Theta rhythms are fairly low frequency sinusoidal waves that occur in all hippocampal subregions during active exploration and rapid eye movement (REM) sleep[8](https://www.nature.com/articles/nrn.2016.21#ref-CR8),[12](https://www.nature.com/articles/nrn.2016.21#ref-CR12). Theta rhythms were first discovered in rabbits[17](https://www.nature.com/articles/nrn.2016.21#ref-CR17) and have since been recorded in many species including cats, rats, mice, bats, monkeys and humans[8](https://www.nature.com/articles/nrn.2016.21#ref-CR8),[18](https://www.nature.com/articles/nrn.2016.21#ref-CR18),[19](https://www.nature.com/articles/nrn.2016.21#ref-CR19),[20](https://www.nature.com/articles/nrn.2016.21#ref-CR20),[21](https://www.nature.com/articles/nrn.2016.21#ref-CR21),[22](https://www.nature.com/articles/nrn.2016.21#ref-CR22). These waves of activity also occur in many cortical and subcortical regions[23](https://www.nature.com/articles/nrn.2016.21#ref-CR23),[24](https://www.nature.com/articles/nrn.2016.21#ref-CR24),[25](https://www.nature.com/articles/nrn.2016.21#ref-CR25),[26](https://www.nature.com/articles/nrn.2016.21#ref-CR26),[27](https://www.nature.com/articles/nrn.2016.21#ref-CR27). Theta rhythms have been the most widely studied rhythm in the rodent hippocampus, in which high-amplitude theta is readily observed during locomotor behaviours[8](https://www.nature.com/articles/nrn.2016.21#ref-CR8). The medial septum–diagonal band of Broca has long been thought to function as the pacemaker for theta rhythms since it was first shown that hippocampal theta is abolished by septal lesions[18](https://www.nature.com/articles/nrn.2016.21#ref-CR18). These results have since been replicated many times and many further details have been revealed regarding the role of the medial septum–diagonal band of Broca in hippocampal theta generation.

***Mechanisms.*** The GABAergic cells of the medial septum that function as theta pacemakers target interneurons in the dentate gyrus, CA3 and CA1 (Ref. [28](https://www.nature.com/articles/nrn.2016.21#ref-CR28)). The septal interneurons rhythmically disinhibit hippocampal pyramidal cells and thereby promote their theta rhythmic firing. Pacemaking medial septum interneurons express parvalbumin and also express hyperpolarization- activated cyclic nucleotide-gated (HCN) channels[29](https://www.nature.com/articles/nrn.2016.21#ref-CR29),[30](https://www.nature.com/articles/nrn.2016.21#ref-CR30), which are likely to promote their pacemaker properties[31](https://www.nature.com/articles/nrn.2016.21#ref-CR31). However, the mechanisms underlying theta generation are more complicated than this simple summary implies. Septal interneurons terminate on more than one type of hippocampal interneuron[28](https://www.nature.com/articles/nrn.2016.21#ref-CR28). In addition, distinct classes of hippocampal interneurons are phase-locked in their firing to different phases of the theta cycle[32](https://www.nature.com/articles/nrn.2016.21#ref-CR32). A recent study of hippocampal interneurons in awake, behaving mice found that parvalbumin-positive basket cells preferentially fire at an earlier theta phase (when place cells preferentially fire) than do somatostatin-positive interneurons in the oriens lacunosum-moleculare[33](https://www.nature.com/articles/nrn.2016.21#ref-CR33). These findings suggest that different types of interneurons in the hippocampus have different functions at distinct phases of the theta cycle.

