

## Accepted Manuscript

Title: Reconciling the different faces of hippocampal theta: the role of theta oscillations in cognitive, emotional and innate behaviors

Authors: Tatiana Korotkova, Alexey Ponomarenko, Caitlin K. Monaghan, Steven L. Poulter, Francesca Cacucci, Tom Wills, Michael E. Hasselmo, Colin Lever



PII: S0149-7634(17)30084-2  
DOI: <http://dx.doi.org/10.1016/j.neubiorev.2017.09.004>  
Reference: NBR 2933

To appear in:

Received date: 29-1-2017  
Revised date: 22-8-2017  
Accepted date: 2-9-2017

Please cite this article as: Korotkova, Tatiana, Ponomarenko, Alexey, Monaghan, Caitlin K., Poulter, Steven L., Cacucci, Francesca, Wills, Tom, Hasselmo, Michael E., Lever, Colin, Reconciling the different faces of hippocampal theta: the role of theta oscillations in cognitive, emotional and innate behaviors. *Neuroscience and Biobehavioral Reviews* <http://dx.doi.org/10.1016/j.neubiorev.2017.09.004>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

## Reconciling the different faces of hippocampal theta: the role of theta oscillations in cognitive, emotional and innate behaviors

Tatiana Korotkova<sup>1,2,§</sup>, Alexey Ponomarenko<sup>1</sup>, Caitlin K. Monaghan<sup>3</sup>, Steven L. Poulter<sup>4</sup>, Francesca Cacucci<sup>5</sup>, Tom Wills<sup>6</sup>, Michael E. Hasselmo<sup>3</sup>, Colin Lever<sup>4,§</sup>.

<sup>1</sup>Behavioural Neurodynamics Group, Leibniz Institute for Molecular Pharmacology (FMP)/ NeuroCure Cluster of Excellence, Chariteplatz 1, CCO, 10117 Berlin, Germany;

<sup>2</sup>Neuronal Circuits and Behavior Research Group, Max Planck Institute for Metabolism Research, Gleueler Str. 50, 50931 Cologne, Germany

<sup>3</sup>Center for Systems Neuroscience, Department of Psychological and Brain Sciences and Graduate Program for Neuroscience, Boston University, 2 Cummington Mall, Boston, Massachusetts, 02215 USA

<sup>4</sup>Department of Psychology, University of Durham, DH1 3LE, U.K.

<sup>5</sup>Department of Neuroscience, <sup>6</sup>Department of Cell and Developmental Biology, Physiology and Pharmacology, University College London, London, WC1E 6BT, UK.

<sup>§</sup>Corresponding authors; tatiana.korotkova@sf.mpg.de, Colin.Lever@durham.ac.uk

### Highlights

- Theta rhythm is crucial for cognitive functions: memory, spatial and time coding
- Theta rhythm is crucial for anxiety-related behaviours
- Theta oscillation properties (phase, frequency, amplitude) are linked with behaviors
- Parallel emergence of hippocampal theta oscillations and behaviors during development

### Abstract

The theta oscillation (5-10 Hz) is a prominent behavior-specific brain rhythm. This review summarizes studies showing the multifaceted role of theta rhythm in cognitive functions, including spatial coding, time coding and memory, exploratory locomotion

and anxiety-related behaviors. We describe how activity of hippocampal theta rhythm generators - medial septum, nucleus incertus and entorhinal cortex, links theta with specific behaviors. We review evidence for functions of the theta-rhythmic signaling to subcortical targets, including lateral septum. Further, we describe functional associations of theta oscillation properties - phase, frequency and amplitude - with memory, locomotion and anxiety, and outline how manipulations of these features, using optogenetics or pharmacology, affect associative and innate behaviors. We discuss work linking cognition to the slope of the theta frequency to running speed regression, and emotion-sensitivity (anxiolysis) to its y-intercept. Finally, we describe parallel emergence of theta oscillations, theta-mediated neuronal activity and behaviors during development. This review highlights a complex interplay of neuronal circuits and synchronization features, which enables an adaptive regulation of multiple behaviors by theta-rhythmic signaling.

**Keywords:** hippocampus, entorhinal cortex, memory, resonance, grid cells, place cells, behaving mice, anxiety, speed, optogenetics

### **1.1 Behavioral correlates of theta rhythm: Introduction**

This review attempts to integrate cognitive, emotional and innate behaviour control-related aspects of hippocampal function, highlighting the crucial role of hippocampal theta rhythm in all of these functions. Research activities on the hippocampus, and hippocampal theta, tend to cluster into related fields. One cluster consists of spatial cognition, intensely studied in rodents, with the work on spatial memory representing a large overlap with a more general memory-oriented field. The field of locomotion and sensorimotor integration overlaps with the spatial cognition field of this first cluster: this is because spatial researchers increasingly recognize that an important contribution to spatial localization emerges from locomotion-derived computations of distance and direction travelled. For the spatial cognition field, then, locomotion-related inputs into the hippocampus are required to update location, and outputs to locomotor regions are required to direct the animal *where* to go. However, the idea that the hippocampus may control locomotion in a more fundamental way has persisted, largely inspired by Vanderwolf (1969) arguing that the key correlate of theta

was voluntary locomotion. In this review, we consider evidence for both the spatial cognition, and the locomotor control, fields of research.

A rather distant research cluster consists of emotion-related fields investigating anxiety, stress and depression. It is worth remembering that the ‘Papez circuit’ approach to limbic anatomy posited the hippocampus as an emotional centre. Broadly speaking, there has been minimal conversation between the cognition-locomotion and emotion-related ‘faces’ of theta. In this review, we not only attempt to highlight interesting work in both clusters, we set out the beginnings of an approach that may begin to bridge these seemingly-separate research areas. We start from the perspective that the hippocampal theta oscillation, while crucially subserving both cognition-locomotion and emotion-related functionality, is an essentially unitary phenomenon. Taking the theta frequency to running speed regression as a starting point, we describe theoretical and empirical work linking a cognition-locomotion component to the slope of this regression, and an emotion-sensitivity component (here, in particular, anxiolysis) to its y-intercept. Our discussion of the development of theta up to adulthood considers both the slope and y-intercept components.

Theta rhythm shows intriguing correlations with a range of different behaviors that include both aspects of movement and of memory function. Extensive data shows theta frequency oscillations in the local field potentials in the hippocampus across species (Green and Arduini, 1954), with similar mechanisms implicated in a range of frequencies labelled as theta (Buzsaki, 2002). Theta rhythm also appears in rat entorhinal cortex (Alonso and Garcia-Austt, 1987; Brandon et al., 2011; Mitchell and Ranck, 1980) and medial prefrontal cortex (Jones and Wilson, 2005; Lee et al., 2005). Intracranial electrodes implanted to detect seizure activity in humans show cortical theta rhythm oscillations associated with performance of memory tasks in humans (Kahana et al., 1999; Lega et al., 2011; Raghavachari et al., 2001; Rizzuto et al., 2006).

Theta rhythm correlates with a range of movement behaviors (Bland and Oddie, 2001; Vanderwolf, 1969; Whishaw and Vanderwolf, 1973) including running on a track (O’Keefe and Nadel, 1978; Skaggs et al., 1996), running wheel (Buzsaki et al., 1983; Hyman et al., 2003), treadmill (Brankack et al., 1993; Fox et al., 1986), and anticipates changes in movement (Morris and Hagan, 1983). Frequency and amplitude of rat theta

increases with running speed (Jeewajee et al., 2008a; Maurer et al., 2005; Rivas et al., 1996; Whishaw and Vanderwolf, 1973), suggesting a role in coding of velocity and location (O'Keefe and Nadel, 1978). We consider theta's links to locomotion, running speed, and location in sections 2 and 4.

Theta rhythm in the hippocampus also correlates with learning and memory function (Berry and Thompson, 1978; Givens and Olton, 1990; Griffin et al., 2004; Seager et al., 2002; Vertes and Kocsis, 1997; Winson, 1978). Lesions of the medial septum and fornix cause memory impairments in tasks including delayed spatial alternation (Aggleton et al., 1995; Givens and Olton, 1990), spatial reversal (M'Harzi et al., 1987), and the 8-arm radial maze (Mitchell et al., 1982). The reduction of theta rhythm correlates with the amount of memory impairment (Givens and Olton, 1994; Winson, 1978). Temporary inactivation of the medial septum causes impairments of spatial memory and also reduces theta rhythm in both the hippocampus (Brioni et al., 1990; Chrobak et al., 1989; Mizumori et al., 1990) and entorhinal cortex (Jeffery et al., 1995). We consider theta's links to learning and memory in section 5.

Less studied than movement and memory correlates, theta rhythm has also been linked to arousal (e.g. Green and Arduini, 1954), and to behavioural inhibition and anxiety (Gray, 1982; Sainsbury, 1998). Benzodiazepines, anxiolytic drugs, reduce both theta frequency and hippocampal-sensitive behavioural inhibition in fixed-interval responding (Woodnorth and McNaughton N, 2002). These links are further explored in sections 3 and 6 below.

## **2.1 Theta rhythm and the coding of spatial location.**

The role of theta rhythm in memory function may be related to a potential role of theta rhythm in the coding of the dimensions of space and time that are essential to episodic memory function (Tulving, 1983). Evidence for this role includes recordings showing a potential role of theta in the coding of a range of spatial dimensions. Numerous studies have explored the phenomenon of place cells in the hippocampus, which respond selectively when a rat visits specific locations in an environment (O'Keefe, 1976; O'Keefe and Dostrovsky, 1971b; Skaggs et al., 1996). Hippocampal place cells show a strong rhythmicity of firing at theta rhythm frequencies, as shown by the autocorrelation of spike times (Climer et al., 2015; O'Keefe and Burgess, 2005;

O'Keefe and Recce, 1993). Place cells also show more fine-grained temporal coding of spike timing relative to the phase of theta rhythm in the form of theta phase precession (O'Keefe and Recce, 1993; Skaggs et al., 1996). When a rat runs through its firing field, a place cell initially spikes at late phases of the theta cycle, and then shifts to progressively earlier phases as the rat continues through the place field (Huxter et al., 2003; O'Keefe and Recce, 1993; Skaggs et al., 1996).

A relationship between spatial coding and theta rhythm also appears in recordings of grid cells in the entorhinal cortex in rats (Hafting et al., 2008; Moser and Moser, 2008). Grid cells respond as a rat visits a regular array of locations in the environment described as falling on the vertices of tightly packed equilateral triangles (Fyhn et al., 2004; Hafting et al., 2008; Hafting et al., 2005). Grid cells also show strong theta rhythm firing, and grid cells in specific layers will show theta phase precession (Hafting et al., 2008). Each time a rat passes through the firing field of a grid cell, the spiking starts at late phases of the LFP theta cycle, and shifts to earlier phases of the theta cycle (Climer et al., 2013; Eggink et al., 2014; Hafting et al., 2008; Jeewajee et al., 2014).

Evidence that the spatial coding of grid cells might depend upon theta rhythm oscillations comes from studies that blocked entorhinal theta rhythm oscillations using infusion of pharmacological agents into the medial septum (Brandon et al., 2011; Koenig et al., 2011). The blockade of theta rhythm oscillations was accompanied by loss of spatial periodicity of grid cells, without loss of head direction cell selectivity by neurons (Brandon et al., 2011). This loss of grid cell spatial coding during the loss of theta rhythm oscillations suggests an important role for theta rhythm in spatial coding, and could explain the spatial memory impairments seen during inactivation of the medial septum (Chrobak et al., 1989). Surprisingly, inactivation of the medial septum does not appear to block the firing of place cells in novel or familiar environments (Brandon et al., 2014).

## **2.2 Theta rhythm and the coding of running speed.**

In addition to the coding of location by place cells and grid cells, extensive experimental data also indicates a relationship between theta frequency and the spatial dimension of running speed. Multiple studies have shown that the frequency and amplitude of theta rhythm in the field potential increases with running speed (Jeewajee

et al., 2008a; Maurer et al., 2005; Rivas et al., 1996; Whishaw and Vanderwolf, 1973), suggesting a role in coding of speed. The difference in field potential frequency is a change of about one hertz over a full range of running speeds from 5 cm/sec to 30 cm/sec, but these effects show robust statistical significance. Interestingly, 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 (aka dorsoventral) axis (Patel et al., 2012). Theta power is significantly lower in the ventral (temporal) hippocampus, where the proportion of theta-rhythmic neurons is lower, compared to the dorsal (septal) hippocampus (Royer et al., 2010).

Neurons in the hippocampal formation and entorhinal cortex also directly code running speed with changes in firing rate (Hinman et al., 2016; Kropff et al., 2015; Lever et al., 2003; O'Keefe et al., 1998; Wills et al., 2012). Neurons that code running speed include grid cells and head direction cells (Hinman et al., 2016; Kropff et al., 2015), whereas neurons sensitive to running speed that do not code other spatial dimensions are referred to as speed cells (Kropff et al., 2015). In addition to these changes in firing rate, many entorhinal neurons also show changes in firing rhythmicity, commonly increasing their frequency with an increase in running speed (Hinman et al., 2016; Jeewajee et al., 2008a; Stensola et al., 2012). This change in rhythmicity with running speed is lost during pharmacological inactivation of the medial septum, even though the change in firing rate is not lost (Hinman et al., 2016). Given that this same inactivation disrupts grid cells, this could imply that speed-rate modulation is dispensable, while theta frequency-speed modulation is critical for normal grid cell function.

The relationship between running speed and theta rhythmicity has been explored in other pharmacological studies of the medial septum. These studies were motivated by studies showing that circuits in the medial septum that regulate theta rhythm are implicated in both memory function (Chrobak et al., 1989), as described above, as well as in the regulation of anxiety (McNaughton N. and Coop, 1991). An intriguing connection between these potential roles concerns impairments in memory encoding and spatial navigation, produced, respectively, by the benzodiazepines (Ghoneim and Mewaldt, 1990) and serotonin 5-HT<sub>1A</sub> receptor agonist buspirone (McNaughton N. and Morris, 1992), drugs used to treat anxiety.

Systemic injections of anxiolytic drugs cause a consistent reduction in the frequency of theta rhythm oscillations across a range of running speeds (Wells et al., 2013). Because the effect is consistent across running speeds, this results in a shift of the y-intercept of a regression line fitting frequency to running speed, without changing the slope of the regression line. Consistent with this result in the hippocampus, recordings of local field potentials and spiking rhythmicity in the entorhinal cortex show a systematic decrease in theta frequency across a range of running speeds, as presented in conference abstracts (Monaghan et al., 2015; Monaghan et al., 2014). In contrast, the novelty of the environment has been shown to change the slope of the relationship between frequency and running speed (Wells et al., 2013). This effect on slope is consistent with the fact that novelty will increase the spacing and size of grid cell firing fields in entorhinal cortex (Barry et al., 2012b).

A sophisticated computational model has linked many aspects of the experimental data on theta rhythm and the coding of spatial location and running speed, using the phenomenon of oscillatory interference (Burgess, 2008; Burgess et al., 2007). This model arose from the initial model of theta phase precession that predicted multiple spatial firing fields (O'Keefe and Recce, 1993). In this model, velocity shifts the theta frequency of oscillators, such that the relative phase of oscillations codes the spatial position of the animal, and summation of oscillations generates grid cell firing fields. This model directly demonstrates the potential link between coding of space and the phenomenon of theta phase precession (Hafting et al., 2008). The model also effectively predicted a relationship between rat running speed and the spacing of grid cell firing fields (Jeevajee et al., 2008a; Stensola et al., 2012), as well as the difference in slope of theta phase precession at different dorsal to ventral positions in entorhinal cortex (Hafting et al., 2008) and hippocampus (Kjelstrup et al., 2008). Consistent with the model, modulation of spiking frequency by the cosine of head direction has been shown in theta rhythmic neurons of the hippocampus and medial septum (Blair et al., 2008; Welday et al., 2011). This model links the circuit dynamics of theta rhythm to the coding of space for behavior (Blair et al., 2008; Blair et al., 2007; Hasselmo, 2008; Hasselmo and Brandon, 2012; Hasselmo et al., 2007; Welday et al., 2011). The specificity of firing could be enhanced by reset by sensory input about environmental barriers (Bush and Burgess, 2014; Hardcastle et al., 2015).

This model is also supported by some aspects of intracellular physiological data, including the difference in the frequency of resonance and subthreshold membrane potential oscillations for entorhinal neurons at different anatomical positions (Giocomo et al., 2007) that has been extensively replicated (Boehlen et al., 2010; Dodson et al., 2011; Giocomo and Hasselmo, 2008a; Giocomo and Hasselmo, 2008b; Giocomo and Hasselmo, 2009; Heys et al., 2010; Pastoll et al., 2012; Shay et al., 2012). Resonance correlates with the time course of rebound from hyperpolarization, and rebound spiking might contribute to grid cell firing (Ferrante et al., 2016; Shay et al., 2016).

