The Function of Oscillations in the Hippocampal Formation

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Abstract

Some of the strongest experimental and computational links between oscillations and cognition concern the oscillations in the hippocampal formation supporting spatial and mnemonic processing. We review experimental and theoretical work concerning well-established hippocampal oscillations such as theta, gamma, and high-frequency ripples and how they relate to spatial, mnemonic, and anxiety-related representation and behaviour. We specifically consider the following computational roles for oscillations: organising processing into discrete chunks, as seen in encoding versus retrieval scheduling; ordinal and metric coding by oscillatory phase; temporal integration by oscillatory phase; and interregional communication. The literature on oscillations has typically been concerned with changes in band-specific power. Here, focusing on the theta oscillation, we summarise how key variables are linked not only to power but also to frequency and to coherence. We conclude that the hippocampal formation provides an invaluable model system for understanding the functional roles of neuronal oscillations and the interaction between oscillations.

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12.1 Different Types of Hippocampal Oscillations

12.1.1 Characteristic Oscillations in the Rodent Hippocampus

It is perhaps worth stating at the outset that the characteristic oscillatory bands historically defined by human scalp EEG are of only limited relevance to those identified by invasive electrophysiological studies of the rodent hippocampus. At the lower-frequency end, researchers of the rodent hippocampus do not consider there to be a distinct 'alpha' (8–12 Hz) oscillation. Rather, it seems that the theta oscillation extends into 'alpha' territory, and theta is typically assigned a range of around 4–12 Hz. Indeed, the upper limit of rodent hippocampal theta seems higher than that typically found in intracranial and magnetoencephalographic (MEG) studies of the human hippocampal formation, an issue we briefly discuss in Sect. 12.1.3. At the higher-frequency end, there is a lot of important hippocampal activity beyond 100 Hz: most notably, the high band (90–150 Hz) of gamma oscillations (30–150 Hz; Bragin et al. 1995; Csicsvari et al. 2003; Scheffer-Teixeira et al. 2011; Belluscio et al. 2012) and ripple oscillations (140–200 Hz, O'Keefe and Nadel 1978, pp. 150–153; Bragin et al. 1999;). For excellent general reviews of hippocampal oscillations, see Buzsaki (2006) and O'Keefe (2007).

The most prominent distinction in the hippocampal EEG of awake behaving rodents is that between 'large irregular activity' (LIA), typically present during stationary behaviours such as eating and grooming, and theta, which is very prominent during behaviours which involve spatial translation of the head (Vanderwolf 1969; O'Keefe and Nadel 1978) or arousal and anxiety (e.g. Green and Arduini 1954; Sainsbury 1998; Seidenbecher et al. 2003). In the next section, we discuss the idea of two types or components of theta. The typical observation is that LIA and theta are exclusive and dominant hippocampal EEG states. That is to say, either LIA occurs or theta occurs, and higher-frequency oscillations accompany LIA or theta. 'Small irregular activity' has also been described (Vanderwolf 1969; Jarosiewicz et al. 2002; Jarosiewicz and Skaggs 2004a, b), which may be an intermediate state between LIA and theta, occurring during sleep and during transitions to alertness. During sleep, the characteristic EEG states are LIA, SIA, theta during REM sleep, and a more recently described slow oscillation which may be linked to neocortical input (Wolansky et al. 2006).

Oscillations intermediate between theta and gamma have generally received comparatively little attention. As noted above, a hippocampal 'alpha' is not really recognised. An oscillation termed 'flutter' has been reported, occurring at around 10–12 Hz, which does not show phase reversal across the CA1 pyramidal layer, and is most prominent when an environment is familiar rather than novel (Nerad and Bilkey 2005). Berke et al. (2008) reported transient beta oscillations in CA3 and CA1 fields in the 23–30 Hz ('beta2') range which were highly modulated by environmental novelty. These beta oscillations were most prominent on the second and third laps of continuous linear tracks and were greatly attenuated when an environment was familiar. Grossberg (2009) has interpreted this oscillation within the framework of adaptive resonance theory and has suggested that it reflects a

learning-eliciting signal of the mismatch between bottom-up sensory-based and top-down expectation-based mechanisms. Vanderwolf (2001) noted a set of specifically olfactory stimuli which elicits ~20 Hz beta waves in the dentate hilus, but not the Cornu Ammonis fields (CA1 and CA3), of the hippocampal formation. Various stimuli in other sensory modalities do not elicit these beta waves. Importantly, these odours do not provoke sniffing but rather behavioural withdrawal. Vanderwolf (2001) interpreted these stimuli as signalling the possible presence of predators. (The idea that the hippocampus is sensitive to both environmental novelty and anxiety-eliciting stimuli is one that we return to in Sect. 12.3.4.) The similarity of the novelty beta waves in CA fields and the 'predator' beta waves in the dentate, apart from their frequency, is not clear.

Flutter and the novelty-related beta oscillations co-occur with theta (Nerad and Bilkey 2005; Berke et al. 2008); their potential co-occurrence with other EEG states is currently unclear. Hippocampal gamma oscillations (Bragin et al. 1995; Csicsvari et al. 2003) have been much more studied and can be found throughout the hippocampal formation. Like flutter and beta oscillations, gamma oscillations can be coincident with theta oscillations, but it is clear that gamma can also occur in sharp wave/ripple states (e.g. Sullivan et al. 2011). The modulation of gamma by theta is an important theme according to the usual rule whereby the lower-frequency oscillation (theta) appears to modulate the higher-frequency oscillation (gamma). Theta-gamma interactions are a recurring theme in the study of theta and gamma. In Sect. 12.1.4, we consider gamma oscillations in more detail, focusing on subtypes of gamma and theta-gamma coupling in CA1. In Sect. 12.2.2, we consider a theoretical model of working memory relying on gamma oscillations nested within theta (Lisman and Idiart 1995). Senior et al. (2008) identified two broad classes of CA1 pyramidal cells according to their relationship to theta, one class firing on theta phases associated with highest gamma power and another firing at all stages of theta phase precession. These authors suggested that only the latter class could support the mechanism required by Lisman and Idiart (1995). In Sect. 12.3 (passim), we review evidence suggesting functional roles for theta-gamma interactions.

The oscillatory band above (high) gamma is the highest-frequency oscillation seen in the normal hippocampus and is known as the ~200 Hz 'ripple' oscillation (O'Keefe and Nadel 1978), spanning a frequency band of around 140–220 Hz as characterised by Buzsaki and colleagues (Sullivan et al. 2011). The ripple oscillation has attracted a great deal of interest over the last 20 years. In Marr's (1971) influential model of hippocampal function, information is transferred from the hippocampus to the neocortex during sleep. It is now well established that during slow-wave sleep and LIA, high-amplitude sharp waves and ripples coincident with the sharp waves frequently occur; if the electrodes are in the pyramidal layer, it is very striking that many pyramidal cells fire simultaneously with the ripples. Ripples have maximal amplitude in the pyramidal layer. The idea that the sharp-wave burst/ripple activity might represent the Marr-esque information transfer phase in which hippocampal information is passed onto neocortex was first proposed in the 1980s by McNaughton (1983) and in particular by Buzsaki (1989). The suggestion was

that theta represents the online learning state and the sharp-wave burst/ripple activity the offline consolidation state. These suggestions proved to be prescient (Wilson and McNaughton 1994; Skaggs and McNaughton 1996) and have led to a considerable body of interesting work advancing our understanding of memory consolidation processes in intrahippocampal and hippocampo-neocortical networks during sleep and rest. We refer the reader to the excellent reviews on sharp-wave burst/ripple activity and memory consolidation, including in this volume (Sutherland and McNaughton 2000; O'Neill et al. 2010; Jadhav and Frank 2014). LIA may have other memory-related roles than consolidation. It is increasingly thought that sharp-wave burst/ripple activity may reflect prospective aspects of spatial processing (Pfeiffer and Foster 2013). Finally, perhaps some periods of LIA represent offline 'housekeeping' processes: O'Keefe (2007) has suggested that synaptic renormalisation and overall gain control processes may occur during LIA.

In summary, the available evidence from rodents supports the following picture of the hippocampal EEG. There are two dominant EEG states, the LIA state and the theta state. (SIA is an intermediate state between the two.) The two states LIA and theta are likely mutually exclusive. Sharp wave and ripple oscillations typically co-occur with LIA, while flutter and beta co-occur with theta, and gamma co-occurs with either the LIA or theta states. Theta may represent an online state supporting encoding and retrieval, while the sharp wave/ripple activity may represent an offline state supporting consolidation, 'what if' cognition, and synaptic reorganisation processes.

12.1.2 Two Components of Hippocampal Theta

Studies focusing on theta amplitude/power have long noted that hippocampal theta has an atropine-sensitive component and atropine-resistant component (Kramis et al. 1975). The general observation is that systemic injection of nonspecific muscarinic antagonists such as atropine and scopolamine eliminates the theta that is observed during alert immobility (aroused/anxious states) and certain anaesthetised states but fairly minimally affects the theta observed during locomotion (Kramis et al. 1975; Buzsaki 2002). Lesions to the septum eliminate both kinds of hippocampal theta. Thus the conception has emerged of two 'types' of theta, one atropine sensitive (type II), linked to arousal and anxiety, and one atropine resistant (type I), linked to spatial translation and movement. Since theta is essentially always present during locomotion, and several studies have shown that theta power and frequency positively correlate with running speed during naturalistic behaviour (reviewed, Lever et al. 2009; and see Hinman et al. 2011; Wells et al. 2013), there is little doubt that type I theta is linked to movement. There is less consensus as to the best characterisation of type II theta. For instance, Sainsbury (1998) views type II theta in sensory terms, while Bland and colleagues (Bland and Oddie 2001; Bland et al. 2007) view this 'sensory' type II theta as limited to the sensory signalling which cues preparation for locomotion. Buzsaki (2002) reviews evidence suggesting that the atropine-resistant theta is conveyed by

the entorhinal afferents onto dentate, CA3, and CA1 cells and partly involves NMDA-receptor activation; notably, for instance, entorhinal lesions render hippocampal theta atropine sensitive, while combined blockade of muscarinic and NMDA receptors abolishes hippocampal theta.

While conceptions of the two contributions to theta are typically not formalised, some researchers appear to implicitly conceive these types of theta as *alternative categories*; either the atropine-sensitive type II theta occurs during immobility-related behaviour (when one might otherwise expect to see LIA), or the atropine-insensitive type I theta occurs during locomotion-related behaviour. Concomitant with this is the identification of particular frequency bands with the two types of theta, lower for type II theta and higher for type I theta. Thus a representative view is 'Atropine-sensitive type 2 theta activity (4–8 Hz) has been shown to occur in the hippocampal formation during periods of immobility, whereas atropine-resistant type 1 theta (8–14 Hz) is observed during exploration' (Seidenbecher et al. 2003). We should note, however, that there are indications that type II theta can have a higher limit. For instance, Sainsbury (1998) reports that a guinea pig in the presence of a snake can show type II theta in the 10–12 Hz range. An additional confusion comes from the developmental aspect of movement-related theta frequency increasing from 4–5 Hz when exploration begins in rat pups at age 16 days to 8–9 Hz seen in the adult (Wills et al. 2010). This may help to explain the relative low frequencies seen in models of theta in slice preparations: slices are typically taken from young animals (up to around 20 days old).

In contrast to characterisation of two mutually exclusive types of theta, in the models of Bland (Bland and Oddie 2001; Bland et al. 2007) and Burgess (2008), both type I and type II mechanisms simultaneously contribute to theta during locomotion-related behaviour. In the Burgess (2008) model, these contributions are complementary. It has long been noted that theta frequency increases, broadly linearly, with running speed (see references above). The (Burgess 2008) model links the type I and type II theta mechanisms to dissociable components of the relationship of theta frequency ($f_\theta(t)$) to running speed ($s(t)$):

$$f_\theta(t) = f_0 + < \beta > s(t),$$

where the rate of increase with running speed ($<\beta>$, 'slope') reflects the presence of 'velocity-controlled oscillators' in the septo-hippocampal system (Burgess 2008; Welday et al. 2011): neurons whose firing shows theta-band modulation whose frequency increases with running speed, as also seen in place (Geisler et al. 2007) and grid cells (Jeewajee et al. 2008a). This slope component is identified with type I mechanisms in being movement related and entorhinal cortex dependent; the second component (f_0, 'intercept') is identified with type II theta mechanisms, in being independent of both movement and entorhinal cortex (Burgess 2008, pp. 1168–9). Thus, the model predicts a dissociation between the factors affecting the intercept and slope of the relationship of theta frequency to running speed, with the intercept component linked to arousal/anxiety and the slope, more obviously, to spatial representation mechanisms updated by translational movement.

In Sects. 12.3.3 and 12.3.4, we discuss new evidence in support of this model showing that the intercept is related to anxiety/anxiolytic drugs and the slope to spatial representation and spatial novelty.

