? The determination of targeted mechanisms to restore loss-of-function will inform on the extent to which theta and gamma rhythms are related to cognitive deficits due to neuronal loss or reorganization, for example, the cell population involved, and/or if other mechanism could be at play such as compensatory mechanisms or alternative pathways (cf. Box 1). The development of new technologies, as optogenetics (Boyden, Zhang, Bamberg, Nagel, & Deisseroth, 2005), would surely be of use to address such questions regarding the intermixed role of network dynamics in epilepsy. We will now tackle functional cognitive deficits during TLE, major comorbidities of the disease, see which impact TL rhythmopathies and network reorganization has on cognition in TLE brains.

### 5.3 | Cognitive deficits in TLE

#### 5.3.1 | Cognitive and behavioral impairments as major TLE comorbidities

In addition to epileptic seizures, cognitive and behavioral (emotional, social) impairments are serious TLE comorbidities (Berg & Scheffer, 2011). For many epileptic patients, these comorbidities may affect their lives even more than epilepsy per se (Loring, Meador, & Lee, 2004). The reason for this is the dynamic evolution of these comorbidities with the evolution of the disease, as the more pathological activity (SRS and IA) occurs, the more it reinforces comorbidities, which become chronic and a hallmark feature of the disease (Hermann, Seidenberg, & Jones, 2008; Lenck-Santini & Holmes, 2008; Liu et al., 2003).

**BOX 1 Compensatory mechanisms**

In their article, Inostroza, Cid, Menendez de la Prida, and Sandi (2012) mentioned that the drop of the number of cells they observed in the lateral and basolateral amygdala was poorly reflected in density values due to the compensatory effect of a reduced volume. A conditioned taste aversion task also showed that the aversion formed in the post-SE brain was, interestingly, able to use the spared cerebral region for the formation of the memory trace (Sroubek, Hort, Komárek, Langmeier, & Brozek, 2001), as in some cases, the non-epileptogenic hemisphere is likely to compensate the TLE deficit. It is an important point to mention, as compensatory mechanisms contribute to the complexity of translational research. Indeed, besides the difficulty of interpreting pathological activities in the brain, as the brain at the normal level is far from being entirely understood, another critical point in the study of brain diseases is that the compensatory mechanisms occurring quickly in the brain during and after an abnormal event tend to re-establish brain homeostasis (Marder & Goaillard, 2006). Therefore, it is very difficult to interpret what we see in pathological conditions, that is, to distinguish between pathological features of brain disease and the compensatory mechanisms occurring to counterbalance hidden pathological activities of the brain. This question remains open, critical and very difficult to solve. The best example is to imagine a prehistorically man coming in our century and trying to interpret how a car is functioning based on the red back light of its brakes. The red lights are activated both when the car decreases its speed to stop, or at a steep and dangerous corner when the car is still moving further but breaking (slowing down). However, for someone watching from behind, it is impossible to say if the car is going to stop or just decreasing its speed if this person does not know the context or the machinery of the car neither its different options to use its brakes. It is exactly the same for the neuroscientist trying to interpret what she records from neuronal brain activity in pathological conditions.

Therefore, cognitive and behavioral comorbidities are associated with several pathological factors interacting between each other (Figure 11). For example, the same way that pathological alterations of oscillatory activity patterns are associated with cognitive processes alterations, as we just described in the previous section, without knowing yet by which exact mechanism, epileptic seizures, IA, anti-epileptic drugs (AED) and network dynamics alterations due to epilepsy add up to this already complex landscape.

Cognitive deficits can be separated in two categories: permanent versus transient (Kleen, Scott, Lenck-Santini, & Holmes, 2012). Permanent deficits were reported to be induced by the etiology of epilepsy whereas transient deficits may rely on dynamic changes caused by epileptiform activity (IA and SRS) and AED (Aarts, Binnie, Smit, & Wilkins, 1984; Binnie, Kasteleijn-Nolst Trenité, Smit, & Wilkins, 1987), for a review see (Aldenkamp & Arends, 2004a).

### 5.3.2 | Behavioral impairments

Morphological reorganizations of structural networks have been shown to be at the origin of behavioral alterations (Adamec, 1991; Franke & Kittner, 2001). In terms of the latter, anxiety is clearly the major behavioral comorbidity of TLE models, especially in kindling of amygdala, HPC and PRC (Adamec & McKay, 1993; Hannesson et al., 2005, 2008; Inostroza et al., 2012; Mortazavi, Ericson, Story, Hulce, & Dunbar, 2005) but also in pilocarpine-treated animals (Lopes et al., 2016); for review see (Kleen et al., 2012). Anxiety impacts on exploratory behavior within open arenas (Kalynchuk, Pinel, & Treit, 1998; Kalynchuk, Pinel, Treitj, et al., 1998), on object recognition (Hannesson et al., 2005) and on social cognition (Haimovici, Wang, Cohen, & Mintz, 2001). An interesting question to investigate is whether these behavioral changes could be prevented by enrichment-based behavior (cf. Box 2).

Some authors concluded that "altered emotional behaviors are not inherent to the epileptic condition in experimental TLE; instead they likely reflect alterations in anxiety levels" (Inostroza et al., 2012), suggesting that emotional outcomes of distinct animal models (*lithium–pilocarpine* and *kainate* TLE models in their study) with similar SRS severity and frequency profiles strongly correlated with structural lesion profiles and cortisol levels (Box 3). SRS occurrence, reflecting the epileptic condition per se, may thus not be the sole precipitating factor of TLE behavioral alterations. Thus, AED may be addressed accordingly in order to decrease TLE patients' associated comorbidities. Defining the cerebral substrates of these comorbidities is key in order to develop strategies to preserve and/or restore the integrity of such neuronal substrates.