### **3.1 Subcortical circuits underlying the behavioral correlates of theta rhythm**

The subcortical circuits involved in generating and regulating theta oscillations are multiple, complex, and have still not yet been fully delineated. Theta rhythm is controlled by several subcortical nuclei. Medial septum, the supramammillary nucleus, nucleus incertus and posterior hypothalamus are involved in theta generation whereas serotonin-containing neurons of the median raphe nucleus promote non-theta state in the hippocampus (reviewed in Kirk, 1998; Oddie and Bland, 1998; Pan and McNaughton N, 2004; Vertes and Kocsis, 1997; Vinogradova 1995). The medial supramammillary nucleus (SuM) sends projections to the medial septum (Vertes, 1992), SuM cells exhibit theta-rhythmic activity and are phase-locked to hippocampal theta (Kirk and McNaughton N, 1991; Kocsis and Vertes 1997). Median raphe nucleus (MR) promotes hippocampal non-theta (desynchronized) state (Graeff et al., 1980). MR lesions induced hippocampal theta activity during immobility (Maru et al., 1979), suggesting an inhibitory influence of MR on the hippocampal theta generation. MR projects strongly to the medial septum and hippocampus (McKenna and Vertes 2001). Majority of neurons in median raphe nucleus (MR) exhibit theta-associated theta activity (Viana Di Prisco et al., 2002). Pharmacologically induced blockade of the MR elicited theta-bursts in the medial septum and hippocampal theta (Kitchigina et al., 1999; Kinney et al., 1995). Hippocampal theta was also produced by pharmacological suppression of the median raphe nucleus with serotonin<sub>1A</sub> agonists (Vertes et al., 1994), whereas non-serotonergic (possibly glutamatergic) median raphe projections to the MS can facilitate the generation of hippocampal theta in the absence of medial septal cholinergic tone (Crooks et al., 2012). Key regions regulating theta oscillations are also connected with

other nuclei, including interpeduncular nucleus (IP), which is reciprocally connected with the supramammillary nucleus (Shibata et al., 1986), the nucleus incertus (Ma, Gundlach, 2015) and median raphe (reciprocal inhibitory connections, Lima et al., 2017), suggesting that IP might also be involved in regulation of theta oscillations.

A comprehensive discussion of these circuits is beyond the scope of this review, and consistent with our functional focus on spatial cognition and memory, locomotion, and emotion-sensitivity, we focus upon three subcortical regions: 1) the medial septum and diagonal band of Broca (hereafter ‘medial septum’); 2) the lateral septum; and 3) the nucleus incertus. We review the medial septum (section 3.2), because it is the most important integrator of multiple ascending influences upon theta, and is crucial for hippocampal theta, and thus all theta’s functional associations. We discuss the lateral septum (section 4.2), mainly for its role in the links between theta and locomotion, after first reviewing more generally the links between hippocampal activity, theta and locomotion (section 4.1). The lateral septum’s importance arises in part from its position in receiving massive projections from the hippocampus, and sending projections to the ventral tegmentum area and lateral hypothalamus. We discuss the nucleus incertus (section 3.3), which has dense projections to the medial septum and ventral hippocampus, not just to draw attention to recent work on this hitherto little-studied region, but in particular to highlight its relevance to probing mechanisms underlying links between hippocampal theta on the one hand, and arousal, stress and anxiety on the other.

### **3.2 Subcortical circuits underlying the behavioral correlates of theta rhythm: medial septum**

As noted above, theta oscillations in dorsal hippocampus have long been associated with exploratory activity. The frequency and amplitude of hippocampal theta oscillations is proportional to running speed (McFarland et al., 1975), see section 2.2. Circuits involved in theta rhythm generation receive multiple inputs from brain regions coding sensory- and motor-related information (Bland and Vanderwolf, 1972a; Oddie and Bland, 1998; Vertes et al., 2004), that can underlie adjustment of theta oscillations to behavioral states. The activity of many neurons in theta-generating regions, including hippocampus (Geisler et al., 2010; Huxter et al., 2003; McNaughton B.L. et al., 1983),

medial septum (MS) (Justus et al., 2017) and medial entorhinal cortex (MEC) (Hinman et al., 2016; Kropff et al., 2015), correlates with running speed. Lesions of MS greatly impair hippocampal theta oscillations (Buzsaki et al., 1983; Rawlins et al., 1979). Locomotion-dependent activity of MS cells, interconnected with subcortical regions, including several hypothalamic nuclei, is thought to underlie matching of theta frequency to changing running speed (Bland et al., 2006). Optogenetic stimulation of MS cells at theta frequency (without specificity for cell type) in freely moving rats affected hippocampal theta oscillations in a speed-dependent manner, being stronger at slower speeds (Blumberg et al., 2016).

Several studies have focused on dissecting out the roles of different cell types in MS. The MS comprises several cell types, projecting in other brain regions, including hippocampus: GABAergic (Freund and Antal, 1988; Kiss et al., 1990), cholinergic (Mesulam et al., 1983), and glutamatergic (Colom et al., 2005; Manns et al., 2001; Manseau et al., 2005). Silencing of PV cells in medial septum during REM sleep led to decrease of theta oscillations and to impairment of spatial as well as fear-conditioned contextual memory (Boyce et al., 2016). Optogenetic activation of cholinergic MS cells affected hippocampal theta oscillations during quiet waking, but not during active waking in rats (Mamad et al., 2015). Likewise, optostimulation of cholinergic MS cells increased theta power in anesthetized mice but it decreased or had no effect on either theta power or locomotion in behaving mice (Vandecasteele et al., 2014). Stimulation of cholinergic fibers also increased firing of hippocampal inhibitory interneurons and made more precise coupling of pyramidal cell firing to theta phase (Dannenberg et al., 2015). Optogenetic activation of glutamatergic MS cells led to initiation of locomotion, preceded by theta oscillations, in head-fixed mice (Fuhrmann et al., 2015). In freely behaving mice, activation of glutamatergic neurons in the MS strongly synchronized hippocampal theta rhythms, whereas selective activation of MS glutamatergic projections to the hippocampus did not affect theta rhythms (Robinson et al., 2016), suggesting that MS glutamatergic neurons affect hippocampal theta oscillations through modulation of other septal neurons, e.g. parvalbumin (PV) cells, or hypothalamic generators of theta oscillations. Thus, behavioral effects of somatic MS optostimulation can partly be mediated by a direct activation of non-hippocampal targets in addition to

the entrainment of hippocampal theta oscillations. This complex interplay between MS, hippocampus and hypothalamic theta generators remains to be elucidated.

GABAergic cells in MS express PV (Freund, 1989) and play a key role in the generation and maintenance of hippocampal theta rhythm (Bender et al., 2015; Bland et al., 1999; Borhegyi et al., 2004; Hangya et al., 2009; Kocsis and Vertes, 1997; Wulff et al., 2009). PV cells in the MS provide extensive collateral innervation within the MS (Borhegyi et al., 2004), and their projections to hippocampus selectively target PV interneurons (Freund and Antal, 1988). Genetic ablation of inhibitory inputs to hippocampal PV interneurons (Wulff et al., 2009) or optogenetic silencing of these cells (Amilhon et al., 2015) disrupts theta oscillations. Theta-rhythmic inhibition of hippocampal PV interneurons by MS PV cells (Borhegyi et al., 2004) determines theta-rhythmic firing of pyramidal cells (Toth et al., 1997). In turn, pyramidal cells via MS-projecting interneurons (Blasco-Ibanez and Freund, 1995; Jinno et al., 2007; Manseau et al., 2008; Mattis et al., 2014; Toth et al., 1993) provide rhythmic feedback to MS, thus supporting maintenance of the theta rhythm (Hangya et al., 2009).

### **3.3 Subcortical circuits underlying the behavioral correlates of theta rhythm: nucleus incertus**

As discussed in section 6 below, the hippocampus has long been associated with the potentially linked functions of arousal, stress-regulation and anxiety. How septo-hippocampal theta in particular might be linked to these functions remains unclear. Briefly, one approach has been to explore the ‘stress-reactive’ nucleus incertus in the pontine brainstem (reviewed in Ryan et al, 2011; Ma and Gundlach, 2015), which consists of largely GABAergic projection neurons, many of which express relaxin-3. The nucleus incertus has very dense projections not only to neurons in the medial septum and diagonal band which project to the hippocampal formation, but also to ventral regions of the hippocampal formation (i.e. temporal pole in rodents), notably to the ventral dentate gyrus and ventral subiculum (Goto et al, 2001; Ma and Gundlach, 2015). As discussed in section 6.1 below, it is the ventral, rather than the dorsal, hippocampus that has been associated with anxiety, especially unconditioned anxiety (Bannerman et al, 2004), thus exploring the nucleus incertus’ projections may be particularly relevant to understanding the hippocampal role in anxiety and stress. In the

anaesthetized rat, stimulation of the nucleus incertus elicits hippocampal theta, and disruption of the nucleus incertus attenuates theta elicited by stimulation of the reticularis pontis oralis (Nunez et al, 2006). A Granger causality analysis revealed causal interdependence between the neuronal activity in nucleus incertus and the hippocampus in the theta-state (Martivez-Bellver et al., 2017). Taken together, these findings suggest that the nucleus incertus has a rather significant role in controlling septo-hippocampal theta, including the reticular-elicited theta which has been used to assay anxiolytic drug efficacy (discussed in sections 6.1 and 6.2). One provocative mechanistic finding is that relaxin-3-positive neurons in the nucleus incertus are excited by ICV infusion of CRF and fire at a particular phase of hippocampal theta, while relaxin-3-negative neurons are unaltered/inhibited by CRF, and show no link to hippocampal theta (Ma et al, 2013). This direct link between stress signals and hippocampal theta may help to further explore emotional contributions to hippocampal theta in a way that integrates cellular variables, oscillations and function in the behaving animal. Relatedly, in section 6 below, we consider an approach to dissociating emotion-sensitive from cognitive components of theta frequency.

#### **4.1 Hippocampal population activity during theta oscillations and rapid regulation of locomotion**

While the correlation between hippocampal theta and locomotion has been known for a long time, it has remained elusive whether hippocampal theta follows locomotion (e.g. for spatial computations, see section 2 above), or can actually control locomotion. Vanderwolf (Vanderwolf, 1969) implicated changes in theta rhythmic activity in behavioral control of complex voluntary movements, whereas Grastyan and colleagues (Grastyan et al., 1965) suggested a role for theta oscillations in motivated behaviors. A study where theta oscillations in the hippocampus were induced (using electrical stimulation of MS) independent of behavior, showed a dissociation of hippocampal theta oscillations from its behavioral correlates (Kramis and Routtenberg, 1977), suggesting that theta oscillations do not directly induce locomotion. Lesions of hippocampus or septum are known to increase locomotor activity (Jarrard, 1968) and running speed (Kim and Frank, 2009), orienting reactions (reviewed in (Vinogradova, 1995) and the frequency of self-stimulation (Buno and Velluti, 1977), while electrical

stimulation of hippocampus led to the inhibition of voluntary movement (Bland and Vanderwolf, 1972b). Gaining control over regularity of theta oscillations using optogenetic theta-rhythmic stimulation of MS GABAergic projections in hippocampus, Bender et al., 2015 showed that hippocampal theta oscillations causally influence locomotion. Spontaneous theta oscillations episodes, comprising cycles of a more regular amplitude, occur during running at a slower and less variable speed (Fig. 1). Accordingly, optogenetic stimulation of MS GABA inputs, which rendered theta oscillations more regular, led to a more stable and slower running speed, while non-theta rhythmic stimulation of MS GABA inputs onto hippocampus did not affect locomotion (Bender et al., 2015). These findings suggest that hippocampus not only receives a movement-dependent bottom-up modulation from subcortical regions but also provides the top-down feedback to directly regulate locomotion.

LFP theta oscillations involve a manifold of neuronal activity dynamics (Buzsaki et al., 1983), ranging from rhythmic modulation of discharge probability to theta phase precession (O'Keefe and Recce, 1993) and cross-frequency coupling with gamma oscillations (Bragin et al., 1995; Buhl et al., 2003; Colgin et al., 2009; Wulff et al., 2009; Korotkova et al., 2010). This signaling involves pyramidal cells and various types of interneurons (Klausberger and Somogyi, 2008), i.e. the cells which participate in the generation of the theta rhythm, leading to a functional cross-talk between experience-dependent information processing and synchronization. Indeed, mutual relationships between properties of pyramidal cells' output and features of theta oscillations have been demonstrated. On the one hand, information about an animal's position can be extracted both from firing of pyramidal cells (section 2 above) and from spatiotemporal variations of theta oscillations amplitude (Agarwal et al., 2014); the firing of fast spiking interneurons, key generators of theta currents, is modulated by place cells according to animal's position (Maurer et al., 2006); and the routing of the spatial signal from MEC and CA3 to CA1 is tightly related to generation of theta-coupled gamma oscillations in distinct frequency bands (Colgin et al., 2009). On the other hand, theta-mediated rhythmic inhibition modifies firing probability during experience-dependent activation of a place cell, as firing probability computed for a particular theta phase is more consistent across theta cycles of more similar amplitudes (Bender et al., 2015). At a population level, the dynamics of the hippocampal output

involves at least three factors. The first determinant is the temporal consistency of the theta rhythmic inhibition related to fluctuations of population synchrony and LFP theta amplitude. The second dynamic factor is the nesting of slow and fast gamma oscillations to specific phases of the theta rhythm, (Colgin et al., 2009; Schomburg et al., 2014). The third factor is a population firing rate coding, which depends on global remapping of representations upon changes of spatial environment (Wills et al., 2005), on rate remapping due to variability of sensory input (Leutgeb et al., 2005; O'Keefe and Conway, 1978), reward representations (Dupret et al., 2010; McKenzie et al., 2014), or different types and sequences of memory episodes occurring in the same location (Ferbinteanu and Shapiro, 2003; Wood et al., 2000). Further, subcortical inputs adjust theta synchrony depending on ongoing behavior (Bland et al., 2006, Fuhrmann et al., 2015), and direct cholinergic and aminergic neuromodulatory inputs regulate hippocampal processing (Dannenberg et al., 2015; Takeuchi et al., 2016; Vandecasteele et al., 2014).

While it is clear that the processes described above shape temporal changes of the hippocampal population activity, specific readouts and functions of these changes remain elusive. Experiments performed in the 1960s to 1980s suggested that hippocampal efferents signal novelty (Meeter et al., 2004), assist orienting responses and planning of voluntary movements (Vanderwolf, 1969) and at the circuit level serve a function of behavioural inhibition (Gray 1982). These and other diverse behavioral phenomena could not be, however, clearly connected to selective cellular responses at any specific timescale, until the discovery of place cells (O'Keefe and Dostrovsky, 1971) and subsequent demonstration of a striking example of a temporal coding in the brain - hippocampal theta phase precession (O'Keefe and Recce, 1993). Recently, ensembles of hippocampal neurons have been demonstrated to directly trigger behaviors associated with their formation (Liu et al., 2012). Intricate dependence of place and grid cells' firing on experience, encoding of which involves firing sequences, organized with millisecond precision, makes experimental replay of their temporal activity particularly challenging. An essential temporal aspect of it, gamma oscillations (Colgin et al., 2009; Csicsvari et al., 2003; Schomburg et al., 2014), have been shown to support spatial working memory, when optogenetically facilitated in the CA1 to MEC pathway (Yamamoto et al., 2014).

Episodes of hippocampal theta oscillations, which have cycles of a similar amplitude, for hundreds of milliseconds or even seconds, are accompanied by a more constant hippocampal output and by running with a more regular and slower running speeds. Optogenetically increasing regularity of theta oscillations' amplitude led to the same effect on locomotion (Bender et al., 2015). This indicates a causal influence of the temporal variability of the hippocampal population output on the movement pattern regulation. Experience-dependent flexibility of hippocampal representations, different density of place fields depending on salient features of environment (Dupret et al., 2010; McKenzie et al., 2014) as well as variations in sensorimotor and cognitive processing (Ferbinteanu and Shapiro, 2003; Long et al., 2014; Leutgeb et al., 2005; O'Keefe and Conway, 1978; Wood et al., 2000) are the factors likely contributing to the variability of theta amplitude and of the hippocampal population output over time. These results suggest that dynamic collective aspects of hippocampal representations are essential for rapid control of behavior.

