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# **Communication through coherence with inter-areal delays** Andre M Bastos<sup>1,2,\*</sup>, Julien Vezoli<sup>1,\*</sup> and Pascal Fries<sup>1,3</sup>



The communication-through-coherence (CTC) hypothesis proposes that anatomical connections are dynamically rendered effective or ineffective through the presence or absence of rhythmic synchronization, in particular in the gamma and beta bands. The original CTC statement proposed that uni-directional communication is due to rhythmic entrainment with an inter-areal delay and a resulting non-zero phase relation, whereas bi-directional communication is due to zero-phase synchronization. Recent studies found that interareal gamma-band synchronization entails a non-zero phase lag. We therefore modify the CTC hypothesis and propose that bi-directional cortical communication is realized separately for the two directions by uni-directional CTC mechanisms entailing delays in both directions. We review evidence suggesting that inter-areal influences in the feedforward and feedback directions are segregated both anatomically and spectrally.

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## Introduction

Rhythmic neuronal synchronization in the gamma-frequency band has been described in the primary visual cortex (areas 17 and 18) of anesthetized cats [1]. These recordings demonstrated that separate groups of cells within the same area could establish oscillatory synchrony when their receptive fields were simultaneously stimulated by a single visual stimulus spanning both receptive fields. This oscillatory synchrony was evident in the cross-correlation function between the spike trains as a peak at approximately zero lag (Figure 1A), with additional oscillatory side lobes. These observations were the basis for the proposal that oscillatory synchrony at zero-phase lag could be a mechanism for binding cells into a functional assembly [2]. Further observations supported this proposal: pairs of cells between area 17 and area 18, between two visual areas with welldefined hierarchical relationship (area 17 and PMLS) [3], and between areas 17 of the two cerebral hemispheres [4] were all reported to engage in oscillatory synchrony with near-zero phase lag when activated by appropriate stimuli. Furthermore, when the physical distance between the cell pairs in primary visual cortex increased, pairs with synchronous spikes were almost always associated with zero-phase oscillations [5], supporting the notion that oscillations might be necessary for assembly formation over long distances. In support of this, simultaneous recordings from multiple areas of the cat neocortex showed long-range beta-band synchrony at zero phase between the field potentials of primary and secondary visual areas, somatosensory and motor cortex [6]. Finally, other studies helped solidify the link between synchronous oscillatory activity and cognitive functions like perception and attention [7,8].

These studies provided experimental evidence that synchrony could provide the mechanism for binding disparate neuronal groups into a coherent assembly (Binding By Synchrony, or BBS) [2,9]. BBS considered primarily zero-phase oscillatory synchrony as the underlying mechanism that binds together a neuronal group representing an active percept. Another hypothesis about the functional role of rhythmic neuronal synchronization is the Communication Through Coherence (CTC) hypothesis. CTC and BBS are distinct, yet consistent with each other, and experiments testing the CTC hypothesis have also provided strong evidence for the BBS hypothesis [10]. CTC states that local rhythmic synchronization leads to rhythmic modulations in synaptic input gain, and a sending group of neurons will have the highest impact on a receiving group, if its inputs consistently arrive when gain is high. This entails that effective connectivity requires synchronization between sender and receiver [11<sup>••</sup>,12– 14]. Indeed, enhanced synchronization between V1 and V4 has been found for V1 neurons activated by an attended as compared to an un-attended stimulus, likely leading to the selective enhancement of effective connectivity for attended signals [10,15\*\*]. Furthermore, a metric of effective connectivity within and between brain