### 5.3.3 | Cognitive impairments in TLE patients

Cognitive deficits are frequent in TLE patients (Helmstaedter & Kockelmann, 2006). Related to extensive structural abnormalities beyond the HPC connectome, TLE patients present a panel of various cognitive alterations, from memory impairments to executive functions, language, intellectual quotient, object verbal naming and sensorimotor skills (Hermann, Seidenberg, Schoenfeld, & Davies, 1997; Oyegbile et al., 2004; Riley et al., 2010; Robertson, Evans, Walterfang, Ng, & Velakoulis, 2008); for review see (Bell, Lin, Seidenberg, & Hermann, 2011) and (Allone et al., 2017). Those cognitive

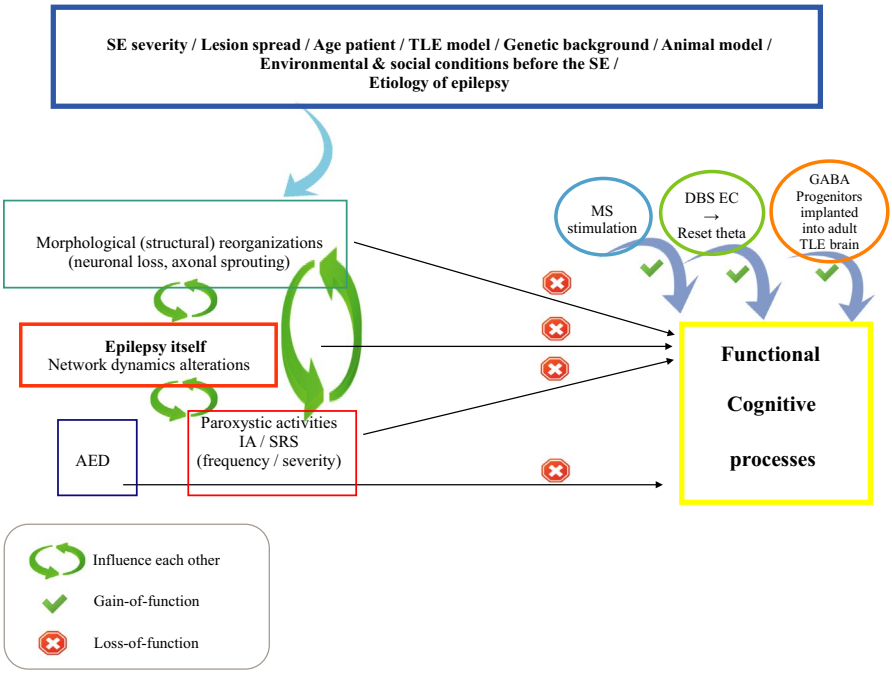


**FIGURE 11** TLE variables and their impact on functional cognitive processes. Morphological reorganizations (e.g., neuronal loss and axonal sprouting), TLE-associated network dynamics alterations (e.g., synaptic reorganizations, changes in neurogenesis, alteration of GABAergic and glutamatergic transmissions, rhythmopathies, hypersynchrony), paroxystic activities (SRS and IA), as well as AED, all have a negative impact on functional cognitive processes. These variables all reinforce each other during epileptogenesis. For example, paroxystic activities associated with TLE compromise morphological network reorganization at the origin of more severe epileptic activities (SRS) which in turn worsen network dynamics, at the origin of more severe functional deficits. Increased epileptic activities may augment AED administration, which will increase its side effects on cognitive processes. It is thus very difficult to know which variable the original cause of functional abnormalities is and how to isolate it from one another. Several strategies have been proposed to restore altered cognitive functions, for example, deep brain stimulation (DBS) of the EC which has been shown to efficiently reset theta rhythm, the stimulation of the MS to strengthen theta input, and GABA progenitors implanted into the adult TLE brain

alterations in TLE patients have been grouped in three distinct types of cognitive profiles: (a) mild deficits (47% of patients; for a review see (Höller & Trinka, 2014), (b) memory deficits (24%) and (c) memory and executive functions deficits (29%) (cf. the recent review of Allone et al., 2017). These three profiles provide different results, depending on the type of epilepsy and cognitive evolution (Hermann, Seidenberg, Lee, Chan, & Rutecki, 2007). For example, the cognitive decline in TLE patients with a unilateral HPC sclerosis is progressive (Marques et al., 2007). However, other authors suggested that there may be a critical phase during childhood and/or adolescent development when episodic memory may be more easily impaired (Helmstaedter & Elger, 2009). Performances of patients diagnosed with mesial TLE associated with right HPC sclerosis and right paraHPC lesion showed impairment of spatial accuracy assessed by memory-guided saccades correlated with the degree of right paraHPC lesion (Colnaghi et al., 2017). This study supports a right lateralization of the control of spatial processing and yields a link between functional alteration and degree of lesion profile. Regarding verbal and non-verbal memory, reduced left HPC volume was associated with delayed verbal memory while its right analog was less clearly involved in non-verbal memory (Griffith et al., 2003). The integrity of the left HPC together with TL white matter integrity are critical in TLE patients, as the mean diffusivity of the left inferior longitudinal fasciculus and the left EC white matter have been yielded strong predictors of memory decline, in particular of verbal memory, combined with measures of HPC volume (McDonald et al., 2014). While the main fiber tract connecting the inferofrontal and anterior TL (uncinate fasciculus) is involved in episodic retrieval and conscious recollection, the cingulum, connecting the medial TL to the posterior cingulate cortex in humans, plays a role in learning and retention processes. White matter fiber tracts, which provide connectivity within cortical regions, between cortical and subcortical regions as well as between inter-hemispheric brain areas, have also been linked with cognitive abilities, especially memory and language in TLE patients (Schoene-Bake et al., 2009). This shows that cognitive dysfunctions in TLE patients are associated with network abnormalities rather than specific structural modification of a given brain area. Regarding long-term memory, the integrity of the superior longitudinal fasciculus, the cingulum and the contralateral TL have been reported to play a

