Neural circuits underlying the generation of theta oscillations

Michele Pignatelli *, Anna Beyeler, Xavier Leinekugel *

Institut des Maladies Neurodégénératives (IMN), UMR 5293, CNRS and Université Bordeaux 1 & 2, Avenue des Facultés, Bat. B2, Talence, France

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ABSTRACT

Theta oscillations represent the neural network configuration underlying active awake behavior and paradoxical sleep. This major EEG pattern has been extensively studied, from physiological to anatomical levels, for more than half a century. Nevertheless the cellular and network mechanisms accountable for the theta generation are still not fully understood. This review synthesizes the current knowledge on the circuitry involved in the generation of theta oscillations, from the hippocampus to extra hippocampal structures such as septal complex, entorhinal cortex and pedunculopontine tegmentum, a main trigger of theta state through direct and indirect projections to the septal complex. We conclude with a short overview of the perspectives offered by technical advances for deciphering more precisely the different neural components underlying the emergence of theta oscillations.

1. Introduction

The development of multi-electrode recordings allowed to study the temporal relationships between neuronal discharges and EEG patterns. This led to the current view that EEG oscillations serve as a temporal reference for information coding by spike times. Nevertheless, the mechanisms and circuits underlying the generation of EEG oscillations are still a matter of active investigation. In vertebrates, active brain state is associated with high cholinergic activity, cortical desynchronization and hippocampal theta rhythm (Buzsáki et al., 2003; Moruzzi and Magoun, 1949; Vanderwolf, 1969; Zhang et al., 2010). Hippocampal theta rhythm (Buzsáki et al., 2003; Green and Arduini, 1954; Saper et al., 2010; Vanderwolf, 1969) is a well known EEG pattern characterized by coherent oscillations in the 4–10 Hz frequency band observable during active awake behavior and paradoxical sleep (Bland, 1986; Buzsáki, 2002). In addition to the consistent amount of observations reported in rodents, theta oscillations can be detected as well in humans and primates through intracranial EEG (Kahana et al., 2001), being reported in both cortical network and hippocampus under condition of active navigation (Kahana et al., 1999) or paradoxical sleep (Cantero et al., 2003), the latter characterized by short bursts of 4–7 Hz oscillations. In the animal, hippocampal theta oscillations are detected under urethane anesthesia as well, either spontaneously or after noxious stimulation and accompanied by muscle atonia and whisker twitching as during paradoxical sleep (Clement et al., 2008). Following extensive multisite recordings in behaving and anesthetized rodents, the expression of theta oscillations found its cardinal generator in the hippocampus (Green and Arduini, 1954) from which theta waves propagate through volume conduction to a large part of the brain (Sirota et al., 2008). It is even possible to induce oscillations in the theta frequency band in the isolated rat hippocampal circuit *in vitro* (Bland et al., 1988; Goutagny et al., 2009; Konopacki et al., 1987a,b). The hippocampus seems to be constituted by coupled theta oscillators disposed in series along the septo-temporal axis and giving rise *in vivo* to traveling septo-temporal theta waves (Lubenov and Siapas, 2009). However, these hippocampal oscillators are largely driven by extra hippocampal inputs. In this review, we will describe the interplay between the different structures involved in the generation of theta oscillations in rodents, from the intra-hippocampal currents and main hippocampal inputs to the deep structures that trigger and sustain the theta-associated, active brain state.

2. Theta oscillations in the hippocampus

Laminar multisite recording of hippocampal theta oscillations in the rat allowed the investigation of the distribution of the synaptic currents involved in the genesis of the hippocampal theta

waves (see Fig. 1). Specifically, oscillatory activation of the perforant path arising from layer II–III cells of the entorhinal cortex (Amaral and Witter, 1989), generates prominent theta oscillations in the molecular layer of the dentate gyrus, accompanied by phased locked firing of granule cells (Muñoz et al., 1990) and interneurons (Sik et al., 1997). Current source density analysis of the laminar profile of CA1 field potentials recorded during theta oscillations revealed the presence of current sources in the pyramidal cell layer coupled to current sinks in the stratum lacunosum moleculare, suggesting synchronous somatic inhibition and dendritic excitation (Kamondi et al., 1998). Because lesion of the entorhinal cortex suppressed the sink in the stratum lacunosum moleculare (Kamondi et al., 1998) and around the hippocampal fissure (Ylinen et al., 1995), it has been suggested that while parvalbumin positive interneurons, in particular axoaxonic basket cells (Klausberger et al., 2003), send inhibitory inputs to the pyramidal