Inter-areal gamma-band synchronization entails time delays. For each cross-correlogram in this figure, the arrow above the panel indicates the alignment event, i.e. what happens at time zero, and the arrow inside the panel indicates what is averaged relative to this alignment event. (A) Cross-correlogram between two multi-unit recordings from cat primary visual cortex showing zero-phase lag synchronization when the stimulus moves over both neurons' receptive fields. Modified from [1]. (B) Jitter-corrected cross-correlogram between V1 and V2 spikes showing inter-areal gamma coherence with a delay between V1 and V2. Modified from [16<sup>••</sup>]. (C) Spike-triggered averages of V1 LFPs relative to V4 spikes, consistent with an inter-areal delay. Modified from [15<sup>••</sup>]. (D) Spike-triggered average of FEF LFPs relative to V4 spikes, suggesting an inter-areal delay of approximately 10 ms. Modified from [21]. (E) Cross-correlogram between two neurons in the superficial layers of monkey V1, showing gamma coherence with a 3m delay between the deeper and the 300 micron more superficial cell. Modified from [37<sup>••</sup>]. (F) Granger-causal influence between V1 and V4 recording sites showing directed influence in the gamma band in both directions. Granger-causal influences are due to delayed interactions. Modified from [10].

areas was found to depend on the precise phase relation between local gamma-band rhythms [12]. Yet, the fundamental CTC prediction, that the phase of the local gamma rhythm modulates synaptic input gain, so far received equivocal experimental support. On the one hand, simultaneous recordings in anesthetized monkey V1 and V2 suggested 'that the coupling of V1-V2 spiking activity follows more closely the V1 than the V2 gamma rhythm' [16<sup>••</sup>]. On the other hand, when fast-spiking interneurons in somatosensory cortex were optogenetically driven with a 40 Hz pulse train, both neuronal [17<sup>••</sup>] and behavioral [18<sup>••</sup>] responses to vibrissae deflections were modulated by the phase of the deflection relative to the 40 Hz cycle. Similar effects have been demonstrated for the physiological beta rhythm in the cortico-spinal projection [19], and will need to be tested for naturally occurring cortico-cortical beta-band and gamma-band synchronization.

The original statement of the CTC hypothesis [11<sup>••</sup>] differentiated between uni-directional and bi-directional communication. 'For unidirectional communication, an oscillation in a sending group might entrain an oscillation that is intrinsically generated in the receiving group or it might even simply drive an oscillation in the receiving group. In this case, the conduction delay would, for a given frequency, directly translate into a relative [nonzero] phase [...]'. For bi-directional inter-areal communication, the original CTC statement assumed that neurons participating in a communication link were synchronized at zero phase both within and between areas. As reviewed above, experiments had demonstrated such zero-phase synchronization. CTC considered inter-areal conduction delays explicitly and suggested that they were short relative to the respective cycle lengths. Thereby, two communicating areas, oscillating at zero phase, send output at the same time in the oscillation cycle, and their mutual inputs arrive shortly afterward, still within the excitatory phase of the same cycle. A given cycle length, i.e. given oscillation frequency, can in this scheme only subserve communication up to a certain conduction delay. This led to the prediction that longer delays, observed between more distant brain areas, result in communication through coherence at lower frequencies. While this has sometimes been assumed to be the case [20], it has recently been shown that inter-areal neuronal synchronization, even over very large cortico-cortical distances, occurs also in the gamma-frequency band [10,15°,21,22°].

Modeling studies proposed a number of solutions to the problem of how to engage neuronal groups in zero-phase synchrony despite conduction delays. For example, Vicente and colleagues showed that two neuronal groups, if they were both bi-directionally connected to a third population, could display oscillatory coherence at zero phase [23]. Since this motif of common input is often observed in anatomical networks involving cortical [24] or sub-cortical sources [25], areas with widespread anatomical connectivity were envisioned to stabilize phase relationships by bringing the oscillations to zero phase across the network despite non-negligible spike transmission times. Several modeling studies explored the underlying connectivity structures that could produce zero-phase offsets, and converged on the importance of common inputs and recurrent connections to coordinate such a zero-phase phenomenon [26,27]. Other mechanisms were explored to maintain zero phase over long conduction delays, such as the spike-doublet phenomenon [28]. Although these models demonstrated the biophysical plausibility of zero-phase synchronization despite long conduction delays, several conditions need to be met. Typically, the situation needs to be symmetric, i.e. the two synchronized local circuits should be similar e.g. in their local organization and activity level, their conduction delays to the respective other circuit, and the strength of their feed-forward inhibition. While these conditions might be met for inter-hemispheric connections, they are likely often not met for connections between visual areas at different hierarchical levels. Indeed, there is increasing experimental evidence that different visual areas are gamma-band synchronized with a non-zero phase lag.