12.1.3 Hippocampal Theta Across Species

In the freely moving rat, theta is the dominant oscillation in the hippocampus (Vanderwolf 1969), and amplitudes of one millivolt are not unusual. By contrast, finding hippocampal theta oscillations in humans has proven elusive until recently. Other than a relatively small number of intracranial EEG recordings in humans (iEEG, Halgren et al. 1978; Arnolds et al. 1980) with unclear behavioural correlates, there was very little evidence relating the hippocampal theta rhythm measured in the rodent to electrophysiological activity elicited by human mnemonic function. Furthermore, human and monkey hippocampal theta oscillations (4–8 Hz) appear to be much more transient in duration than the rodent hippocampal theta rhythm measured during exploration (Jacobs and Kahana 2010). This is only further confounded by differences in frequency, where often the LFP is not dominated by the centre of the theta band like with rodents, but by either lower 1–4 Hz delta frequencies or higher frequencies in the 8–12 Hz alpha band (Lega et al. 2012; Jacobs and Kahana 2010; Buzsaki et al. 2013).

One problem for across-species comparisons is that the historical scalp-EEG-derived frequency boundaries used in human research are somewhat arbitrary, and the frequency of characteristic oscillations (e.g. eyes-closed alpha) may vary considerably even in aged-matched subjects, such that a priori fixed-band analyses may mask real effects (Klimesch 1999). A key challenge for reconciling animal-human data is that theta-behaviour links have mostly been characterised in freely moving rodents, while no recordings exist of theta during human locomotion, where virtual reality video games are more commonly used. One feasible possibility for species-matching is to record theta from ambulating mammals including humans in virtual reality setups where the subject's ambulation updates the visual scene (Harvey et al. 2009; Chen et al. 2013). Further evidence of the utility of VR systems for measuring theta comes from targeted electrode recordings in rodents showing the presence of movement-related hippocampal theta during ambulation in a virtual reality system and even when experiencing virtual visual motion without physically moving (Chen et al. 2013).

Still, it is uncertain whether human hippocampal delta oscillations during virtual exploration (Ekstrom et al. 2005; Watrous et al. 2011) are more analogous to theta in rodents or whether the 8 Hz amplitude increases seen during some components of goal-directed virtual navigation (Ekstrom et al. 2005; Kaplan et al. 2012) and purely mnemonic tasks (Fell et al. 2011; Lega et al. 2012) are more comparable to rodent theta (Watrous et al. in press). Notably some ~8 Hz oscillatory activity extends well into the 8–12 Hz alpha band (Fell et al. 2011; Lega et al. 2012), which is interesting given hypotheses that posit that alpha inhibition in the neocortex makes neural representations more sparse during memory formation

(Axmacher et al. 2006). Further, the proposed cognitive mechanism of transient hippocampal theta triggering top-down alpha inhibition in the neocortex (Axmacher et al. 2006) may relate to early ideas on the hippocampal theta rhythm and behavioural inhibition (Douglas 1969).

12.1.4 Gamma Oscillations and Theta-Gamma Coupling

Much has been learned about gamma oscillations and theta-gamma interactions by recording from silicon probes in the behaving rat (Bragin et al. 1995; Csicsvari et al. 2003). The well-established finding that hippocampal gamma power is appreciably higher during theta states than non-theta states (e.g. Bragin et al. 1995; Csicsvari et al. 2003) has long suggested the possibility that theta modulates gamma. Notably, for instance, the amplitude of gamma varies as a function of the theta cycle, and the frequency of theta and gamma is positively correlated (Bragin et al. 1995; Belluscio et al. 2012). Recently, hippocampal gamma has increasingly been subdivided into different frequency bands, with a view to better understanding the physiological basis of theta-gamma coupling and the neuroanatomy of gamma in the hippocampal formation. As we shall see, subdividing gamma also helps to clarify theta's role in encoding versus retrieval scheduling, discussed in Sect. 3.2.

A clear consensus has not yet fully emerged, but three gamma bands have been identified in hippocampal region CA1, here called low, middle, and high gamma (Scheffer-Teixeira et al. 2011; Belluscio et al. 2012). Belluscio et al. (2012) assign ranges of 30–50, 50–90, and 90–150 Hz to these three bands. Scheffer-Teixeira et al. (2011) identified two separate gamma bands in the high range, centred at around 80 Hz and 140 Hz, respectively. An influential study of theta-gamma coupling by Colgin et al. (2009) identified the slow band (~25–50 Hz) but did not subdivide the broad fast band (~65–140 Hz). Whether this could be related to the location of the recording electrodes with respect to CA1 layers is currently unclear. The absolute values of the characteristic peaks of these bands will likely vary with individual differences, similarly to alpha (Klimesch 1999), and with behaviour. For example, gamma frequency increases with running speed (Ahmed and Mehta 2012). (This may reflect theta-gamma frequency coupling; as mentioned above, theta frequency reliably increases with running speed.)

Scheffer-Teixeira et al. (2011) examined phase-amplitude coupling between theta phase and the amplitude of different gamma bands in CA1. Phase-amplitude coupling refers to the amplitude modulation of a higher-frequency oscillation by a lower-frequency oscillation. These authors found that activity in the two gamma ranges (one peaking at ~80 Hz, 'middle gamma'; one at ~140 Hz, 'high gamma') was controlled by theta phase. Using electrodes located at different depths in CA1, Scheffer-Teixeira and colleagues showed that the strength of the theta-middle-gamma coupling appeared to peak in the lacunosum-moleculare layer, which is the layer where entorhinal axonal terminals synapse onto CA1 dendrites. In other words,

theta-middle-gamma coupling probably reflects a state of enhanced communication between entorhinal-CA1 projection neurons and their CA1 targets.

Belluscio et al. (2012) used current source density analysis to identify the anatomical location of the different gamma bands. Consistent with Scheffer-Teixeira et al. (2011), Belluscio and colleagues locate middle gamma to the stratum lacunosum-moleculare, indicating that entorhinal afferents drive the middle gamma. Consistent with Colgin et al. (2009), Belluscio and colleagues show that slow gamma had the largest sink in the mid-stratum radiatum, indicating that CA3 afferents drive the slow gamma. Scheffer-Teixeira et al.'s theta-phase-gamma-amplitude coupling study was unable to detect significant theta phase modulation of low gamma activity, but the other studies found that this gamma was linked to the descending phase of pyramidal-layer theta (slow-gamma-to-theta coupling, Colgin et al. 2009; peak slow-gamma power, Belluscio et al. 2012).

In summary then, CA3–CA1 communication is preferentially mediated by slow gamma on the descending phase of CA1 pyramidal-layer theta, while entorhinal-CA1 communication, according to the Scheffer-Teixeira and Belluscio studies, is mediated by middle gamma at the peak of pyramidal-layer theta. The different theta phase preference of the coupling between entorhinal cortex and CA1, on the one hand, and CA3 and CA1, on the other, is a theme we return to (Sect. 12.3.2) in the discussion of encoding versus retrieval scheduling. If encoding is primarily entorhinal driven and preferentially occurs at one phase of theta, and retrieval is primarily CA3 driven and preferentially occurs at another phase of theta, then theta phase may be one of the mechanisms scheduling encoding and retrieval (Hasselmo et al. 2002; Manns et al. 2007; Lever et al. 2010; Douchamps et al. 2013). In Sect. 12.3.2, we discuss experimental work on place cells in support of this proposal.

12.1.5 Human Hippocampal Gamma and High-Frequency Activity

Similar to across-species differences in theta, discrepancies related to shorter duration and lower frequencies have been observed when investigating the human/non-human primate homologues of fast gamma (>100 Hz) and sharp wave/ripple activity. 80–150 Hz ripple activity typically lasting around 50 ms has been observed in both humans (Axmacher et al. 2008) and non-human primates (Skaggs et al. 2007; Logothetis et al. 2012), which is lower than the traditional 140–220 Hz activity in rodent recordings. Despite these differences, Axmacher et al. (2008) found that increased ripple events during a short nap after a memory encoding task predicted successful post-nap memory recall, which matched later findings in rodents also showing behavioural relevance for ripples (e.g. Girardeau et al. 2009; Ramadan et al. 2009; Jadhav et al. 2012). Furthermore, robust >200 Hz hippocampal activity has also been observed; however, it appears to directly relate to epilepsy pathology (Bragin et al. 1999; for review see Engel et al. 2009). Other non-pathological >100 Hz fast gamma activity in the parahippocampal gyrus was found during slow-wave sleep, but hippocampal gamma was mostly below 100 Hz

(Le Van Quyen et al. 2010). In Sect. 12.3, we discuss findings involving human and non-human primate hippocampal gamma (<100 Hz) and memory performance in further detail.

12.2 Computational Functions of Oscillations

In this section we attempt to define some of the potential functional roles of oscillatory brain activity, so as to provide a framework for discussion of the experimental data relating hippocampal oscillations to cognition and behaviour. Memory will be one focus for this discussion, given the undisputed role of the hippocampus in memory, following Scoville and Milner's seminal (1957) paper. The theta rhythm will be another focus, given the predominance of the theta rhythm in the hippocampal electrophysiology of behaving rodents (Vanderwolf 1969). A third phenomenon, relevant to several of the examples discussed, is the theta phase precession of place cell firing (O'Keefe and Recce 1993). This provides one of the most robust examples of a behavioural correlate of the temporal organisation of neuronal firing. We briefly describe this finding here, to be available for reference in many of the discussions below.

Place cells in the hippocampus fire whenever the animal moves through a specific portion of its environment (the cell's firing field; O'Keefe and Dostrovsky 1971). In parallel with this firing rate code for location, there is a temporal organisation to firing relative to the ongoing theta rhythm in the local field potential (LFP), such that the theta phase of firing systematically advances from later to earlier phases as the animal moves through the firing field (O'Keefe and Recce 1993) see Fig. 12.1. Since the finding of theta phase precession in hippocampal place cells, a similar phenomenon has been shown to exist in the grid cells found in layer II of medial entorhinal cortex (Hafting et al. 2008). These cells fire whenever the animal enters any one of an array of firing fields that are arranged across the environment at the vertices of a regular triangular grid (Hafting et al. 2005). The systematic advance of theta phase of firing from later phases to earlier phases is seen as the animal traverses any of the firing fields.

Below we discuss some of the potential functional roles of oscillatory brain activity, including organising processing into discrete chunks, representing the order of events by firing phase, representing metrical information such as distance by firing phase, using phase differences to perform temporal integration of variables encoded as frequency differences, and using phase coupling to route interregional communication.

12.2.1 Organisation of Processing into Discrete Chunks

An oscillation can be seen as dividing processing into cycles or parts of cycles. This can serve as an organisational principle in the same way as the processing cycles of the CPU of a computer: processing occurs within each theta cycle, so that the

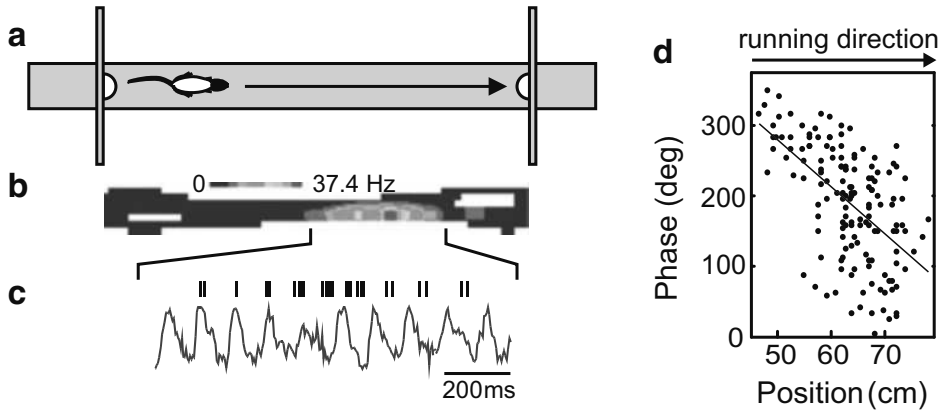

Fig. 12.1 Theta phase precession of place cell firing. (**a**) As a rat runs along a linear track, a place cell in the hippocampus fires as the animal moves through the firing field (**b**). The firing rate code for location is also a temporal code (**c**) spikes (*ticks*) are fired at successively earlier phases of the theta rhythm of the local field potential (*blue trace*), referred to as 'theta phase precession'. The theta phase of firing correlates with the distance travelled through the place field (**d**), even when pooled over runs that might be fast or slow. Adapted from (Huxter et al. 2003)

outputs of the process are discretised, one per cycle. These discrete outputs have some advantages over a seamlessly evolving process. For example, it becomes well defined to compare one output to the next so as to detect change. This type of organisational role is most often associated with lower frequencies, including hippocampal theta, with higher frequencies such as gamma often being considered part of the processing that is being organised. Indeed, this type of organisation may reflect a more general hierarchical organisation in which lower-frequency oscillations modulate higher-frequency oscillations (Lakatos et al. 2005) and in which lower frequencies provide organisation over larger spatial scales (von Stein and Sarnthein 2000; Buzsaki and Draguhn 2004).

