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Review
Neural Cross-Frequency Coupling: Connecting Architectures, Mechanisms, and Functions

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Neural oscillations are ubiquitously observed in the mammalian brain, but it has proven difficult to tie oscillatory patterns to specific cognitive operations. Notably, the coupling between neural oscillations at different timescales has recently received much attention, both from experimentalists and theoreticians. We review the mechanisms underlying various forms of this cross-frequency coupling. We show that different types of neural oscillators and cross-frequency interactions yield distinct signatures in neural dynamics. Finally, we associate these mechanisms with several putative functions of cross-frequency coupling, including neural representations of multiple environmental items, communication over distant areas, internal clocking of neural processes, and modulation of neural processing based on temporal predictions.

Mechanistic and Functional Characteristics of Cross-Frequency Coupling

Brain oscillations are observed *in vivo* and *in vitro* in almost any neuronal population of the neo- and paleocortex. While it is relatively easy to measure oscillations and observe their modulations in various sensory states and cognitive operations, it remains largely unclear what role, if any, they play in neural information processing or, more generally, in cognition [1,2]. An intriguing feature of neural oscillations is that rhythms of distinct frequencies show specific coupling properties [3–5]. The best-studied example of **cross-frequency coupling** (CFC, see Glossary) is between theta (4–8 Hz) and gamma (>30 Hz) oscillatory activity in the rodent hippocampus [5–7]. Several other observations of CFC, reported in a variety of species, brain regions, experimental conditions, and recording techniques, have been linked to distinct cognitive processes [7–10], but the functional significance of CFC remains enigmatic and its neuronal substrate obscure. The current working hypothesis is that different functions ascribed to CFC, including the representation of multiple items [7,11], communication between distant areas [12], and parsing of sensory stimuli with complex temporal structure [8], could arise from specific CFC patterns.

To clarify the potential roles of CFC, mechanistic and functional levels of description need to be brought together. These two strands of research have so far largely grown independently. To wit, functional models of CFC generally elude committing to precise underlying neural mechanisms, and dynamical models of CFC typically do not generate specific predictions about CFC signatures and related functions. The goal of this review is to draw a closer link between CFC mechanisms and functions. First, we introduce a novel classification of CFC phenomena according to the underlying architectures: whether they are generated by intermingled or by independent neuronal circuits, and whether the ensuing cross-frequency modulation is weak or

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Cross-frequency coupling (CFC), in other words the association of multiple frequency neural oscillations, is present across different frequency bands and neural systems.

Circuit mechanisms determine CFC characteristics: oscillations generated in distinct versus overlapping circuits, and continuously active versus intermittent fast oscillation (FO).

Dynamic network properties determine CFC signatures: phase–phase coupling occur under weakly coupling and do not co-occur with phase–frequency coupling; phase–amplitude coupling is present when the FO is intermittent or sparse spiking; amplitude–amplitude coupling requires asymmetrical slow oscillations.

CFC is mechanistically implicated in three cognitive operations: multi-item representation, long-distance communication, and stimulus parsing.

Modeling shows that theta–gamma CFC is an intracortical mechanism for parsing speech.

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strong. We then relate each architecture to an existing computational model, and connect the various CFC signatures to specific neural mechanisms. Finally, we address how such neural mechanisms may specifically underpin the commonly proposed CFC functions. Our novel framework allows us to go beyond describing the various CFC phenomena because it lays down a conceptual scaffold for the distinct CFC signatures as experimental markers of specific neural mechanisms and cognitive functions.

CFC Architectures and Mechanisms

The first requirement for a network to generate CFC is to produce neural oscillations at two distinct frequencies. Three elementary architectures allow neuronal circuits to synchronize spiking activity and generate periodic rhythms: (i) synaptic coupling between inhibitory neurons, (ii) synaptic coupling across inhibitory and excitatory neurons, and (iii) electrical coupling via gap junctions – see [1]. When synaptic coupling generates synchrony, the decay time of inhibition is a major determinant of the oscillation frequency [13]. Subpopulations of interneurons, with slower and faster synaptic dynamics, as found in both the hippocampus and the neocortex [6,14], can give rise to coupled neural oscillations at distinct frequencies. We focus here exclusively on CFC between two neural oscillations that we refer to as fast and slow oscillations, abbreviated FO and SO, respectively.

The second requirement for a neural network to produce CFC lies in the coupling between the neural circuits that generate the individual oscillations. Depending on the nature of the coupling different CFC classes can be distinguished. Intermingled CFC networks (Figure 1A) refer to architectures where circuits generating individual oscillations share a common subpopulation, while independent CFC networks refer to separate populations generating the two oscillations. This case further divides into two subtypes: bidirectional coupling (Figure 1B), where two reciprocally coupled populations generate individual oscillations, and unidirectional coupling (Figure 1C) where unidirectional connections from the population generating one rhythm actively modulate the other rhythm. So far, theoretical models of unidirectional coupling only considered the case where FO are driven by SO, although the reverse mechanism of FO driving SO might also exist [15]. Finally, unidirectional CFC with external drive (Figure 1D) corresponds to the case where SO is not an internally generated oscillation but is a (pseudo-)rhythmic sensory signal modulating FO in sensory circuits (see section 'Temporal Parsing of Continuous Stimuli').

In addition to the specific neural architectures, circuit parameters such as cross-circuit coupling strength also determine the temporal pattern of the cross-coupled oscillations. An important factor that characterizes the dynamics of CFC is whether the FO is present or not throughout the slow cycle [16]. Accordingly, we distinguish between continuous CFC, where the fast oscillations remain constantly active (Figure 1E), and intermittent CFC where FO is only present in a restricted interval of the SO cycle (Figure 1F,G). Both can be predicted from the phase diagram, which shows the conditions for fast oscillations to occur as a function of external inputs (Figure 1E–G) [13,17–19]. In the phase diagram, each phase of the SO cycle is associated with a given subset of coordinates, and the whole SO cycle determines a periodic trajectory. If the external modulation by the SO is weak enough that the FO state stays within the oscillatory region throughout the SO cycle (e.g., for weak coupling, Box 1), FO remains continuously active throughout the SO cycle. If, conversely, the SO is strong enough to drive the FO system in and out of the oscillatory region of the phase diagram (FO passes a bifurcation point at the boundary between the oscillatory and non-oscillatory region), FO occurs intermittently for SO phases where the FO system stays within the oscillatory boundaries. Within this scheme, FO can alternate with quiescent periods during which there is no spiking activity in the network (Figure 1F), with an asynchronous regime where spiking is not synchronized across neurons (Figure 1G), or any other dynamic state. Existing computational models of intermittent CFC have only focused on alternation with quiescent state [16,20].

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