**BOX 2 Social environmental conditions of the animals used in our models**

In their study, Fares et al. (2013) recently showed that an enriched environment allows the recovery of impaired cognitive functions after SE (Fischer, Sananbenesi, Wang, Dobbin, & Tsai, 2007). However, in typical animal model studies, rats are kept in isolated conditions, in an environment lacking social and contextual enrichment level. These conditions are known to be stressful, leading to high levels of cortisol and anxiety (Manouze et al., 2019). Indeed, rats are social animals, and if we want to compare studies performed on animal models with human studies, our experimental conditions are not optimal and are therefore more difficult to apply and interpret to human patients. This variable should be seriously considered as a bias in animal model studies, and social and environmental enriched conditions should be used consistently in the future (Duffy, 2001; Manouze et al., 2019; Teather, Magnusson, Chow, & Wurtman, 2002). In our previous studies (Chauvière et al., 2009, 2012), rats were housed in individual cages but used only two to three weeks after they arrived at the laboratory, period during which they were handled three to five times a day during half an hour by the experimentalist to socialize them with the latter and make them familiar with further experimental conditions. However, this was probably insufficient, and we seriously consider improving social and housing conditions for further studies. This could explain the distinct results with Becker et al. (2015) who found no spatial cognitive deficits in SE rats; however, the authors used the KA model while we used the pilocarpine model; therefore, it is difficult to draw any firm conclusion here (cf. Box 3). More recently, a study showed that environmental enrichment compensated for the VMT inactivation (Ali et al., 2017), see also (Valero-Aracama, Sauvage, & Yoshida, 2015).

**BOX 3 Dependence of cognitive deficits on TLE model and strain of the animals**

It has been recently shown that HPC-dependent spatial memory is not necessarily affected in TLE, depending on the model and strain of the animals used in the model, and that comorbidity between spatial deficits and anxiety is more related with the underlying brain lesions than with the epileptic condition per se. In their study, Inostroza et al. (2012) compared spatial impairments and anxiety-related performances in two types of TLE models, ***lithium–pilocarpine*** and ***kainate***, and two types of rat strains, ***Wistar*** and ***Sprague-Dawley***, and found different results for both sets of conditions. Despite a similar level of seizure severity in both experimental TLE models, they observed different spatial learning deficits and different anxiety evaluation depending on the strain of the animal within the ***kainate*** model (Inostroza et al., 2012). Furthermore, their MRI data clearly showed larger lesions in ***lithium–pilocarpine*** than in ***kainate***-treated animals for both strains, mostly affecting the HPC, the lateral and basolateral amygdala and the more ventral aspect of the neocortex. These lesions correlate with the behavioral performances, for example, spatial memory deficits could be explained by the reduced HPC volume. HPC binding functions may be altered, thus information encoding may be partial, and/or abnormal. The distinct lesion pattern in ***lithium–pilocarpine*** versus ***kainate***-treated animals already occurs 24 hr after the SE, suggesting that behavioral differences truly reflect strain and model features (Covolan & Mello, 2000; Racine, Steingart, & McIntyre, 1999; Xu, McIntyre, Fahnestock, & Racine, 2004), at least during early stages of epileptogenesis (cf. Box 5). The authors finally proposed that model and strain differences can be further exploited to validate TLE models better suitable for cognitive studies in epilepsy. These data bring attention to the importance of carefully choosing the appropriate experimental model for this endeavor.

key role in human working memory, with a higher vulnerability for TLE patients with left HPC sclerosis (Winston et al., 2013). Social cognition is also impaired in TLE patients (Bora & Meletti, 2016).

Several factors have been proposed to be at the origin of cognitive deficits impacting patients' everyday lives between SRS: (a) epilepsy itself and its underlying altered distributed networks, (b) IA, during and between seizures, (c) SRS, (d) the etiology of epilepsy, especially the nature and timing of occurrence of the initial precipitating injury, (e) AED (for reviews see Bell et al., 2011; Lenck-Santini & Scott, 2015; Figure 12). Thus, not only SRS do have an impact on cognitive processes. The reorganization of neuronal networks, for example the buildup from surviving neurons that got spared from neuronal loss, also leads to abnormal connections which may therefore transmit disrupted information to downstream targets, therefore leading to impaired cognitive behavior. We will now address the latter in TLE animal models.