In support of this view are findings from a study in which different interneuron classes were silenced in head-fixed mice as they ran on a treadmill containing visual and tactile cues[34](https://www.nature.com/articles/nrn.2016.21#ref-CR34). Silencing of parvalbumin-positive interneurons, which are mainly perisomatic-targeting, increased place cell spiking in the early part of a cell's place field, which corresponds to late phases of theta[35](https://www.nature.com/articles/nrn.2016.21#ref-CR35),[36](https://www.nature.com/articles/nrn.2016.21#ref-CR36). By contrast, inhibition of somatostatin-positive interneurons, which mainly target dendrites, tended to increase place cell firing in the later part of the place field[34](https://www.nature.com/articles/nrn.2016.21#ref-CR34), which corresponds to early phases of theta[35](https://www.nature.com/articles/nrn.2016.21#ref-CR35),[36](https://www.nature.com/articles/nrn.2016.21#ref-CR36). These findings suggest that parvalbumin-positive interneurons have a role in selecting which place cells become active during theta. The findings also suggest that somatostatin- positive interneurons could inhibit the activity of place cells as the animal reaches the end of their place fields, thereby allowing the network to update its representation of location according to ongoing behaviour and current environmental cues.

Consistent with the findings that different types of interneurons fire at different theta phases, it has been shown that different types of interneuron mechanisms are involved in theta generation. First, theta rhythmic inhibition of interneurons is crucial for theta rhythm generation, as described above. In addition, mice lacking functional GABA type A receptors (GABAARs) in parvalbumin-positive interneurons show attenuated theta rhythms[37](https://www.nature.com/articles/nrn.2016.21#ref-CR37). Another important interneuron-mediated mechanism of theta generation is the rhythmic suppression of pyramidal cell activity. In support of this mechanism, it was found that specifically silencing theta-modulated parvalbumin-positive and somatostatin-positive interneurons in behaving mice increased firing rates of place cells within their place fields[34](https://www.nature.com/articles/nrn.2016.21#ref-CR34). In addition, place cells produced longer bursts of spikes when somatostatin-positive interneurons were silenced[34](https://www.nature.com/articles/nrn.2016.21#ref-CR34). Moreover, other studies have shown that theta-modulated interneurons not only inhibit spiking but also induce theta-synchronized firing in pyramidal cells. In hippocampal slices, theta rhythmic activation of interneurons induced post-inhibitory rebound spiking, which produced theta-synchronized firing across multiple pyramidal cells[5](https://www.nature.com/articles/nrn.2016.21#ref-CR5). Consistent with these findings, in a recent study of parvalbumin-positive interneurons in mice that were freely behaving in their home cage, it was shown that theta rhythmic activation of parvalbumin-positive interneurons induced rebound spiking and theta rhythmic firing in pyramidal cells[38](https://www.nature.com/articles/nrn.2016.21#ref-CR38).

Non-GABAergic mechanisms are also involved in theta production. First, excitatory currents are essential during theta[39](https://www.nature.com/articles/nrn.2016.21#ref-CR39),[40](https://www.nature.com/articles/nrn.2016.21#ref-CR40). A study of head-fixed mice running on a cue-rich treadmill found that silencing interneurons did not affect place cells outside of their place fields[34](https://www.nature.com/articles/nrn.2016.21#ref-CR34), showing that excitatory inputs are necessary to activate specific place cells within a theta cycle. Second, the intrinsic properties of pyramidal neurons that promote theta resonance may also have a role in theta production. For example, HCN1 is thought to facilitate theta rhythmic firing in neurons[41](https://www.nature.com/articles/nrn.2016.21#ref-CR41),[42](https://www.nature.com/articles/nrn.2016.21#ref-CR42) and HCN1 blockade reduces theta entrainment of pyramidal cell spikes induced by rhythmic activation of parvalbumin-positive interneurons[38](https://www.nature.com/articles/nrn.2016.21#ref-CR38). However, the precise role of HCN channels in theta production remains unclear because it has also been reported that enhanced theta rhythms occur in HCN1-knockout mice[43](https://www.nature.com/articles/nrn.2016.21#ref-CR43). Last, cholinergic inputs from the medial septum also contribute to theta generation. Cholinergic projections from the medial septum are required for theta rhythms that occur while the animal is not engaged in active behaviours, which are termed atropine-sensitive theta[44](https://www.nature.com/articles/nrn.2016.21#ref-CR44). Cholinergic stimulation may provide excitation[45](https://www.nature.com/articles/nrn.2016.21#ref-CR45) to the hippocampus during such inactive states, when movement-related inputs that drive atropine-resistant theta[44](https://www.nature.com/articles/nrn.2016.21#ref-CR44) are absent. In addition, a major role for cholinergic inputs in theta generation may be the suppression of another type of rhythm, sharp wave–ripples, which function in a manner that is antagonistic to theta[46](https://www.nature.com/articles/nrn.2016.21#ref-CR46),[47](https://www.nature.com/articles/nrn.2016.21#ref-CR47) ([Box 2](https://www.nature.com/articles/nrn.2016.21#Sec4)).