The view of theta as parcellating computation into discrete chunks (see, e.g. O'Keefe and Nadel 1978) is nicely consistent with several experimental observations, briefly summarised below. Theta modulation of the overall activity of principal cells in the hippocampus produces preferred firing phases and non-preferred firing phases (Mitchell and Ranck 1980; Fox et al. 1986). Theta modulation of synaptic plasticity produces phases permissive of LTP or not (Pavlides et al. 1988) or distinguishing LTP from LTD (Huerta and Lisman 1995, 1996; Hyman et al. 2003). Theta modulation of higher-frequency oscillations such as gamma provides discrete periods of gamma power (Bragin et al. 1995; Canolty et al. 2006) or discrete periods of differential responsiveness to different sources and frequencies of gamma-modulated input (Chrobak and Buzsaki 1998; Colgin et al. 2009).

Several potential functional consequences of organising processing into discrete phases of an underlying oscillation have been suggested. In one early example, Gardner-Medwin (1976), following Marr (1971) in modelling CA3 as an auto-associative network, suggested that pattern completion was an incremental process that occurred across each theta cycle. Pattern completion is the process by which a

subset of cues from an event trigger reactivation of the full neural representation of that event. Starting with a high firing threshold (high inhibition), only the most strongly driven neurons would fire which would be those mostly likely to be consistent with the input pattern initiating retrieval. A gradual reduction in firing threshold allowed more neurons to be activated, via recurrent activity from those initially activated, eventually completing the stored pattern with very few erroneously active neurons. The next theta cycle then starts with high phasic inhibition, curtailing the activity of the previous cycle and allowing pattern completion of a new pattern, i.e. whichever stored pattern is most consistent with the pattern of input to CA3 on that cycle.

In a related, second example, Hasselmo et al. (2002) proposed a subdivision of the theta cycle in CA1 into phases associated with encoding into memory (permissive of LTP and driven by sensory input from entorhinal cortex) and phases associated with retrieval (resistant to LTP and driven by pattern-completed input from CA3). This proposal, and supporting evidence for it, is discussed in more detail below; see Sect. 12.3.2.

A third example concerns the gamma rhythm. If gamma oscillations are a natural consequence of local feedback inhibition (Whittington et al. 1995), then it is possible that populations of neurons representing distinct objects might compete in a winner-take-all fashion to dominate activity within a gamma cycle. As in the above example of pattern completion, phasic inhibition curtails that activity in the previous cycle, allowing a new competition for activity in the next cycle. In this manner, the neurons firing in the same gamma cycle might be thought to represent different aspects of the same object, i.e. object binding via firing synchrony (Singer and Gray 1995; Fries 2005). We discuss this type of mechanism further in the context of interregional phase coupling and the 'communication through coherence' hypothesis (Fries 2005); see Sect. 12.3.5.

12.2.2 Ordinal Coding by Oscillatory Phase

Extending the idea of winner-take-all competition between items within each gamma cycle (see above), Lisman and Idiart (1995) proposed a hierarchical theta-gamma organisation of sequence memory. In this model, sequences of items could be represented such that each item corresponded to activity in one gamma cycle, and the entire sequence was represented in the gamma cycles within one theta cycle. A process of after-depolarisation (ADP, following the usual after-hyperpolarisation, AHP) with a timescale of one theta period meant that the neurons representing each item reactivated at the same point in the next theta cycle, allowing the sequence to be maintained indefinitely. This cyclic process of competition, activation, and suppression parallels the process of 'competitive queuing' used in psychological models of memory for sequential order (Grossberg 1972; Houghton 1990; Burgess and Hitch 1992) and in patterns of neural firing in primates performing sequential tasks (Averbeck et al. 2002; Bullock 2004). The model provides predictions for how many items can be remembered in order

(the number of gamma cycles per theta cycle) and for patterns of theta and gamma oscillations in working memory tasks (which we return to in Sect. 12.3).

The example of theta phase precession of place cell firing is also relevant here. A population of place cells with spatially overlapping firing fields distributed along a linear track will fire in a sequential but temporally overlapping way as the animal runs along the track. However, as a consequence of the theta phase precession of individual cells, there will be temporal structure to the pattern of firing within each theta cycle: those place cells firing at later phases will have firing fields centred ahead of the animal, while those firing at earlier phases will have firing fields centred behind the animal. Thus, the spatial order of firing fields on the track will be present in the temporal order of firing within each theta cycle. While this effect is most clear on a linear track (O'Keefe and Recce 1993), the same pattern can also be seen in animals foraging in open environments (Burgess et al. 1994; Skaggs et al. 1996). This effect can also be thought of as the location represented by the population of place cells 'sweeping forwards' from behind the animal to in front of it during each theta cycle (Skaggs et al. 1996; Gupta et al. 2012).

If we consider the sequential activation of place cells as the animal runs along a linear track, the ordered firing of place cells within each theta cycle, combined with spike-time-dependent long-term potentiation, allows the formation of associations from a place cell firing earlier on the track to one firing later on the track. In principle this could explain theta phase precession in terms of a place cell's early phase firing being driven by environmental input to the place cell and firing nearer to the start of the track being driven by learned associations from place cells firing nearer to the start of the track, and occurring at later phases due to synaptic conduction delays (Tsodyks et al. 1996). The Lisman and Idiart (1995) model can be adapted to model this situation, predicting that a discrete number of place locations are represented in each gamma cycle within a theta cycle (Jensen and Lisman 1996), and the Tsodyks et al. (1996) model can be adapted to include theta phase precession in open environments by including similar neuronal AHP/ADP dynamics to the Lisman model (Navratilova et al. 2012).

12.2.3 Metrical Coding by Oscillatory Phase

A large-scale oscillation, such as that reflected in the local field potential, provides a clock against which the phases of the activity of different neurons can be used to represent continuous or metrical quantities. For example, Hopfield (1995) outlined a situation in which incoming sensory information encoded in firing rates could be represented as phase advances relative to a global subthreshold membrane potential oscillation (MPO): the greater the depolarising input to each neuron, the earlier it would take the MPO over the firing threshold, i.e. the earlier the phase of firing relative to the global oscillation. This scheme can implement scale-invariant pattern recognition in a natural way, if there is a logarithmic translation of depolarisation into phase advance.

The theta phase precession of place cell firing can also be seen as a metrical phase code. A key observation of O'Keefe and Recce (1993) was that the phase of firing codes the distance travelled through the firing field (and more so than the time spent in the firing field, even though the data include spikes fired during fast and slow runs through the firing field). Thus the theta phase of firing provides metrical information concerning distance travelled: providing a fine-scale code for position within-field to go with the firing rate code and providing additional spatial information to that in the firing rate alone (Jensen and Lisman 2000). In fact, the firing phase appears to code for distance travelled independently of the firing rate, which could vary to independently encode nonspatial variables (Huxter et al. 2003).

12.2.4 Temporal Integration by Oscillatory Phase

Temporal integration is a key component of all mnemonic processing that requires knowledge of what has happened in the recent past. A simple mechanism for this is provided by the phase of one oscillator (an 'active' oscillation) compared to another oscillator (a 'baseline' oscillation). If the active oscillation varies its frequency relative to the baseline oscillation, then its phase relative to the baseline oscillation will be the time integral of the frequency difference. Thus, by encoding information as a variation in frequency, the phase of the active oscillation automatically performs temporal integration of that information.

The phase precession effect can be seen in terms of temporal integration by phase coding. O'Keefe and Recce (1993) showed that place cell firing is temporally modulated at a frequency slightly higher than the LFP theta frequency. If the increase in frequency is proportional to running speed, then the theta phase of firing will represent distance travelled (i.e. the temporal integration of running speed; Lengyel et al. 2003). Populations of place cells can be considered as 'speed-controlled oscillators' in this way (Geisler et al. 2007). Because the firing rate of place cells is spatially modulated, the LFP will be consistent with the oscillation in overall population firing rate, even though each individual place cell has a higher frequency of oscillation (Burgess et al. 1993; Geisler et al. 2010).

The temporally repeating nature of phase codes, the spatially repeating nature of grid cell firing patterns, and the assumption that grid cells perform 'path integration' (i.e. represent translation by integrating movement) suggest that a similar phase-coding mechanism might underlie grid cell firing. To perform accurate path integration, and to produce coherent 2-dimensional firing patterns, requires that the animal's distance travelled is tracked along more than a single direction. To do this, several 'velocity-controlled oscillators' (VCOs) could vary their frequency relative to baseline proportional to the component of velocity along different 'preferred' directions. Then their phases relative to baseline will encode the distances travelled along their preferred directions, and grid cell firing could reflect constructive interference between inputs from VCOs with coincident phases (Burgess et al. 2005, 2007; Burgess 2008; Hasselmo 2008). Again, the baseline LFP

frequency is consistent with the mean frequency of all of the VCOs coding for different preferred directions (Burgess 2008).

Thus, type I 'movement-related' theta may represent a baseline oscillation frequency against which phase coding can perform temporal integration of movement speed (in the case of place cells) or the component of movement speed along preferred directions (in the case of the putative inputs to grid cells). A key observation here is that 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 is irrelevant to spatial coding. This suggests that type I 'movement-related' mechanisms of theta generation are specifically reflected in the *slope* of the frequency-speed relationship, while type II mechanisms (e.g. associated with alert immobility and anxiety, Kramis et al. 1975; Sainsbury 1998) are specifically reflected in the *intercept* of the frequency-speed relationship (Burgess 2008). We consider evidence for this suggestion about two components of theta frequency in Sect. 12.3.4.

Of course place cell firing and grid cell firing will also reflect inputs carrying environmental information, such as boundary vector cells (Hartley et al. 2000; Lever et al. 2009), to provide spatial stability to any temporal integration of movement (e.g. Burgess and O'Keefe 2011; Cheung and Vickerstaff 2010), and this input need not be theta modulated. They may also reflect recurrent inputs from other place or grid cells, increasing stability (Burgess et al. 2007) and potentially supporting an alternative 'continuous attractor' mechanism for integration (Zhang 1996; Fuhs and Touretzky 2006; McNaughton et al. 2006; Burak and Fiete 2008).

12.2.5 Oscillations and Interregional Communication

Just as oscillations can provide potentially useful temporal organisation of processing within a region, they can also support efficient interregional processing. Thus, if processing is temporally organised into chunks (as discussed in Sect. 12.2.1), but is spread across two brain regions, then coherent temporal organisation is required across both regions. For example, if processing is organised such that information concerning different objects occurs in different cycles of gamma, and this information is spread across multiple brain regions, then local gamma rhythms must be coherent for the correct object bindings to be maintained. Equally, if neural activity in two regions each tend to oscillate (e.g. due to local feedback inhibition), coupling the activity in both regions via interregional synaptic transmission will tend to lead to coherence in the local oscillations. This view, of oscillatory coherence as diagnostic of functional interregional coupling, is elaborated in the 'communication through coherence' hypothesis (Fries 2005).

There are several other proposed functions for oscillations in interregional communication. For example, a hierarchical generative model of perception supposes alternating phases of 'bottom-up' inference and 'top-down' prediction involving projections between perceptual areas and higher areas representing hidden variables or causes (e.g. Mumford 1994; Dayan et al. 1995), with

implications for the hippocampus as supporting and maintaining the highest level representation (e.g. Kali and Dayan 2004). This type of temporal organisation of processing modes (like the separation into encoding and retrieval modes discussed in Sects. 12.2.1 and 12.3.2) would be well suited to oscillatory control of the entire processing stream from hippocampus down to sensory neocortex. Such an arrangement would require a coherent oscillation in all of these disparate areas, e.g. modulation of activity in sensory areas by hippocampal theta.

We note that the occurrence of sharp wave/ripples in the hippocampus (O'Keefe and Nadel 1978; Buzsaki et al. 1983) has been suggested to represent a processing mode in which information is communicated to neocortex (Buzsaki 1989). This interesting suggestion is discussed in detail in Jadhav and Frank (2014). More generally, electronic communications often increase the number of distinct information streams carried by a single channel by multiplexing: i.e. using each successive cycle of a high-frequency oscillation to carry a different stream, so that all streams are carried within one cycle of a lower-frequency oscillation. Such a role has been proposed for theta-gamma coupling (Nadasdy 2009, see 2010 for review; Lisman and Idiart 1995)

12.3 Experimental Findings Relating Oscillations to Cognition and Behaviour

12.3.1 Oscillatory Power and Performance

When processing is temporally organised, as discussed in Sect. 12.2, then normal operation of the process will likely produce an oscillatory modulation of activity. In this case, the presence of oscillations can be diagnostic of efficient processing. Here we review evidence consistent with this position: correlations between the presence of oscillatory power in the relevant frequency band and performance on the associated cognitive or behavioural task.