### 5.3.4 | Cognitive impairments in TLE animal models

Chronic stage epileptic animals display many cognitive deficits, especially of spatial memory (Chauvière et al., 2009;

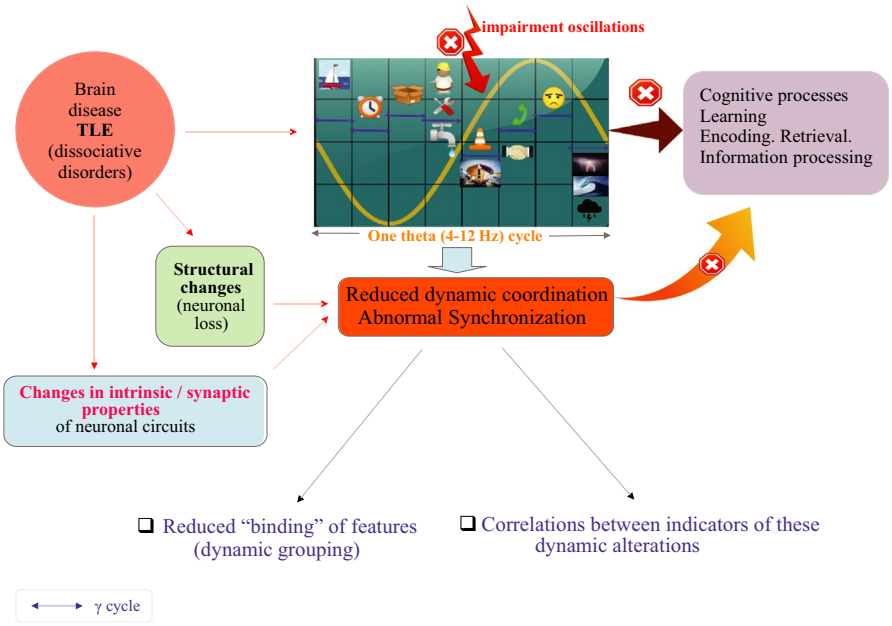


**FIGURE 12** TLE rhythmopathies. Based on Figure 3, any disturbance (e.g., power, frequency, coupling) of the underlying rhythms (theta, gamma) carrying episodic features in distinct assembly sequences would lead to cognitive deficits (e.g., altered information processing, impaired learning). Indeed, such rhythmopathies would induce reduced dynamic coordination and abnormal synchronization, at the origin of reduced binding of features (dynamic grouping), abnormal oscillatory and synchronized activity, as well as correlations between indicators of these dynamic alterations. Such processes interfere with structural alterations (e.g., neuronal loss and axonal sprouting) and changes in intrinsic and synaptic properties of the neuronal circuits which emphasize the underlying functional network impairment associated with TLE and its related dissociative disorders

Leite, Nakamura, Lemos, Masur, & Cavalheiro, 1990; Lenck-Santini & Holmes, 2008; Letty, Lerner-Natoli, & Rondouin, 1995; Shatskikh, Raghavendra, Zhao, Cui, & Holmes, 2006) for review see (Lenck-Santini & Scott, 2015; Meador, 2007; Murphy, 2013). Although we did not find any non-spatial deficit as defined by a lack of novel object exploration in pilocarpine-treated rats (Chauvière et al., 2009), as confirmed recently by Becker et al. (2015), but see also (Detour, Schroeder, Desor, & Nehlig, 2005), other authors found an impairment of non-spatial memory (object recognition) in SE rats (Hannesson et al., 2005; Pearson, Schulz, & Patel, 2014).

Spatial cognitive deficits have been characterized to depend on (a) the TLE model: They occur in different animal models (Inostroza et al., 2011; Kearney et al., 2001; Majak & Pitkänen, 2004); cf. Box 3); (b) the genetic background (rat strains): The ability to compensate these deficits seems to be related to the animal strains used for the TLE models, both in rats (Hort, Brožek, Komárek, Langmeier, & Mareš, 2000) and in mice (Royle, Collins, Rupniak, Barnes, & Anderson, 1999); (c) SRS frequency (Kotloski, Lynch, Lauersdorf, & Sutula, 2002; Nissinen, Halonen, Koivisto, & Pitkänen, 2000; Sutula, Lauersdorf, Lynch, Jurgella, & Woodard, 1995); (d) SRS severity (Mohajeri et al., 2003); (e) the severity of the lesion, the latter being itself function of the SE duration (Fujikawa, 1996; Mello & Cavalheiro, 1989); (f) the age of the animals when the first SE occurs since the immature brain seems less sensitive to epileptic activity (Holmes, 1991) due either to a lower propagation of this activity, or to neurons being more resistant to the apoptotic phenomena (Stafstrom, Chronopoulos, Thurber, Thompson, & Holmes, 1993); for review see (Cilio et al., 2003; Kubová, Druga, Haugvicová, Suchomelová, & Pitkanen, 2002; Lado, Sankar, Lowenstein, & Moshé, 2000); (g) the spread of the network involved in SRS (for review see Hannesson & Corcoran, 2000): indeed, kindling of different TL structures will not generate the same deficits (e.g., spatial deficits within the dorsal HPC, but not within the PRC, the ventral HPC or the amygdala, inducing other types of cognitive deficits); (h) the latency of recovery between the SE and the first day of test (Hort, Brozek, Mares, Langmeier, & Komarek, 1999; Leung, Martin, & Stewart, 1994); (i) the task used (Barry et al., 2016); (j) environmental and social conditions before the SE: It has been shown that an enriched environment improves cognitive performances (cf. Box 2), both in rats (Akman, Hu, Fu, & Holmes, 2003; Rutten et al., 2002) and in mice (Duffy, 2001) but apparently not for all cognitive tests (Teather et al., 2002) while maternal deprivation decreased cognitive performances (Huang et al., 2002); (k) AED (Bolanos et al., 1998); (l) the "mental reserve" phenomenon according to which cognitive performances of animals tested before SE may have an influence on their performances after the SE, but this factor has been found dependent on the type of cognitive task and remains controversial (Akman et al., 2003; Leung, Brzozowski, & Shen, 1996; Leung et al., 1994).