#### **4.2 Subcortical read-out of theta rhythmic hippocampal signaling via lateral septum**

The major subcortical output of the hippocampus is the lateral septum (LS), a GABAergic nucleus which receives non-reciprocal inputs from hippocampal pyramidal cells (Risold and Swanson, 1996) as well as from medial prefrontal cortex (Carus-Cadavieco et al., 2017) and is connected with several subcortical regions including lateral hypothalamus (Risold and Swanson, 1996), the ventral tegmental area (Luo et al., 2011) and amygdala (Sheehan et al., 2004). Chemogenetic inhibition of hippocampus to LS projections leads to an increase in running speed (Bender et al., 2015), pointing to a circuitry, the disruption of which underlies behavioral hyperactivity after lesions of hippocampus or LS (Sheehan et al., 2004). Further, theta oscillations are coordinated between hippocampus and lateral septum (Bender et al., 2015). This prominent coordination is specific for the theta band: coordination at gamma frequencies is much lower between hippocampus and LS than between medial prefrontal cortex and LS (Carus-Cadavieco et al., 2017). Optogenetic inhibition of the hippocampus to LS pathway precludes the regularizing effect of hippocampal theta oscillations on locomotion, suggesting that changes in hippocampal theta synchronization are translated

into rapid adjustment of running speed during spontaneous exploration via the LS. Further, theta oscillations are also suggested to be involved in regulation of motivated behavior. Ongoing hippocampal theta oscillations increased in amplitude and frequency before and after reward-associated lever pressing; the rats tended to lever press during particular phases of theta (Buno and Velluti, 1977); the phase of the theta wave at which lever pressing occurred was opposite to that at which lever releasing occurred (Semba and Komisaruk, 1978). Theta-frequency stimulation of hippocampus via LS-induced disinhibition activates dopaminergic VTA neurons, and this pathway supports reinstatement of reward memories (cocaine-seeking) by contextual stimuli, thus linking context with reward (Luo et al., 2011). LS neurons show place- and reward-related activity, suggesting possible coding of contextual information associated with reward (Takamura et al., 2006).

Another prominent efferent region of LS is the lateral hypothalamus (LH), which is crucial for control of locomotion (Gladfelter and Brobeck, 1962; Grastyan et al., 1965; Grillner et al., 2008; Sinnamon, 1993) and arousal (Herrera et al., 2016; Mileykovskiy et al., 2005). Many LH cells progressively increase their firing upon locomotion onset (Bender et al., 2015). Approach behaviors elicited by stimulation of LH, but not withdrawal behaviors, correlate with hippocampal theta oscillations (Grastyan et al., 1965). Theta-rhythmic activation of LS projections to the LH replicates the reduction of running speed, induced by more regular hippocampal theta oscillations (Bender et al., 2015) during spontaneous locomotion. LS afferents to the LH are also activated during cocaine preference (Sartor and Aston-Jones, 2012), suggesting involvement of this pathway in motivated behaviors.

### **5.1 Theta rhythm and coding of time for episodic memory.**

In addition to its role in coding the “where” of memory, theta rhythm may also contribute to encoding the “when” of episodic memory. In addition to coding spatial location, neurons in the hippocampus and entorhinal cortex respond selectively at consistent time points within each trial of a behavioral task (Kraus et al., 2015; Kraus et al., 2013; MacDonald et al., 2013; MacDonald et al., 2011; Pastalkova et al., 2008). These responses have been referred to as “time cells” (McDonald et al., 2011). The firing of time cells could allow events or items to be associated with a specific time

point coded by neural activity as well as a specific location coded by place cells. In an explicit timing task (DRL) hippocampal cells tend to code time features of the task that are not linked to narrow “time points” (Young and McNaughton N., 2000).

Neurons in the hippocampus and entorhinal cortex that code spatial location often code time intervals as well. This was initially shown in neurons of the hippocampus as a rat ran in a running wheel during the delay interval between different responses in a spatial alternation task (Pastalkova et al., 2008). Further studies explored these responses on a treadmill that allowed studies of systematic changes in the treadmill speed. On the treadmill, it was shown that neurons can code either the time of running or the distance of running, and many neurons that code these dimensions also fire as place cells in different locations in the task (Kraus et al., 2013). Modeling shows that the same framework used for modeling grid cells with theta rhythm oscillations (Burgess, 2008) could contribute to coding of time intervals by time cells (Hasselmo, 2008; Hasselmo, 2012; Hasselmo and Stern, 2014). This use of oscillations to code time intervals resembles previous models of time intervals (Brown et al., 2000; Miall, 1989). Consistent with predictions of this model, neurons in the entorhinal cortex that fire as grid cells during foraging in an open field will also fire as time cells during running on a treadmill (Kraus et al., 2015). Models of episodic memory show how the coding of time and space by theta rhythm oscillations could account for episodic retrieval (Hasselmo, 2009; Hasselmo, 2012) that could underlie the hippocampal activity found in functional magnetic resonance imaging (Brown et al., 2010; Brown and Stern, 2014).

## **5.2 Theta rhythm separation of encoding and retrieval.**

The behavioral data above indicates a role of theta rhythm in memory function, but the mechanisms for this role are not known. One possible model shows how specific physiological processes at different phases of theta rhythm oscillations could enhance encoding by separating the dynamics of encoding and retrieval on different phases of the theta rhythm (Hasselmo et al., 2002). In this model, during the encoding phase of each theta cycle, input from entorhinal cortex is strong, as shown by current source density analysis (Brankack et al., 1993; Buzsaki et al., 1986). Synaptic input from region CA3 is weaker at this phase, but synaptic modification at the CA3 synapses is

strong, storing associations between the presynaptic activity in CA3 and the postsynaptic activity from entorhinal cortex. Physiological data shows that long-term potentiation is strongest at this phase of the EEG (Hölscher et al., 1997; Huerta and Lisman, 1995; Hyman et al., 2003).

During a separate retrieval phase of each theta cycle, input from entorhinal cortex is weaker, but the excitatory input from region CA3 is stronger (Brankack et al., 1993; Buzsaki et al., 1986). The strong input from CA3 means postsynaptic activity is driven by previously modified synapses, retrieving previously stored associations. At this time, the cell body receives the least inhibition, allowing retrieval to drive the spiking output of the neurons. Long-term potentiation is reduced during this time, so that the retrieval activity is not stored as a new event. Simulations show that separate phases of encoding and retrieval allow effective separation of new external input from prior retrieval (Hasselmo et al., 2002).

Physiological data on theta rhythm are consistent with the encoding/retrieval model. At one phase of theta, the dendrites are depolarized (Kamondi et al., 1998), allowing encoding of entorhinal input, while the cell body is hyperpolarized, preventing spiking due to interference from retrieval of previous associations, (Hasselmo et al., 2002). Membrane potential changes could arise due to different morphological classes of inhibitory interneurons that spike at different phases of theta rhythm (Klausberger et al., 2003; Klausberger and Somogyi, 2008). Inhibitory axo-axonic and basket cells could inhibit the cell bodies and axons of excitatory cells to reduce spiking output during encoding (Cutsuridis and Hasselmo, 2010). At the opposite phase, oriens lacunosum-moleculare cell spiking inhibits the layer where entorhinal input contacts the distal dendrites, reducing external input during retrieval of associations at previously modified synapses in stratum radiatum (Hasselmo et al., 2002; Kunec et al., 2005).

The model helps the understanding of impairments of memory encoding during loss of theta rhythm (Chrobak et al., 1989; Givens and Olton, 1994; M'Harzi et al., 1987; Winson, 1978). The model is consistent with physiological data showing that the phase of theta rhythm resets during stimulus encoding (Givens, 1996), and in rats performing a delayed non-match to sample task, spiking occurs at different phases of theta for match (retrieval) versus non-match (encoding) stimuli (Manns et al., 2007). One study tested predictions made by combining the cholinergic model (Hasselmo et al., 1996) and theta

phase model (Hasselmo et al, 2002) of encoding vs retrieval separation (Douchamps et al, 2013). In the cholinergic model, high levels of acetylcholine promote the encoding mode. As predicted, replicating an earlier study (Lever et al, 2010), environmental novelty shifted CA1 place cell firing to a later phase of theta (towards the pyramidal-layer theta peak), consistent with a bias towards novelty-elicited coding; scopolamine (a cholinergic antagonist) shifted cell firing in a familiar environment to an earlier phase of theta (towards the pyramidal-layer theta trough), consistent with an anti-encoding bias favouring retrieval. Moreover, in a novel environment, scopolamine blocked the later-phase-in-novelty effect, and blunted place cell remapping, consistent with both models (Hasselmo et al, 1996; Hasselmo et al, 2002). The behavioural relevance of these kinds of observations was tested by an optogenetic study that used closed-loop stimulation to show a pattern of memory enhancement consistent with the idea that stimulation at one phase of theta promoted encoding while stimulation at another phase promoted retrieval (Siegle and Wilson, 2014). Consistent with the encoding phase of the model, high frequency gamma oscillations are coherent between entorhinal cortex and region CA1 at one phase of theta (Colgin et al., 2009), and coherent between CA3 and CA1 at a different phase (Belluscio et al, 2012; Colgin et al, 2009; Schomburg et al, 2014).

### **6.1 Dual functionality of the hippocampal formation?: links to theta rhythm**

There is no theoretical consensus as to how best to uniquely characterise hippocampal function. Broadly speaking, two sets of functional associations persist, one cognitive, the other emotional. In the first set, the hippocampus supports spatial cognition, episodic and other memory, with these functions typically linked to coding for, and detecting initially novel contexts (to which individual contents can be associated), (e.g. Burgess et al., 2002; Hasselmo et al., 1996; O'Keefe and Nadel, 1978; Schiller et al., 2015). Briefly, paradigmatic findings in this set include the discovery of hippocampal spatial cells (reviewed in: Hartley et al., 2014), online and offline (re)activation of experience-specific cell firing sequences (reviewed in O'Neill et al., 2010; Redish, 2016; Schiller et al., 2015) and evidence for hippocampal support of context-dependent memory (e.g. O'Keefe and Nadel, 1978; Phillips and LeDoux, 1992; Redondo et al., 2014). In the second set, rather differently, the hippocampus plays a crucial role in anxiety, likely linked to roles in stress and depression. Paradigmatic

findings in this set include demonstrations of anxiety-modulating effects following hippocampal disruption (reviewed in Engin and Treit, 2007; Gray and McNaughton N., 2000), the importance of hippocampal neurogenesis in controlling anxiety (e.g. Revest et al., 2009) and depression (e.g. Santarelli et al., 2003), and hippocampal control over the HPA axis (Herman and Cullinan, 1997; Sapolsky and Meaney, 1986).

Remarkably few theoretical studies try to bridge the gap between these two sets of functional associations. While the anxiety-based approach accounts for the considerable context-conditioned fear literature in terms of ‘anticipatory anxiety’ (Gray and McNaughton N., 2000), its attempt to incorporate the growing spatial literature has not been influential. While a context-based memory approach naturally explains context-conditioned fear literature, it fails to account for hippocampal contributions to unlearned anxiety. The problem of bridging these literatures seems more acute when we consider that proponents of different theories of hippocampal function place theta at the heart of their theory. For instance, O’Keefe and Nadel (1978) reinterpreted observations from Vanderwolf (1969) linking theta to voluntary movement to suggest that theta acted as an index of spatial translation, and it is now clear that there are robust links between theta phase and spatial variables in linear tracks and open fields (Climer et al., 2013; Huxter et al., 2008; Jeewajee et al., 2014; O’Keefe and Recce, 1993; Skaggs et al., 1996). Similarly Gray (1982) argued that hippocampal theta was crucial for behavioural inhibition, emphasising how all drugs which were clinically effective anxiolytic drugs impaired rodent septo-hippocampal theta.

By far the most influential approach to duality of hippocampal function has been to posit that the dorsal and ventral hippocampus are distinct structures, with space/memory assigned to dorsal hippocampus (posterior in primates), and anxiety to ventral hippocampus (anterior in primates) (Bannerman et al., 2004; Fanselow and Dong, 2010; Strange et al., 2014). This view receives clear support from lesion studies in animals (Bannerman et al., 2004; Kjelstrup et al., 2002; Pentkowski et al., 2006), and neuroimaging studies in primates including humans (Bach et al., 2014; Loh et al., 2016; O’Neil et al., 2015; Oler et al., 2010). This anatomy-based approach clearly captures an important truth about the parcellation of hippocampal function. However, an extreme version of this approach is incompatible with hippocampal physiology, not least because hippocampal theta is found throughout the dorso-ventral axis and resembles a single

travelling wave (Lubenov and Siapas, 2009; Patel et al., 2012). In other words, while amplitude can vary, and phase does vary systematically, along the dorso-ventral axis (Hinman et al., 2011; Patel et al., 2012), as far as frequency is concerned the dorsal and ventral hippocampus both share the same theta in the intact behaving rat. Indeed, the vast majority of studies inspiring and supporting the Gray and N. McNaughton theory of anxiety (Gray, 1982; Gray and McNaughton N., 2000), including where anxiolytic drugs reduce the frequency of reticular-elicited theta, have sampled *dorsal* hippocampal theta (e.g. dorsal sampling: Engin et al., 2008; Gray and McNaughton N., 2000; McNaughton N. et al., 2007; Seidenbecher et al., 2003; Shin et al., 2009; Siok et al., 2009; Yeung et al., 2012) (dorsal & ventral sampling: Adhikari et al., 2010; Cornwell et al., 2008; Engin et al., 2016).

## **6.2 Dual functionality of the hippocampal formation: two components of theta frequency**

In summary, it remains unclear how the hippocampal processing subserving such different functions, space/memory on the one hand, and anxiety on the other, might be mechanistically related to each other, when both share an important physiological substrate: septo-hippocampal theta. One reasonable theoretical starting assumption is that the processing of one set of functions should not interfere with the processing of the other. If theta frequency is linked to both spatial translation and anxiety, it would be maladaptive for anxiety to be reduced if running speed were to be reduced, or path integration mechanisms impaired. One would expect to show some independence of theta mechanisms relating to spatial cognition and anxiety. Here, we highlight one such approach, begun by Wells et al. (2013).

The oscillatory-interference model of grid cell mechanisms (discussed above in section 2.2) suggested that theta frequency overall might result from the additive contribution of two components, one corresponding to the slope of the theta frequency to running speed relationship, and one corresponding to the variable offset of this relationship, defined by its intercept on the speed (Y) axis at 0cm/s (Burgess, 2008). Importantly, in this model, the two contributions to frequency are independent. The scale of spatial coding is determined by the rate of change of frequency with running speed, while the absolute value of the baseline frequency itself (the intercept) is

irrelevant to spatial coding.

The idea that spatial scale increases in environmental novelty (Barry et al., 2012b) is a strong prediction of the oscillatory interference models (Burgess, 2008; Burgess et al., 2007), given that theta frequency is reduced in environmental novelty (Jeewajee et al., 2008b). More specifically, the Burgess (2008) model predicts that the increase in spatial scale in novelty results from a decrease in the slope of the theta frequency to running speed relationship. Thus the Wells et al. (2013) study made specific predictions regarding the spatial cognition functional association of hippocampal theta: a novel spatial context would reduce the *slope* of the theta frequency to running speed relationship, without any obligatory effect on intercept, and this would increase spatial scale, with the level of slope change predicting the level of scale change (place field size).

Combining the Burgess (2008) model with insights from the Gray and McNaughton N. (2000) theoretical approach, the Wells et al. (2013) study derived a new prediction regarding the ‘anxiety’ functional association of hippocampal theta. Intriguingly, all clinically-effective anxiolytic drugs (i.e. prescribed for Generalised Anxiety Disorder) reduce the average frequency of hippocampal theta elicited by stimulation of the reticular formation (‘reticular-elicited theta’). This frequency-reduction effect of reticular-elicited theta is seen across a wide range of *anxiolytic* drugs, despite their substantial neurochemical dissimilarities (McNaughton et al 1986; McNaughton and Coop, 1991; Engin et al., 2008; McNaughton N. et al., 2007; Siok et al., 2009; Yeung et al., 2012), but is not seen with *antipsychotic* drugs (Gray and McNaughton N., 2000). In addition, ‘immobility-related’ type II theta occurs during predator-elicited arousal/anxiety (Sainsbury et al., 1987), and during ‘anticipatory anxiety’ (Gray and McNaughton N., 2000) following standard-footshock conditioning (Seidenbecher et al., 2003). Accordingly, since: a) anxiety may be linked to type-II theta; b) anxiolytics reduce reticular-elicited theta frequency; and c) the Burgess (2008) model links type II theta mechanisms to intercept, the prediction was that anxiolytics should reduce the *intercept* of the theta frequency to running speed relationship, without any obligatory effect on slope. In summary, a double dissociation was predicted whereby anxiolytics would specifically reduce y-intercept, and environmental novelty would specifically reduce slope.

