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Phase organization of network computations

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Abstract

Coupled oscillations are hypothesized to organize the processing of information across distributed brain circuits. This idea is supported by recent evidence, and newly developed techniques promise to put such theoretical framework to mechanistic testing. We review evidence suggesting that individual oscillatory cycles constitute a functional unit that organizes activity in neural networks, and that oscillatory phase (defined as the fraction of the wave cycle that has elapsed relative to the start of the cycle) is a key oscillatory parameter to implement the functions of oscillations in limbic networks. We highlight neural manipulation techniques that currently allow for causal testing of these hypotheses.

Introduction

Oscillatory activity has been associated with the encoding, communication, and storage of information in nervous systems. As such, distinct oscillatory frequencies are correlated with distinct behavioral states. In the hippocampus, theta oscillations are observed during exploration, while ripple oscillations, which coincide with population firing patterns that may represent the activation of memory traces, occur during sleep and awake immobility (1, 2). In neocortex, gamma oscillations have been associated with attention (3), and working memory (4), while alpha and beta bands may orchestrate the representation and selection of rules (5). While we can indeed draw a correspondence between oscillatory frequency and behavior, phenomena such as oscillatory cycle asymmetry (6), non-uniform distributions of spike-LFP phase relationships, such as phase-locking and precession (7), and theta-cycle skipping (8), suggest that distinct phases of a cycle have their own function in information processing. Based on these observations, the phase of oscillations has been hypothesized to be a temporal organizer of neural activity, one that allows the processing and transferring of information within and between brain circuits.

The oscillatory cycle as a functional unit

As animals explore an environment, a subset of hippocampal neurons display increased firing rates when the animal occupies restricted spatial locations of the environment. Therefore, ensembles of these cells afford a place-code based on neuronal firing rate (9). The rate code is sufficiently robust to allow us to predict the animal's location at any given time (10). What then, is the role of phase in hippocampal place coding? As the animal traverses a given neuron's receptive field, the phase corresponding to individual spikes changes in consecutive cycles of the theta oscillation (4–12 Hz, ~10 cycles per place-field), with spikes advancing progressively towards the peak of the theta cycle, a phenomenon called theta phase-precession (7). As illustrated in Figure 1, theta phase-precession allows a more precise encoding of location, providing a measure of the distance that the animal has travelled within the receptive field; importantly, it also means that different spatial information is encoded at different phases. This phase asymmetry has an additional consequence at the population level (Figure 1): Within a single theta cycle, spikes from place cells with overlapping fields represent where the animal was, where it is, and where it will be in the form of so-called theta sequences (11, 12). This suggests that the single theta cycle is a functional unit capable of representing distinct temporal-spatial content at different phases.

In addition to the segregation of information at different phases within a cycle, there is also distinct processing across successive oscillatory cycles. In the medial entorhinal cortex (mEC), spikes from neurons selective for the animal head-direction skip every other theta cycle when they fire in their preferred phases, while they fire in every cycle when in non-preferred phases. In other words, different cycles segregate at least two populations of neurons with distinct head-directionality (8). Thus, in addition to phase-specific processing, head-direction neurons exhibit a cycle-specific processing, one that segregates information between consecutive cycles and might contribute to computations that span multiple theta cycles. Pharmacological disruption of this functional cycle-offset was found to suppress the unique grid-shaped place selectivity of mEC neurons, suggesting a functional role in space representation (8). Cycle skipping has been observed in other areas of the entorhinal cortex (reviewed by Brandon et al., 2013), and elsewhere in the limbic system, namely in neurons from the thalamic nucleus reuniens, and specifically in those that were not involved in head-direction coding, suggesting its contribution to the processing of other types of information (13). Cycle-specific processing is also demonstrated in hippocampal CA3 place-selective populations, whose activity can represent different contexts by spontaneously switching back and forth between two contextual representations in consecutive theta cycles. Although mixed representations within a cycle were rare, when they happen, the segregation of representations occurred chiefly during the second half of the theta cycle (14), reflecting phase specific contextual segregation, possibly to preserve the integrity of both representations and enhance the discriminative power between environments. These results indicate the ability for the theta oscillation to segregate information sources at distinct within-cycle phases and also across cycles, potentially contributing to longer computations.