In summary, we highlighted that network reorganization of TL structures leads to cognitive alterations in TLE brains and that these alterations mainly correlate with oscillatory mechanisms. We will now propose a scenario on how TL cognitive deficits emerge during epileptogenesis, making hypotheses on how distinct but intertwined variables—as oscillations, structural and functional network connectivity as well as TLE activities—might influence each other.

## 5.4 | Hypotheses and proposed scenario

### 5.4.1 | Interictal activity, theta rhythm and cognition

We propose that IA may have an indirect impact on cognition by altering theta rhythm. We observed a transient IA effect on theta oscillations both in TLE patients and in TLE animal model during early stages of epileptogenesis (J. Krieg, L. Chauvière, A. Ghestem, F. Bartolomei, C. Bénar, & C. Bernard, unpublished data; Ge et al., 2013 ). IA was neither phase-locked with theta oscillations nor resetting them; however, IA transiently impaired their amplitude stability. While the former suggests that IA was neither influenced (positively or negatively) by any specific theta phase nor did drive theta genesis, the latter suggests that IA and theta rhythm may share common mechanisms and/or resources. As IA is hypothesized to be a local emerging feature (Miles & Wong, 1983) in comparison with theta rhythm which shares network properties, IA may rather share common resources. To support this hypothesis, IA wave after the spike, recruiting inhibitory mechanisms (de Curtis, Manfridi, & Biella, 1998; Demont-Guignard, Benquet, Gerber, & Wendling, 2009), may transiently use GABAergic resources to the detriment of theta oscillations which also recruits GABAergic circuits (Buzsáki, 2006; Gloveli et al., 2005).

### 5.4.2 | Theta rhythm and circuit impairments

Based on the aforementioned, theta stability could then be a marker of the evolution of damaged HPC tissue in TLE patients. Thus, GABAergic circuit impairment during the chronic stage (El-Hassar et al., 2007) may therefore be reflected by (a) the impairment of theta oscillations' stability, power and frequency and (b) by the difficulty of recruiting GABAergic circuits. Since theta was already impaired early after SE (Chauvière et al., 2009), circuit remodeling post-SE may also decrease the cooperation between theta generators. The significant MS neuronal loss, especially of GABAergic neurons, compared to glutamatergic and cholinergic neurons, both relatively spared during the chronic stage (Garrido Sanabria et al., 2006), supports this hypothesis. As GABAergic neurons provide theta frequency and control HPC excitability (Garrido Sanabria et al., 2006), a loss of these inhibitory neurons would have a dual impact on functional network properties. In addition, HPC pyramidal cells express *hyperpolarization-activated cation channels* (HCN channels; HCN1 and HCN2 isomers) which get activated by hyperpolarization of the membrane potential and underlie the $I_h$ current. $I_h$ may be responsible for the tuning of CA1 pyramidal cell dendrites to theta input, and decrease in $I_h$ would compromise such resonance properties. Theta resonance has indeed been reported altered during epileptogenesis in a TLE rat model, associated with a lower expression (and/or mislocalization) of HCN subunits and with a power and frequency decrease of theta oscillations in vivo (Marcelin et al., 2009). This acquired channelopathy occurring during epileptogenesis may affect temporal coding by triggering selective tuning of pyramidal cells dendrites to theta inputs. To corroborate these data, a subpopulation of GABAergic neurons expressing HCN channels acts as HPC theta "pacemaker," transmitting rhythmic information from MS to HPC (Hangya, Borhegyi, Szilágyi, Freund, & Varga, 2009). However, while MS neuronal loss is present during the chronic stage, it is absent during the latent period when theta rhythm was already found altered (Chauvière et al., 2009; Kilias et al., 2018; Marcelin et al., 2009). This could therefore not explain the early functional impairment of theta rhythm but may reinforce the phenomenon during the chronic stage. Other mechanism may be at play during the latent period, for example, the functional reorganization of the circuit and the loss of some interneurons, like O-LM cells, would be sufficient to impair the cooperation between theta generators; though most of the interneurons remain functional.

### 5.4.3 | Hippocampal and entorhinal coupling and directionality

Related to other mechanisms at play during the latent period, HPC-EC coupling was found increased during the latter, then returned to control levels during the chronic stage. In contrast, HPC-EC information flow was permanently reversed from the early stage of epileptogenesis, with EC now driving the HPC (L. Chauvière, A. Ghestem, F. Wendling, F. Bartolomei, & C. Bernard, unpublished data). Information flow reversal has been proposed to favor SRS genesis in epileptic tissue (Avoli, Biagini, & Curtis, 2006; Avoli et al., 2002). In vivo, it could be associated with early and persistent spatial memory deficits (Chauvière et al., 2009) and with seizure genesis/propagation. Directionality (information flow) represents a meta-parameter of system dynamics; yet these results suggest that the way the system is processing/transmitting information is dramatically modified after SE. The underlying mechanisms likely include the post-SE reorganization of the neuronal circuitry. The initial SE triggers the loss of O-LM interneurons, which controls the EC input to the HPC (Cossart, Dinocourt, et al., 2001). Consequently,

the temporoammonic pathway (Figure 1d) may be largely facilitated, and its activation can trigger burst firing in CA1 (Cossart, Tyzio, et al., 2001). Interestingly, the change of directionality did not depend upon IA presence during rest epochs. However, the coupling was IA-dependent as HPC-EC coupling was similar to control groups for epochs without IA and increased during early epileptogenesis for epochs with IA. We propose that the increased coupling merely reflects changes in the circuitry, within and between TL structures. Facilitated transfer of information between the HPC and EC may facilitate the construction of an epileptogenic network. Interestingly, late during epileptogenesis, the coupling returned to control levels even in the presence of IA, a result that can be interpreted as a sign of progressive degradation of the circuit. The changes in HPC-EC coupling and information flow may not only represent the construction of an epileptogenic network but also be causally related to the functional TLE cognitive deficits. The reversal of information flow being stable around the first spontaneous seizure (SZ1) in our study, compared to IA dynamics, supports the fact that the change in directionality would be more related to network remodeling after SE than to IA.