For example, it has been shown that between areas V1 and V2 in the monkey, spike-spike cross-correlograms display gamma oscillations with an average phase shift of 2.7 ms, with V2 spikes following V1 spikes (Figure 1B) [16<sup>••</sup>]. Another recent study found that spikes in V4 were coherent with fields in V1 of awake monkeys, with the V1 gamma preceding the V4 spikes by a few milliseconds (Figure 1C) [15<sup>••</sup>]. Areas separated by greater cortical distances display greater phase delays. For example, FEF and area V4 show inter-areal spike-LFP coherence in the gamma band with a phase shift corresponding to approximately 10 ms (Figure 1D) [21]. In human cortex, frontalto-visual gamma coherence has been associated with even longer ( $\sim$ 20 ms) delays [22<sup>••</sup>]. Similar observations have also been made outside visual cortex, e.g. in the hippocampus, where a gamma oscillation emerging in CA3 entrains CA1 [29]. Note that these non-zero phase relations likely reflect several distinct processes necessary for inter-neuronal influences, like pre-synaptic spike transmission and post-synaptic dendritic charge accumulation and diffusion. While it is difficult to predict the combined delay due to all these processes, particularly in the context of rhythmic coupling, the reported paired recordings directly provide the resulting net phase relation. Here, we integrate these new insights with previous evidence and propose a modified CTC hypothesis for the bi-directional communication between cortical areas.

If gamma-band synchronization between two cortical areas A and B entails a relative phase consistent with

an A-to-B conduction delay, this suggests that the gamma rhythm is generated in A and either entrains a gamma rhythm generated in B, or simply drives a gamma rhythm in B. As mentioned above, this corresponds to CTC for uni-directional communication, and it provides the core CTC mechanism: When gamma in B is phase locked to the gamma in A, then input from A to B can consistently arrive at moments of high input gain. Yet, at first sight it appears as if this could subserve only the communication in the A-to-B direction. If output in one gamma cycle of A triggers spiking in a phase-lagged gamma cycle of B, then feedback from B to A will arrive in A after the excitatory phase of the gamma cycle in which A had sent its output. Thus, CTC would subserve communication in the feedforward direction, but would not at the same time strengthen the corresponding feedback. One potential solution could be that feedback arrives at the excitable phase of the following gamma cycle. Assuming that interareal delays are fixed, this would require that gamma cycle lengths are fixed, and thus that the gamma frequency is fixed. By contrast, gamma frequency changes dynamically with stimulus parameters [30–33] and with selective attention [10]. However, laminar anatomy together with laminar electrophysiology suggests a different scenario, in which CTC subserves bi-directional cortical communication separately in the two directions.

Anatomical tracing studies suggest that those neurons of a given area that receive input and those that send output are almost completely separate [34<sup>••</sup>,35]. Thus, one set of neurons might entrain to incoming rhythmic input, and a different set might provide rhythmic output. Those separate, yet neighboring, sets of neurons might locally communicate via rate-based mechanisms and/or be synchronized in a non-rhythmic way [5]. Alternatively, receiving and sending neurons within a given area might have a particular non-zero phase relation to each other, which should be visible if the separate sets of neurons were not intermingled, but segregated e.g. in layers. In fact, neurons receiving feedforward input are primarily located in layer 4 [35]. These layer 4 neurons send intracolumnar projections to supragranular layers [36]. Supragranular neurons send output projections feedforward and also feedback to nearby areas, e.g. from supragranular V2 to supragranular V1 [34<sup>••</sup>]. Intriguingly, Livingstone showed in the granular and supragranular layers of monkey V1 that gamma-band synchronization entails a systematic inter-laminar delay of 1 ms per 100 micron, with more superficial neurons lagging deeper neurons [37<sup>••</sup>]. We show an example pair of neurons from Livingstone that was recorded at a separation of 300 micron and showed gamma-band synchronization with a 3 ms delay (Figure 1E). This suggests the mechanism illustrated in Figure 2: Bi-directional cortical communication might be realized by CTC acting separately in the two directions, with both inter-areal and inter-laminar delays (see the