### 6.3 Different types of anxiolytic drug reduce the y-intercept of the theta-frequency-to-running speed relationship.

This prediction was fulfilled in the experimental results (Wells et al., 2013). Figure 2 shows schematic illustrations of the data. Figure 2F shows the effect of systemic injection of two well-established clinically effective anxiolytic drugs (Chlordiazepoxide, a benzodiazepine agonist; Buspirone, a 5HT-1A agonist) and one putative anxiolytic drug (O-2545, a CB1 agonist) which reduced thigmotaxis, as expected from a classic anxiolytic drug. At the doses tested, all the anxiolytic drugs elicited a reduction in the y-intercept without affecting slope. Further support for the generality of these findings comes from unpublished work (presented in Lever et al., 2016) showing that systemic injection of pregabalin also reduces the y-intercept (Figure 2F). Pregabalin is a presynaptically-acting anti-epileptic drug which binds to the  $\alpha_2\text{-}\delta\text{-}1$  subunit of voltage-gated calcium-channels on presynaptic sites, effectively blocking these channels. Significantly, it is now clear that Pregabalin is also an effective anxiolytic drug (in the European Union, where it is licensed for anxiolysis).

It is interesting that the specific effect of y-intercept reduction in hippocampal theta from the freely moving rat is shared by all these anxiolytic drugs tested, despite the considerable variance in primary targets (benzodiazepine site of GABA-A receptor, 5HT-1A receptor, CB1 receptor,  $\alpha_2\text{-}\delta\text{-}1$  subunit of calcium-channel) and the presynaptic and postsynaptic locations of these targets (e.g. presynaptic  $\alpha_2\text{-}\delta\text{-}1$  subunit containing calcium-channel, postsynaptic benzodiazepine site of GABA-A receptor). Furthermore, this specific y-intercept reduction effect during freely moving theta is consistent across different drug classes, unlike that obtained from the reticular-stimulation model, where anxiolytic drugs reduce the slope and/or intercept of the frequency-to-intensity function (Gray and McNaughton N., 2000; McNaughton N. et al., 2007). For instance, at the doses tested, Chlordiazepoxide reduced only the slope, while Buspirone reduced only the intercept, of this function (summarised in (John et al., 2014)) in the reticular-stimulated theta.

How widely across septo-hippocampal theta sites does this specific effect on frequency extend? Interestingly, the observations from hippocampal theta have been replicated and extended by demonstrations that systemic injections of a benzodiazepine

(Diazepam) and a 5HT-1A agonist anxiolytic (8-OH-DPAT) all reduce the y-intercept of theta recorded from the entorhinal cortex of freely moving rats (Fig 2G depicting schematic illustrations; Monaghan et al., 2015; Monaghan et al., 2014).

Taken together, this shared and specific effect of different classes of systemically-administered anxiolytic drugs on septo-hippocampal theta in behaving rats strongly hints at an underlying common mechanism of anxiolysis, an understanding of which is absent from reviews of anxiolytic drugs (e.g. Sandford et al., 2000). Even if the y-intercept reduction is a proxy to a more fundamental mechanism of systemic anxiolysis, these findings should help to stimulate rational approaches to drug design, e.g. (John et al., 2014; McNaughton N. et al., 2007).

#### **6.4 The slope of the theta-frequency-to-running speed relationship: modulation by environmental novelty**

Figure 2 shows a schematic figure of the effect of introducing the rat into a novel spatial context, i.e. a novel configuration of cues (which elicited remapping) in the same geocentric location as a familiar baseline environment. In line with a central prediction of the oscillatory interference model (Burgess, 2008), the contextual novelty elicited a reduction in the slope without significantly affecting intercept (Wells et al., 2013) (Figure 2D). Moreover, as predicted by the Burgess (2008) model, place fields of CA1 place cells expanded in the novel environments (Figure Figure 2D), and a robust correlation was observed between the change in slope across the baseline and novel environments, and the change in the spatial scale (i.e. average field size) of the place cells. Partial correlation analysis showed that slope change predicted spatial scale change controlling for the effect of novelty status, but not vice versa. These results were consistent with the (Barry et al, 2012b) study, where environmental novelty elicited an expansion in the spatial scale of entorhinal grid cells (Figure 2E). In the oscillatory interference model (Burgess, 2008), this is due to flattening of slope, which the (Barry et al, 2012) study did not examine. Specifically, what controls spatial scale in the model is the gain of the intrinsic (i.e. interburst) theta frequency of cell firing due to speed, which is harder to analyse than the LFP (but see Hinman et al, 2016).

Furthermore, the hippocampal theta study (Wells et al, 2013) also found that, rearing on the hind legs, a hippocampus-dependent behaviour highly sensitive to

environmental novelty (Lever et al., 2006), increased when slope was flatter (Figure 2D), and that rearing frequency was robustly predicted by changes in slope, but not intercept. This further supported the theoretical link between slope and environmental novelty.

The Wells et al. (2013) study also observed a dissociation between slope and intercept that was not theoretically predicted. Only a few studies have investigated the positive relationship between temperature and theta frequency (e.g. Whishaw and Vanderwolf, 1971). The Wells et al. (2013) study showed that, in the locomoting rat at least, temperature is positively correlated with the slope, but not the intercept, of the frequency-speed relationship. The dissociation may also prove useful in understanding mechanisms driving underlying type I theta frequency modulation.

### **6.5 Dual functionality and theta frequency: overview**

Taken together, this set of findings dissociating intercept reduction and slope reduction provide good support for the additive two component model of hippocampal theta in Burgess (2008), and offer a new physiological perspective upon dual hippocampal functionality. Whether oscillatory interference is a crucial mechanism for grid cell generation remains controversial (Barry et al., 2012a; Brandon et al., 2011; Koenig et al., 2011; Yartsev et al., 2011), but it seems intuitive that the slope component of theta frequency is linked to distance estimation (see also McNaughton B.L. et al., 2006). Recent hints of this are the demonstrations that: 1) darkness in mice flattens the slope component of theta frequency, and also disrupts grid fields (Chen et al., 2016) (Figure 2E); 2) medial septum inactivation flattens the slope of the intrinsic spiking rhythmicity of individual neurons (Hinman et al, 2016) and also disrupts grid fields (Brandon et al, 2011). Whether space is physical or semantic (Constantinescu et al., 2016), whether physically traversed or imagined (Horner et al., 2016), a crucial process for mapping is estimating the distance (and direction) from one place to another, and theta may contribute to this process. Accordingly, the demonstration that the y-intercept and slope components can be modulated independently in the freely behaving rat is potentially significant. In summary, the preliminary and published work described here (e.g. Lever et al., 2016; Monaghan et al., 2015; Monaghan et al., 2014; Wells et al., 2013) may help to lay the empirical groundwork for a quantitative approach to

hippocampal theta that bridges parallel streams of research on hippocampal cognitive and emotional processing.

### **7.1 The post-natal development of theta and the cognitive map**

Rats and mice, like humans, are altricial animals, born possessing only very limited sensory and motor capabilities (Alberts, 1984). By the age of three weeks, however, rats are capable of independent feeding, movement, and display hippocampus-dependent spatial learning and memory (for a review see (Wills et al., 2014)). In the following sections, we will discuss the post-natal emergence of the hippocampal theta rhythm in the rat, relating this to the development of wider hippocampal neural networks underlying spatial cognition, as well as the emergence of spatial behaviour. We aim to show that the development of the theta oscillation during this three-week window can provide insights how it supports hippocampal function.

### **7.2 Early emergence of network oscillations in the hippocampal formation**

For approximately the first week of life, rats are not capable of sustained independent locomotion, and instead spend their time amongst a small group (or ‘huddle’) of littermates (Alberts and Brunjes, 1978). During this period, theta is not present in the hippocampal local field potential (LFP). Instead, the earliest co-ordinated network activity *in vivo* takes the form of large, slow deflections which reverse polarity across the CA1 pyramidal cell layer, which are seen from post-natal day 2 (P2) onwards (Leinekugel et al., 2002; Mohns et al., 2007). These are consistent with the Large Irregular Activity (LIA) state of the adult hippocampus, seen during rest and immobility in adults (Vanderwolf, 1969), and may also correspond to the giant depolarising potentials (Ben-Ari et al., 1989) seen in immature hippocampal slices *in vitro* (Leinekugel et al., 2002). The early emergence of such large, synchronous activity bursts has led to the proposal that they are required to develop basic network connectivity in the hippocampal formation (Ben-Ari, 2001; Buzsáki, 2015). Interestingly, the 140-200Hz fast oscillations (or ‘ripples’), which accompany LIA spikes in the CA1 layer (Buzsaki et al., 1992; O’Keefe and Nadel, 1978), emerge later, from one week of age onwards (Buhl et al., 2005; Mohns et al., 2007).

Rats are capable of crawling from approximately P9 (though *spontaneous* movement away from the nest occurs much later, at around two weeks) (Altman and Sudarshan, 1975; Gerrish and Alberts, 1996; T. J. Wills et al., 2014). At approximately this age, hippocampal theta is seen in vivo in awake animals for the first time (Mohs and Blumberg, 2008). (Though theta can be observed earlier in animals under urethane anaesthesia (Brockmann et al., 2011; Hartung et al., 2016)). Immature rats spend a large proportion of their time in a behavioural state known as ‘active sleep’ characterised by twitches of the limbs, head and eyes (Gramsbergen et al., 1970), and the earliest bouts of hippocampal theta co-occur with such myoclonic twitches during active sleep. These earliest instances of theta are also associated with bouts of gamma oscillations and bursts of hippocampal neural firing (Mohs et al., 2007; Mohs and Blumberg, 2008), raising the possibility that theta, early in development, may facilitate the fine-scale synchronisation of neural firing across hippocampal networks (Mohs and Blumberg, 2010).

Theta in adult rats (and other rodents) has been described as consisting of two different components, dissociable by their pharmacology and behavioural correlates: type I theta is related to movement, and is insensitive to blockade of the cholinergic projections to the hippocampus, type II theta occurs during alert immobility and is disrupted by application of cholinergic antagonists (Kramis et al., 1975). At P10, both types of theta appear to be present: atropine-sensitive theta emerges concurrently with theta associated with voluntary movement (Leblanc and Bland, 1979). This is consistent with the development of the cholinergic neurons in the medial septum, which develop gradually between P1 and P16, but display molecular markers of acetylcholine production by P10 (Bender et al., 1996). However, it has also been suggested that the early association of theta with myoclonic twitches (at P8) indicates that type I theta is the earliest to emerge (Mohs and Blumberg, 2008). As type I theta is thought to be supported by GABA-ergic projections from the medial septum to hippocampal interneurons (Buzsaki, 2002), early development of type I theta would be consistent with the very early development of GABA-ergic neurons in the medial septum (Bender et al., 1996), and the early development of inhibitory synapses onto CA1 pyramidal cells (Danglot et al., 2006). The finding that early hippocampal theta bursts can entrain the firing of neurons in other brain regions, for example the pre-frontal and para-

hippocampal cortices, indicates that the role of theta in synchronising developing networks may also extend beyond the hippocampal formation (Brockmann et al., 2011; Hartung et al., 2016).

The earliest bouts of theta display a markedly lower frequency than that observed in adults, displaying a frequency of around 5Hz (Leblanc and Bland, 1979; Mohs and Blumberg, 2008). Similar theta frequency increases are observed in other species (Marley and Key, 1963; Creery and Bland, 1980), suggesting that this might be a general pattern of mammalian brain development. *In vivo* recordings of hippocampal neural activity during exploration between P16 and P30 (Langston et al., 2010; Wills et al., 2010) show that the frequency of theta continues to increase gradually throughout this period, but remains lower than that of adult rats even after three weeks of age (Wills et al., 2010). As discussed in previous sections, the instantaneous frequency of theta is modulated by running speed in adult rats, and the intercept and the slope of the speed-frequency curve may reflect different aspects of hippocampal function (see sections 6.2, 6.3 and 6.4). During development, the frequency of theta is also positively modulated by running speed, from the earliest ages at which exploration occurs (Wills et al., 2010). Both the slope and the intercept of the speed-frequency curve increase during development, though the time course of their respective increases appears dissociable, with large changes in intercept occurring between P18 and P24, despite much slower, gradual changes in slope (Wills et al., 2010). Interestingly, other speed-related signals in the hippocampal formation, such as the speed-modulation of grid cells in the entorhinal cortex (Hinman et al., 2016), are also present early in development (Wills et al., 2012).

### **7.3 Modulation of neural firing by theta during development**

The hippocampus contains several different classes of neurons whose firing is modulated by the position and orientation of the animal in space. A series of recent studies have shown that different types of spatially modulated neurons follow different developmental trajectories: head direction cells emerge first, abruptly, becoming adult-like as soon as animals open their eyes (Tan et al., 2015). Place cells are present as soon as animals begin to explore their environment (around P15, but with considerably reduced spatial tuning than in adulthood, and continue to mature gradually over the following 2-4 weeks (Scott et al., 2010; Wills et al., 2010). Finally, grid cells emerge

abruptly at around three weeks of age (Wills et al., 2010). For a review, see (Tan et al., 2016). In the adult, the probability of spiking of both place cells and grid cells is modulated by the phase of the ongoing theta oscillation (Fox et al., 1986; Hafting et al., 2008): in this section we will discuss how this temporal modulation of spiking by theta emerges during development.

Place cell spiking occurs preferentially on the negative phase of the locally recorded (CA1) theta oscillation (Fox et al., 1986), and the resulting theta frequency bursting is most clearly measured as a set of repeating peaks, at theta frequency, in the temporal auto-correlogram of the spike train. This theta-modulation of place cell spiking is present at the earliest ages tested (P16), but at lower levels than observed in adults (Langston et al., 2010; Wills et al., 2010). Interestingly, the degree of theta-modulation of place cells appears to reach adult-like levels at P22 (Wills et al., 2010), approximately coincident with the emergence of hippocampal spatial behaviours. An open question is whether the preferred phase of place cell firing also changes during development: different phases of the theta cycle have been proposed to coordinate the CA1 place cell firing with firing in different input areas, for example CA3 or entorhinal cortex (Hasselmo et al., 2002): changes in the preferred phase during development could reflect changes in the relative weights of input from these different regions.

The modulation frequency of adult place cell spiking (or ‘intrinsic frequency’) has a marginally greater frequency than the ongoing LFP theta, with the result that the phase of LFP theta at which spiking occurs precesses slightly as rats move through a place field (O’Keefe and Recce, 1993). Spike phase correlates better with distance travelled through the place field than with other variables (Huxter et al., 2003), leading to the idea that phase precession may represent a temporal code for space. Phase precession is a feature of grid cell, as well as place cell, firing, and these observations inspired ‘oscillatory interference’ models of spatial firing (Blair et al., 2008; Burgess et al., 2007; Zilli and Hasselmo, 2010). The common mechanism shared by such models is that a frequency difference between two oscillations, (where one of oscillation is frequency-modulated by velocity), can track the distance an animal has travelled and thereby produce spatially stable firing.

During development, the intrinsic frequency of both grid and place cells is higher than that of LFP theta, from the earliest ages at which spatial responses are

present (P16) (Langston et al., 2010; Wills et al., 2010). Phase precession through a place field is present at least as early as P17 in place cells (Langston et al., 2010; Wills et al., 2010), demonstrating that this temporal organisation of place cell spiking is potentially adult-like during earliest exploration. One avenue for further investigation is to use recently developed analysis methods (Climer et al., 2015) to test whether, during development, intrinsic frequency is modulated by running speed as it is in adult rats (Jewajee et al., 2008; Stensola et al., 2012; Hinman et al., 2016).

## **Outlook**

The findings reviewed here show that hippocampal theta oscillations are crucial for diverse brain functions, ranging from anxiety and locomotion to cognitive processes. They also highlight the mechanisms through which hippocampal theta oscillations are involved in such a wide range of behaviors. First, the precision of hippocampal signalling and the temporal regularity of hippocampal output is related to several components of theta oscillations - frequency, amplitude and different phases of theta cycles. While frequency of hippocampal theta likely depends on bottom-up movement-dependent signals from cortical and subcortical theta generators, regularity of theta amplitude adjusts top-down output to subcortical targets, which then directly regulates locomotion. Influence of hippocampal theta rhythmic output regularity on locomotion may further reflect differential involvement of hippocampus in circuitries controlling spatial navigation depending on the familiarity of environment and other salient stimuli. Dissociation of theta signaling components, such as intercept reduction and slope reduction offers a new physiological perspective upon dual hippocampal functionality, helping to bridge the rather different views of hippocampal function in cognitive processes and anxiety. This quantitative approach to hippocampal theta may help to lay the empirical groundwork that bridges parallel streams of research on hippocampal cognitive and emotional processing. The complex interplay between multiple theta generators can also ensure precision of hippocampal signaling, crucial for separation of encoding and retrieval as well for theta phase precession. Impairments of this precision may underlie impairments of memory encoding upon loss of theta rhythm. Second,

different functions of theta oscillations can be mediated through signalling to various projections of hippocampus. Projection-specific inhibition or excitation of these pathways will enable investigation of particular pathways' contributions in different behaviors. Closed-loop, optogenetically induced, modifications or disruptions of theta oscillations during specific phases of behavioral tasks can probe for the necessity of theta oscillations for particular functions.