Before we do, we should comment on the nature of this evidence. Correlation-type evidence dominates in the analysis of the importance of oscillatory activity to brain function. Hippocampal-dependent spatial and mnemonic processing is no exception to this. Unlike the targeting of, say, specific genes and receptor subunits, one cannot act selectively on oscillations without disrupting the interacting components from which the oscillations emerge. Oscillations are an emergent property, and Buzsaki has written eloquently on the difficulty, indeed perhaps the 'logical absurdity in the quest of expunging oscillations selectively' (Buzsaki 2006, p. 359). Accordingly, observing the consequences of eliminating oscillatory activity selectively may be an elusive goal.

One point of leverage in analysing cause and effect relationships regarding septo-hippocampal theta has been to disrupt the function of the medial septum. Early studies in this vein using lesions (Winson 1978) suggested that septo-hippocampal theta was crucial to spatial learning. More recently, two studies (Koenig et al. 2011; Brandon et al. 2011) have inactivated medial septum (MS)

and shown an interesting dissociation in the representations underlying spatial cognition. MS inactivation strongly disrupts grid cell firing, while only minimally affecting head direction cell firing. Place cells are somewhat affected, but surprisingly mildly. Such evidence provides important clues to theta's role in spatial cognition and the memory dependent upon that cognition, but there is the obvious significant caveat; it cannot be ruled out that other effects of MS inactivation, such as the acute deprivation of acetylcholine, drive the disruption to grid cell signalling.

With the almost impossible quest of selectively expunging oscillations in mind, then, we turn to the correlations between oscillatory activity and performance.

12.3.1.1 Human Theta and Cognition

The introduction of virtual reality navigation tasks for epileptic patients that have hippocampal depth electrodes has given researchers the ability to use similar spatial memory tasks as ones used with rodents and investigate the same correlates in the human hippocampus (Burgess et al. 2002). Kahana et al. (1999) published the first study of movement-related theta oscillations from the human brain, including the medial temporal lobe, and follow-up studies recording from hippocampal neurons found neural firing that correlated with place, goal, and direction (Ekstrom et al. 2003; Jacobs et al. 2010) and also grid-like firing patterns (Jacobs et al. 2013).

Further research has attempted to classify the exact human analogue of type I hippocampal theta with iEEG (Ekstrom et al. 2005; Watrous et al. 2011) and MEG (de Araujo et al. 2002; Cornwell et al. 2008; Kaplan et al. 2012). Robust but transient increases in delta (1–4 Hz) oscillations have been observed (Ekstrom et al. 2005; Watrous et al. 2011) in addition to power increases at other frequencies (~8 Hz), depending on the specific task during virtual navigation (see Sect. 12.1.3 for further discussion of across-species differences). Similar to rodents, movement-related theta is highest in amplitude at movement initiation and is also accompanied by a reduction in theta power (not frequency like in rodents) in novel environments (Kaplan et al. 2012). Notably, Cornwell et al. (2008) observed an increase in hippocampal theta power during goal-directed virtual movement versus aimless virtual movement and also that hippocampal theta power correlated with performance in navigating a virtual reality water maze. Another study has found that movement-initiation-related theta power increases during encoding of object locations within a virtual environment correlate with subsequent memory for the object locations (Kaplan et al. 2012). This study may provide a link between human theta and the proposal that movement-related theta plays a role in exploratory behaviour in rodents (O'Keefe and Nadel 1978).

In humans, frontal midline theta is often viewed as a surrogate to the hippocampal theta usually observed in rodent recordings (Mitchell et al. 2008), and numerous studies have related human frontal midline theta oscillations to memory performance (see Klimesch et al. 2001; Addante et al. 2011 for examples). However with advances in intracranial recordings and non-invasive MEG source reconstruction, investigations into the theta rhythm of the human hippocampus and medial temporal lobe are becoming more prevalent. An emerging literature of MEG and iEEG studies has demonstrated correlations between theta power in the

hippocampus/medial temporal lobe and memory performance (Cornwell et al. 2008; Guderian et al. 2009; Fell et al. 2011; Poch et al. 2011; Kaplan et al. 2012; Lega et al. 2012; Guitart-Masip et al. 2013). Furthermore, recent findings have implicated the importance of single unit phase-locking to the hippocampal theta rhythm (Rutishauser et al. 2010). Rutishauser et al. (2010) found the precision of phase-locking of amygdala and hippocampal neurons to the LFP theta rhythm during memory encoding predicted whether an encoded item would be successfully remembered. This finding indicates that hippocampal phase concentration could serve as a diagnostic of system state. In addition to hippocampal theta, a distinct theta rhythm has been reported in the human entorhinal cortex (Mormann et al. 2008), preliminary evidence suggests that direct stimulation of entorhinal cortex resets hippocampal theta and improves performance on a spatial memory task (Suthana et al. 2012), and stimulation eliciting memories is associated with theta-band synchronisation of multiple areas (Barbeau et al. 2005).

Earlier studies have focused on using paradigms like the Sternberg working memory task to investigate working memory maintenance. Theta oscillatory activity during working memory has been reported in the human hippocampus using MEG (Tesche and Karhu 2000) and also iEEG (Raghavachari et al. 2001). A hippocampal source of theta during working memory has been supported by MEG studies of patients with bilateral hippocampal atrophy (Cashdollar et al. 2009), in which the patients were impaired at retaining associative information and showed reduced occipital-temporal theta synchrony compared to healthy control participants. There have also been studies looking at declarative memory rather than working memory. These studies have mainly focused on correlating theta activity during encoding with subsequent memory performance. One MEG study found that subsequent memory performance correlated with pre-stimulus MTL theta during memory encoding (Guderian et al. 2009), while another found that theta amplitude, including signal attributed to the MTL, was higher for recollection than recognition (Guderian and Duzel 2005). Parallel findings relating theta to subsequent memory have been made with intracranial hippocampal recordings (Sederberg et al. 2003, 2007) and with combined fMRI/EEG (Sato et al. 2010). These subsequent memory effects have also been observed with hippocampal gamma power (Sederberg et al. 2007). Finally, a transient increase in hippocampal theta for encoding of unpredictable compared to predictable events in an iEEG study has also been reported (Axmacher et al. 2010a).

12.3.1.2 Human Hippocampal Theta in Psychiatry and Anxiety

Attempts have been made to translate spatial navigation-related theta findings into clinical domains. For instance, virtual navigation tasks show potential to be applied to psychiatry, where research has shown reduced hippocampal theta in depressed patients compared to healthy controls during virtual navigation (Cornwell et al. 2010). While investigating threatening (unpredictable shocks) versus non-threatening (no threat of shocks) environments during navigation in a virtual Morris water maze, Cornwell et al. (2012) found that self-reported anxiety during navigation in threatening environments correlated with 2–6 Hz power in the left anterior

MTL. They also found that better individual spatial memory performance in threatening environments correlated with left posterior MTL 4–8 Hz power. Increasing use of MEG in cognitive neuroscience, potentially combined with simultaneous investigation using iEEG recordings from the hippocampus, may help to bridge some of the gaps between direct measurements from the hippocampus of oscillatory activity in patient populations and non-invasive but indirect measurements of oscillatory activity in healthy participants.

12.3.2 Theta Phase and Encoding Versus Retrieval Scheduling

In Sect. 12.2, we outlined different potential functions of oscillations and identified one of these as organising processing into discrete chunks (Sect. 12.2.1). Several potential functional consequences of organising processing into discrete phases of an underlying oscillation have been suggested. In this section, we consider the idea that theta organises the encoding and retrieval stages of hippocampal memory processing. It appears that there are several memory-modulating processes which are dominant at different phases of the theta oscillation. These include when feedforward and feedback-related input are dominant, when synaptic potentiation or depression is dominant, and when inhibition is dominant. The theta oscillation appears to organise these in such a way that one theta phase is propitious for encoding, while another theta phase is propitious for pattern completion-based retrieval.

12.3.2.1 Models of Encoding Versus Retrieval Scheduling

Memory systems need to encode novel information in the face of interference from previously encoded associations (proactive interference). That food was previously abundant in a specific location should not prevent us from learning that there is no food in that location now. That a prominent ex-girlfriend was called ‘Olivia’ should not prevent us from learning that the sister of a new girlfriend is also called by that name.

In counteracting proactive interference, a general solution is to separate encoding and retrieval processes and to propitiously co-align facilitatory processes (such as synaptic potentiation or depression) appropriate to each memory state. Two sets of models have been proposed for the hippocampus, one involving neuromodulators, notably acetylcholine (Hasselmo and Schnell 1994; Hasselmo et al. 1996; Meeter et al. 2004; see Gupta and Hasselmo 2014), and acting on longer timescales (seconds), and one involving the theta oscillation (Hasselmo et al. 2002; Kunec et al. 2005), and thus acting on subsecond timescales. In theta-based models, the phase of ongoing theta oscillations temporally separates encoding and retrieval and determines the different synaptic plasticity regimes that encoding and retrieval require. These models, originated by Hasselmo and colleagues, have been reviewed in detail very recently (Hasselmo 2012). Accordingly, after a short summary of the modelling approach, our presentation here focuses on new empirical support for

these models: two studies of rodent hippocampal place cell firing consistent with control of encoding and retrieval scheduling by theta phase (Douchamps et al. 2013; Jezek et al. 2011).

CA1 has two major inputs, one from the entorhinal cortex (perforant path), which might convey feedforward sensory information, and one from CA3 (Schaffer collaterals), which might convey retrieved information following recurrent-collateral-mediated pattern completion (Marr 1971; McNaughton and Morris 1987; Treves and Rolls 1994). A relatively high proportion of synaptic input onto CA3 pyramidal cells actually comes from other CA3 pyramidal cells ('recurrent collaterals'). Marr (1971) suggested that this anatomical feature meant that CA3 cells could subserve an evolving pattern completion process, whereby partial input (a subset of cues from an event) could trigger stages of mutual co-activation eventually activating the full set of cells originally associated with the complete inputs (i.e. recalling the whole event). As described in Sect. 12.2.1, Gardner-Medwin (1976) suggested a particular implementation of this idea, whereby the initial process of partial input pattern presentation, then mutual co-activation, and then pattern completion would take place within a single theta cycle.

In the (Hasselmo et al. 2002) model of CA1 encoding and retrieval, encoding takes place preferentially at the peak of theta as recorded from the CA1 pyramidal layer, when entorhinal cells are maximally active and CA3 cells are minimally active. At this phase, long-term potentiation of the excitatory CA3-CA3 recurrent connections, and the CA3-CA1 Schaffer collateral connections, should be maximal. In contrast, retrieval takes place preferentially around the trough of theta, when CA3 cells are maximally active and entorhinal cells are minimally active (though sufficient to cue retrieval). This allows the network to be driven mainly by activity at previously modified synapses. At this phase, there should be no long-term potentiation, to preserve the purity of the retrieved traces and the novel associations. In the Hasselmo et al. (2002) instantiation of the model, long-term depression occurs at this theta phase.

One of the empirical foundations of the theta-based Hasselmo et al. (2002) model is the strong relationship between theta phase and plasticity (Pavlides et al. 1988). In CA1, LTP at Schaffer collateral synapses (i.e. CA3 to CA1) is preferentially induced by stimulation at the peak of local theta, while stimulation at the trough does not induce LTP and can induce LTD or depotentiation (Hölscher et al. 1997; Huerta and Lisman 1993, 1995, 1996; Hyman et al. 2003). The model's assumption that entorhinal and CA3 input arrive at different phases of theta, based originally on Brankack et al. (1993), is supported by recent studies (Mizuseki et al. 2009). The current data are certainly consistent with the view that the entorhinal activity peak, and entorhinal-CA1 coupling peak, occurs at the peak of pyramidal-layer theta. Current indications are that the CA3 activity peak and the CA3–CA1 coupling peak occur on the descending, pre-trough phase of pyramidal-layer theta. (See Sect. 12.1.4 for discussion of the theta-gamma coupling data.) Determining the precise theta phase preference of entorhinal-driven and CA3-driven activity is complicated by recent findings that theta phase of firing depends on anatomical location, particularly along the long axis (Lubenov and

Siapas 2009; Patel et al. 2012). Thus, it will be important in future work to ensure that the electrodes are in those regions of entorhinal cortex and CA3 that project to the CA1 cells under study.

12.3.2.2 Place Cell Studies Support Theta-Based Encoding and Retrieval Scheduling

We recently conducted an experiment designed to test predictions from both the cholinergic-based and theta-based encoding versus retrieval scheduling models (Douchamps et al. 2013). In the cholinergic-based model, high levels of acetylcholine promote an encoding mode. Acetylcholine is released in novelty, enhances long-term potentiation, and suppresses input relating to CA3 recurrent activity (i.e. suppresses CA3–CA3 and CA3–CA1 synaptic activity). Thus levels of acetylcholine control the balance between encoding and retrieval.