### 5.4.4 | Dual role of interictal activity

Altogether these data support the hypothesis that at early stages of epileptogenesis, when the network is not yet totally remodeled, with functional interneurons, though already leading to early cognitive deficits, IA may have only transient deleterious effects on cognitive functions. This may affect the functional state of the network only at IA occurrence, or even generate a protective effect which may compensate the imbalanced global homeostasis of the network (cf. Box 1), though we suggested above that IA may also have an indirect impact on cognitive functions by impairing theta rhythm. However, once the network is impaired enough to induce SRSs, IA would have no direct effect anymore on functional network dynamics but only an indirect effect as it would simply add more imbalance (perturbation) to the already imbalanced network. At this stage, network remodeling would impair underlying (cognitive) functions with or without IA. For example, during the late stage of epileptogenesis, before the network switches to the chronic stage (just before SZ1), when epilepsy tends to already develop with a network reorganized enough to start generating SRSs, IA may mimic a stimulus which induces oscillatory (theta/gamma) "phase-reset" in order to favor cognitive performances. In this case, IA would mimic a beneficial physiological mechanism to re-establish (compensate) global network homeostasis. We nevertheless found that IA was not resetting theta oscillations (J. Krieg, L. Chauvière, A. Ghestem, F. Bartolomei, C. Bénar, & C. Bernard, unpublished data; cf. section 5.4.1). IA activity may well be an emerging property of the network, as a deficit in memory consolidation may not be due to IA but to network restructuration, for example having an effect on ripple oscillations, crucial in memory consolidation. Similar to the effect on theta rhythm during memory encoding, as we proposed earlier. IA wave after the spike could also be protective during early stages of epileptogenesis (Chang et al., 2018; Marder & Goaillard, 2006). The epileptogenic process, described as being continuous (Bartolomei, Chauvel, & Wendling, 2008; Kadam, White, Staley, & Dudek, 2010; Tassi et al., 2009), could be maintained in an epileptogenic state by IA, maintaining the network in a pathological state when it switches its dynamics after SZ1 (Chauvière et al., 2012).

Furthermore, the correlation between IA and spatial deficits was observed when the underlying network was not yet fully reorganized at the early stage of epileptogenesis but not afterward (J. Krieg, L. Chauvière, A. Ghestem, F. Bartolomei, C. Bénar, & C. Bernard, unpublished data). This is consistent with the proposed general "anti-epileptogenic" action of IA (Box 4), a property which disappears with the degradation of the neuronal circuit (Avoli et al., 2002). We indeed propose that IA, depending on its time of occurrence, that is, before or after the occurrence of SRSs, may have distinct impact on network functions: an anti-epileptogenic effect and an anti-binding effect (Figure 12; Chang et al., 2018; Kubista, Boehm, & Hotka, 2019).

### 5.4.5 | Interictal activity and the binding phenomenon

One possibility linking IA, rhythmic activities and cognitive functions is that IA may trigger the binding phenomenon, being then associated with an "anti-binding" phenomenon (Bartolomei et al., 2013). Indeed, gamma rhythm, within the HPC-neocortical loop, largely occurs in a hypersynchronous way at the beginning of the epileptiform discharges in animal models. Then, during these discharges, gamma activity

**BOX 4 A protective effect of interictal activity?**

Surprisingly, IA has been reported more influent in the non-epileptogenic hemisphere, in the propagation zone (Bettus et al., 2008). Based on our previous findings (Chauvière et al., 2012), we can hypothesize that IA is a mechanism selected by the brain to first compensate the instability of the network till the chronic stage of the disease, then reinforcing the already reorganized underlying networks at the origin of cognitive deficits, hence the buildup of epileptogenic networks (Bartolomei, Bettus, Stam, & Guye, 2013; Bartolomei et al., 2008; Chang et al., 2018; Kubista et al., 2019).