Maturation of theta oscillations in parallel with development of more complex behaviors in early postnatal days and weeks also points out the importance of theta-rhythm. During development, the intrinsic frequency of both grid and place cells is higher than that of LFP theta, from the earliest ages at which spatial responses are present (P16). Phase precession through a place field is present at least as early as P17 in place cells, demonstrating that this temporal organisation of place cell spiking is potentially adult-like during earliest exploration. One avenue for further investigation is to use recently developed analysis methods to test at what age intrinsic frequency is modulated by running speed in developing pups, as it is in adults, and as oscillatory interference models would predict.

These and future findings help to understand how oscillations participate in generation and regulation of complex behaviors, what role they play in healthy brain and how impairments of oscillations are linked to brain disorders.

### **Acknowledgements**

We thank Neil Burgess for discussions and Franziska Bender for preparing Figure 1. This work was supported by NIH (R01 MH60013, M.H.; R01 MH61492, M.H.) and the Office of Naval Research MURI grant N00014-16-1-2832 (M.H.), The Human Frontier Science Program (HFSP; RGY0076/2012, TK), Deutsche Forschungsgemeinschaft (DFG; Exc 257 NeuroCure, TK and AP; Priority Program 1665, 1799/1-1(2), AP), The German-Israeli Foundation for Scientific Research and Development (GIF; I-1326-421.13/2015, TK), the Biotechnology and Biological Sciences Research Council (BB/G01342X/1, BB/G01342X/2, and BB/M008975/1, CL), the ERC ('DEVSPACE') and the Royal Society, UK (UF100746).

## References

- Adhikari A, Topiwala MA, Gordon JA. 2010. Synchronized activity between the ventral hippocampus and the medial prefrontal cortex during anxiety. *Neuron* 65(2):257-69.
- Agarwal G, Stevenson IH, Berenyi A, Mizuseki K, Buzsáki G, Sommer FT. 2014. Spatially distributed local fields in the hippocampus encode rat position. *Science* 344(6184):626-30.
- Aggleton JP, Neave N, Nagle S, Hunt PR. 1995. A comparison of the effects of anterior thalamic, mamillary body and fornix lesions on reinforced spatial alternation. *Behav Brain Res* 68(1):91-101.
- Alberts JR. 1984. Sensory-perceptual studies in the Norway rat: A view toward comparative studies., in: Kail, R., Spear, N.S. (Eds.), *Comparative Perspectives on Memory Development*. Erlbaum, Hillsdale, NJ.
- Alberts JR, Brunjes PC. 1978. Ontogeny of thermal and olfactory determinants of huddling in the rat. *J.Comp Physiol Psychol.* 92: 897–906.
- Alonso A, Garcia-Austt E. 1987. Neuronal sources of theta rhythm in the entorhinal cortex of the rat. I. Laminar distribution of theta field potentials. *Experimental Brain Research* 67(3):493-501.
- Altman J, Sudarshan K. 1975. Postnatal development of locomotion in the laboratory rat. *Anim Behav.* 23: 896–920.
- Amilhon B, Huh CY, Manseau F, Ducharme G, Nichol H, Adamantidis A, Williams S. 2015. Parvalbumin Interneurons of Hippocampus Tune Population Activity at Theta Frequency. *Neuron* 86(5):1277-89.
- Bach DR, Guitart-Masip M, Packard PA, Miro J, Falip M, Fuentemilla L, Dolan RJ. 2014. Human hippocampus arbitrates approach-avoidance conflict. *Curr Biol* 24(5):541-7.
- Bannerman DM, Rawlins JN, McHugh SB, Deacon RM, Yee BK, Bast T, Zhang WN, Pothuizen HH, Feldon J. 2004. Regional dissociations within the hippocampus--memory and anxiety. *Neurosci Biobehav Rev* 28(3):273-83.
- Barry C, Bush D, O'Keefe J, Burgess N. 2012a. Models of grid cells and theta oscillations. *Nature* 488(7409):E1-2; discussion E2-3.
- Barry C, Ginzberg LL, O'Keefe J, Burgess N. 2012b. Grid cell firing patterns signal environmental novelty by expansion. *Proc Natl Acad Sci U S A* 109(43):17687-92.
- Belluscio MA, Mizuseki K, Schmidt R, Kempter R, Buzsáki G. 2012. Cross-frequency phase-phase coupling between  $\theta$  and  $\gamma$  oscillations in the hippocampus. *J Neurosci* 32(2):423-35.
- Ben-Ari Y. 2001. Developing networks play a similar melody. *Trends Neurosci.* 24: 353–360.
- Ben-Ari Y, Cherubini E, Corradetti R, Gaiarsa JL. 1989. Giant synaptic potentials in immature rat CA3 hippocampal neurones. *J.Physiol* 416: 303–325.
- Bender F, Gorbati M, Cadavieco MC, Denisova N, Gao X, Holman C, Korotkova T, Ponomarenko A. 2015. Theta oscillations regulate the speed of locomotion via a hippocampus to lateral septum pathway. *Nat Commun* 6:8521.
- Bender R, Plaschke M, Naumann T, Wahle P, Frotscher M. 1996. Development of cholinergic and GABAergic neurons in the rat medial septum: different onset of choline acetyltransferase and glutamate decarboxylase mRNA expression. *J.*

- Comp. Neurol. 372: 204–14.
- Berry SD, Thompson RF. 1978. Prediction of learning rate from the hippocampal electroencephalogram. *Science* 200(4347):1298-300.
- Blair HT, Gupta K, Zhang K. 2008. Conversion of a phase- to a rate-coded position signal by a three-stage model of theta cells, grid cells, and place cells. *Hippocampus* 18(12):1239-55.
- Blair HT, Wolday AC, Zhang K. 2007. Scale-invariant memory representations emerge from moire interference between grid fields that produce theta oscillations: a computational model. *J Neurosci* 27(12):3211-29.
- Bland BH, Bird J, Jackson J, Natsume K. 2006. Medial septal modulation of the ascending brainstem hippocampal synchronizing pathways in the freely moving rat. *Hippocampus* 16(1):11-9.
- Bland BH, Oddie SD. 2001. Theta band oscillation and synchrony in the hippocampal formation and associated structures: the case for its role in sensorimotor integration. *Behav Brain Res* 127(1-2):119-36.
- Bland BH, Oddie SD, Colom LV. 1999. Mechanisms of neural synchrony in the septohippocampal pathways underlying hippocampal theta generation. *Journal of Neuroscience* 19(8):3223-3237.
- Bland BH, Vanderwolf CH. 1972a. Diencephalic and hippocampal mechanisms of motor activity in the rat: effects of posterior hypothalamic stimulation on behavior and hippocampal slow wave activity. *Brain Res* 43(1):67-88.
- Bland BH, Vanderwolf CH. 1972b. Electrical stimulation of the hippocampal formation: behavioral and bioelectrical effects. *Brain Res* 43(1):89-106.
- Blasco-Ibanez JM, Freund TF. 1995. Synaptic input of horizontal interneurons in stratum oriens of the hippocampal CA1 subfield: structural basis of feed-back activation. *Eur J Neurosci* 7(10):2170-80.
- Blumberg BJ, Flynn SP, Barriere SJ, Mouchati PR, Scott RC, Holmes GL, Barry JM. 2016. Efficacy of nonselective optogenetic control of the medial septum over hippocampal oscillations: the influence of speed and implications for cognitive enhancement. *Physiol Rep* 4(23).
- Boehlen A, Heinemann U, Erchova I. 2010. The range of intrinsic frequencies represented by medial entorhinal cortex stellate cells extends with age. *J Neurosci* 30(13):4585-9.
- Borhegyi Z, Varga V, Szilagy N, Fabo D, Freund TF. 2004. Phase segregation of medial septal GABAergic neurons during hippocampal theta activity. *J Neurosci* 24(39):8470-9.
- Boyce R, Glasgow SD, Williams S, Adamantidis A. 2016. Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. *Science* 352(6287):812-6.
- Bragin A, Jando G, Nadasdy Z, Hetke J, Wise K, Buzsaki G. 1995. Gamma (40-100 Hz) oscillation in the hippocampus of the behaving rat. *J Neurosci* 15(1 Pt 1):47-60.
- Brandon MP, Bogaard AR, Libby CP, Connerney MA, Gupta K, Hasselmo ME. 2011. Reduction of theta rhythm dissociates grid cell spatial periodicity from directional tuning. *Science* 332(6029):595-9.
- Brandon MP, Koenig J, Leutgeb JK, Leutgeb S. 2014. New and distinct hippocampal place codes are generated in a new environment during septal inactivation. *Neuron* 82(4):789-96.
- Brankack J, Stewart M, Fox SE. 1993. Current source density analysis of the

- hippocampal theta rhythm: associated sustained potentials and candidate synaptic generators. *Brain Research* 615(2):310-327.
- Brioni JD, Decker MW, Gamboa LP, Izquierdo I, McGaugh JL. 1990. Muscimol injections in the medial septum impair spatial learning. *Brain Res* 522(2):227-34.
- Brockmann MD, Pöschel B, Cichon N, Hanganu-Opatz IL. 2011. Coupled oscillations mediate directed interactions between prefrontal cortex and hippocampus of the neonatal rat. *Neuron* 71: 332–47.
- Brown GD, Preece T, Hulme C. 2000. Oscillator-based memory for serial order. *Psychol Rev* 107(1):127-81.
- Brown TI, Ross RS, Keller JB, Hasselmo ME, Stern CE (2010) Which way was I going? Contextual retrieval supports the disambiguation of well learned overlapping navigational routes. *J Neurosci* 30:7414-7422.
- Brown TI, Stern CE (2014) Contributions of medial temporal lobe and striatal memory systems to learning and retrieving overlapping spatial memories. *Cereb Cortex* 24:1906-1922.
- Buhl DLL, Buzsáki G. 2005. Developmental emergence of hippocampal fast-field “ripple” oscillations in the behaving rat pups. *Neuroscience* 134: 1423–1430.
- Buhl DL, Harris KD, Hormuzdi SG, Monyer H, Buzsaki G. 2003. Selective impairment of hippocampal gamma oscillations in connexin-36 knock-out mouse in vivo. *J Neurosci* 23(3):1013-8.
- Buno W, Jr., Velluti JC. 1977. Relationships of hippocampal theta cycles with bar pressing during self-stimulation. *Physiol Behav* 19(5):615-21.
- Burgess N. 2008. Grid cells and theta as oscillatory interference: theory and predictions. *Hippocampus* 18(12):1157-74.
- Burgess N, Barry C, O'Keefe J. 2007. An oscillatory interference model of grid cell firing. *Hippocampus* 17(9):801-12.
- Burgess N, Maguire EA, O'Keefe J. 2002. The human hippocampus and spatial and episodic memory. *Neuron* 35(4):625-641.
- Bush D, Burgess N. 2014. A hybrid oscillatory interference/continuous attractor network model of grid cell firing. *J Neurosci* 34:5065-5079.
- Buzsaki G. 2002. Theta oscillations in the hippocampus. *Neuron* 33(3):325-40.
- Buzsáki G. 2015. Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. *Hippocampus* 25: 1073–188.
- Buzsaki G, Czopf J, Kondakor I, Kellenyi L. 1986. Laminar distribution of hippocampal rhythmic slow activity (RSA) in the behaving rat: current-source density analysis, effects of urethane and atropine. *Brain Res* 365(1):125-37.
- Buzsaki G, Horvath Z, Urioste R, Hetke J, Wise K. 1992. High-frequency network oscillation in the hippocampus. *Science* 256: 1025–1027.
- Buzsaki G, Leung LW, Vanderwolf CH. 1983. Cellular bases of hippocampal EEG in the behaving rat. *Brain Res* 287(2):139-71.
- Carus-Cadavieco M, Gorbati, M., Ye, L., Bender, F., Van der Veldt, S., Kosse, C., Börgers, C., Lee, SY., Ramakrishnan, C., Hu, Y., Denisova, N., Ramm, F., Volitaki, E., Burdakov, D., Deisseroth, K., Ponomarenko, A., Korotkova, T. 2017. Gamma oscillations organize top-down signaling to hypothalamus and enable food seeking. *Nature* 542(7640): 232-236.
- Chen G, Manson D, Cacucci F, Wills TJ. 2016. Absence of Visual Input Results in the Disruption of Grid Cell Firing in the Mouse. *Curr Biol* 26(17):2335-42.

- Chrobak JJ, Stackman RW, Walsh TJ. 1989. Intraseptal administration of muscimol produces dose-dependent memory impairments in the rat. *Behav. Neural Biol.* 52(3):357-369.
- Climmer JR, DiTullio R, Newman EL, Hasselmo ME, Eden UT. 2015. Examination of rhythmicity of extracellularly recorded neurons in the entorhinal cortex. *Hippocampus* 25(4):460-73.
- Climmer JR, Newman EL, Hasselmo ME. 2013. Phase coding by grid cells in unconstrained environments: two-dimensional phase precession. *Eur J Neurosci* 38(4):2526-41.
- Colgin LL, Denninger T, Fyhn M, Hafting T, Bonnevie T, Jensen O, Moser MB, Moser EI. 2009. Frequency of gamma oscillations routes flow of information in the hippocampus. *Nature* 462(7271):353-7.
- Colom LV, Castaneda MT, Reyna T, Hernandez S, Garrido-Sanabria E. 2005. Characterization of medial septal glutamatergic neurons and their projection to the hippocampus. *Synapse* 58(3):151-64.
- Constantinescu AO, O'Reilly JX, Behrens TE. 2016. Organizing conceptual knowledge in humans with a gridlike code. *Science* 352(6292):1464-8.
- Cornwell BR, Johnson LL, Holroyd T, Carver FW, Grillon C. 2008. Human hippocampal and parahippocampal theta during goal-directed spatial navigation predicts performance on a virtual Morris water maze. *J Neurosci* 28(23):5983-90.
- Creery BL, Bland BH. 1980. Ontogeny of fascia dentata electrical activity and motor behavior in the Dutch belted rabbit (*Oryctolagus cuniculus*). *Exp Neurol.* 67(3):554-72.
- Crooks R, Jackson J, Bland BH. 2012. Dissociable pathways facilitate theta and non-theta states in the median raphe--septohippocampal circuit. *Hippocampus* 22(7):1567-76.
- Csicsvari J, Jamieson B, Wise KD, Buzsaki G. 2003. Mechanisms of gamma oscillations in the hippocampus of the behaving rat. *Neuron* 37(2):311-22.
- Cutsuridis V, Hasselmo ME. 2012. GABAergic contributions to gating, timing, and phase precession of hippocampal neuronal activity during theta oscillations. *Hippocampus.* 22(7):1597-621.
- Danglot L, Triller A, Marty S. 2006. The development of hippocampal interneurons in rodents. *Hippocampus* 16: 1032–1060.
- Dannenberg H, Pabst M, Braganza O, Schoch S, Niediek J, Bayraktar M, Mormann F, Beck H (2015) Synergy of direct and indirect cholinergic septo-hippocampal pathways coordinates firing in hippocampal networks. *J Neurosci* 35:8394-8410.
- Dodson PD, Pastoll H, Nolan MF. 2011. Dorsal-ventral organization of theta-like activity intrinsic to entorhinal stellate neurons is mediated by differences in stochastic current fluctuations. *J Physiol* 589(Pt 12):2993-3008.
- Douchamps V, Jeewajee A, Blundell P, Burgess N, Lever C. 2013. Evidence for encoding versus retrieval scheduling in the hippocampus by theta phase and acetylcholine. *J Neurosci.* 2013 May 15;33(20):8689-704.
- Dupret D, O'Neill J, Pleydell-Bouverie B, Csicsvari J. 2010. The reorganization and reactivation of hippocampal maps predict spatial memory performance. *Nat Neurosci* 13(8):995-1002.
- Eggink H, Mertens P, Storm E, Giocomo LM. 2014. Hyperpolarization-activated cyclic nucleotide-gated 1 independent grid cell-phase precession in mice.