We used both models to derive predictions about the theta phase of firing of CA1 pyramidal cells, under the assumption that encoding prevails in novelty and retrieval in familiarity. In a familiar environment, the mean theta phase of neural firing occurs just after the trough of LFP theta recorded from the pyramidal layer. Using spiking activity in this condition as a baseline, we made three predictions as follows. First, in a novel environment under saline (Novel + Saline), preferred theta phase should shift *later*, closer to the pyramidal-layer theta peak, reflecting increased levels of entorhinal-driven encoding. Second, in a novel environment under scopolamine (Novel + Scopolamine), this muscarinic cholinergic antagonist should antagonise ACh's presumed role in novelty-elicited suppression of CA3 excitatory input to CA1 and should disrupt the later-theta-phase-in-novelty effect. Third, in a familiar environment under scopolamine (Familiar + Scopolamine), this cholinergic antagonist should shift preferred phase *earlier*, closer to the theta trough, by removing baseline cholinergic suppression of the CA3 projections onto CA1.

As Fig. 12.2 shows, we found evidence in clear support for all three of these predictions. Figure 12.2 shows the theta phase distribution of ensemble spiking activity for two representative ensembles in the control condition (Familiar + Saline) and in the three experimental conditions referred to above (Novel + Saline, Novel + Scopolamine, Familiar + Scopolamine). Figure 12.2a depicts an example of a raw and theta-bandpass-filtered LFP trace from the pyramidal layer. Figure 12.2b shows two cycles from this trace for illustrative purposes as the theta reference for the spike phase distributions shown in Fig. 12.2c–j. Figure 12.2c, d shows that theta phase distribution was unchanged under saline in the familiar environment. Figure 12.2e, f shows that preferred theta phase shifted to a later phase in the novel environment, closer to that of the pyramidal-layer theta peak. They also show that the phase distribution of spikes upon reexposure to the familiar environment (grey lines) closely resembles that seen in the baseline trial (black lines). In a previous study (Lever et al. 2010), we had shown this later-phase-in-novelty effect, but due to differing theta references could not be certain that resulting phase was closer to the pyramidal-layer theta peak. Figure 12.2 g, h illustrates how scopolamine injection shifted the phase distribution of spike firing

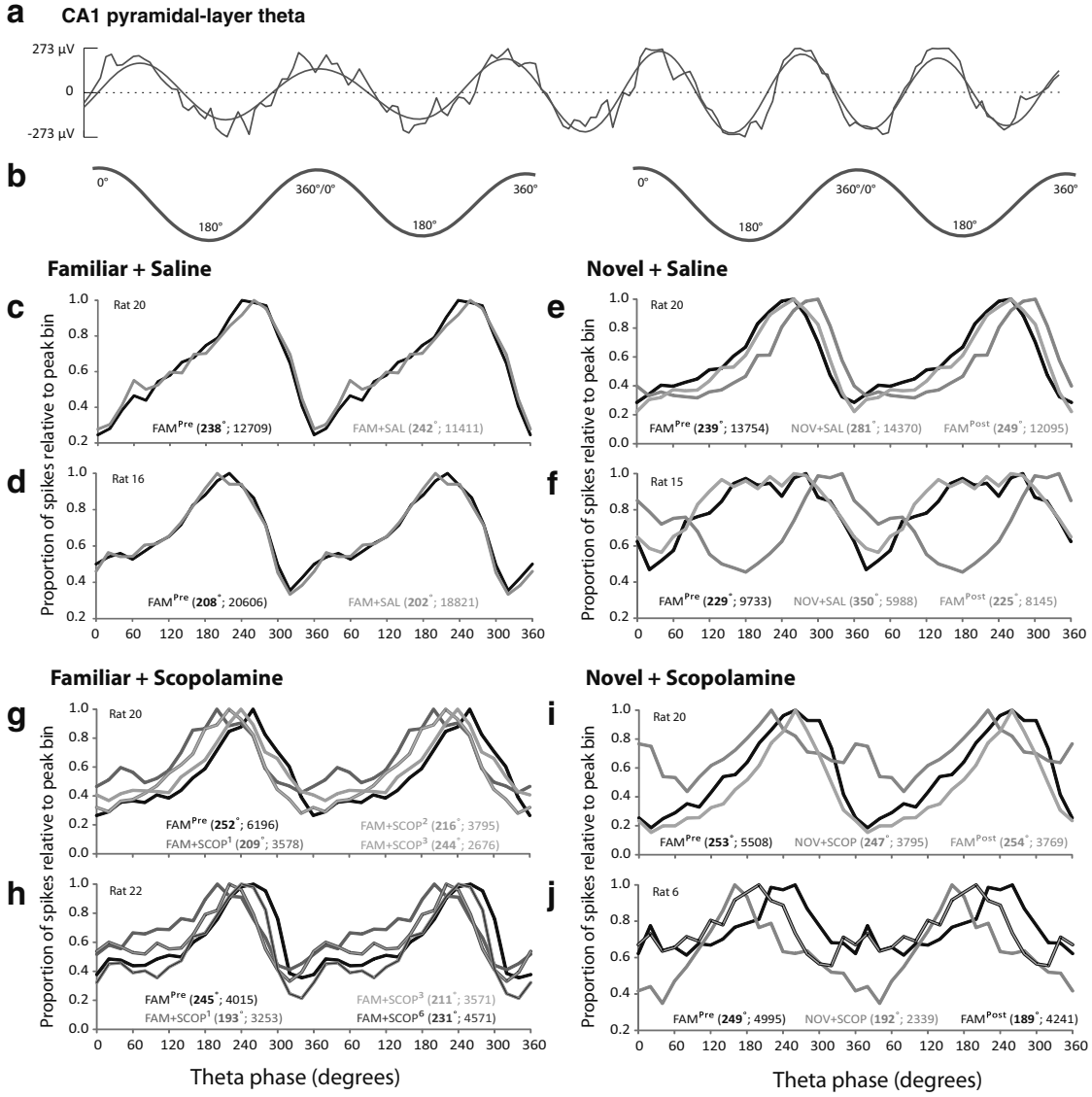

Fig. 12.2 Theta phase controls encoding and retrieval scheduling in the hippocampus. CA1 ensembles show later preferred firing phases in novelty, an effect disrupted by scopolamine, and show earlier firing phases under scopolamine in familiarity. Examples of the firing phase distributions of CA1 ensembles in individual rats. (**a**) Raw (*blue*) and filtered (6–12 Hz; *grey*) LFP trace recorded from CA1 pyramidal layer showing ~6 theta cycles. (**b**) Two theta cycles from trace in **a** are shown for illustrative purposes as the theta reference for the spike phase distributions below. (**c, d**) The preferred phase is very stable in the familiar environment before and after saline injection (FAM + SAL). (**e, f**) Novelty (NOV + SAL) elicits a later preferred phase compared to the baseline familiar trial T3 (FAM^{Pre}), but the distribution reverts to baseline on return to the familiar environment (FAM^{Post}). (**g, h**) Scopolamine elicits an earlier preferred phase in the familiar environment (FAM + SCOP); then the phase progressively approaches baseline phase as drug wears off over 3 (**g**) or 6 (**h**) sessions. (**i,j**) Scopolamine blocks the novelty-elicited coherent shift to a later firing phase characteristic of the undrugged state (NOV + SCOP). In C-J, preferred phase and total spike count of each ensemble shown in parentheses. Adapted from Douchamps et al. (2013)

in a familiar environment to an earlier phase, closer to the pyramidal-layer theta trough (red lines). Note that, in both rats, as the drug wore off, preferred phase gradually approached the phase seen in the baseline trial. Finally, Fig. 12.2i, j illustrates how scopolamine disrupts the shift towards the pyramidal-layer theta peak (c.f. Fig. 12.2e, f). There is some peak-related firing in the ensemble shown in Fig. 12.2i, which was also seen in another rat, but overall the results were clear: the novelty-elicited shift to a later preferred phase characteristic of the undrugged state was disrupted by scopolamine. In summary, all three predictions were confirmed.

We additionally tested a prediction based on the cholinergic model alone that scopolamine would disrupt 'remapping'. Remapping occurs when the hippocampus produces divergent representations (maps) of different environments (Muller and Kubie 1987). Greater difference in the environments, and more experience in the environments, elicits greater divergence in the maps (Lever et al. 2002; Leutgeb et al. 2004, 2005; Wills et al. 2005; Fyhn et al. 2007; McHugh et al. 2007; Nakashiba et al. 2012). Remapping is a well-established phenomenon and is related to encoding a representation of a new environment (Kentros et al. 1998; Nakazawa et al. 2003; Lever et al. 2002; Leutgeb et al. 2004, 2005; Wills et al. 2005; Sava and Markus 2008; Nakashiba et al. 2012). Accordingly, we reasoned that scopolamine should disrupt encoding and thus attenuate the distinctiveness of the map in the novel environment. This prediction was also confirmed: levels of remapping were reduced in the novel environment under scopolamine as compared to under saline (as broadly consistent with Ikonen et al. 2002). Taken together, the fact that all our predictions were confirmed offers strong support for both the cholinergic-based and theta-based models and suggests that the processes they model are complementary and should be integrated into a common framework (Hasselmo 2012; Easton et al. 2012; Barry et al. 2012).

The Douchamps et al. study was mostly focused on hippocampal encoding in response to novel environments, using place cell activity in a familiar environment as a baseline. We now turn to the study of Jezek et al. (2011), which investigated the process of retrieving pre-existing representations ('maps') of two highly experienced environments. These authors developed an elegant paradigm whereby they could instantaneously change the sensory cues (colour/lighting) triggering CA3 place cell maps of two very familiar environments. They asked what happened to CA3 place cell ensemble activity following the instantaneous cue change from the first to the second environment. Typically, ensemble activity flip-flopped between all-or-none representations of either the first or the second environment before settling on the second. Perhaps surprisingly, representations of the first environment were still occurring several seconds and occasionally tens of seconds after the instantaneous cue switch, broadly consistent with an earlier demonstration of slow-timescale place cell attractor dynamics in CA1 (Wills et al. 2005).

A key result in the Jezek et al. study was that the flip-flop transitions between maps occurred on a theta frequency timescale. Analysis showed that the best-performing period for separating the two maps was a theta cycle whose beginning was defined by the lowest point of CA3 pyramidal cell firing. Mixed ensemble activity, where both maps were co-active, was rare in a single theta cycle (~121 ms) and particularly so in the second half of the theta cycle.

In the first whole theta cycle after both first-to-second and second-to-first map transitions, representations were typically mature: they did not become more similar to the baseline representations over successive theta cycles. This implied that the fast-timescale attractor mechanism needed only one theta cycle for full pattern completion.

In summary, sharp transitions between CA3 spatial maps occurred preferentially at the theta phase of minimal pyramidal firing, and mixed maps were much rarer in the second half cycle, as expected if attractor dynamics dominate that half cycle. These findings are clearly consistent with the theta-based encoding versus retrieval scheduling models where hippocampal encoding and retrieval occur at theta frequency, and each cycle is alternately dominated by extrinsic sensory input and intrinsic recurrent/feedback input (Hasselmo et al. 2002; Kunec et al. 2005).

In conclusion, recent place cell studies provide good support of the idea that encoding and retrieval are scheduled by theta phase.

12.3.3 Theta Phase Coding of Metrical Spatial Information

Part of the interest in the theta phase precession of place cell firing comes from the observation that firing phase correlates better with distance travelled through the firing field than with other variables such as the time spent in the firing field (O'Keefe and Recce 1993). Thus, when pooling data over runs of variable speed, the intrinsic firing frequency of the place cell must adjust to exceed the LFP theta frequency by a greater amount during fast runs than slow runs, so that the correlation with distance is maintained. Even more intriguing is that simple explanations linking the firing phase to the overall depolarisation level of the neuron (Harris et al. 2002; Mehta et al. 2002) are inconsistent with the observation that variation run by run in firing phase is unrelated to variation in firing rate (Huxter et al. 2003) and that the theta phase of firing is unrelated to intracellular measures of depolarisation (Harvey et al. 2009).

The robust relationship between firing phase and location, in which firing phase adds spatial information beyond that contained in firing rate (Jensen and Lisman 2000), has led to the idea that theta phase precession plays a role in path integration. This idea is implemented by the 'dual oscillator' model of place cell firing, in which firing phase calculates distance travelled (O'Keefe and Recce 1993; Lengyel et al. 2003), and the oscillatory interference model of grid cell firing, in which 'velocity-controlled oscillators' encode the distances travelled along specific preferred directions which are combined in the grid cell firing pattern (Burgess et al. 2005; 2007; Burgess 2008; Blair et al. 2008; Hasselmo 2008) see Sect. 12.2.4.