decreases. An "over-binding" phenomenon has thus been proposed at the very beginning of SRSs, suggested to be at the origin of the formation of wrong associations due to synaptic modifications and leading to abnormal dynamic gating, thus routing, of information, at the origin of cognitive deficits (Figure 12). Thus, IA could be considered as an "anti-binding" phenomenon, similar to the "non-learning" one when IA occurs during sleep (Medvedev, 2002). At the very beginning of seizures, there are very high HPC-neocortical gamma coherence and power which largely decrease (Medvedev, 2001; Medvedev et al., 2011). These results suggest a desynchronization of the protected mechanisms against the "over-binding" phenomenon; it is as IA may "reset" the functional state of the brain, that is, the temporal binding phenomenon of neuronal activities. Referring to the first scenario we proposed in this review, in normal conditions (cf. section 4), HPC binding of information into an integrated episodic representation as well as "*pre-binding*" (pre-processing/ pre-selective grouping) of complex information upstream the HPC could be impaired through IA as it may interfere with theta oscillatory mechanism by which selective relevant information gets bound together and stored within its cycle. This "anti-binding" mechanism (alteration of dynamic coordination and temporally structured potentiation of relevant converging related inputs) triggered by IA is interesting since these wrong associations could explain the phenomenon of "deja-vu" occurring at the very beginning of the seizures, resulting from a very high gamma synchrony which creates false memories. During IA, it has been observed an increase of interdependence between signals (Mormann et al., 2005). This could create wrong associations and transfer of aberrant message to downstream targets, at the origin of cognitive deficits and confusion, for example, between imagined thoughts and reality regarding the latter, as in schizophrenia, probably sharing common mechanisms with TLE and cognitive deficits. Indeed, schizophrenic patients failed at tasks requiring feature binding mechanisms (Uhlhaas & Singer, 2006) with a decrease in power and synchrony of gamma oscillations and a pronounced loss of the patients' ability to synchronize gamma rhythms over remote brain regions. This may apply as well to other pathology characterized by IA, as Alzheimer's disease models display IA at very early stages (Palop et al., 2007), for which a similar negative impact on cognitive performance is possible (for reviews see Chin & Scharfman, 2013; Noebels, 2011). Autism spectrum disorders may also share such features (e.g., see (Velíšková, Silverman, Benson, & Lenck-Santini, 2018) for a recent review).

### 5.4.6 | Epileptic seizures, *Status Epilepticus* and interictal activity

The early development of SRSs correlates with the SE severity rather than with epileptogenesis (Hellier et al., 1999). The rate of SRSs progressively increases with time post-SE till reaching a plateau (Bertram & Cornett, 1994; Hellier, Patrylo, Buckmaster, & Dudek, 1998). We propose that this plateau may be the hallmark of a stable (irreversible) epileptic state whereby the network, once reorganized (remodeled) enough to trigger SRSs, may lead IA to stabilize but not modify as such the network state.

### 5.4.7 | Proposed scenario during TLE

Based on our proposed scenario during normal conditions (cf. section 4), we hypothesize that during TLE, when theta rhythm gets severely impaired, the coordination it provides between cell ensembles coding the same information may also be altered, thus conveying an aberrant message to downstream targets, inducing disruptive episodic memory and cognitive deficits. This alteration in temporal coordination may indeed have an impact on the way the HPC binds and stores information within gamma cycles nested in theta cycles to be further retrieved as unique episodes. As theta plays a major role in learning processes by providing precise temporal organization of pyramidal cell spike firing within its cycles, potentiating relevant inputs around its depolarizing peak before shunting inhibition occurs, an impairment of this rhythm (Arabadzisz et al., 2005; Barry et al., 2016; Chauvière et al., 2009; Inostroza et al., 2013; Kilias et al., 2018; Salami et al., 2014) would have deleterious effects on cognitive processes relying on such timed sequence of firing distribution (Itskov, Pastalkova, Mizuseki, Buzsaki, & Harris, 2008; Vertes & Kocsis, 1997). Indeed, theta impairment post-SE results in abnormal temporal coding of information, for example impaired phase precession and altered time compression of firing between neuron pairs (Lenck-Santini & Holmes, 2008); for review see (Lenck-Santini & Scott, 2015). Abnormalities in the timing of neuronal activities may amplify across distributed TL networks, generating a misinterpretation from higher consciousness networks in qualifying the information pertinent or not (Figure 8, Figure 12). From there, misleading thoughts may occur and afferent information may be wrongly associated with existing episodes, if at all. For example, schizophrenic patients interpret their own voice as the voice of someone else, unable to process it as familiar, thus interpreting it as novel, explaining their auditory hallucinations and the feeling of being controlled by "higher entities". Schizophrenic patients are also unable to make a distinction between real and imagined thoughts. It is as if their brain networks cannot learn, store and/or recall this information correctly. This may also well be the case during latent and chronic TLE, altering the way information gets processed between distributed neuronal ensembles. In addition, IA may worsen this altered landscape, as recently reported (Gelinas, Khodagholy, Thesen, Devinsky, & Buzsáki, 2016). We can also imagine that during development (toward pubescence

over early stages), when oscillations play a critical role in network formation and stabilization, a detrimental effect on activity coordination may have a bigger impact on cognitive processes. Nevertheless, while cognitive deficits were not visible—or not detected yet—in developing rats after SE, pubescent and older rats displayed similar deficits as adult SE rats (Stafstrom et al., 1993). We could hypothesize that during development, networks may not yet be determined in the function they will assure during pubescent or adulthood, as inhibitory circuits remained excitatory in developing animals compared to adults, for example. Other mechanisms may also be at play below a certain age as a critical way to store information.

Finally, whereas we did not find any gamma impairment (Chauvière et al., 2009), preliminary results from pilocarpine-treated rats recorded over fifteen TL brain regions showed decreased functional connectivity between remote brain regions of TL networks while local connections were strengthened, probably at the origin of SRSs. This was confirmed by a recent study using neuroimaging in TLE patients (Lee et al., 2018). Such abnormalities were also reported in other brain diseases as Alzheimer's (Koenig et al., 2005; Stam, Jones, Nolte, Breakspear, & Scheltens, 2007) and autism (Wilson, Rojas, Reite, Teale, & Rogers, 2007). These findings thus pave the way of studying dynamic temporal coordination and building processes to investigate dissociative symptoms of several brain diseases and synchronization of oscillatory brain dynamics as endophenotypes of these diseases share dissociative disorders (Figure 12).