Adding to the range of complex mechanisms known to contribute to theta generation is the discovery that theta rhythms can occur in the absence of medial septum pacemaker inputs in a whole hippocampal *in vitro* preparation[48](https://www.nature.com/articles/nrn.2016.21#ref-CR48). This finding suggests that theta can also emerge from local circuit interactions in the hippocampus. Nonetheless, it is clear that medial septum inputs are important for driving theta in behaving animals, as numerous studies have shown that medial septum lesions or inactivation disrupt theta generation[18](https://www.nature.com/articles/nrn.2016.21#ref-CR18),[49](https://www.nature.com/articles/nrn.2016.21#ref-CR49),[50](https://www.nature.com/articles/nrn.2016.21#ref-CR50),[51](https://www.nature.com/articles/nrn.2016.21#ref-CR51),[52](https://www.nature.com/articles/nrn.2016.21#ref-CR52).

***Functions.*** In the 1970s, several fundamental studies showed that the extent to which theta was present in an electroencephalogram predicted how quickly animals learned or how well they remembered[53](https://www.nature.com/articles/nrn.2016.21#ref-CR53),[54](https://www.nature.com/articles/nrn.2016.21#ref-CR54),[55](https://www.nature.com/articles/nrn.2016.21#ref-CR55). These findings led to the theory that theta has an essential role in learning and memory. Since then, much evidence for this theory has been provided by studies relating theta to mnemonic task performance and synaptic plasticity[50](https://www.nature.com/articles/nrn.2016.21#ref-CR50),[56](https://www.nature.com/articles/nrn.2016.21#ref-CR56),[57](https://www.nature.com/articles/nrn.2016.21#ref-CR57),[58](https://www.nature.com/articles/nrn.2016.21#ref-CR58),[59](https://www.nature.com/articles/nrn.2016.21#ref-CR59),[60](https://www.nature.com/articles/nrn.2016.21#ref-CR60),[61](https://www.nature.com/articles/nrn.2016.21#ref-CR61),[62](https://www.nature.com/articles/nrn.2016.21#ref-CR62),[63](https://www.nature.com/articles/nrn.2016.21#ref-CR63),[64](https://www.nature.com/articles/nrn.2016.21#ref-CR64),[65](https://www.nature.com/articles/nrn.2016.21#ref-CR65),[66](https://www.nature.com/articles/nrn.2016.21#ref-CR66),[67](https://www.nature.com/articles/nrn.2016.21#ref-CR67). However, the theory has been called into question by a recent study[51](https://www.nature.com/articles/nrn.2016.21#ref-CR51) involving recordings from place cells. Place fields emerge as animals gain experience with new environments[68](https://www.nature.com/articles/nrn.2016.21#ref-CR68),[69](https://www.nature.com/articles/nrn.2016.21#ref-CR69),[70](https://www.nature.com/articles/nrn.2016.21#ref-CR70) and it is often assumed that the development of place cell representations corresponds to spatial learning. It was therefore surprising that this study[51](https://www.nature.com/articles/nrn.2016.21#ref-CR51) showed that, in rats, place fields were formed when the animal was in novel environments despite theta rhythms and theta entrainment of spikes being blocked by septal inactivation. In addition, flying bats have place cells even though these place cells show little to no theta rhythmicity in their firing[71](https://www.nature.com/articles/nrn.2016.21#ref-CR71). These findings show that theta rhythmicity is not required for the formation of place fields and thus imply that theta is not necessary for the formation of spatial memory representations at the single cell level.