- Hippocampus 24:249-256.
- Engin E, Smith KS, Gao Y, Nagy D, Foster RA, Tsvetkov E, Keist R, Crestani F, Fritschy JM, Bolshakov VY and others. 2016. Modulation of anxiety and fear via distinct intrahippocampal circuits. *Elife* 5:e14120.
- Engin E, Stellbrink J, Treit D, Dickson CT. 2008. Anxiolytic and antidepressant effects of intracerebroventricularly administered somatostatin: behavioral and neurophysiological evidence. *Neuroscience* 157(3):666-76.
- Engin E, Treit D. 2007. The role of hippocampus in anxiety: intracerebral infusion studies. *Behavioural Pharmacology* 18(5-6):365-74.
- Fanselow MS, Dong HW. 2010. Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron* 65(1):7-19.
- Ferbinteanu J, Shapiro ML. 2003. Prospective and retrospective memory coding in the hippocampus. *Neuron* 40(6):1227-39.
- Ferrante M, Shay CF, Tsuno Y, William Chapman G, Hasselmo ME. 2016. Post-Inhibitory Rebound Spikes in Rat Medial Entorhinal Layer II/III Principal Cells: In Vivo, In Vitro, and Computational Modeling Characterization. *Cereb Cortex*.
- Fox SE, Wolfson S, Ranck Jr. JB. 1986. Hippocampal theta rhythm and the firing of neurons in walking and urethane anesthetized rats. *Brain Research* 62(3):495-508.
- Freund TF. 1989. GABAergic septohippocampal neurons contain parvalbumin. *Brain Res* 478(2):375-81.
- Freund TF, Antal M. 1988. GABA-containing neurons in the septum control inhibitory interneurons in the hippocampus. *Nature* 336(6195):170-3.
- Fuhrmann F, Justus D, Sosulina L, Kaneko H, Beutel T, Friedrichs D, Schoch S, Schwarz MK, Fuhrmann M, Remy S. 2015. Locomotion, theta oscillations, and the speed-correlated firing of hippocampal neurons are controlled by a medial septal glutamatergic circuit. *Neuron* 86(5):1253-64.
- Fyhn M, Molden S, Witter MP, Moser EI, Moser MB. 2004. Spatial representation in the entorhinal cortex. *Science* 305(5688):1258-64.
- Geisler C, Diba K, Pastalkova E, Mizuseki K, Royer S, Buzsaki G. 2010. Temporal delays among place cells determine the frequency of population theta oscillations in the hippocampus. *Proc Natl Acad Sci U S A* 107(17):7957-62.
- Gerrish CJ, Alberts JR. 1996. Environmental temperature modulates onset of independent feeding: warmer is sooner. *Dev. Psychobiol.* 29: 483-495.
- Ghoneim MM, Mewaldt SP. 1990. Benzodiazepines and human memory: a review. *Anesthesiology* 72(5):926-38.
- Giocomo LM, Hasselmo ME. 2008a. Computation by oscillations: implications of experimental data for theoretical models of grid cells. *Hippocampus* 18(12):1186-99.
- Giocomo LM, Hasselmo ME. 2008b. Time constants of h current in layer ii stellate cells differ along the dorsal to ventral axis of medial entorhinal cortex. *J Neurosci* 28(38):9414-25.
- Giocomo LM, Hasselmo ME. 2009. Knock-out of HCN1 subunit flattens dorsal-ventral frequency gradient of medial entorhinal neurons in adult mice. *J Neurosci* 29(23):7625-30.
- Giocomo LM, Zilli EA, Fransen E, Hasselmo ME. 2007. Temporal frequency of subthreshold oscillations scales with entorhinal grid cell field spacing. *Science* 315(5819):1719-22.

- Givens B. 1996. Stimulus-evoked resetting of the dentate theta rhythm: relation to working memory. *Neuroreport* 8(1):159-63.
- Givens B, Olton DS. 1994. Local modulation of basal forebrain: effects on working and reference memory. *J Neurosci* 14(6):3578-87.
- Givens BS, Olton DS. 1990. Cholinergic and GABAergic modulation of the medial septal area: Effect on working memory. *Behav. Neurosci.* 104:849-855.
- Gladfelter WE, Brobeck JR. 1962. Decreased spontaneous locomotor activity in the rat induced by hypothalamic lesions. *Am J Physiol* 203:811-7.
- Goto M, Swanson LW, Canteras NS. 2001. Connections of the nucleus incertus. *J Comp Neurol* 438(1):86-122.
- Graeff FG, Quintero S, Gray JA. 1980. Median raphe stimulation, hippocampal theta rhythm and threat-induced behavioral inhibition. *Physiol Behav.* 25(2):253-61.
- Gramsbergen A, Schwartz P, Precht HF. 1970. The postnatal development of behavioral states in the rat. *Dev. Psychobiol.* 3: 267–280.
- Grastyan E, Karmos G, Vereczkey L, Martin J, Kellenyi L. 1965. Hypothalamic Motivational Processes as Reflected by their Hippocampal Electrical Correlates. *Science* 149(3679):91-3.
- Gray JA. 1982. *The Neuropsychology of Anxiety: an inquiry into the functions of the septo-hippocampal system.* Oxford: Oxford University Press.
- Gray JA, McNaughton N. 2000. *The Neuropsychology of Anxiety: Oxford University Press.*
- Green JD, Arduini AA. 1954. Hippocampal electrical activity in arousal. *Journal of Neurophysiology* 17:533-557.
- Griffin AL, Asaka Y, Darling RD, Berry SD. 2004. Theta-contingent trial presentation accelerates learning rate and enhances hippocampal plasticity during trace eyeblink conditioning. *Behav Neurosci* 118(2):403-11.
- Grillner S, Wallen P, Saitoh K, Kozlov A, Robertson B. 2008. Neural bases of goal-directed locomotion in vertebrates--an overview. *Brain Res Rev* 57(1):2-12.
- Hafting T, Fyhn M, Bonnevie T, Moser MB, Moser EI. 2008. Hippocampus-independent phase precession in entorhinal grid cells. *Nature* 453(7199):1248-52.
- Hafting T, Fyhn M, Molden S, Moser MB, Moser EI. 2005. Microstructure of a spatial map in the entorhinal cortex. *Nature* 436(7052):801-6.
- Hangya B, Borhegyi Z, Szilagy N, Freund TF, Varga V. 2009. GABAergic neurons of the medial septum lead the hippocampal network during theta activity. *J Neurosci* 29(25):8094-102.
- Hardcastle K, Ganguli S, Giocomo LM (2015) Environmental boundaries as an error correction mechanism for grid cells. *Neuron* 86:827-839.
- Hartley T, Lever C, Burgess N, O'Keefe J. 2014. Space in the brain: how the hippocampal formation supports spatial cognition. *Philosophical Transactions of the Royal Society B: Biological Sciences* 369(1635):20120510.
- Hartung H, Brockmann MD, Pöschel B, De Feo V, Hanganu-Opatz IL. 2016. Thalamic and Entorhinal Network Activity Differently Modulates the Functional Development of Prefrontal–Hippocampal Interactions. *J. Neurosci.* 36: 3676–3690.
- Hasselmo ME. 2008. Grid cell mechanisms and function: contributions of entorhinal persistent spiking and phase resetting. *Hippocampus* 18(12):1213-29.
- Hasselmo ME. 2009. A model of episodic memory: mental time travel along encoded

- trajectories using grid cells. *Neurobiol Learn Mem.* 92(4):559-73.
- Hasselmo ME. 2012. *How we remember: Brain mechanisms of episodic memory.* Cambridge, MA: MIT Press.
- Hasselmo ME, Bodelon C, Wyble BP. 2002. A proposed function for hippocampal theta rhythm: separate phases of encoding and retrieval enhance reversal of prior learning. *Neural Comput* 14(4):793-817.
- Hasselmo ME, Brandon MP. 2012. A model combining oscillations and attractor dynamics for generation of grid cell firing. *Front Neural Circuits* 6:30.
- Hasselmo ME, Giocomo LM, Zilli EA. 2007. Grid cell firing may arise from interference of theta frequency membrane potential oscillations in single neurons. *Hippocampus* 17(12):1252-71.
- Hasselmo ME, Stern CE. 2014. Theta rhythm and the encoding and retrieval of space and time. *Neuroimage* 85 Pt 2:656-66.
- Hasselmo ME, Wyble BP, Wallenstein GV. 1996. Encoding and retrieval of episodic memories: Role of cholinergic and GABAergic modulation in the hippocampus. *Hippocampus* 6(6):693-708.
- Herman JP, Cullinan WE. 1997. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. *Trends Neurosci* 20(2):78-84.
- Herrera CG, Cadavieco MC, Jago S, Ponomarenko A, Korotkova T, Adamantidis A. 2016. Hypothalamic feedforward inhibition of thalamocortical network controls arousal and consciousness. *Nat Neurosci* 19(2):290-8.
- Heys JG, Giocomo LM, Hasselmo ME. 2010. Cholinergic modulation of the resonance properties of stellate cells in layer II of medial entorhinal cortex. *J Neurophysiol* 104(1):258-70.
- Hinman JR, Brandon MP, Climer JR, Chapman GW, Hasselmo ME. 2016. Multiple Running Speed Signals in Medial Entorhinal Cortex. *Neuron* 91(3):666-79.
- Hinman JR, Penley SC, Long LL, Escabi MA, Chrobak JJ. 2011. Septotemporal variation in dynamics of theta: speed and habituation. *J Neurophysiol* 105(6):2675-86.
- Hölscher C, Anwyl R, Rowan MJ. 1997. Stimulation on the positive phase of hippocampal theta rhythm induces long-term potentiation that can be depotentiated by stimulation on the negative phase in area CA1 *in vivo*. *The Journal of Neuroscience* 17:6470-6477.
- Horner AJ, Bisby JA, Zotow E, Bush D, Burgess N. 2016. Grid-like Processing of Imagined Navigation. *Curr Biol* 26(6):842-7.
- Huerta PT, Lisman JE. 1995. Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 *in vitro*. *Neuron* 15(5):1053-1063.
- Huxter J, Burgess N, O'Keefe J. 2003. Independent rate and temporal coding in hippocampal pyramidal cells. *Nature* 425(6960):828-32.
- Huxter JR, Senior TJ, Allen K, Csicsvari J. 2008. Theta phase-specific codes for two-dimensional position, trajectory and heading in the hippocampus. *Nat Neurosci* 11(5):587-94.
- Hyman JM, Wyble BP, Goyal V, Rossi CA, Hasselmo ME. 2003. Stimulation in hippocampal region CA1 in behaving rats yields long-term potentiation when delivered to the peak of theta and long-term depression when delivered to the trough. *J Neurosci* 23(37):11725-31.
- Jarrard LE. 1968. Behavior of Hippocampal Lesioned Rats in Home Cage and Novel Situations. *Physiology & Behavior* 3(1):65-&.

- Jeewajee A, Barry C, Douchamps V, Manson D, Lever C, Burgess N. 2014. Theta phase precession of grid and place cell firing in open environments. *Philos Trans R Soc Lond B Biol Sci* 369(1635):20120532.
- Jeewajee A, Barry C, O'Keefe J, Burgess N. 2008a. Grid cells and theta as oscillatory interference: electrophysiological data from freely moving rats. *Hippocampus* 18(12):1175-85.
- Jeewajee A, Lever C, Burton S, O'Keefe J, Burgess N. 2008b. Environmental novelty is signaled by reduction of the hippocampal theta frequency. *Hippocampus* 18(4):340-8.
- Jeffery KJ, Donnett JG, O'Keefe J. 1995. Medial septal control of theta-correlated unit firing in the entorhinal cortex of awake rats. *Neuroreport* 6(16):2166-70.
- Jinno S, Klausberger T, Marton LF, Dalezios Y, Roberts JD, Fuentealba P, Bushong EA, Henze D, Buzsaki G, Somogyi P. 2007. Neuronal diversity in GABAergic long-range projections from the hippocampus. *J Neurosci* 27(33):8790-804.
- John T, Kiss T, Lever C, Erdi P. 2014. Anxiolytic drugs and altered hippocampal theta rhythms: the quantitative systems pharmacological approach. *Network* 25(1-2):20-37.
- Jones MW, Wilson MA. 2005. Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. *PLoS Biol* 3(12):e402.
- Justus D, Dalugge D, Bothe S, Fuhrmann F, Hannes C, Kaneko H, Friedrichs D, Sosulina L, Schwarz I, Elliott DA and others. 2017. Glutamatergic synaptic integration of locomotion speed via septoentorhinal projections. *Nat Neurosci* 20(1):16-19.
- Kahana MJ, Sekuler R, Caplan JB, Kirschen M, Madsen JR. 1999. Human theta oscillations exhibit task dependence during virtual maze navigation. *Nature* 399(6738):781-4.
- Kamondi A, Acsady L, Wang XJ, Buzsaki G. 1998. Theta oscillations in somata and dendrites of hippocampal pyramidal cells in vivo: activity-dependent phase-precession of action potentials. *Hippocampus* 8(3):244-261.
- Kim SM, Frank LM. 2009. Hippocampal lesions impair rapid learning of a continuous spatial alternation task. *PLoS One* 4(5):e5494.
- Kinney GG, Kocsis B, Vertes RP. 1995. Injections of muscimol into the median raphe nucleus produce hippocampal theta rhythm in the urethane anesthetized rat. *Psychopharm (Berl)* 120(3):244-8.
- Kiss J, Patel AJ, Freund TF. 1990. Distribution of septohippocampal neurons containing parvalbumin or choline acetyltransferase in the rat brain. *J Comp Neurol* 298(3):362-72.
- Kirk IJ. 1998. Frequency modulation of hippocampal theta by the supramammillary nucleus, and other hypothalamo-hippocampal interactions: mechanisms and functional implications. *Neurosci Biobehav Rev*. Mar;22(2):291-302.
- Kirk IJ, McNaughton N. 1991. Supramammillary cell firing and hippocampal rhythmical slow activity. *Neuroreport* 2:723-725.
- Kitchigina VF, Kudina TA, Kuttyeva EV, Vinogradova OS. 1999. Neuronal activity of the septal pacemaker of theta rhythm under the influence of stimulation and blockade of the median raphe nucleus in the awake rabbit. *Neuroscience* 94(2):453-63.
- Kjelstrup KB, Solstad T, Brun VH, Hafting T, Leutgeb S, Witter MP, Moser EI, Moser MB. 2008. Finite scale of spatial representation in the hippocampus. *Science*

- 321(5885):140-3.
- Kjelstrup KG, Tuvnes FA, Steffenach HA, Murison R, Moser EI, Moser MB. 2002. Reduced fear expression after lesions of the ventral hippocampus. *Proc Natl Acad Sci U S A* 99(16):10825-30.
- Klausberger T, Magill PJ, Marton LF, Roberts JD, Cobden PM, Buzsaki G, Somogyi P. 2003. Brain-state- and cell-type-specific firing of hippocampal interneurons in vivo. *Nature* 421(6925):844-8.
- Klausberger T, Somogyi P. 2008. Neuronal diversity and temporal dynamics: the unity of hippocampal circuit operations. *Science* 321(5885):53-7.
- Kocsis B, Vertes RP. 1997. Phase relations of rhythmic neuronal firing in the supramammillary nucleus and mammillary body to the hippocampal theta activity in urethane anesthetized rats. *Hippocampus* 7(2):204-14.
- Koenig J, Linder AN, Leutgeb JK, Leutgeb S. 2011. The spatial periodicity of grid cells is not sustained during reduced theta oscillations. *Science* 332(6029):592-5.
- Korotkova T, Fuchs EC, Ponomarenko A, von Engelhardt J, Monyer H. 2010. NMDA receptor ablation on parvalbumin-positive interneurons impairs hippocampal synchrony, spatial representation and working memory. *Neuron*, 68(3):557-69.
- Kramis RC, Routtenberg A. 1977. Dissociation of hippocampal EEG from its behavioral correlates by septal and hippocampal electrical stimulation. *Brain Res* 125(1):37-49.
- Kramis R, Vanderwolf CH, Bland BH. 1975. Two types of hippocampal rhythmical slow activity in both the rabbit and the rat: relations to behavior and effects of atropine, diethyl ether, urethane, and pentobarbital. *Exp.Neurol.* 49: 58–85.
- Kraus BJ, Brandon MP, Robinson RJ, 2nd, Connerney MA, Hasselmo ME, Eichenbaum H. 2015. During Running in Place, Grid Cells Integrate Elapsed Time and Distance Run. *Neuron* 88(3):578-89.
- Kraus BJ, Robinson RJ, 2nd, White JA, Eichenbaum H, Hasselmo ME. 2013. Hippocampal "Time Cells": Time versus Path Integration. *Neuron* 78(6):1090-101.
- Kropff E, Carmichael JE, Moser MB, Moser EI. 2015. Speed cells in the medial entorhinal cortex. *Nature* 523(7561):419-24.
- Kunec S, Hasselmo ME, Kopell N. 2005. Encoding and retrieval in the CA3 region of the hippocampus: a model of theta-phase separation. *J Neurophysiol* 94(1):70-82.
- Langston RF, Ainge JA, Couey JJ, Canto CB, Bjerknes TL, Witter MP, Moser EI, Moser MB. 2010. Development of the spatial representation system in the rat. *Science* 328: 1576–1580.
- Leblanc, M.O., Bland, B.H., 1979. Developmental aspects of hippocampal electrical activity and motor behavior in the rat. *Exp.Neurol.* 66, 220–237.
- Lee MG, Hassani OK, Alonso A, Jones BE. 2005. Cholinergic basal forebrain neurons burst with theta during waking and paradoxical sleep. *J Neurosci* 25(17):4365-9.
- Lega BC, Jacobs J, Kahana M. 2011. Human hippocampal theta oscillations and the formation of episodic memories. *Hippocampus* 22(4):748-61.
- Leutgeb S, Leutgeb JK, Barnes CA, Moser EI, McNaughton BL, Moser MB. 2005. Independent codes for spatial and episodic memory in hippocampal neuronal ensembles. *Science* 309(5734):619-23.
- Lever C, Burton S, Jeewajee A, Wills TJ, Cacucci F, Burgess N, O'Keefe J. 2010. Environmental novelty elicits a later theta phase of firing in CA1 but not