The oscillatory interference model of grid cell firing (see Burgess 2008, and Sect. 12.2.4) makes specific predictions relating a grid cells' frequency of firing rate modulation ('intrinsic frequency' f_i) to the spatial scale of the grid (G), running speed (s), and the LFP theta frequency extrapolated to zero speed (f_0):

$$f_i(t) = f_0 + \frac{2(\pi + 1)}{\sqrt{3\pi G}} s(t).$$

When looking in grid cell data from Barry et al. (2007) and from the Moser laboratory, we found this relationship to be broadly verified (Jeewajee et al. 2008a). The baseline frequency (observable as LFP theta and equivalent to the mean frequency of all the VCOs with different preferred directions) should not vary with running direction; in fact the prediction for theta frequency (f_θ) as a function of running speed is

$$f_\theta(s(t)) = f_0 + < \beta > s(t),$$

where $< \beta >$ is a constant of proportionality which is inversely proportional to average grid scale.

The model also predicts that 'velocity-controlled oscillators' (VCOs) exist, whose frequency varies from the baseline frequency to encode the component of running speed along different preferred directions. The VCOs driving a grid cell could in principle be dendritic MPOs or input from other neurons (Burgess et al. 2005, 2007), but the former option is not biophysically plausible (Remme et al. 2010). Thus, VCOs should be neurons whose intrinsic frequency varies as a cosine function of running direction and a linear function of running speed. Welday et al. (2011) recorded from 'theta cells', i.e. presumed interneurons with strongly theta-modulated firing, along the septo-hippocampal circuit. They recorded for long enough to be able to make separate estimates of intrinsic frequency as a function of running direction and running speed, and found the predicted relationship. See Fig. 12.3 for a schematic summary of this oscillatory interference model of grid cell formation, in which a grid cell acts as a coincidence detector of multiple VCO inputs (Hasselmo 2008).

As well as supporting a specific novel prediction of the oscillatory interference model, the finding of Welday et al. (2011) potentially changes how we view theta cells. Not simply being involved in feedback inhibition and theta generation, they appear to be playing a key role in path integration by encoding the component of movement velocity along different preferred directions. Welday et al. (2011) point out that the firing of these VCOs provides a basis set from which any arbitrary spatial firing pattern could be constructed via oscillatory interference (including grid-like patterns as a subset). Thus oscillatory modulation of firing rates may have a very specific role in encoding information, beyond the more general functions usually ascribed to oscillatory firing, such as those outlined in Sect. 12.2.

The predicted link between theta rhythmicity and grid scale, and the observation that theta frequency reduces when the animal is put into a new environment (Jeewajee et al. 2008b) prompted us to examine the effect of environmental novelty on grid scale (Barry et al. 2012). Consistent with the model, we saw that grid scale expands under environmental novelty and slowly contracts as the new environment

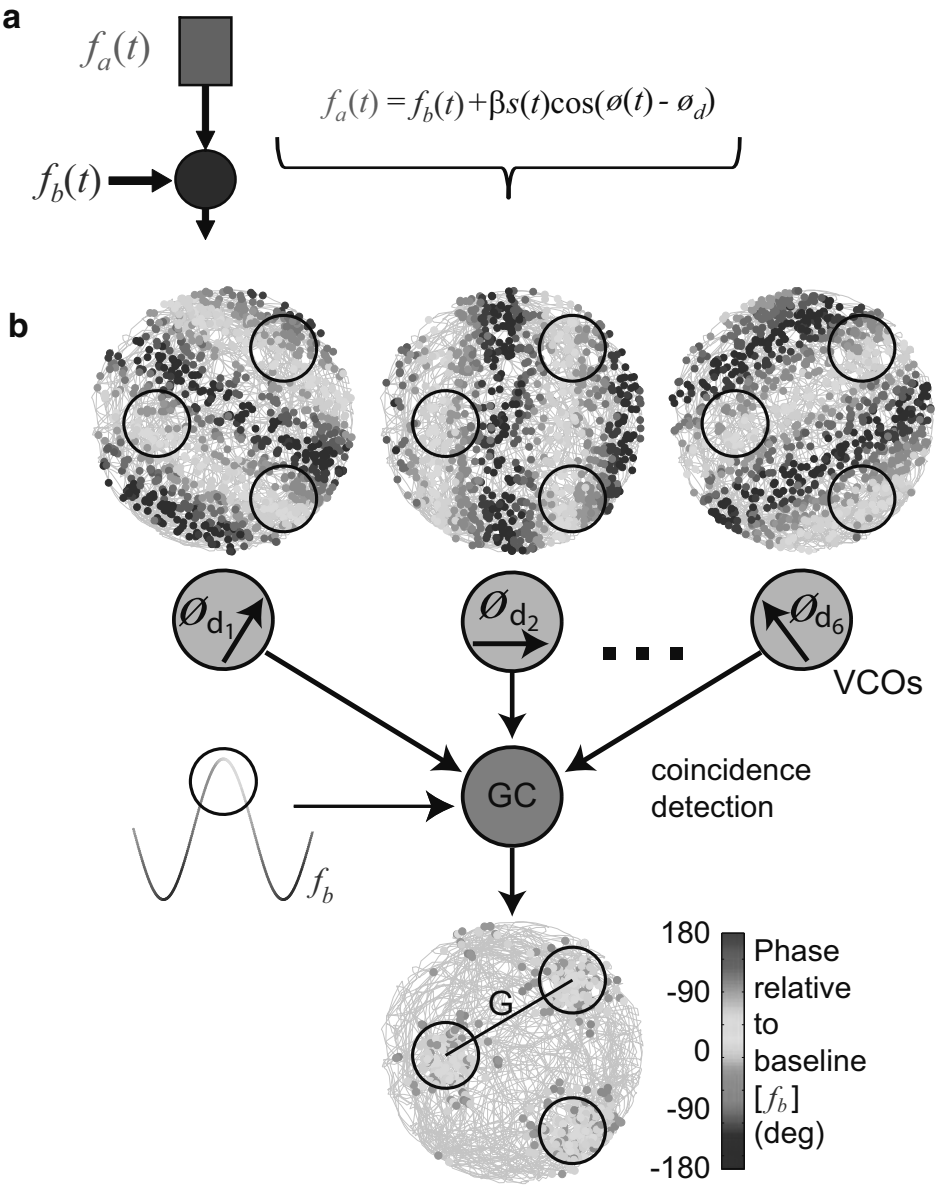

Fig. 12.3 The oscillatory interference model of grid cell firing. (**a**) A 'velocity-controlled oscillator' (VCO) is an active oscillation that has a frequency f_a which varies around the baseline frequency (f_b, identified with the local field potential) according to running speed $s(t)$ and running direction $\phi(t)$ relative to the VCO's preferred running direction ϕ_d. The dependency on running speed and direction causes the phase of the active oscillation relative to baseline to reflect displacement along the preferred direction (see mid *top panel* of **b**). (**b**) Multiple VCOs with different preferred directions combine with each other and the somatic baseline input to produce grid firing. Grid scale depends on the constant β as: $G = 2/\sqrt{3}\beta$. Adapted from (Burgess and O'Keefe 2011)

becomes familiar, while grid cells' intrinsic frequency reduces. The more specific prediction is that the reduction in theta frequency with novelty is due to a reduction of the slope of the relationship to running speed rather than a reduction in the intercept, as discussed in Sect. 12.3.4.

12.3.4 Dissociating Two Components in the Theta Frequency to Running Speed Relationship

The hippocampal formation is thought to play key roles in two very distinct sets of brain functioning: (1) spatial and context-dependent memory, linked to novelty detection, and (2) anxiety, linked to stress and depression. Each of these functions was the subject of highly influential books published over 30 years ago. O'Keefe and Nadel (1978) theorised on the hippocampal role in spatial cognition and episodic memory, while Gray (1982) set out the case that the hippocampus was involved in behavioural inhibition and anxiety. Interestingly, both O'Keefe and Nadel (1978) and Gray (1982) assumed that theta was crucial to the function they studied, with O'Keefe and Nadel (1978) suggesting that theta acted as a record of spatial translation and Gray (1982) noting that drugs which were effective as anxiolytic drugs in humans impaired septo-hippocampal theta in rodents.

Since, as we argue in this chapter, the temporal organisation of hippocampal online processing is dominated by the theta oscillation, it would be expected that hippocampal theta has increasingly been implicated in both the functional sets outlined above, and this is indeed the case. To give a quick pass through this literature in the last decade, many studies cited here have continued to implicate hippocampal theta in anxiety/anxiolytic drug action (e.g. Adhikari et al. 2010; Cornwell et al. 2012; Gordon et al. 2005; Gray and McNaughton 2000; Seidenbecher et al. 2003; Shin et al. 2009), memory-related novelty processing (e.g. Hasselmo et al. 2002; Lever et al. 2010; Rutishauser et al. 2010; Kaplan et al. 2012), and spatial cognition (e.g. Brandon et al. 2011; Buzsaki 2006; Giocomo et al. 2007; Huxter et al. 2003, 2008; Jezek et al. 2011; Jones and Wilson 2005; Koenig et al. 2011; Maurer et al. 2006; O'Keefe 2007; Skaggs et al. 1996).

By and large, however, there has been little attempt to understand how the hippocampal processing relating to spatial cognition (O'Keefe and Nadel 1978) and anxiety (Gray 1982) might be related to each other, despite their common substrate. One reasonable theoretical starting point is that the processing of one should not, of necessity, interfere with the processing of the other. In recent work, we have explored the potential independence of theta mechanisms relating to spatial cognition and anxiety (Wells et al. 2013).

In Sects. 12.1.2, 12.2.4, and 12.3.3 above, we 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 axis at 0 cm/s (Burgess 2008). Importantly, in this model, the spatial translation and arousal/anxiety-related 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. 2012) was a prediction of the oscillatory interference models (Burgess et al. 2007; Burgess 2008), 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 we made specific predictions regarding the 'spatial cognition' functional association of hippocampal theta: environmental novelty 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 (e.g. place field size).

We also made a corresponding prediction regarding the 'anxiety' functional association of hippocampal theta. It has long been noted that all clinically effective anxiolytic drugs (i.e. those effective for generalised anxiety disorder) reduce the average frequency of hippocampal theta elicited by stimulation of the reticular formation under anaesthesia ('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 (Gray and McNaughton 2000; McNaughton et al. 2007; Engin et al. 2008; Siok et al. 2009; Yeung et al. 2012), but is not seen with *antipsychotic* drugs (Gray and McNaughton 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 2000) following standard-footshock conditioning (Seidenbecher et al. 2003). Accordingly, since (a) arousal/anxiety is explicitly 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, we used the model to predict that anxiolytics should reduce the *intercept* of the theta frequency to running speed relationship, without any obligatory effect on slope.

In summary, we predicted a double dissociation whereby anxiolytics would specifically reduce intercept, and environmental novelty would specifically reduce slope. This is what we observed (Wells et al. 2013). Figure 12.4a,b,c shows the effect of systemic injection of two well-established clinically effective anxiolytic drugs (4a, CDP, a benzodiazepine agonist; 4b, buspirone, a 5HT-1A agonist) and one putative anxiolytic (4c, O-2545, a CB1 agonist). All the anxiolytic drugs elicit a reduction in the intercept (without affecting slope). Figure 12.4d-f shows the effect of introducing the rat into novel environments (in the same geocentric location as a familiar baseline environment). In line with a central prediction of the oscillatory interference model (Burgess 2008), in all cases, the novelty elicits a reduction in the slope (without significantly affecting intercept). Place fields of CA1 place cells expanded in the novel environments, and a significant 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. This result is also predicted by the (Burgess 2008) model.