If information is indeed segregated by oscillatory phases and cycles, accessing this information by distant brain areas requires cycle and phase-specific coordinated activity, or

phase-coherence (15). Instances suggesting that one brain region can "read" the contents encoded in another, through oscillatory coherence, have been broadly reported; namely, during multi-feature representation (16, 17), and sensory information integration (18). Coherent neural activity has been reported between multiple brain areas and the hippocampus at the theta frequency, which is a time scale that is relevant for plasticity, memory formation, and decision-making (19–24). The phase-coordinated activation of these regions has been suggested to contribute to a variety of task-related functions, such as working memory, reward prediction, and decision-making (20, 25–27).

Recently reported interactions between hippocampal CA3, CA1, and mEC suggest that oscillatory phase could indeed segregate and organize the integration of different types of information. Colgin et al. found that gamma-oscillations in CA1 are dominated by slow or high frequencies at distinct theta phases, and that each gamma band is associated with increased coherence with different input areas: CA3 at slow gamma frequencies, or mEC at fast gamma frequencies(28, 29, 30). In addition, synaptic plasticity in the CA3 input also changes with phase (31). The phase-specific theta-gamma coupling suggests that coherence at distinct theta phases would allow for the selection/exclusion of neural activity from distinct inputs, namely CA3 versus entorhinal cortex in the case of CA1 (32••, 33). Based on these observations, hippocampal theta has been proposed to serve as a switch between the encoding and retrieval of information in different phases of the theta cycle (for a recent review see Hasselmo and Stern, 2014), a hypothesis that has recently received experimental support by silencing CA1 cells under distinct behavioral demands – encoding and retrieval - and at different phases of the hippocampal theta (34••). In this work, stimulation of hippocampal inhibitory interneurons (e.g., "silencing" of principal neurons) enhanced performance, if enacted at the peak of theta during the "encoding" segment of the task, or at the trough of theta during the "retrieval" segment. This is the first causal evidence of performance changes as a result of phase-specific activity manipulation at high temporal resolution.

Is phase-coding related to cognitive processing?

Changes in coherent activity between neural populations have been associated with various cognitive demands. Namely, coherence between hippocampus and cingulate cortex (35), the medial prefrontal cortex (19, 21, 22), and amygdala (36) have been reported during decision-making and reward expectation, and enhanced mPFC-striatum coherence during motor behavior and associative learning (37, 38). There is also evidence that, during working memory tasks, mPFC neurons fire at a more restricted range of theta phases (19, 21, 22). In addition, the preferred hippocampal phase of mPFC spikes switches when animals are close to the choice point in a Y maze (26), as if these cortical neurons were accessing a particular type of information, processed in a particular phase of the hippocampal LFP. Lastly, a relative increase in low-frequency theta (5–7 Hz) coherence between hippocampus and cingulate cortex accompanies a switch in the relative timing of hippocampal and cingulate spikes, when animals are close to choice points in a multi-choice task, and the amount of choice-relevant information processed increases (35). Spikes that initially are essentially simultaneous, develop a hippocampus-cingulate delay of about ~80ms. Such timing relation might serve, or even represent, the integration and processing

of incoming hippocampal information by cingulate neuronal populations, something seen in previous studies relating hippocampus and entorhinal cortex (39).

Future directions

While distinct phases within an oscillatory cycle likely segregate distinct information, allowing for its specific processing, they may also serve more complex computations spanning across multiple oscillatory cycles. An example is given by hippocampal sharp-wave ripples (SWR), which often occur in bursts. During each SWR burst, content corresponding to a long spatial trajectory is replayed in compressed form and partitioned among the individual ripples in the burst (10). In an analogous manner, multiple theta cycles might carry distinct information from the same episode, using mechanisms such as the aforementioned cycle skipping, which implies a degree of control over which cell populations become active in subsequent cycles to represent different aspects of experience. Such a mechanism would preserve the integrity of an extended experience by linking its constituent segments, and would allow this information to be read by other structures during longer computations, for instance, those related to decision-making.