However, it is important to note that memory is a distributed process involving coordinated groups of neurons, not isolated neurons, and, accordingly, several studies suggest that theta is required for the formation of memories represented by [neuronal ensembles](https://www.nature.com/articles/nrn.2016.21#Glos3). A recent study in rats showed that theta rhythm blockade by inactivation of the medial septum impaired performance on a delayed spatial alternation mnemonic task and disrupted organized ensembles of place cells that are activated in a specific order[52](https://www.nature.com/articles/nrn.2016.21#ref-CR52). Such organized neuronal ensembles are termed [theta sequences](https://www.nature.com/articles/nrn.2016.21#Glos4)[36](https://www.nature.com/articles/nrn.2016.21#ref-CR36),[72](https://www.nature.com/articles/nrn.2016.21#ref-CR72),[73](https://www.nature.com/articles/nrn.2016.21#ref-CR73) ([Fig. 1](https://www.nature.com/articles/nrn.2016.21#Fig1)) and this work suggested that theta sequences, rather than isolated place cells, are important for memory operations. In support of this view, theta sequences have been shown to be experience dependent[74](https://www.nature.com/articles/nrn.2016.21#ref-CR74) and to represent meaningful concepts that involve sequences of locations[75](https://www.nature.com/articles/nrn.2016.21#ref-CR75),[76](https://www.nature.com/articles/nrn.2016.21#ref-CR76) (such as the path to a reward). In addition, theta sequences do not simply reflect hard-wired connections in the hippocampal network, but rather they change dynamically according to the behavioural intentions of the animal[76](https://www.nature.com/articles/nrn.2016.21#ref-CR76). These results suggest that theta rhythms link different cells together in functional ensembles that support memory operations by providing integrated representations of complex concepts and experiences.

Theta may also integrate various types of sensory information received by the hippocampus — such as olfactory and visual input — by linking neurons that code different aspects of the same experience. Theta rhythms are well suited to coordinating multimodal sensory information because they correlate with movements used to acquire sensory stimuli, including sniffing and whisking[56](https://www.nature.com/articles/nrn.2016.21#ref-CR56),[77](https://www.nature.com/articles/nrn.2016.21#ref-CR77). These correlations may be important for the optimal intake of sensory information. For example, during an olfactory discrimination task, performance was poor when rats sniffed more slowly than theta frequency[78](https://www.nature.com/articles/nrn.2016.21#ref-CR78). Moreover, theta rhythm in the hippocampus was not coupled to whisking when rats were merely whisking in air rather than actively sampling olfactory stimuli[79](https://www.nature.com/articles/nrn.2016.21#ref-CR79). In addition, a recent study reported that saccade generation reset the phase of hippocampal theta in monkeys carrying out a visual memory task[22](https://www.nature.com/articles/nrn.2016.21#ref-CR22), which suggests that saccades prime the hippocampus to take in visual information. Together, these results suggest that theta coordination of neuronal activity and the active sampling of sensory stimuli produce an integrated representation of the current environment.

Furthermore, each theta cycle may represent a fundamental unit of information within an episodic memory. Support for this idea was provided by studies in rats showing that distinct representations of different environments[80](https://www.nature.com/articles/nrn.2016.21#ref-CR80), or of the same environment but with the location of rewards changed[81](https://www.nature.com/articles/nrn.2016.21#ref-CR81), were mainly segregated across separate theta cycles. Similar theta segregation occurred across head direction-coding neuronal ensembles in the medial entorhinal cortex (MEC) and the parasubiculum of rats[82](https://www.nature.com/articles/nrn.2016.21#ref-CR82). [Head direction cells](https://www.nature.com/articles/nrn.2016.21#Glos5) that fired on the same theta cycles were tuned to similar head directions, whereas cells that fired on separate theta cycles preferred different head directions. Together, these studies suggest that spikes carrying related information are linked within a theta cycle, whereas dissimilar (and thus potentially conflicting) signals are segregated on different theta cycles.

The functions described above are associated with theta that occurs during active states. However, theta is also prominent in the hippocampus during REM sleep, albeit with a lower frequency and a different regional profile than theta that occurs during waking[83](https://www.nature.com/articles/nrn.2016.21#ref-CR83). Interestingly, place cell spiking patterns that occur during active states have been shown to reoccur in theta during subsequent REM sleep, raising the possibility that REM sleep-associated theta may have a role in memory consolidation[84](https://www.nature.com/articles/nrn.2016.21#ref-CR84).