cell layer, the entorhinal cortex provides periodic excitatory inputs to the apical dendrites of the pyramidal cells (Kamondi et al., 1998). In addition, because oriens-lacunosum moleculare interneurons and pyramidal cells share similar preferred theta phase of firing (Klausberger et al., 2003) CA1 pyramidal cells receive rhythmic somatic hyperpolarization coupled to rhythmic dendritic depolarization, resulting in a net decrease of the input resistance during theta oscillations (Buzsáki, 2002; Kamondi et al., 1998). However, while both deep and superficial CA1 pyramidal cells fire preferentially at the trough of theta oscillations during active exploration, only deep pyramidal cells shift their preferred phase of firing to the peak of theta during paradoxical sleep (Mizuseki et al., 2011). Interestingly, CA1 and CA3 pyramidal cells are active on opposite theta phases suggesting that interleaving CA3 neuronal sequences may bind CA1 assemblies (Dragoi and Buzsaki, 2006). In addition to the laminar characteristics of theta
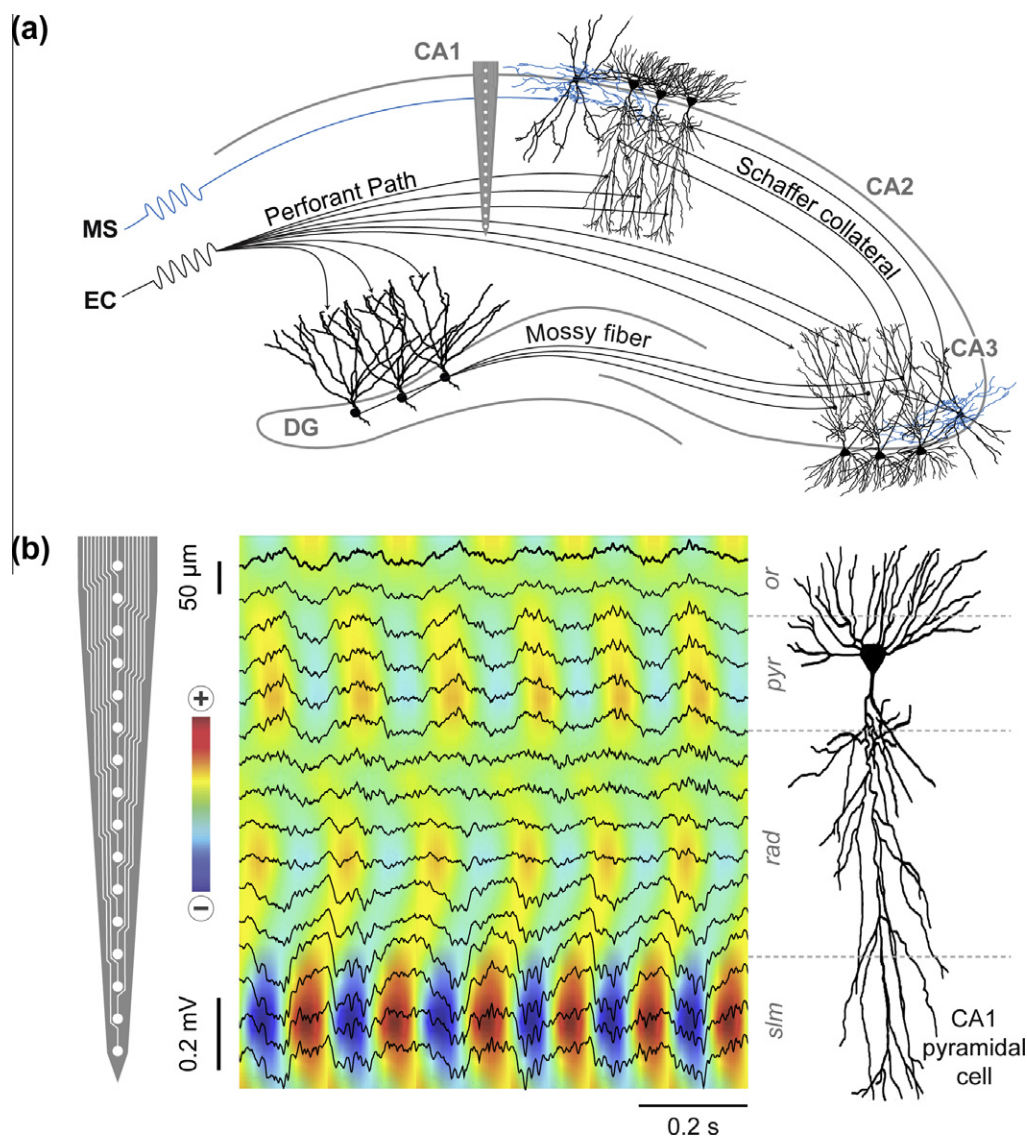
Fig. 1. Hippocampal circuitry underlying theta oscillations. (a) Excitatory (black) and inhibitory (blue) transmission involved in electrogeneration of theta oscillations. The *medial septum* (MS) provides rhythmic inhibitory inputs to CA1 *basket cells* (soma and dendrites in black plus axon in blue), which in turn provide rhythmic perisomatic inhibition to CA1 pyramidal cells. The entorhinal cortex (EC) provides rhythmic excitatory inputs at theta frequency through the *perforant path* to the granule cells of the dentate gyrus (DG) and to the apical dendrites of CA1 and CA3 pyramidal cells. The rhythmic activity from DG granule cells is conveyed through the *mossy fibers* to the CA3 pyramidal cells and then, through the *Schaffer collaterals,* to CA1 pyramidal cells. (b) Current source density analysis of theta oscillations in the CA1 region during REM sleep, obtained with a silicone probe (16 sites, 50 μm spaced). Note the presence of rhythmic somatic hyperpolarization (source in stratum pyramidale) coupled to rhythmic dendritic depolarization (sink in stratum lacunosum moleculare). Current sources in red and sinks in blue. Abbreviations: *or* stratum oriens, *pyr* stratum pyramidale, *rad* stratum radiatum, *slm* stratum lacunosum moleculare.

oscillations, *in vivo* multisite electrophysiological recordings have shown that the coherence of theta oscillations (Royer et al., 2010; Sabolek et al., 2009) and the relationship between theta power and locomotion speed (Hinman et al., 2011) decreases along the septo-temporal axis.