- subiculum. *Hippocampus* 20(2):229-34.
- Lever C, Burton S, O'Keefe J. 2006. Rearing on hind legs, environmental novelty, and the hippocampal formation. *Rev Neurosci* 17(1-2):111-33.
- Lever C, Cacucci, F., Wills T., Burton, S., McClelland, A., Burgess, N., O'Keefe J. 2003. Spatial coding in the hippocampal formation: input, information type, plasticity and behaviour. In: Jeffery K, editor. *The Neurobiology of Spatial Behaviour*. Oxford: Oxford University Press.
- Lever C, Hines M, Poulter S, Douchamps V, McGregor A. 2016. Spatial cognition or Anxiety? Can dissociable theta frequency correlates reconcile opposing views of hippocampal function? *IBNS Abstracts*. Budapest, Hungary.
- Liu X, Ramirez S, Pang PT, Puryear CB, Govindarajan A, Deisseroth K, Tonegawa S. 2012. Optogenetic stimulation of a hippocampal engram activates fear memory recall. *Nature* 484(7394):381-5.
- Long LL, Hinman JR, Chen CM, Stevenson IH, Read HL, Escabi MA, Chrobak JJ. 2014. Novel acoustic stimuli can alter locomotor speed to hippocampal theta relationship. *Hippocampus* 24(9):1053-8.
- Loh E, Kurth-Nelson Z, Berron D, Dayan P, Duzel E, Dolan R, Guitart-Masip M. 2016. Parsing the Role of the Hippocampus in Approach-Avoidance Conflict. *Cereb Cortex*.
- Lubenov EV, Siapas AG. 2009. Hippocampal theta oscillations are travelling waves. *Nature* 459(7246):534-9.
- Leinekugel X, Khazipov R, Cannon R, Hirase H, Ben Ari Y, Buzsaki G. 2002. Correlated bursts of activity in the neonatal hippocampus in vivo. *Science* 296: 2049–2052.
- Lima LB, Bueno D, Leite F, Souza S, Gonçalves L, Furigo IC, Donato J Jr, Metzger M. Afferent and efferent connections of the interpeduncular nucleus with special reference to circuits involving the habenula and raphe nuclei. *J Comp Neurol*. 2017. 525(10):2411-2442.
- Luo AH, Tahsili-Fahadan P, Wise RA, Lupica CR, Aston-Jones G. 2011. Linking context with reward: a functional circuit from hippocampal CA3 to ventral tegmental area. *Science* 333(6040):353-7.
- M'Harzi M, Palacios A, Monmaur P, Willig F, Houcine O, Delacour J. 1987. Effects of selective lesions of fimbria-fornix on learning set in the rat. *Physiol Behav* 40(2):181-8.
- Ma S, Blasiak A, Olucha-Bordonau FE, Verberne AJ, Gundlach AL. 2013. Heterogeneous responses of nucleus incertus neurons to corticotrophin-releasing factor and coherent activity with hippocampal theta rhythm in the rat. *J Physiol* 591(16):3981-4001.
- Ma S, Gundlach AL. 2015. Ascending control of arousal and motivation: role of nucleus incertus and its peptide neuromodulators in behavioural responses to stress. *J Neuroendocrinol* 27(6):457-67.
- MacDonald CJ, Carrow S, Place R, Eichenbaum H. 2013. Distinct hippocampal time cell sequences represent odor memories in immobilized rats. *J Neurosci* 33(36):14607-16.
- MacDonald CJ, Lepage KQ, Eden UT, Eichenbaum H. 2011. Hippocampal "time cells" bridge the gap in memory for discontinuous events. *Neuron* 71(4):737-49.
- Mamad O, McNamara HM, Reilly RB, Tsanov M. 2015. Medial septum regulates the hippocampal spatial representation. *Front Behav Neurosci* 9:166.

- Manns ID, Mainville L, Jones BE. 2001. Evidence for glutamate, in addition to acetylcholine and GABA, neurotransmitter synthesis in basal forebrain neurons projecting to the entorhinal cortex. *Neuroscience* 107(2):249-63.
- Manns JR, Zilli EA, Ong KC, Hasselmo ME, Eichenbaum H. 2007. Hippocampal CA1 spiking during encoding and retrieval: relation to theta phase. *Neurobiol Learn Mem* 87(1):9-20.
- Manseau F, Danik M, Williams S. 2005. A functional glutamatergic neurone network in the medial septum and diagonal band area. *J Physiol* 566(Pt 3):865-84.
- Manseau F, Goutagny R, Danik M, Williams S. 2008. The hippocamposeptal pathway generates rhythmic firing of GABAergic neurons in the medial septum and diagonal bands: an investigation using a complete septohippocampal preparation in vitro. *J Neurosci* 28(15):4096-107.
- Marley E., Key B.J., 1963. Maturation of the Electrocorticogram and Behaviour in the Kitten and Guinea-pig and the Effect of Some Sympathomimetic Amines. *Electroencephalogr Clin Neurophysiol.* 1963 Aug;15:620-36.
- Martínez-Bellver S, Cervera-Ferri A, Luque-García A, Martínez-Ricós J, Valverde-Navarro A, Bataller M, Guerrero J, Teruel-Martí V. 2017. Causal relationships between neurons of the nucleus incertus and the hippocampal theta activity in the rat. *J Physiol.* 595(5):1775-1792.
- Maru E, Takahashi LK, Iwahara S. 1979. Effects of median raphe nucleus lesions on hippocampal EEG in the freely moving rat. *Brain Res.* 163(2):223-34.
- Mattis J, Brill J, Evans S, Lerner TN, Davidson TJ, Hyun M, Ramakrishnan C, Deisseroth K, Huguenard JR. 2014. Frequency-dependent, cell type-divergent signaling in the hippocamposeptal projection. *J Neurosci* 34(35):11769-80.
- Maurer AP, Cowen SL, Burke SN, Barnes CA, McNaughton BL. 2006. Phase precession in hippocampal interneurons showing strong functional coupling to individual pyramidal cells. *J Neurosci* 26(52):13485-92.
- Maurer AP, Vanrhoads SR, Sutherland GR, Lipa P, McNaughton BL. 2005. Self-motion and the origin of differential spatial scaling along the septo-temporal axis of the hippocampus. *Hippocampus* 15(7):841-52.
- McFarland WL, Teitelbaum H, Hedges EK. 1975. Relationship between hippocampal theta activity and running speed in the rat. *J Comp Physiol Psychol* 88(1):324-8.
- McKenna JT, Vertes RP. 2001. Collateral projections from the median raphe nucleus to the medial septum and hippocampus. *Brain Res Bull* 54(6):619-30.
- McKenzie S, Frank AJ, Kinsky NR, Porter B, Riviere PD, Eichenbaum H. 2014. Hippocampal representation of related and opposing memories develop within distinct, hierarchically organized neural schemas. *Neuron* 83(1):202-15.
- McNaughton BL, Barnes CA, O'Keefe J. 1983. The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. *Exp Brain Res* 52(1):41-9.
- McNaughton BL, Battaglia FP, Jensen O, Moser EI, Moser MB. 2006. Path integration and the neural basis of the 'cognitive map'. *Nat Rev Neurosci* 7(8):663-78.
- McNaughton N, Coop CF. 1991. Neurochemically dissimilar anxiolytic drugs have common effects on hippocampal rhythmic slow activity. *Neuropharmacology* 30(8):855-63.
- McNaughton N, Kocsis B, Hajos M. 2007. Elicited hippocampal theta rhythm: a screen for anxiolytic and procognitive drugs through changes in hippocampal function? *Behavioural Pharmacology* 18(5-6):329-46.

- McNaughton N, Morris RG. 1992. Buspirone produces a dose-related impairment in spatial navigation. *Pharmacol Biochem Behav* 43(1):167-71.
- McNaughton N, Richardson J, Gore C. 1986. Reticular elicitation of hippocampal slow waves: common effects of some anxiolytic drugs. *Neuroscience* 19: 899-903.
- Meeter M, Murre JM, Talamini LM. 2004. Mode shifting between storage and recall based on novelty detection in oscillating hippocampal circuits. *Hippocampus* 14(6):722-41.
- Mesulam MM, Mufson EJ, Wainer BH, Levey AI. 1983. Central cholinergic pathways in the rat: an overview based on an alternative nomenclature (Ch1-Ch6). *Neuroscience* 10(4):1185-201.
- Miall R. 1989. The storage of time intervals using oscillating neurons. *Neural Comput* 1:359-371.
- Mileykovskiy BY, Kiyashchenko LI, Siegel JM. 2005. Behavioral correlates of activity in identified hypocretin/orexin neurons. *Neuron* 46(5):787-98.
- Mitchell SJ, Ranck JB, Jr. 1980. Generation of theta rhythm in medial entorhinal cortex of freely moving rats. *Brain Res* 189(1):49-66.
- Mitchell SJ, Rawlins JN, Steward O, Olton DS. 1982. Medial septal area lesions disrupt theta rhythm and cholinergic staining in medial entorhinal cortex and produce impaired radial arm maze behavior in rats. *J Neurosci* 2(3):292-302.
- Mizumori SJY, Perez GM, Alvarado MC, Barnes CA, Mcnaughton BL. 1990. Reversible inactivation of the medial septum differentially affects 2 forms of learning in rats. *Brain Research* 528(1):12-20.
- Mohns EJ, Blumberg MS. 2010. Neocortical activation of the hippocampus during sleep in infant rats. *J.Neurosci.* 30: 3438–3449.
- Mohns EJ, Blumberg MS. 2008. Synchronous bursts of neuronal activity in the developing hippocampus: modulation by active sleep and association with emerging gamma and theta rhythms. *J.Neurosci.* 28: 10134–10144.
- Mohns EJ, Karlsson KA, Blumberg MS. 2007. Developmental emergence of transient and persistent hippocampal events and oscillations and their association with infant seizure susceptibility. *Eur.J.Neurosci.* 26: 2719–2730.
- Monaghan CK, Chapman GW, Hasselmo M. 2015. Medial septal infusion of a serotonin 1A receptor agonist anxiolytic reduces theta frequency in the medial entorhinal cortex. . *Soc. Neurosci. Abstr.* 41:85.02.
- Monaghan CK, Chapman GW, Hasselmo ME. 2014. Effects of a benzodiazepine and a serotonin 1A receptor agonist on neural activity in the rat medial entorhinal cortex. . *Soc. Neurosci. Abstr.* 40:466.06.
- Morris RGM, Hagan JJ. 1983. Hippocampal electrical activity and ballistic movement. In W. Seifert (Ed.), *Neurobiology of the Hippocampus*: 321-331. London: Academic press.
- Moser EI, Moser MB. 2008. A metric for space. *Hippocampus* 18(12):1142-56.
- Nunez A, Cervera-Ferri A, Olucha-Bordonau F, Ruiz-Torner A, Teruel V. 2006. Nucleus incertus contribution to hippocampal theta rhythm generation. *Eur J Neurosci* 23(10):2731-8.
- O'Keefe J. 1976. Place units in the hippocampus of the freely moving rat. *Exp Neurol* 51(1):78-109.
- O'Keefe J, Burgess N. 2005. Dual phase and rate coding in hippocampal place cells: theoretical significance and relationship to entorhinal grid cells. *Hippocampus* 15(7):853-66.

- O'Keefe J, Burgess N, Donnett JG, Jeffery KJ, Maguire EA. 1998. Place cells, navigational accuracy, and the human hippocampus. *Philos Trans R Soc Lond B Biol Sci* 353(1373):1333-40.
- O'Keefe J, Conway DH. 1978. Hippocampal place units in the freely moving rat: why they fire where they fire. *Exp Brain Res* 31(4):573-90.
- O'Keefe J, Dostrovsky J. 1971. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Res* 34(1):171-5.
- O'Keefe J, Nadel L. 1978. *The Hippocampus as a Cognitive Map*. Oxford, UK: Oxford University Press.
- O'Keefe J, Recce ML. 1993. Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* 3:317-330.
- O'Neil EB, Newsome RN, Li IH, Thavabalasingam S, Ito R, Lee AC. 2015. Examining the Role of the Human Hippocampus in Approach-Avoidance Decision Making Using a Novel Conflict Paradigm and Multivariate Functional Magnetic Resonance Imaging. *J Neurosci* 35(45):15039-49.
- O'Neill J, Pleydell-Bouverie B, Dupret D, Csicsvari J. 2010. Play it again: reactivation of waking experience and memory. *Trends in Neurosciences* 33(5):220-229.
- Oddie SD, Bland BH. 1998. Hippocampal formation theta activity and movement selection. *Neurosci Biobehav Rev* 22(2):221-31.
- Oler JA, Fox AS, Shelton SE, Rogers J, Dyer TD, Davidson RJ, Shelledy W, Oakes TR, Blangero J, Kalin NH. 2010. Amygdalar and hippocampal substrates of anxious temperament differ in their heritability. *Nature* 466(7308):864-8.
- Pan WX, McNaughton N. 2004. The supramammillary area: Its organization, functions and relationship to the hippocampus. *Prog Neurobiol* 74:127-166.
- Pastalkova E, Itskov V, Amarasingham A, Buzsaki G. 2008. Internally generated cell assembly sequences in the rat hippocampus. *Science* 321(5894):1322-7.
- Pastoll H, Ramsden HL, Nolan MF. 2012. Intrinsic electrophysiological properties of entorhinal cortex stellate cells and their contribution to grid cell firing fields. *Front Neural Circuits* 6:17.
- Patel J, Fujisawa S, Berenyi A, Royer S, Buzsaki G. 2012. Traveling theta waves along the entire septotemporal axis of the hippocampus. *Neuron* 75(3):410-7.
- Pentkowski NS, Blanchard DC, Lever C, Litvin Y, Blanchard RJ. 2006. Effects of lesions to the dorsal and ventral hippocampus on defensive behaviors in rats. *Eur J Neurosci* 23(8):2185-96.
- Phillips RG, LeDoux JE. 1992. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behavioral Neuroscience* 106(2):274-285.
- Raghavachari S, Kahana MJ, Rizzuto DS, Caplan JB, Kirschen MP, Bourgeois B, Madsen JR, Lisman JE. 2001. Gating of human theta oscillations by a working memory task. *J Neurosci* 21(9):3175-83.
- Rawlins JN, Feldon J, Gray JA. 1979. Septo-hippocampal connections and the hippocampal theta rhythm. *Exp Brain Res* 37(1):49-63.
- Redish AD. 2016. Vicarious trial and error. *Nat Rev Neurosci* 17(3):147-159.
- Redondo RL, Kim J, Arons AL, Ramirez S, Liu X, Tonegawa S. 2014. Bidirectional switch of the valence associated with a hippocampal contextual memory engram. *Nature* 513(7518):426-430.
- Revest JM, Dupret D, Koehl M, Funk-Reiter C, Grosjean N, Piazza PV, Abrous DN. 2009. Adult hippocampal neurogenesis is involved in anxiety-related behaviors.