The evidence reviewed here indicates that oscillatory phase could be critical for the encoding and exchange of information in limbic structures, and a fundamental property that provides neural networks with a temporal framework that segregates the writing/reading of distinct types of information. We posit that coupled oscillations are the way neuronal populations organize and sample information in time, with different computations potentially spreading through the progressive phases within a cycle. An important prediction of this hypothesis, which is now causally addressable, is that dynamically changing the phase-locking of limbic neuronal populations to ongoing oscillations could essentially regulate their contribution to particular components (stages) of cognition (behavior), and disruptions of phase-synchrony will lead to cognitive impairments.

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- Individual oscillatory cycles constitute a functional unit that organizes activity in neural networks

- Oscillatory phase is a key property of oscillations in limbic networks

- Different phases can represent distinct computations and information

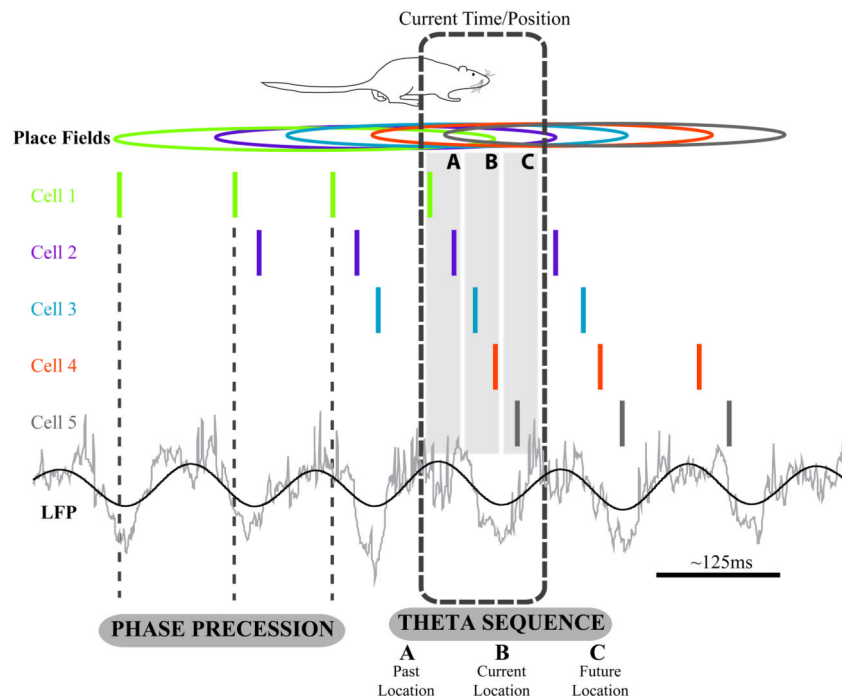- Computations may be organized across multiple oscillatory cycles

Figure 1. Oscillatory cycles and phase organize place cell activity in hippocampus
The overlapping place fields of five principal cells are represented schematically and color-coded. The corresponding vertical bars represent the spikes from each place cell as the animal traverses the receptive fields from left to right. Below is the raw local field potential (LFP), overlaid with the same signal filtered in the theta band (4–12Hz, black), to illustrate the theta rhythm that dominates during locomotion and exploration. As the animal moves across each place field, the spikes of that cell occur at progressively earlier phases of the hippocampal theta rhythm (phase precession; e.g., green spikes). As a consequence, for any given theta cycle, the spikes of place fields extending behind ('A') and ahead ('C') of the animal occur at different phases, effectively generating a compressed representation of a spatial trajectory (theta sequence, spikes in 'ABC'). Note that, without the phase information, the position within a receptive field could not be estimated from the spikes of that cell alone; also, without theta sequences, the representation of the same spatial trajectory would require computation over several cycles.