3. Hippocampus-associated regions implicated in theta oscillations

3.1. Medial Septum (MS)

In the behaving rat, hippocampal theta oscillations are accompanied by high cholinergic tone (Jasper and Tessier, 1971; Zhang et al., 2010). In order to tune the network state into theta regime, the hippocampal activity diverges from a resting state characterized by sharp-wave-ripple complexes (Csicsvari et al., 2000) also known as large irregular activity. This transition is triggered and sustained by the pacemaker activity of the medial septum (Petsche et al., 1962), a structure well known for its direct cholinergic projections to the hippocampus. The MS together with the vertical and horizontal limb of the diagonal band of Broca (VDB and HDB) is a midline structure part of a vast region known as basal forebrain (Zaborszky et al., 2005). The MS projects to specific hippocampal subregions (Crutcher et al., 1981) such as: (i) dentate gyrus (the supragranular zone of the septal pole and the hilus), (ii) CA1 (stratum oriens and stratum lacunosum moleculare), (iii) CA2–CA3 (stratum oriens and stratum radiatum). The subiculum, presubiculum and parasubiculum are targeted as well (Crutcher et al., 1981). The MS contains an heterogeneous population of projecting cells characterized by cholinergic (Mesulam et al., 1983), GABAergic (Freund, 1989; Kiss et al., 1990; Leranth and Frotscher, 1989) or glutamatergic (Colom et al., 2005; Manns et al., 2001) neurotransmission. Interestingly, only GABAergic and glutamatergic cells display pacemaker properties *in vitro* (Huh et al., 2010; Markram and Segal, 1990; Varga et al., 2008). *In vivo,* MS cells are known to fire at theta frequency, in phase with the negative peak of the theta signal recorded in the CA1 pyramidal layer (Dragoi et al., 1999). In addition, the firing of the MS cells is suppressed during sharp-waves ripples (Dragoi et al., 1999). Inhibition of the MS cell activity, through targeted lidocaine (Koenig et al., 2011; Mizumori et al., 1990; Winson, 1978) or muscimol (Bland et al., 1996; Brandon et al., 2011) injection, leads to complete suppression of the theta oscillations. However, while i.p. injection of the muscarinic antagonist, atropine (Bradley and Nicholson, 1962), suppresses the theta oscillations associated with paradoxical sleep, it leaves almost intact the one related to locomotion, usually absent under urethane anesthesia (Kramis et al., 1975). Furthermore, direct injection of atropine into the hippocampus leads to a decrease of the theta power (Li et al., 2007) and selective lesion of MS cholinergic neurons with IgG-saporin (Lee et al., 1994), or MS GABAergic neurons with kainic acid (Yoder and Pang, 2005), significantly reduces theta power, suggesting that both populations of neurons are involved in the generation of theta oscillations. Septohippocampal cholinergic afferents are known to establish synaptic contacts in the dentate gyrus (Clarke, 1985; Frotscher, 1991), preferentially with neuropeptide-Y interneurons (Dougherty and Milner, 1999) and cholinergic activity can trigger intrinsic theta oscillations in the hippocampus as demonstrated by *in vitro* intracellular recordings under bath perfusion with the cholinergic agonist, carbachol (Bland et al., 1988). The MS GABAergic cells expressing parvalbumin (Freund, 1989) and targeting the hippocampal basket cells (Freund and Antal, 1988; Tóth et al., 1997), have been reported to drive hippocampal activity (Hangya et al., 2009) and the hippocampal feedback to the medial (Tóth et al., 1993) and lateral septum (Leranth and Frotscher, 1989) may

support the synchronization between the two structures. Interestingly, MS glutamatergic cells expressing the vesicular glutamate transporter 2 (VGLUT-2) (Hajszan et al., 2004) have been reported to project to the hippocampus and to produce rhythmic discharges in the theta range (Huh et al., 2010) but their role in the genesis of the hippocampal theta oscillations remains to be established.

3.2. Entorhinal Cortex (EC)

The EC provides much of the cortical information to the hippocampal formation. This important region is identified by its projections targeting the dentate gyrus of the hippocampus: the perforant path. In the hippocampus, the septo-temporal organization of the EC fibers is associated to specific subregions of the EC (Dolorfo and Amaral, 1998): (i) the septal part of the hippocampus receives afferents from a portion of the lateral EC (LEC) adjacent to the rhinal fissure and from the medial EC (MEC), (ii) the central part is innervated by the medial portion of the LEC and by rostral portion of the MEC, whereas (iii) the temporal part is innervated by the most medial portion of the LEC and by most rostral portion of the MEC. The EC sends direct glutamatergic inputs to the stratum lacunosum moleculare of CA1, CA3 and to the molecular layer of the dentate gyrus (Amaral and Witter, 1989; Van Groen et al., 2003) but only the MEC seems strongly involved in the generation of the hippocampal theta oscillations (Deshmukh et al., 2010). MEC lesion reduces hippocampal theta oscillations in drug free animals and in atropine treated animals (Montoya and Sainsbury, 1985), suggesting that atropine resistant theta oscillations involve the MEC. However, septal lesion or septal injections of lidocaine or muscimol abolish theta oscillations in the MEC of freely behaving animals (Brandon et al., 2011; Koenig et al., 2011; Mitchell et al., 1982). Combined septal injection of kainic acid (preferentially eliminating GABAergic cells) and IgG-saporin (preferentially eliminating cholinergic cells) suppresses locomotion-related theta oscillations (Yoder and Pang, 2005), suggesting that septal GABAergic cells may drive the MEC theta inputs to the hippocampus. Nevertheless, the MEC circuitry generates local theta oscillations that reverse in layer II and MEC units are phase locked to the local theta signal (Dickson et al., 1995; Mitchell and Ranck, 1980; Mizuseki et al., 2009; Stewart et al., 1992). Moreover, layer II stellate cells and deep layer cells (Schmitz et al., 1998) expressing I_{pNa+} and I_h currents (Alonso and Llinás, 1989; Dickson et al., 2000), display subthreshold oscillatory activity within the theta range and the cholinergic agonist, carbachol, can induce theta oscillations in MEC slices (Gołebiewski et al., 1994; Konopacki and Gołebiewski, 1992). Interestingly, layer V pyramidal cells, the link between the hippocampus and many cortical regions, respond to consecutive stimuli with graded changes in firing frequency linked to cholinergic muscarinic receptor activation and characterized by sustained levels of firing frequency that can be either increased or decreased in an input-specific manner (Egorov et al., 2002). As the hippocampus, the MEC circuit usually displays a resting state and its transition towards theta state is triggered and supported by the activation of MS, VDB and HDB (Jeffery et al., 1995; Mizumori et al., 1992). Therefore, the theta activity of both EC and hippocampus seems to rely on MS, VDB and HDB although with a certain degree of specialization. In fact, while the EC inputs are mainly attributed to VDB and HDB, the hippocampal inputs seem restricted to MS and VDB (Gaykema et al., 1990).