- Mol Psychiatry 14(10):959-67.
- Risold PY, Swanson LW. 1996. Structural evidence for functional domains in the rat hippocampus. *Science* 272(5267):1484-6.
- Rivas J, Gaztelu JM, Garcia-Austt E. 1996. Changes in hippocampal cell discharge patterns and theta rhythm spectral properties as a function of walking velocity in the guinea pig. *Exp Brain Res* 108(1):113-8.
- Rizzuto DS, Madsen JR, Bromfield EB, Schulze-Bonhage A, Kahana MJ. 2006. Human neocortical oscillations exhibit theta phase differences between encoding and retrieval. *Neuroimage* 31(3):1352-8.
- Robinson J, Manseau F, Ducharme G, Amilhon B, Vigneault E, El Mestikawy S, Williams S. 2016. Optogenetic Activation of Septal Glutamatergic Neurons Drive Hippocampal Theta Rhythms. *J Neurosci* 36(10):3016-23.
- Royer S, Sirota A, Patel J, Buzsaki G. 2010. Distinct representations and theta dynamics in dorsal and ventral hippocampus. *J Neurosci* 30(5):1777-87.
- Ryan PJ, Ma S, Olucha-Bordonau FE, Gundlach AL. 2011. Nucleus incertus--an emerging modulatory role in arousal, stress and memory. *Neurosci Biobehav Rev* 35(6):1326-41.
- Sabolek HR, Penley SC, Hinman JR, Bunce JG, Markus EJ, Escabi M, Chrobak JJ. 2009. Theta and gamma coherence along the septotemporal axis of the hippocampus. *J Neurophysiol* 101(3):1192-200.
- Sainsbury RS, Heynen A, Montoya CP. 1987. Behavioral correlates of hippocampal type 2 theta in the rat. *Physiol Behav* 39(4):513-9.
- Sainsbury RS. 1998. Hippocampal theta: a sensory-inhibition theory of function. *Neurosci Biobehav Rev* 22(2):237-41.
- Sandford JJ, Argyropoulos SV, Nutt DJ. 2000. The psychobiology of anxiolytic drugs. Part 1: Basic neurobiology. *Pharmacol Ther* 88(3):197-212.
- Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O and others. 2003. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 301(5634):805-9.
- Sapolsky RM, Meaney MJ. 1986. Maturation of the adrenocortical stress response: neuroendocrine control mechanisms and the stress hyporesponsive period. *Brain Res* 396(1):64-76.
- Sartor GC, Aston-Jones GS. 2012. A septal-hypothalamic pathway drives orexin neurons, which is necessary for conditioned cocaine preference. *J Neurosci* 32(13):4623-31.
- Schiller D, Eichenbaum H, Buffalo EA, Davachi L, Foster DJ, Leutgeb S, Ranganath C. 2015. Memory and Space: Towards an Understanding of the Cognitive Map. *The Journal of Neuroscience* 35(41):13904-13911.
- Scott RC, Richard GR, Holmes GL, Lenck-Santini PP. 2011. Maturation dynamics of hippocampal place cells in immature rats. *Hippocampus* 21(4):347-353.
- Schomburg EW, Fernandez-Ruiz A, Mizuseki K, Berenyi A, Anastassiou CA, Koch C, Buzsaki G. 2014. Theta phase segregation of input-specific gamma patterns in entorhinal-hippocampal networks. *Neuron* 84(2):470-85.
- Seager MA, Johnson LD, Chabot ES, Asaka Y, Berry SD. 2002. Oscillatory brain states and learning: Impact of hippocampal theta-contingent training. *Proc Natl Acad Sci U S A* 99(3):1616-20.
- Seidenbecher T, Laxmi TR, Stork O, Pape HC. 2003. Amygdalar and hippocampal theta

- rhythm synchronization during fear memory retrieval. *Science* 301(5634):846-50.
- Semba K, Komisaruk BR. 1978. Phase of the theta wave in relation to different limb movements in awake rats. *Electroencephalogr Clin Neurophysiol* 44(1):61-71.
- Shay CF, Boardman IS, James NM, Hasselmo ME. 2012. Voltage dependence of subthreshold resonance frequency in layer II of medial entorhinal cortex. *Hippocampus* 22(8):1733-49.
- Shay CF, Ferrante M, Chapman GW, Hasselmo ME. 2016. Rebound spiking in layer II medial entorhinal cortex stellate cells: Possible mechanism of grid cell function. *Neurobiol Learn Mem* 129:83-98.
- Sheehan TP, Chambers RA, Russell DS. 2004. Regulation of affect by the lateral septum: implications for neuropsychiatry. *Brain Res Brain Res Rev* 46(1):71-117.
- Shibata H, Suzuki T, Matsushita M. 1986. Afferent projections to the interpeduncular nucleus in the rat, as studied by retrograde and anterograde transport of wheat germ agglutinin conjugated to horseradish peroxidase. *J Comp Neurol* 248: 272-284.
- Shin J, Gireesh G, Kim SW, Kim DS, Lee S, Kim YS, Watanabe M, Shin HS. 2009. Phospholipase C beta 4 in the medial septum controls cholinergic theta oscillations and anxiety behaviors. *Journal of Neuroscience* 29(49):15375-85.
- Siegle JH, Wilson MA. 2014. Enhancement of encoding and retrieval functions through theta phase-specific manipulation of hippocampus. *Elife*. 3:e03061. doi: 10.7554/eLife.03061.
- Sinnamon HM. 1993. Preoptic and hypothalamic neurons and the initiation of locomotion in the anesthetized rat. *Prog Neurobiol* 41(3):323-44.
- Siok CJ, Taylor CP, Hajos M. 2009. Anxiolytic profile of pregabalin on elicited hippocampal theta oscillation. *Neuropharmacology* 56(2):379-85.
- Skaggs WE, McNaughton BL, Wilson MA, Barnes CA. 1996. Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus* 6:149-172.
- Stensola H, Stensola T, Solstad T, Froland K, Moser MB, Moser EI. 2012. The entorhinal grid map is discretized. *Nature* 492(7427):72-8.
- Strange BA, Witter MP, Lein ES, Moser EI. 2014. Functional organization of the hippocampal longitudinal axis. *Nat Rev Neurosci* 15(10):655-69.
- Takamura Y, Tamura R, Zhou TL, Kobayashi T, Tran AH, Eifuku S, Ono T. 2006. Spatial firing properties of lateral septal neurons. *Hippocampus* 16(8):635-44.
- Takeuchi T, Duzskiewicz AJ, Sonneborn A, Spooner PA, Yamasaki M, Watanabe M, Smith CC, Fernández G, Deisseroth K, Greene RW, Morris RG. 2016. Locus coeruleus and dopaminergic consolidation of everyday memory. *Nature* 537(7620):357-362.
- Tan HM, Bassett JP, O'Keefe J, Cacucci F, Wills TJ. 2015. The development of the head direction system before eye opening in the rat. *Curr. Biol.* 25(4):479-483.
- Tan HM, Wills TJ, Cacucci F. 2017. The development of spatial and memory circuits in the rat. *Wiley Interdiscip. Rev. Cogn. Sci* 8(3)doi:10.1002/wcs.1424
- Toth K, Borhegyi Z, Freund TF. 1993. Postsynaptic targets of GABAergic hippocampal neurons in the medial septum-diagonal band of Broca complex. *J Neurosci* 13(9):3712-24.
- Toth K, Freund TF, Miles R. 1997. Disinhibition of rat hippocampal pyramidal cells by

- GABAergic afferents from the septum. *J Physiol* 500 ( Pt 2):463-74.
- Tulving E. 1983. *Elements of episodic memory*. Oxford, UK: Oxford University Press.
- Vandecasteele M, Varga V, Berenyi A, Papp E, Bartho P, Venance L, Freund TF, Buzsaki G. 2014. Optogenetic activation of septal cholinergic neurons suppresses sharp wave ripples and enhances theta oscillations in the hippocampus. *Proc Natl Acad Sci U S A* 111(37):13535-40.
- Vanderwolf CH. 1969. Hippocampal electrical activity and voluntary movement in the rat. *Electroencephalogr Clin Neurophysiol* 26(4):407-18.
- Vertes RP. 1992. PHA-L analysis of projections from the supramammillary nucleus in the rat. *Journal of Comparative Neurology*, 326:595–622.
- Vertes RP, Hoover WB, Viana Di Prisco G. 2004. Theta rhythm of the hippocampus: subcortical control and functional significance. *Behav Cogn Neurosci Rev* 3(3):173-200.
- Vertes RP, Kinney GG, Kocsis B, Fortin WJ. 1994. Pharmacological suppression of the median raphe nucleus with serotonin1A agonists, 8-OH-DPAT and buspirone, produces hippocampal theta rhythm in the rat. 60(2):441-51.
- Vertes RP, Kocsis B. 1997. Brainstem-diencephalo-septohippocampal systems controlling the theta rhythm of the hippocampus. *Neuroscience* 81(4):893-926.
- Viana Di Prisco G1, Albo Z, Vertes RP, Kocsis B. 2002. Discharge properties of neurons of the median raphe nucleus during hippocampal theta rhythm in the rat. *Exp Brain Res* 145(3):383-94.
- Vinogradova OS. 1995. Expression, control, and probable functional significance of the neuronal theta-rhythm. *Prog Neurobiol* 45(6):523-83.
- Welday AC, Shlifer IG, Bloom ML, Zhang K, Blair HT. 2011. Cosine directional tuning of theta cell burst frequencies: evidence for spatial coding by oscillatory interference. *J Neurosci* 31(45):16157-76.
- Wells CE, Amos DP, Jeewajee A, Douchamps V, Rodgers J, O'Keefe J, Burgess N, Lever C. 2013. Novelty and anxiolytic drugs dissociate two components of hippocampal theta in behaving rats. *J Neurosci* 33(20):8650-67.
- Whishaw IQ, Vanderwolf CH. 1971. Hippocampal EEG and behavior: effects of variation in body temperature and relation of EEG to vibrissae movement, swimming and shivering. *Physiol Behav* 6(4):391-7.
- Whishaw IQ, Vanderwolf CH. 1973. Hippocampal EEG and behavior: changes in amplitude and frequency of RSA (theta rhythm) associated with spontaneous and learned movement patterns in rats and cats. *Behav. Biol.* 8(4):461-484.
- Wills TJ, Barry C, Cacucci F. 2012. The abrupt development of adult-like grid cell firing in the medial entorhinal cortex. *Front Neural Circuits* 6:21.
- Wills TJ, Cacucci F, Burgess N, O'Keefe J. 2010. Development of the hippocampal cognitive map in preweanling rats. *Science* 328: 1573–1576.
- Wills TJ, Lever C, Cacucci F, Burgess N, O'Keefe J. 2005. Attractor dynamics in the hippocampal representation of the local environment. *Science* 308(5723):873-6.
- Wills TJ, Muessig L, Cacucci F. 2014. The development of spatial behaviour and the hippocampal neural representation of space. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 369, 20130409. doi:10.1098/rstb.2013.0409.
- Winson J. 1978. Loss of hippocampal theta rhythm results in spatial memory deficit in the rat. *Science* 201(4351):160-3.
- Wood ER, Dudchenko PA, Robitsek RJ, Eichenbaum H. 2000. Hippocampal neurons encode information about different types of memory episodes occurring in the

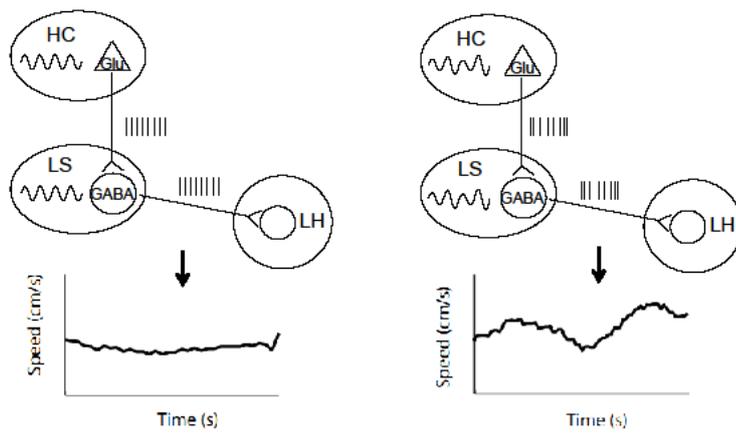
- same location. *Neuron* 27(3):623-33.
- Woodnorth MA, McNaughton N. 2002. Similar effects of medial supramammillary or systemic injections of chlordiazepoxide on both theta frequency and fixed-interval responding. *Cogn Aff Behav Neurosci* 2: 76-83.
- Wulff P, Ponomarenko AA, Bartos M, Korotkova TM, Fuchs EC, Bahner F, Both M, Tort AB, Kopell NJ, Wisden W and others. 2009. Hippocampal theta rhythm and its coupling with gamma oscillations require fast inhibition onto parvalbumin-positive interneurons. *Proc Natl Acad Sci U S A* 106(9):3561-6.
- Yamamoto J, Suh J, Takeuchi D, Tonegawa S. 2014. Successful execution of working memory linked to synchronized high-frequency gamma oscillations. *Cell* 157(4):845-57.
- Yartsev MM, Witter MP, Ulanovsky N. 2011. Grid cells without theta oscillations in the entorhinal cortex of bats. *Nature* 479(7371):103-7.
- Yeung M, Treit D, Dickson CT. 2012. A critical test of the hippocampal theta model of anxiolytic drug action. *Neuropharmacology* 62(1):155-60.
- Young B, McNaughton N. 2000. Common firing patterns of hippocampal cells in a differential reinforcement of low rates of response schedule. *J Neurosci* 20(18):7043-51.
- Zilli EA, Hasselmo ME. 2010. Coupled noisy spiking neurons as velocity-controlled oscillators in a model of grid cell spatial firing. *J.Neurosci.* 30: 13850–13860.

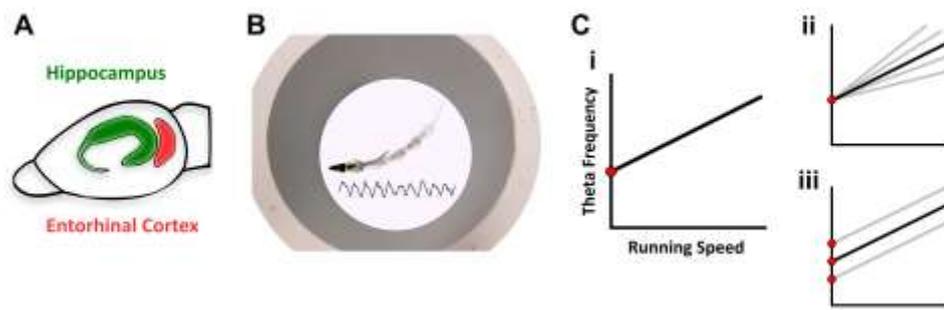
## Figure legends

**Figure 1** A schematic illustration of locomotion speed-regulating downstream theta-rhythmic signaling, which regulates locomotion speed (Bender et al., 2015). HC-hippocampus, LS-lateral septum, LH-lateral hypothalamus. The figure is a courtesy of Franziska Bender.

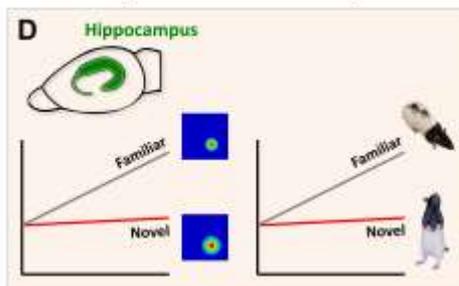
## **Figure 2 Functional dissociation of two components of hippocampal formation theta frequency (schematic illustrations)**

Extracellular electrophysiological recordings in the hippocampal formation (**A**) show theta-band oscillations as the rat forages (**B**). One second trace of the local field potential showing ~10 cycles of theta (filtered 0.25 to 200Hz) is shown below rat (**B**). Whole-trial LFP data can be used to construct plot of instantaneous theta frequency vs running speed, showing correlation that is positive and broadly linear (**Ci**). Right-hand plots show potential modulation of slope (**Cii**) and y-intercept (**Cii**) values. Note Y-Intercept value (i.e. theta frequency at zero running speed), depicted as small red circle in each plot, is calculated from extrapolating frequency-speed regression line, not stationary behaviour. **D-G** show schematic illustrations of modulation of slope component (**D-E**), and y-intercept component (**F-G**). Environmental novelty (new spatial context) elicits reduction of slope in hippocampal and entorhinal theta. Slope reduction in hippocampus is accompanied by larger spatial scale of CA1 place fields (**D, left**) and increase in rearing on hindlegs, a hippocampal dependent novelty-responsive behaviour (**D, right**) (Wells et al, 2013). Environmental novelty elicits larger spatial scale of grid cells (**E, left**: Barry et al, 2012b), which (Burgess, 2008) model predicts is due to slope reduction (prediction, not data). Darkness elicits slope reduction in mice, accompanied by strong disruption to grid cell spatial signal (**E, right**: Chen et al, 2016). Different classes of systemically-administered anxiolytic drugs have the common effect of reducing y-intercept in theta from the hippocampus (**F**) and entorhinal cortex (**G**). Hippocampal theta: Chlordiazepoxide, Buspirone and O-2545 from (Wells et al, 2013); Pregabalin from (Lever et al, 2016); Entorhinal theta: Diazepam and 8-OH-DPAT (schematic illustration based on unpublished work in (Monaghan et al, 2014; Monaghan et al, 2015)).





## Space &amp; Novelty



## Anxiolytic Drugs