We also observed a dissociation between slope and intercept that was not predicted by the model. A few studies, perhaps too few, have investigated the positive relationship between temperature and theta frequency (e.g. Whishaw and Vanderwolf 1971). Our data show that, in the locomoting rat at least, temperature is positively correlated with the slope, but not the intercept, of the frequency-speed

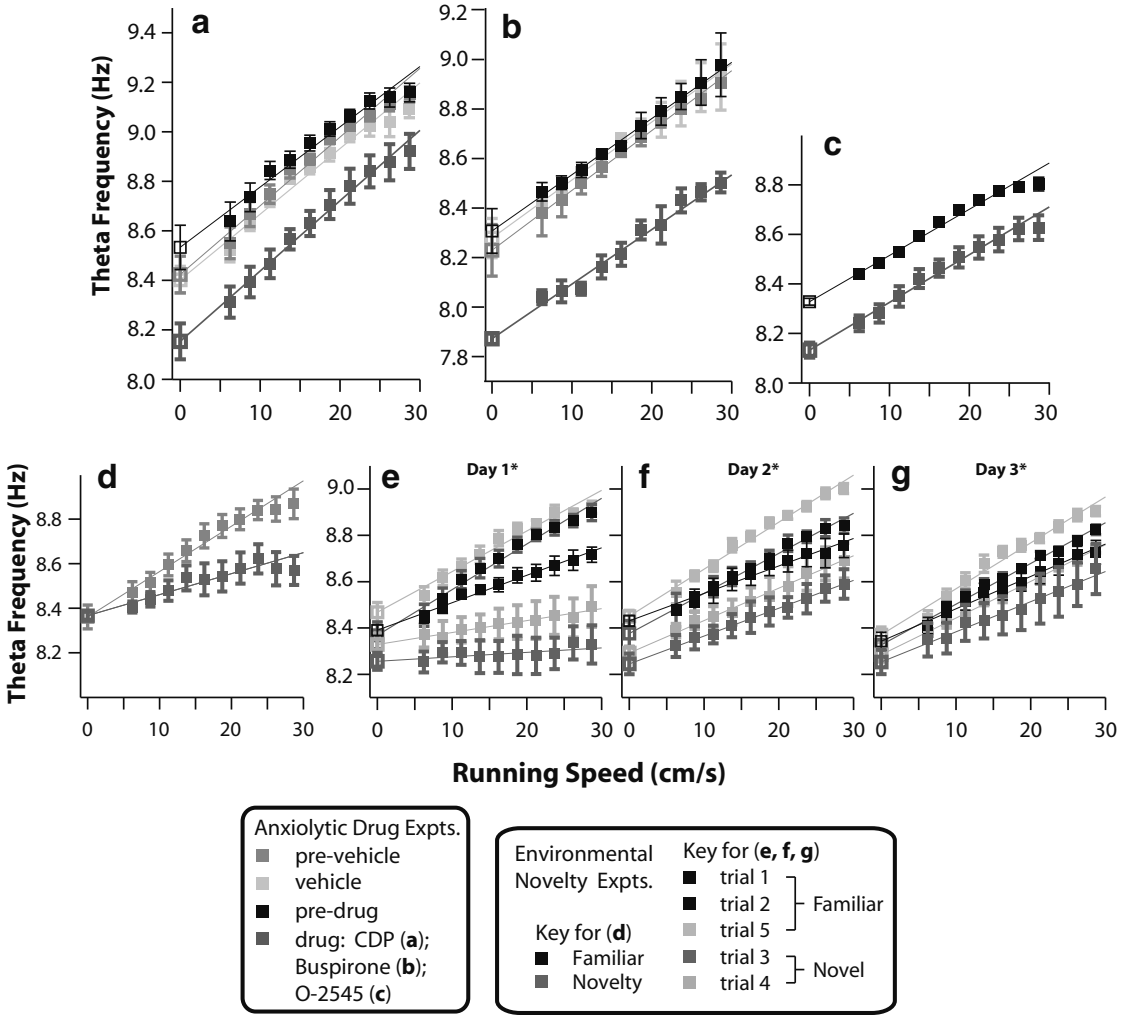

Fig. 12.4 Anxiolytic drugs reduce the intercept of the theta frequency to running speed relationship, while environmental novelty reduces its slope. Three neurochemically different anxiolytic drugs (all i.p. injections: (**a**) CDP, benzodiazepine agonist, 5 mg/kg; (**b**) buspirone, 5HT-1A agonist, 1 mg/kg; (**c**) O-2545, putative anxiolytic, CB1 agonist, 100 μg/ml, 0.5 ml/kg) have the common effect of reducing the 0 cm/s intercept of the theta frequency to running speed relationship. In contrast, exploration of a novel environment reduces the slope of this relationship (**d** and **e**), which then recovers as the novel environment itself becomes familiar (**e, f, g**). Parts **c** and **d** present data from the same rats (i.e. a within-subject's double dissociation of intercept and slope effects is observed). *Open squares* indicate *y*-intercept of regression lines. All recording sites CA1 except **e**, **f**, **g** = various hippocampal sites (dentate, CA1, subiculum). Adapted from Wells et al. (2013)

relationship. The dissociation may also prove useful in understanding mechanisms driving type I theta frequency. This finding also has implications for the study of theta phase precession and spatial cognition. For example, if slope is flatter on the first trials of the day, when the rat's brain is colder, phase precession may be weaker, given some noise, than when the brain is hot and slope is steeper.

Taken together, this set of findings provides good support for the additive two-component model of hippocampal theta in Burgess (2008). More generally,

the findings may lay the groundwork for a quantitative approach to hippocampal theta that unifies parallel streams of research on hippocampal cognitive and emotional processing.

12.3.5 Interregional Coherence and Communication

The idea that oscillatory synchronisation has behavioural relevance came from observations of visual cortex gamma phase synchronisation (Gray and Singer 1989; Gray et al. 1989; for review see Singer and Gray 1995) and work showing that this type of synchrony predicts performance on cognitive tasks (Womelsdorf et al. 2006). Related theoretical approaches have highlighted the importance of 'communication through coherence' and task-relevant communication between different regions through phase-locking within the same frequency (Malsburg 1995; Fries 2005, 2009). Concepts from 'communication through coherence' have been applied to the rodent hippocampus and to the investigation of how interactions between task-relevant regions might guide memory (Wang et al. 1990; Buzsaki 2006; Battaglia et al. 2011). In parallel, recent research investigating how local computations in neocortex could be facilitated by gamma oscillations, and potentially modulated by the phase of lower-frequency oscillations such as theta, has highlighted how synchrony or cross-frequency coupling might underlie interregional interactions (Schroeder and Lakatos 2009a, b; Buzsaki 2006).

Theta-gamma coupling is often hypothesised to function in a sort of master–slave relationship, implying that theta might function as an instrument of sensory selection (Lakatos et al. 2008; Buzsaki 2006). This has caused theta-gamma coupling to be the focus of several studies recording from the rodent hippocampus during spatial navigation. Informed by theoretical work hypothesising that the hippocampus serves as a comparator (Vinogradova 2001), Colgin et al. (2009) found that different gamma frequencies in the medial entorhinal cortex (~65–120 Hz) and CA3 (~25–50 Hz) couple with the ongoing theta rhythm in CA1 in awake behaving rodents (findings detailed in Sect. 12.1.4). Notably, these different gamma sources are usually phase-locked to different phases of the ongoing CA1 theta rhythm and tend to occur in different cycles. Previous studies had found a lower-frequency (25–50 Hz) gamma rhythm in CA3 than in medial entorhinal cortex (Bragin et al. 1995) and that (40–100 Hz) gamma phase coupling between CA3 and CA1 was higher during awake behaviour than REM sleep (Montgomery et al. 2008). Additionally, Montgomery et al. (2008) found that both theta and gamma phase coupling increased between CA3 and dentate during REM sleep. Furthermore, recent work has found that increased CA3–CA1 gamma synchrony predicted increased precision of place cell replay in the awake rodent (Carr et al. 2012). The capability of the CA1 theta rhythm to couple with different frequency oscillations is further supported by work from Belluscio et al. (2012) who found that CA1 theta phase coupled with the amplitude of slow (30–50 Hz), mid- (50–90 Hz), and fast

gamma (90–150 Hz) frequencies both during maze exploration and REM sleep. Cross-frequency coupling between the hippocampal formation and other regions has also been found. Tort et al. (2008) found striatal (~110–150 Hz) gamma amplitude was modulated by the ongoing hippocampal theta phase around the onset of T-maze trials. Furthermore, Sirota et al. (2008) found that neocortical gamma rhythms with different neocortical sources and different frequencies occurred at different phases of the ongoing hippocampal theta rhythm in the freely behaving rodent.

Another form of interregional oscillatory coupling comes from investigation of low-frequency (0.01–0.1 Hz) endogenous fluctuations in the blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) signal in humans. One of the primary endogenous brain networks, commonly referred to as the 'default mode network', centres on the hippocampus, parietal midline, and mPFC (Raichle et al. 2001; Buckner et al. 2008) and shows anatomical overlap with fMRI activity patterns observed during spatial and autobiographical memory tasks (Hassabis and Maguire 2007; Buckner and Carroll 2007). In parallel research with MEG, a study by Hipp et al. (2012) observed ongoing (5–7 Hz) theta synchronicity between the human MTL and other default mode network regions. Related to both electrophysiological and fMRI signals, Logothetis et al. (2012) used hippocampal electrode recordings simultaneously with fMRI to measure hippocampal ripple events in both awake and sleeping primates. The authors found that ripple events were phase-locked to the hippocampal delta rhythm and inhibited endogenous BOLD activity in neocortical areas, but increased activity in subcortical brain regions.

There is now an emerging literature investigating inter-areal coupling in humans using ECoG recordings (Watrous et al. 2013) and non-invasive MEG source connectivity techniques to explore phase interactions that could underlie mnemonic function. Interregional and cross-frequency coupling does not appear to be behaviourally specific and has been observed during spatial memory, evaluative, and anxiety-related behaviours in health and disease, so we will summarise the current literature based on specific field and animal model below.

12.3.5.1 Interregional Coherence and Communication: Integrating Spatial Knowledge and Decision-Making

Interregion coherence may be a general mechanism for task-led interregional communication (see Sect. 12.2.5). Here we summarise evidence for this hypothesis within spatial, mnemonic, and anxiety-related behaviour. [For related discussion of spatial tasks, see Shapiro et al. (2014); for related discussion of anxiety-related tasks, see Blair and Fanselow (2014).] We first describe work on interregional communication in the rodent, where there is more data at the level of ensembles of single neurons, and then turn to humans.

Jones and Wilson (2005) recorded from CA1 and medial prefrontal regions during a spatial working memory task. The task was designed such that they could investigate runs when a choice of direction was required, compared to when there was no choice. As expected, coherence between the local field potentials

in the theta range was significantly higher during choice-related behaviour. The phase-locking of medial prefrontal neuronal firing to CA1 theta, and the cross-correlation of CA1-prefrontal neuron spike trains, was also greater during choice-related behaviour. Other work has shown that mPFC firing rate changes during exploratory behaviour are entrained to hippocampal theta, and that mPFC cells can dynamically alternate between being entrained to the hippocampal theta rhythm and nonphasic firing (Hyman et al. 2005; Siapas et al. 2005).

Sigurdsson et al. (2010) used a similar paradigm to Jones and Wilson to investigate hippocampal-prefrontal coupling in a mouse model of schizophrenia. They contrasted the choice runs versus the sample runs in a discrete-trial, T-maze, working memory task. In wild-type mice, replicating the findings of Jones and Wilson (2005) in rats, they showed that both theta-band coherence of the two regions' LFPs and phase-locking of medial prefrontal neuronal firing to CA1 theta, was higher during choice runs. In the schizophrenia-model mice, however, this theta-band coupling was impaired.

In summary, both studies showed theta-band coherence at the cellular and LFP level between the hippocampus and the prefrontal cortex during choice-related behaviour in a spatial working memory task. The interpretation of these results is that increased theta coherence mediates the communication required to integrate spatial memory with decision-making.

In related findings, Benchenane et al. (2010) measured hippocampal and mPFC theta oscillations in rodents performing a Y-maze decision-making task, where rats learned two reward contingency rules (e.g. to receive a reward, the rat must go to the arm on the right and then go to the arm that lights up). The authors found that after learning a reward contingency and coming upon a choice point in subsequent trials, mPFC-hippocampus coherence increased. Furthermore, the authors also observed increased replay during sleep of mPFC cell firing that previously occurred during time periods with strong hippocampal-mPFC theta synchronisation (Benchenane et al. 2010). Recently, an MEG human decision-making study, without a specific spatial component, found similar theta-band phase-locking between these two structures (Guitart-Masip et al. 2013), suggesting a role for human hippocampal-mPFC theta phase-locking in decision-making and planning.

12.3.5.2 Interregional Coherence and Communication: Anxiety Behaviour

The hippocampus clearly plays a well-established role in spatial and other forms of memory. But it has also long been implicated in anxiety (Gray 1982; Gray and McNaughton 2000; Engin and Treit 2007; Oler et al. 2010), including unconditioned anxiety (Kjelstrup et al. 2002; Bannerman et al. 2004; Pentkowski et al. 2006). Thus, one might expect that the increased communication through coherence shown between the hippocampus and prefrontal cortex during spatial memory-guided choice behaviour (Jones and Wilson 2005; Sigurdsson et al. 2010) will also apply in anxiety behaviour.

The characterisation and delineation of anxiety and fear and the contribution of the hippocampus to these emotions are debated. For instance, the contribution of the

hippocampus to anxiety/fear could be attributed to its support of context-dependent memory. This is a reasonable interpretation of the report by Seidenbecher et al. (2003) which showed increased theta coherence between the dorsal hippocampus and the lateral amygdala during the retrieval of conditioned fear (what Gray and McNaughton (2000) would call 'anticipatory anxiety').