3.3. Subicular Complex (Sub)

The output of CA1 is characterized by columnar projections towards the subiculum, a structure known to project directly and indirectly, through the presubiculum and the parasubiculum, to the EC layer II–III cells (Amaral and Witter, 1989). Subicular

pyramidal cells (Wang et al., 2006) and layer II parasubicular cells (Glasgow and Chapman, 2007, 2008) display intrinsic subthreshold oscillations in the theta range, which depend on I_{pNa+} and I_h currents. In addition, the whole subicular complex is under the control of the septal complex (Crutcher et al., 1981). As a potential consequence, locally generated atropine-sensitive theta oscillations can be observed in the parasubiculum, in phase with the theta oscillations recorded in the stratum lacunosum moleculare, and display phase reversal between the superficial and deep layers (Glasgow and Chapman, 2007). Cellular activity is usually phase locked to the theta signal (Anderson and O'Mara, 2003; Boccara et al., 2010; Cacucci et al., 2004). Interestingly, a more detailed investigation has revealed that only the spiking activity of the superficial layers is phase locked to theta oscillations whereas deep layers fire tonically during theta state (Chrobak and Buzsáki, 1994).

4. Control of the theta pacemaker

The septal complex (MS, VDB and HDB) is under the control of different deep structures (Bland and Oddie, 1998; Vertes and Kocsis, 1997). This control is specifically operated by the cholinergic nuclei of the brainstem, the pedunculo pontine tegmentum and the laterodorsal tegmentum (Mesulam et al., 1983), in two different ways (see Fig. 2). The first, direct pathway, projects directly to the septal complex (Hallanger and Wainer, 1988; Woolf and Butcher, 1986). The second, indirect pathway, is mainly mediated by the hypothalamus (Woodnorth et al., 2003) through its supramammillary nuclei (Kirk and McNaughton, 1991) and posterior hypothalamic nuclei (Oddie et al., 1994). Importantly, the two brainstem nuclei, which are known to mediate cortical desynchronization (Datta and Siwek, 1997), support in their caudal part,
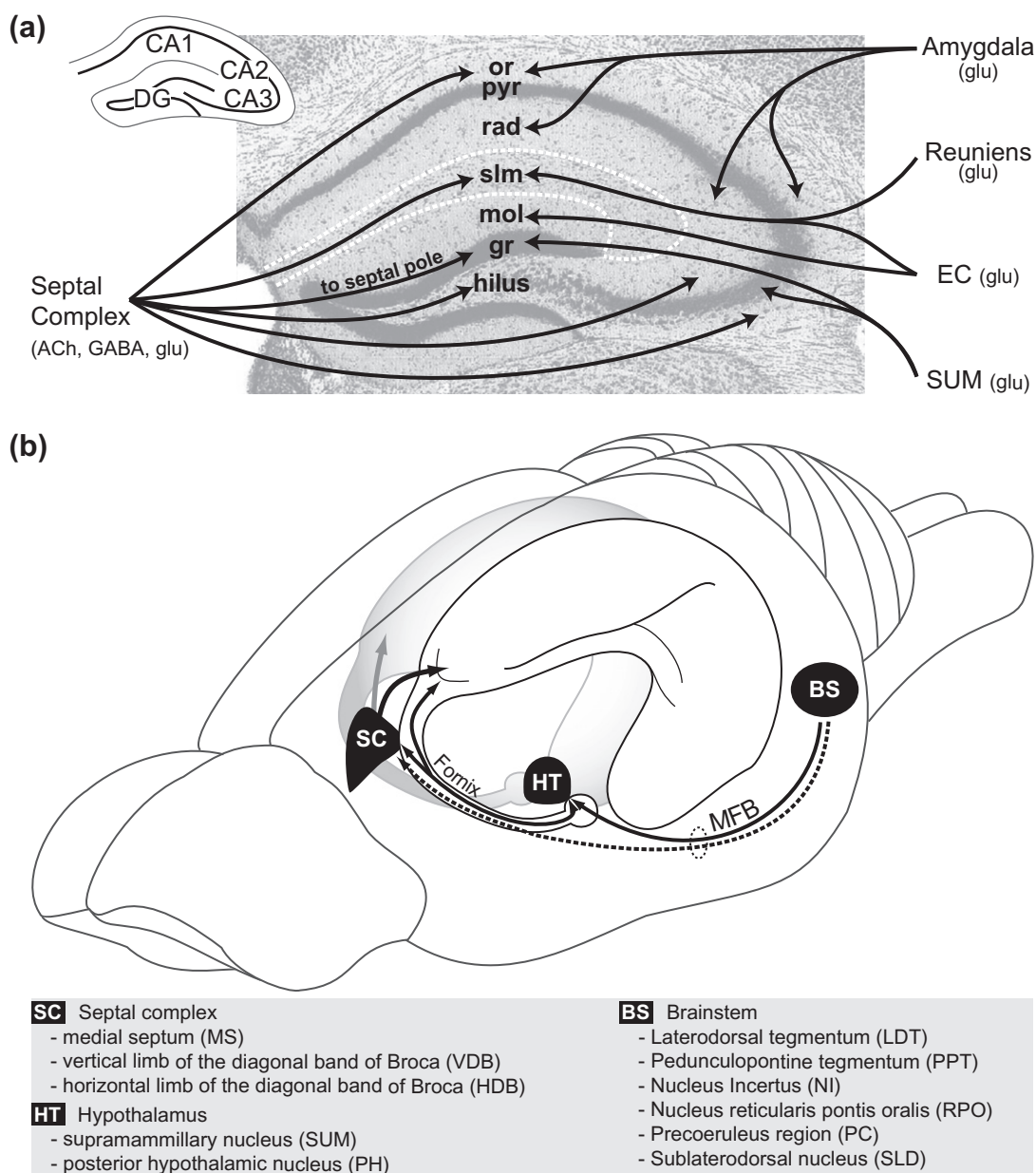
Fig. 2. Neural circuitry involved in the generation of theta oscillations. (a) Layer specific afferents supporting hippocampal theta oscillations (*or*: stratum oriens, *pyr*: stratum pyramidale, *rad*: stratum radiatum, *slm*: stratum lacunosum moleculare, *m*: stratum moleculare, *gr*: stratum granulare). Neurotransmitters: acetylcholine (*ACh*), gamma amino butyric acid (*GABA*), glutamate (*glu*). Abbreviations: EC, entorhinal cortex, SUM, supramammillary nucleus. (b) Direct (dotted line) and indirect pathways mediating the activation of the septal complex (SC). Both of them pass through the medial forebrain bundle (MFB) and the fornix. HT: hypothalamus, BS: brainstem.

composed by the sublaterodorsal nucleus and precoeruleus region, the generation of paradoxical sleep (Lu et al., 2006). Instantaneous increase in power and frequency of the theta oscillations during paradoxical sleep, known as phasic theta (Montgomery et al., 2008), is correlated with phasic pontine activity (Karashima et al., 2005).