## 6 | CONCLUSION

In this review, we have shown that TL is critical in learning and memory processes and that a disruption of distributed TL network coordination leads to cognitive deficits, as in TLE, mainly via the disruption of oscillatory mechanisms underlying precise and dynamic temporal coordination of neuronal ensembles. Thus, timing is key to process information, create new memories and efficiently retrieve them. Further, TL network coordination is essential to extract meaningful information from past experiences to make better choices for future decisions, related planning and actions, and to maintain a normal sense of self by being able to recall episodes of our life, constantly learning and adapting to our environment. Cognitive deficits in TLE animal models and patients can be induced by different factors. Epilepsy per se, via epileptic seizures, the intrinsic network reorganization due to epilepsy, and IA during epileptogenesis are the main sources of cognitive deficits. Today, epilepsy-induced network alterations, which affect neuronal networks involved in the genesis of oscillations underlying TL-dependent cognition, is the major candidate suggested to be at the origin of cognitive deficits. However, more experimental and theoretical evidence would be needed to support this view and provide causal insights. Indeed, the lack of a conceptual framework about oscillations and synchronization processes in normal conditions prevents the building of solid hypotheses during pathological conditions.

Finally, as epileptogenesis is a multifactorial process, with several variables varying at the same time and compensatory mechanisms adding up to this already complex landscape (cf. Box 1), it is difficult to draw any conclusion at this stage. Thus, aiming toward the identification of predictive biomarkers to prevent epilepsy and its comorbidities seems an appropriate current research pathway to embrace. Toward this goal, understanding epileptogenesis in animal models is a critical first step (Box 5).

**BOX 5 Advantage of studying early stage of epileptogenesis in animal models**

In one of our studies (Chauvière et al., 2009), we observed cognitive deficits that emerged in the early stages of epileptogenesis. These deficits were not due to epilepsy per se, since there were no SRSs yet at this stage (seizure-free period). In TLE patients, however, all variables sum up, that is, epilepsy per se, SRSs, and network reorganization, since now SRSs have already occurred and may affect cognition. In addition, AED may also play a role. Therefore, animal models remain a great tool to study epileptogenesis in vivo in order to yield predictive biomarkers of epileptogenesis and try to prevent epilepsy and its comorbidities in humans. Nevertheless, selecting the appropriate model to reproduce TLE in humans is key (cf. Box 3), as post-SE models usually present more widespread damage (i.e., HPC and extra-HPC structures) than the ones exhibited in TLE patients but do not mimic the standard CA1 and CA3 HPC sclerosis frequently observed in TLE patients (Margerison and Corsellis, 1966; Norwood et al., 2010; Sloviter, 2009; for review, see Gorter et al., 2015). Efforts are thus to be made to standardize animal models and improve their closeness to human pathology.

## 7 | FUTURE DIRECTIONS

We suggest several avenues of future research strategies to better understand by which exact mechanisms TL structures design cognitive processes. This would help patients overcome TLE cognitive comorbidities, as well as diseases

sharing dissociative disorders. A better understanding of the precise mechanisms underlying the intermixed, multifactorial relationship between TLE and cognitive deficits would ultimately help disentangle the neural underpinnings of cognitive processes as well as isolate the molecular and cellular network modifications underlying cognitive alterations.

Targeting and applying new appropriate strategies beyond AED may help decrease comorbidities in TLE patients, thus improve their mnemonic and cognitive performances, as recent promising studies have already shown (Fischer et al., 2007; Hunt, Girskis, Rubenstein, Alvarez-Buylla, & Baraban, 2013), especially via the stimulation of TL regions (Lee et al., 2017; Suthana et al., 2012). These studies suggest promising neuromodulatory therapeutic targets. Investigating which mechanisms these interventions apply to restore cognitive functions may shed light on cognitive processes and/or on compensatory mechanisms coming into play during TL functional damage. Which mechanisms are thus targeted, which cell populations and network dynamics are manipulated to restore/enhance cognitive functions?

Lastly, if not totally restoring TL brain functions, investigating strategies to identify predictive biomarkers in animal models to prevent TLE and its comorbidities seems a reasonable alternative. Then, the need to understand underlying mechanisms and measure them with less invasive methods in order to validate them in at-risk patients is critical. Finally, adapting adequate treatment strategies in identified at-risk patients will be the ultimate goal. In normal conditions, the need of identifying causal evidence and underlying mechanisms of how TL integrates information is crucial. If epilepsy is a continuous process, it would evolve with time. Long-term recordings, lasting several months after SRSs, would be a useful tool to investigate the question, that is, to characterize the evolution of network reorganization along epilepsy.

Because TLE, oscillations and cognition are emergent network properties, it is critical to record in as many sites as feasible within these networks. Modern research strategies apply new tools including optogenetics (Lerner, Ye, & Deisseroth, 2016), non-invasive acoustically targeted chemogenetics (Szablowski, Lee-Gosselin, Lue, Malounda, & Shapiro, 2018), functional connectivity measures, as coherence and small-world networks (Wang et al., 2014) and large-scale multisite recordings. These tools will allow for the manipulation and analysis of TL network dynamics to provide answers about: (a) how interconnected TL structures efficiently "communicate" between each other and with higher brain networks to transmit, store and efficiently retrieve information, (b) how this "communication" is distorted in TL diseases, both by yielding causal evidence. Understanding how such mechanisms are distorted during TLE will help disentangle brain diseases sharing common dissociative symptoms, as Alzheimer's disease, autism and schizophrenia.

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## CONFLICT OF INTEREST

The author has no conflict of interest to declare.

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