However, Adhikari et al. (2010) recorded theta from the hippocampus and medial prefrontal cortex while mice were exposed to two anxiety-provoking environments thought to model *unconditioned* anxiety (a bright open field and an elevated plus maze). Though subsequent learning occurs, initial anxiety in the anxiety-provoking environments is usually thought to reflect unconditioned anxiety. Thus the finding of increased CA1/medial prefrontal cortex theta coherence in these tasks is less obviously attributable to the hippocampal role in memory. In keeping with this, and supporting the linking of dorsal hippocampus to space and memory and ventral hippocampus to anxiety (Bannerman et al. 2004; Fanselow and Dong 2010), it was found that the region of CA1 that increased coherence with mPFC was the ventral hippocampus (Adhikari et al. 2010).

Even in the control environment, theta coherence between ventral CA1 and medial prefrontal cortex was much higher than between dorsal CA1 and medial prefrontal cortex. Exposure to the anxiety-provoking environments further increased ventral CA1/medial prefrontal cortex theta power correlations and increased the phase-locking of medial prefrontal cortex multiunit activity to ventral CA1. Anxiety-induced increased theta coherence likely reflected hippocampal-to-mPFC influence, rather than the reverse: (a) ventral CA1/medial prefrontal cortex theta power correlation was maximal when the medial prefrontal cortex EEG signal was shifted backwards by 8 ms; (b) theta frequency increased in anxiety in medial prefrontal cortex, approaching the frequency seen in ventral CA1; (c) phase-locking of mPFC multiunit activity to ventral CA1 theta was maximal when mPFC spikes were shifted backwards by 32 ms. These results are in line with anatomical tracing data showing that direct CA1-mPFC projections come from the ventral, not dorsal, CA1, while prefrontal influence on CA1 is multisynaptic. [Importantly, future work needs to resolve the apparent contradiction between the description of theta as a travelling wave (Lubenov and Siapas 2009; Patel et al. 2012) and the finding of reduced frequency in the ventral, relative to the dorsal, hippocampus (Adhikari et al. 2010)].

In summary, the studies of theta-band coherence between the hippocampus and its efferent regions such as the prefrontal cortex suggest that the increased coherence-communication mechanism may apply to both spatial memory-guided and anxiety behaviours and to both the dorsal and the ventral hippocampus.

12.3.5.3 Interregional Coherence and Communication: Human Memory

Results showing that gamma band synchronisation during encoding precedes successful memory formation, in both non-human primates (Jutras and Buffalo 2010) and humans (Fell et al. 2001), raise the possibility that interregional coherence might underlie memory formation. Fell et al. (2001) measured ~40 Hz oscillatory activity

from the LFP of intracranial electrodes in the hippocampus and rhinal cortex (entorhinal and perirhinal cortices), finding that oscillatory synchronisation preceded successful declarative memory formation. This study indicates that gamma oscillations help interregional coordination during memory encoding. Another study, in non-human primates, found that hippocampal gamma synchronisation during encoding predicted subsequent memory performance in a visual recognition memory task (Jutras and Buffalo 2009). Other work by Fell and colleagues showed that 1–19 Hz rhinal-hippocampal intrafrequency phase-locking also occurred during continuous word recognition, and phase-locking at encoding predicted subsequent memory formation (Fell et al. 2003, 2008). Theta phase-locking between hippocampus, amygdala, and neocortex has also been observed with auditory memory in intracranial patients (Babiloni et al. 2009), but so far task-relevant interactions between 4 and 8 Hz human hippocampal theta oscillations and the neocortex have been missing. Recordings from the surface of prefrontal and parahippocampal cortices in humans suggest that low-frequency (1–10 Hz) phase-locking between the MTL and the PFC is predictive of successful memory recall (Watrous et al. 2013). Two Hz phase-locking between PFC and MTL predicted recall of spatial locations, while 8 Hz phase-locking between PFC and MTL predicted successful recall of serial order. Notably, other ECoG studies with similar frontotemporal electrode placements have found that synchronisation in theta and surrounding frequency bands was higher for recall than baseline (Anderson et al. 2010). In sum, there is growing evidence that interregional synchronisation is important for successful memory formation and retrieval, but there is a dearth of evidence implicating specific tasks or frequency bands.

12.3.6 Cross-Frequency Coupling

A potential mechanism for organising distributed representations, particularly relevant in mnemonic function, is cross-frequency coupling. In the context of memory tasks, cross-frequency coupling usually entails the phase of a low-frequency oscillation, like the hippocampal theta rhythm, showing phase consistency with the amplitude of a higher-frequency oscillation, like gamma (see Sects. 12.2.1, 12.2.2, 12.3.1 for the theoretical implications of cross-frequency coupling). This phase-amplitude coupling could work in the service of memory formation and retrieval by providing a mechanism to organise learned sequences (Jensen and Colgin 2007). Researchers have examined cross-frequency coupling during working memory maintenance in humans to support this hypothesis. In a MEG study, Fuentemilla et al. (2010) applied pattern classifiers to theta and gamma activity elicited during encoding for individual stimuli and subsequently decoded their replay during working memory maintenance. Replay of different stimuli categories (e.g. whether participants were maintaining a picture of an indoor or an outdoor scene) was decoded during maintenance, and the reactivation of maintained items was usually locked to a particular phase of theta, and the consistency of decoded items with theta phase correlated with memory performance.

Follow-up analyses determined that the timing of item reactivations during working memory maintenance was locked to the ongoing theta phase in the hippocampus and dorsolateral prefrontal cortex (dlPFC) (Poch et al. 2011). Further evidence of the importance of cross-frequency coupling during working memory maintenance comes from a paper by Axmacher and colleagues, who observed theta-gamma coupling during working memory maintenance in patients with hippocampal depth electrodes (2010b). The authors also demonstrated that the consistency of hippocampal theta-gamma coupling predicted memory performance, extending the behavioural relevance of cross-frequency coupling further (Axmacher et al. 2010b).

12.4 Summary and Conclusions

In this section, we offer an integrative view of the whole chapter, not necessarily in the order of presentation and without the detailed referencing given above.

12.4.1 Hippocampal EEG States and Their Correlates

Two mutually exclusive states dominate the hippocampal local field potential in awake rodents: LIA and theta. LIA is observed when the animal is idling, theta (around 4–12 Hz) whenever the animal is moving, but also sometimes during immobility such as in the presence of predators. The characteristic frequency band of theta may be somewhat lower in humans than in rodents, but it has not been definitively established if this reflects genuine species differences. Ripple oscillations (140–200 Hz) occur during LIA which may represent memory consolidation and 'what if' cognition mechanisms.

While gamma (30–150 Hz) can be present during LIA, gamma appears to be strongly controlled by theta. The presence and phase of theta modulates the amplitude of gamma, and the frequencies of theta and gamma are often positively correlated. A prominent model of sequence memory proposes that item sequences correspond to a sequence of gamma cycles within one theta cycle, with each item corresponding to one gamma cycle's activity, at a particular phase of theta. The model began as a model of working memory but has been adapted to model theta phase precession of place cell firing. The number of items that can be remembered in order will be constant across varying theta cycle durations so long as theta and gamma frequency are correlated. In summary, in this scenario oscillatory phase (theta) and gamma nesting within theta implement ordinal coding.

12.4.2 Encoding Versus Retrieval Scheduling in CA1: Theta Phase and Theta-Gamma Coupling

Coupling of specific gamma bands to different theta phases could reflect switching between different input channels. Thus, in CA1, entorhinal-CA1 communication

may be preferentially mediated by middle gamma (50–90 Hz) timed to the peak of CA1 pyramidal-layer theta, while CA3–CA1 communication may be preferentially mediated by slow gamma (30–50 Hz) timed to the descending phase of CA1 pyramidal-layer theta. Such theta phase-based theta-gamma coupling appears consistent with theoretical suggestions (old and new) that theta schedules encoding versus retrieval states. The theta-based encoding versus retrieval scheduling models are also consistent with empirical evidence relating theta phase to the strength and direction (potentiation, depression) of long-term synaptic plasticity. In CA1, entorhinal-driven encoding may preferentially occur near the peak of CA1 pyramidal-layer theta, while CA3-driven retrieval may preferentially occur nearer the trough, with each memory state associated with different levels of inhibition and different synaptic plasticity regimes. We reviewed two recent place cell studies which provide good evidence for theta phase correlating with the propensity for encoding versus retrieval. In the study of CA3 place cells, apparent attractor-based retrieval was dominant in one half of the theta cycle. (This was the second half of the cycle, whose start was defined as the phase of lowest CA3 spiking.) In the study of CA1 place cells, an encoding-enhancing manipulation (novelty) elicited a later phase of preferred spiking closer to the pyramidal-layer theta peak, while a retrieval-enhancing manipulation (scopolamine in a familiar environment) elicited an earlier phase of preferred spiking close to the pyramidal-layer theta trough. These results closely match the predictions of encoding versus retrieval scheduling models based on theta phase.

12.4.3 Theta and Memory Performance

While some of the relationships between oscillations and memory are harder to observe in human memory studies, the research summarised in the two paragraphs above strongly suggests a role for theta in the efficiency of memory operations. Consistent with this, an emerging literature of MEG and iEEG studies is increasingly demonstrating correlations between theta power in the hippocampus/medial temporal lobe and memory performance in humans. For instance, a MEG study showed that hippocampal theta power when setting out on a route correlates with performance in navigating a virtual reality water maze. Another study found that increases in movement-initiation-related theta power during exploration/encoding of object locations within a virtual environment correlate with subsequent memory for those object locations.

Furthermore, invasive electrophysiological recording studies in humans have implicated the importance of single unit phase-locking to the hippocampal theta rhythm; the precision of phase-locking of amygdala and hippocampal neurons to the LFP theta rhythm during memory encoding predicted whether an encoded item would be successfully remembered. This suggests that hippocampal theta phase concentration, as well as power, could serve as a diagnostic of system state. Intriguingly, preliminary evidence indicates that directly stimulating the entorhinal cortex resets hippocampal theta phase and improves performance on a spatial

memory task. Thus, the improved performance could derive from the way in which theta phase determines synaptic plasticity and is consistent with theta-based encoding versus retrieval scheduling models.

12.4.4 Spatial Memory and Anxiety: Communication Through Coherence

What is the function of the hippocampus? Two broad sets of functions have been proposed: (1) spatial and episodic memory, linked to novelty detection, and (2) anxiety, linked to stress and depression. Research on both humans and rodents across a variety of behaviours provides good support for the 'communication through coherence' hypothesis whereby two regions show a transient increase in coherence when a particular task requires communication between those two regions. This phenomenon is observed in tasks tapping both of the two broad functions ascribed to the hippocampus: spatial coding and anxiety. In these tasks, the hippocampus communicates with a hippocampus-efferent region such as the medial prefrontal cortex or the amygdala, and theta coherence between the two regions increases. For instance, increased hippocampus-prefrontal theta coherence is observed in tasks which require decision-making based on spatial memory and in tasks including environment-elicited anxiogenesis. This between-region coherence is seen between both the local field potentials and between the firing of cells in the efferent region (medial prefrontal cortex or the amygdala) and the hippocampal LFP theta.

12.4.5 Spatial Memory and Anxiety: Two Components of Theta

Grid cells, and indeed place cells, may subserve path integration. One set of models of grid cells is based on the oscillatory interference of multiple inputs with somewhat different theta-band frequencies. Computational modelling and unit recording studies suggest that at least some theta cells (i.e. theta-modulated interneurons) may play a key role in path integration by encoding the component of movement velocity along different preferred directions. Each such VCO cell will have a different preferred direction. This encoding is not by rate but by frequency (i.e. inter-burst frequency in the theta band) and the resultant patterns of synchrony between cells. Thus oscillatory modulation of firing may have a very specific role in encoding information, beyond the more general functions usually ascribed to oscillatory firing.

We tested a model which 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 intercept of this relationship on the speed axis at 0 cm/s. The first component (the slope) is posited to reflect type I theta mechanisms, relating to spatial translation, and the second (the intercept) is posited to reflect type II theta mechanisms, relating to arousal/anxiety. In agreement with predictions derived from the model, we

showed that (1) environmental novelty reduces the frequency-speed slope in CA1 LFP theta and increases spatial scale in CA1 place cells and that there is a correlation between these variables and (2) anxiolytic drugs reduce the intercept of the frequency-speed slope in CA1 LFP theta. In summary, we show two contributions to theta frequency within a unifying, quantitative framework potentially linking the two rather different functions ascribed to the hippocampus.

12.4.6 Conclusions

A range of specific computational functions have been proposed to be supported by oscillatory processes and by the interactions between oscillations, such as integration, representations of order, providing quantised processing cycles, and facilitating communication between regions. Many of the most robust phenomena and most well-instantiated computational models concern the oscillations found in and around the hippocampal formation and their relationship to spatial and mnemonic processing. Here we have attempted to review some of the experimental and theoretical work in this rapidly growing field, in the hopes that it provides an instructive model system for wider application to neural processing in the brain and in support of other aspects of cognition.

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