4.1. Brainstem control of theta oscillations

4.1.1. Pedunculopontine Tegmentum (PPT) and Laterodorsal Tegmentum (LDT)

The PPT and the LDT contain an heterogeneous cellular population characterized by cholinergic, GABAergic or glutamatergic neurotransmission (Lee et al., 1988). The cells fire tonically during the active state (Steriade et al., 1990). Direct stimulation of PPT-LDT elicits cortical desynchronization, hippocampal theta oscillations accompanied by wakefulness or paradoxical sleep (Datta and Siwek, 1997) and can induce locomotion, as other components of the mesencephalic locomotor region (Milner and Mogenson, 1988; Skinner and Garcia-Rill, 1984). Suppression of the PPT activity, through local injection of procaine, abolishes hippocampal theta rhythm in urethane anaesthetized rats (Nowacka et al., 2002). The anatomical substrates of these effects are represented by two groups of projections: (i) a descending pathway innervating the brainstem and the spinal cord (Rye et al., 1988) and (ii) an ascending pathway projecting to the diencephalon and to the basal forebrain (Hallanger et al., 1987). The descending projections are characterized by cholinergic transmission up to the beginning of the spinal cord and then by non-cholinergic terminals (Rye et al., 1988). The ascending component is mainly characterized by cholinergic transmission, specifically targeting the thalamus, lateral septum, MS, VLB and HLB, amygdala, globus pallidus (internal segment and entopeduncolar nucleus), substantia nigra, subthalamic nucleus, zona incerta, lateral hypothalamus and superior colliculus (Hallanger et al., 1987; Hallanger and Wainer, 1988; Inglis and Winn, 1995; Rye et al., 1987; Woolf and Butcher, 1986). The nucleus reticularis pontis oralis is targeted by the PPT as well (Mitani et al., 1988; Semba et al., 1990; Shiromani et al., 1988). In addition, the PPT is directly modulated by the activity of the following structures: nucleus accumbens, ventral pallidum, caudate putamen (ventrolateral), globus pallidus (medial), subthalamic nucleus, substantia nigra, locus coeruleus, raphe nuclei and finally the parabrachial nucleus and the contralateral PPT (Inglis and Winn, 1995; Semba and Fibiger, 1992; Steininger et al., 1992). Different neuromodualtors are involved in the control of the PPT-LDT activity and in the modulation of theta oscillations: (i) noradrenergic inputs from the locus coeruleus leads to theta activity (Berridge and Foote, 1991) and, (ii) serotoninergic inputs from the median raphe (MR) suppress theta oscillations desynchronizing hippocampal activity (Jackson et al., 2008), whereas inactivation of the MR through muscimol injection can elicit theta oscillations (Kinney et al., 1995).

4.1.2. Sublaterodorsal nucleus (SLD) and Precoeruleus region (PC)

The SLD and PC are two structures located caudally to the LDT and their inactivation is responsible for a significant decrease in paradoxical sleep occurrence together with a reduction of the associated theta oscillations (Lu et al., 2006; Saper et al., 2010). These nuclei contain glutamatergic and GABAergic cells, as well as cholinergic cells in the SLD (Allen-Brain-Atlas). Injection of retrograde tracers into the ventral horn of the spinal cord has revealed direct projections from SLD cells which, importantly, express VGLUT-2 (Fuller et al., 2007). Animals with lesion of the SLD do not display muscle atonia. Therefore SLD, by exciting glycinergic/GABAergic cells of the spinal cord, could elicit the muscle atonia observed during paradoxical sleep. In addition, injection of a retrograde tracer in

the MS has revealed labeled cells in the PC region and selective lesion of the PC suppresses sleep-related hippocampal theta oscillations without affecting muscle atonia and cortical desynchronization (Fuller et al., 2007; Lu et al., 2006).

4.1.3. Nucleus Reticularis Pontis Oralis (RPO)

The RPO is a pontine structure directly innervated by the PPT (Semba et al., 1990) and known to project mainly to the supramammillary nucleus (Vertes et al., 1986). Neurons in the RPO display tonic spiking activity during theta state (Vertes, 1977, 1979). Under urethane anesthesia, stimulation of the RPO leads to theta activity while its inhibition by local procaine injection suppresses the spontaneous and tail-pinch evoked theta oscillations (Bland and Oddie, 1998).

4.1.4. Nucleus Incertus (NI)

The NI is a small nucleus embedded in the periacqueductal gray adjacent to the dorsal tegmental nucleus. It is composed of longitudinal columns of cells coexpressing GABA, relaxin 3 and neuromedin B (Ryan et al., 2011). The NI integrates synaptic inputs from prefrontal and premotor cortex, hippocampus, septal complex, lateral habenula, interpeduncular nucleus, posterior hypothalamus, periaqueductal gray, dorsal raphe and retro-LDT, targeting the output on the prefrontal cortex, premotor cortex, hippocampus, mediodorsal and ventromedial thalamic nucleus, septal complex (in particular to medial part), posterior hypothalamus, supramammillary nucleus, periaqueductal gray, dorsal raphe and retro-LDT (Goto et al., 2001). Electrical stimulation of the NI elicits theta oscillations in urethane-anaesthetized rats while injection of muscimol prevents theta oscillations evoked by RPO stimulation (Nuñez et al., 2006).

4.1.5. Ventral tegmental nucleus of Gudden (VTn)

The VTn is located in the medial part of the pontine tegmental area. It is related to Papez's circuit through its GABAergic connections with the medial mammillary nucleus (Allen and Hopkins, 1990) and, in addition, it receives direct afferents from the LDT (Irle et al., 1984). The VTn cells are reported to rhythmically discharge during theta activity, in awake behaving and urethane-anaesthetized rats (Bassant and Poindessous-Jazat, 2001; Kocsis et al., 2001).

4.1.6. Dorsal Raphe (DR)

The DR is the major serotoninergic nucleus of the brain (Steinbusch and Nieuwenhuys, 1981). The DR projects to the piriform, insular, frontal, occipital, entorhinal, perirhinal, frontal orbital, anterior cingulate, and infralimbic cortices, hippocampal formation, as well as the intralaminar nuclei of the thalamus, septal complex (in particular the lateral septum, VDB and HDB), SUM, ventral tegmental area and the PPT (Vertes, 1991). The main afferents arise from orbital, cingulate, infralimbic, dorsal peduncular, and insular cortices, ventral pallidum, lateral habenula, claustrum, zona incerta, central nucleus of the amygdala, lateral, dorsal and posterior hypothalamic areas (Peyron et al., 1998). Stimulation of the DR can elicit scopolamine sensitive theta oscillations, suggesting that the effect is mediated by the cholinergic system (Peck and Vanderwolf, 1991). Around 55% of the cellular population of the DR is reported to rhythmically fire in phase with theta oscillations in the behaving rat (Kocsis and Vertes, 1992).

4.2. Hypothalamic control of theta oscillations

4.2.1. Supramammillary nucleus (SUM)

SUM cells receive direct innervations from the nucleus reticularis pontis oralis (Vertes et al., 1986), the septal complex and the LDT (Gonzalo-Ruiz et al., 1999), and project to the septal

complex (Borhegyi et al., 1998) and to the hippocampus (Vertes, 1992), innervating the granule cell layer of the dentate gyrus and the pyramidal cell layer of the CA2-CA3 region (Maglóczky et al., 1994). In the rat, its cellular population is composed of glutamatergic cells (Kiss et al., 2002) producing synchronous discharges phase-locked to the theta signal (Kirk and McNaughton, 1991). Electrical stimulation of the nucleus reticularis pontis oralis, following procaine injection in the SUM, leads to a reduced theta power and frequency in urethane-anaesthetized rats, whereas injection of procaine in the MS reduces exclusively theta power (Kirk and McNaughton, 1993), suggesting that the SUM could exert a direct control on the frequency of theta oscillations. However, selective lesions of the SUM have failed to suppress hippocampal theta activity in the behaving animal (Thinschmidt et al., 1995), suggesting the restricted role of a theta modulator. Even so, based on the existence of reciprocal connections between SUM and septo-hippocampal systems (Borhegyi and Freund, 1998; Borhegyi et al., 1998), it is proposed a state-dependent bidirectional coupling characterized by alternated leadership between the two oscillators (Kocsis, 2006).

4.2.2. Mammillary bodies (MB)

The SUM can also be considered as a component of the mammillary bodies (MB), a central relay of the limbic system (Vann and Aggleton, 2004), which receives direct inputs from the subiculum (Meibach and Siegel, 1975) and which cellular activity is phase-locked to the theta signal (Kocsis and Vertes, 1994). However, these structures are remarkably different both anatomically and physiologically. The anatomical difference lies in the thalamic target of the projections: (i) the SUM projects preferentially to the nucleus reuniens, a site which provides direct innervation to the CA1 stratum lacunosum moleculare (Vertes, 1992; Vertes et al., 2006) and characterized by tonic discharges during theta state (Morales et al., 2007), whereas (ii) the MB projects to the anterior thalamic nuclei (Allen and Hopkins, 1990), in which rhythmic discharges phase locked to the theta rhythm have been reported (Vertes et al., 2001). The physiological difference between SUM and MB appears after septal inactivation, leading to the persistence of theta activity in the SUM but its suppression in the MB (Kirk et al., 1996). Overall, these experimental evidences indicate that the MS drives the MB whereas the SUM is independent.

4.2.3. Posterior nucleus of the hypothalamus (PH)

The PH is a nucleus adjacent to the MB. Reciprocally connected to the PPT (Hallanger and Wainer, 1988; Steininger et al., 1992), it also innervates the SUM, the septal complex and the reuniens nucleus of the thalamus (Vertes et al., 1995). The nucleus mainly contains glutamatergic cells expressing VGLUT-2 (Ziegler et al., 2002) and displaying tonic firing during theta state (Bland et al., 1995). In addition, selective inactivation of the PH by muscimol (Bocian and Konopacki, 2007) or procaine injection (Oddie et al., 1994), in rats under urethane anesthesia, impairs theta oscillations.

5. Additional regions involved in theta oscillations

5.1. Medial Prefrontal Cortex (mPFC)

The mPFC is one of the principal targets of the CA1 pyramidal cells from the ventral part of the hippocampus (Swanson, 1981). The CA1 pyramidal cell terminals, distributed in layer I and layer V, provide excitation to both mPFC pyramidal cells and interneurons (Gabbott et al., 2002). The mPFC is typically identified by the thalamic afferents originating in the mediodorsal nucleus (Condé et al., 1990) and receives, in addition, afferent projections from the agranular insular cortex, the entorhinal and piriform cortices, the subiculum, the endopiriform nucleus, the amygdalo-piriform transition, the amygdalohippocampal area, the lateral tegmentum, the parabrachial nucleus (Condé et al., 1995) and importantly from the septal complex (Gaykema et al., 1990), the ventral tegmental area (Sesack et al., 1998) and the LDT (Satoh and Fibiger, 1986). Therefore, since the mPFC is under the control of the hippocampus, EC, septal complex and LDT, the detection of synaptically driven theta oscillations in this structure is not surprising. In fact, the presence of pyramidal cells and parvalbumin positive interneurons phase locked to theta oscillations has been reported in the rat mPFC (Hartwich et al., 2009; Hyman et al., 2005; Jones and Wilson, 2005a; Sirota et al., 2008; Tsujimoto et al., 2006), although delayed relative to CA1 pyramidal cells (Siapas et al., 2005). The efferent projections of the mPFC are targeted on cingulate, entorhinal and perirhinal cortical structures, the dorsomedial and ventral striatum, basal forebrain nuclei, basolateral amygdala, lateral hypothalamus, mediodorsal, midline and intralaminar thalamic nuclei, periaqueductal gray region, ventral midbrain tegmentum, LDT, PPT, and raphe nuclei (Apergis-Schoute et al., 2006; Gabbott et al., 2005; Gaykema et al., 1991; Sesack et al., 1989; Vertes, 2002). Interestingly, the ventral striatum, one of the principal targets of the mPFC, contains theta modulated cells (van der Meer and Redish, 2011). In summary, the mPFC is reciprocally connected to most of the regions involved in theta generation and can be considered as a global modulator of theta activity. Simultaneous multisite electrophysiological recordings, targeting both hippocampus and mPFC, have shown: (i) a correlation between the two structures paralleled by the increased coupling in the 7 Hz range during behaviors involving spatial working memory (Jensen, 2005; Jones and Wilson, 2005b; Paz et al., 2008), and (ii) an increase in the coherence between the two theta signals, which reaches a maximum at the choice point of a Y-maze, in particular following acquisition of the task (Benchenane et al., 2010).

5.2. Amygdala

The amygdala is a complex anatomical structure critical for producing appropriate emotional and behavioral responses to biologically relevant sensory stimuli, representing a cardinal link between the sensory systems, the limbic system and all the subcortical structures involved in emotional responses such as the hypothalamus, the brainstem and the striatum (McDonald, 1998). In the cat, the projection cells and the interneurons of the basolateral amygdala are significantly phase locked to theta oscillations (Paré and Gaudreau, 1996). To support this observation, the amygdala receives direct innervation from different regions implicated in theta oscillations such as: ventral hippocampus (Kishi et al., 2006), prefrontal cortex (Cassell and Wright, 1986; McDonald et al., 1996), lateral entorhinal cortex (McDonald and Mascagni, 1997), ventral subiculum (Canteras and Swanson, 1992), HDB (Meibach and Siegel, 1977), parabrachial area (Bernard et al., 1993) and a small contribution from the PPT and LDT (Hallanger and Wainer, 1988). The efferent projections are as well directed to most of the regions implicated in theta oscillations: (i) from the basomedial nucleus to the HDB, the mPFC and the lateral and ventromedial nuclei of the hypothalamus (Jolkkonen et al., 2002; Petrovich et al., 1996), (ii) from the basal nucleus to the stratum oriens and stratum radiatum of CA3 and CA1 and from lateral nucleus to layer III of the entorhinal cortex (Pikkarainen et al., 1999), (iii) from the posterior nucleus to the stratum lacunosum-moleculare of the temporal CA1 subfield, the adjacent molecular layer of the proximal temporal subiculum, the parahippocampal region, and the entorhinal cortex (Canteras et al., 1992; Kemppainen et al., 2002), (iv) from the medial and central nuclei to the midline thalamic nuclei (McKenna and Vertes, 2004; Otake et al., 1994) and (v) from the central nucleus to the PPT (Semba

and Fibiger, 1992). Synchronization of theta activities in the amygdalohippocampal network represents a neuronal correlate of conditioned fear, potentially facilitating neuronal communication during memory retrieval (Seidenbecher et al., 2003). While theta coupling increases between all areas during retrieval of conditioned fear, it decreases during extinction learning (Lesting et al., 2011). Furthermore, overnight bidirectional changes in fear memory are selectively correlated with modifications in theta coherence between the amygdala, medial prefrontal cortex, and hippocampus during paradoxical sleep (Popa et al., 2010). Finally, septal lesions were found to potentiate the freezing response elicited by contextual stimuli (Sparks and LeDoux, 1995).

5.3. Reuniens nucleus of the thalamus (RE)

The RE is a midline structure known to mediate arousal and awareness, receiving direct cholinergic afferents from the PPT (Hallanger et al., 1987; Van der Werf et al., 2002; Vertes et al., 1995). Furthermore, it is considered as an interface between the prefrontal cortex and the hippocampus since pyramidal cells of the prefrontal cortex innervate RE cells projecting to the stratum lacunosum moleculare of CA1 (Vertes, 2002; Vertes et al., 2007). In the hippocampus, RE terminals establish asymmetric synapses with both GABAergic and non-GABAergic dendrites (Dolleman-Van der Weel and Witter, 2000). The RE sends region specific glutamatergic fibers to the septal complex (Bokor et al., 2002), EC, subiculum and the amygdala (Dolleman-Van der Weel and Witter, 1996; Su and Bentivoglio, 1990; Vertes et al., 2006). The RPO, PH, SUM and PPT all innervate the RE (Hallanger et al., 1987; Newman and Ginsberg, 1994). RE cells coexpress calretinin (Cicchetti et al., 1998; Wouterlood et al., 2008) and VGLUT-2 (Wouterlood et al., 2008) and display tonic firing during theta state in rats under urethane anesthesia (Morales et al., 2007).

6. Future directions

The dynamic of the extracellular currents along the hippocampal septo-temporal axis and the relative contribution of each independent hippocampal oscillator to the theta field still represents an open question that could be addressed by selective inactivation of hippocampal or entorhinal subregions associated with multisite recordings along the longitudinal axis and network modeling (Buzsáki, 2002).

The power of the theta oscillations exhibits fluctuations correlated to the behavioral state of the animal (Wyble et al., 2004) and phasic theta episodes are reported during paradoxical sleep (Montgomery et al., 2008). The dynamic interplay between all the extra hippocampal oscillators and the resulting integration at the hippocampal level provides an intricate substrate to modulate theta power. Alternatively, the significant correlation between theta power and pontine waves occurrence (Karashima et al., 2004) may suggest a pivotal modulation of the PPT on the extra hippocampal theta generators. Moreover, because sensory-related theta has a slower frequency than locomotion-related theta (4–9 Hz against 6–12 Hz) (Kramis et al., 1975), their expected coexpression during behavior is a potential source of oscillatory interference. From the signal theory, the interference between two summed theta waves of slightly different frequencies would result in a rhythmically modulated theta wave. Therefore, one might expect theta power to be rhythmically modulated during spontaneous behavior. Simultaneous recordings of hippocampal theta together with different anatomical elements of its generating circuit during controlled behavioral protocols should help understand the role played by these structures in the generation and modulation of hippocampal theta, allowing to explore new dimensions of theta oscillations and potentially helping us understand the temporal organization of sensory-motor processes.

Interestingly, the dorsocaudal region of the rat MEC contains a topographically organized neural map of the spatial environment constituted by the grid cell, which is activated whenever the animal position coincides with any vertex of a regular grid of equilateral triangles spanning the surface of the environment (Hafting et al., 2005). The map is anchored to external landmarks, but persists in their absence. Grid cells exhibit firing at regular spatial locations and temporal modulation with theta oscillation. It has been recently shown in rats, that MS inactivation, through muscimol

Table 1
Synaptic and network properties of the regions implicated in theta oscillations.

	Neurotransmitters				Network properties				Brain states		
	ACh	5HT	Glutamate	GABA	Pacemaker	Oscillator	Driver	Modulator	Awake	REM	Urethane
CA1 pyr			+			+			+	+	+
CA3 pyr			+			+			+	+	+
DG			+			+			+	+	+
SC	+		+	+	+	+			+	+	+
EC			+			+			+	+	+
Sub			+			+			+	+	+
SUM			+			+			ND	ND	+
MB			+			+			ND	ND	+
PH			+					+	ND	ND	+
PPT											
LDT	+						+		+	+	+
SLD											
PO			+				+			+	
RPO			+					+	ND	ND	+
NI				+				+	ND	ND	+
VTn			+			+			+	+	+
DR		+				+	+		+	+	ND
PFC			+			+			+	+	+
Amy			+			+			+	+	ND
RE			+					+	ND	ND	+

+, reported in the litterature.
ND, expression of theta not demonstrated in this structure in the corresponding brain state.
Pacemaker, displays intrinsic theta activity.
Oscillator, displays inducible theta activity upon adequate stimulation.
Driver, required for theta oscillations in other structures.
Modulator, able to modulate the power or frequency of theta oscillations in other structures.

or lidocaine, leads to suppression in the spatial periodicity of the grid cells, unaffecting the spatial representation of the hippocampal place cells (Brandon et al., 2011; Koenig et al., 2011). In addition, grid cells persist after hippocampal inactivation (Hafting et al., 2008). It would be interesting to understand how the pacing activity of the MS affects the interplay occurring between the cortical and the subcortical inputs in the generation of spatial representation of the MEC and to address, through selective lesion of the septo-entorhinal pathway, what is the impact of a disorganized entorhinal input on theta activity of the hippocampus.

Other critical issues are to decipher the exact sequential activation of all the structures involved in the theta generation (see Table 1) as well as the mechanisms involved in the synchronization of the theta oscillators during specific behavioral tasks (Benchenane et al., 2010; Jensen, 2005; Seidenbecher et al., 2003). These issues could be examined by combining simultaneously, in different configurations, multiple intracellular (Poulet and Petersen, 2008) and massive extracellular recordings (Csicsvari et al., 2003). The precise timing between circuit elements may highlight potential targets useful to address specific behavioral paradigms. Finally, despite the considerable effort reported by all the past anatomical studies, a methodic dissection aimed to quantify the structural and ultrastructural contribution of all the deep structures to the theta generation can still provide useful information about the theta circuit. Detailed information relative to the projections and synaptic targets of the cholinergic and glutamatergic cells of the PPT and LDT, the glutamatergic cells of the MS, the SUM and the PH, the noradrenergic cells of the locus coeruleus and the serotoninergic cells of the raphe nuclei can still provide important insights.

7. Conclusions

The progress of our understanding of theta generators closely correlates with technological advances. The identification of theta generators was primarily based on electrophysiological recordings such as unit activity and field potential followed by electrolytic lesions to allow histological verification. The spiking activity was classified in relation to theta signal as (i) theta-phase modulated (units phase locked to theta signal), (ii) theta-ON (tonic activity during theta) and (iii) theta-OFF (no activity during theta) (Colom and Bland, 1987). Electrical stimulation and surgical or chemical lesions allowed a systematic inspection of the regions involved in theta generation (Robinson and Vanderwolf, 1978). In addition, anatomical studies based on combined applications of retrograde and anterograde tracers coupled to ultrastructural observation provided the necessary morphological support to the physiological results. Nevertheless, a real progress appears with the use of pharmacological tools first applied systemically (atropine, scopolamine, physostigmine, urethane, ...) and then locally by targeted injections. Glutamate was employed to provide excitation of local populations of neurons, and lidocaine, procaine or muscimol to provide their inhibition. Furthermore, the advent of the immunocytochemistry has lead rapidly towards a targeted cellular dissection of single theta generators. However, the precision of both anatomical and pharmacological techniques was often limited by the relative control of the volume of tracers or drugs injected. With such techniques, selective stimulation of a specific cellular population was out of reach. In fact, electrical stimulation and lidocaine injection can alter not only the somas but also passing axons, resulting in less straightforward interpretation.

Today, the advent of molecular biology offers new perspectives to the field. Selective tagging coupled to the expression of optogenetic tools (Gradinaru et al., 2010) allow the stimulation or inhibition of selective cellular populations, increasing the precision from the regional to the single cell scale. The convergence of physiological, anatomical and molecular tools finally allows the perspective of a new generation of experimental investigations.

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