thick red and blue arrows in the lower left). Inter-laminar delays might delay the supragranular gamma phase such that reentrant feedback arrives at the excitable phase of the same – delayed – gamma cycle. This mechanism should function with variable gamma frequencies, as long as inter-areal and inter-laminar delays remain stable. The precise laminar level at which reentrant feedback hits a matching phase might be determined by spike-timing dependent plasticity mechanisms. For pairs of very distant areas, reentrant feedback would arrive too late to hit a matching phase. Intriguingly, we found that for those area pairs, gamma-band influences exist essentially only in the feedforward direction [38<sup>••</sup>].

Note that the presented scenario simplifies the local rhythm as an oscillating line with a particular phase at a particular time. In reality, the rhythm is a process that entails excitatory and inhibitory neurons firing in a characteristic sequence [29,39–41]. Future research will need to investigate how inter-laminar and inter-areal synchronization with the observed delays is brought about by locally triggered and/or feedforward inhibition. Predictions from this scenario are confirmed by several recent studies. The Livingstone result was recently replicated and extended by current-source density recordings from laminar multi-contact electrodes [42]. Other studies showed that neuronal signals recorded from different cortical depths show consistent phase differences [40,43,44]. Also, the delayed inter-areal gamma-band synchronization should be visible as Granger-causal (GC) influences in the gamma band, because a GC influence indicates that variance in one signal explains otherwise unexplained variance in another signal several milliseconds later. Indeed, we recently demonstrated GC influences between V1 and V4 in both directions (Figure 1F) [10].

Furthermore, a combination of laminar anatomy and electrophysiology with inter-areal GC influence analysis suggests an additional mechanism that maintains bidirectional communication between pairs of areas that span multiple hierarchical levels. While feedforward projections between these areas originate primarily from supragranular layers, feedback projections originate primarily from infragranular layers [34\*\*]. This anatomical asymmetry strongly suggests that the above-mentioned models of long-range zero-phase synchrony based on symmetricity do not apply between hierarchically distant areas. Rather, feedback and feedforward communication appear not only anatomically but also functionally distinct. Locally, infragranular neurons show synchronization primarily at slower frequencies than gamma, such as alpha and beta [45-47]. Correspondingly, feedback communication deriving from infragranular neurons is expected to use slower frequencies (Figure 2, right side), a prediction that we have recently verified  $[38^{\bullet\bullet}]$  (see also [42,48]): Directed inter-areal influences in the beta and gamma



### Figure 2

CTC with inter-areal delays between hierarchically arranged areas. Schematic illustration of the modified CTC hypothesis incorporating delays between areas and between the layers of a given area. Purple lines illustrate supragranular gamma oscillations with a systematic delay from layer 4 toward layer 1. Such systematic delays have been found with paired recordings at two depths [37\*\*] and with multi-contact laminar probes [42]. Red arrows indicate feedforward signals, entering in the lower left into layer 4, and proceeding through supragranular layers onwards to layer 4 of the next higher area. Blue arrows indicate supragranular feedback between closely neighboring areas. The thick red and blue arrows highlight one complete cycle of feedforward and reentrant feedback signaling. Note that the reentrant feedback arrives at the excitable phase of the local gamma, because it targets more superficial sub-layers, which are delayed relative to layer 4. Brown lines illustrate infragranular beta oscillations, green arrows infragranular feedback.

bands were systematically related to the laminar origin of the corresponding anatomical projections. Across 28 pairs of visual areas, we found that an increasing asymmetry in the GC influence was strongly correlated to an increasing anatomical asymmetry (neurons increasingly projecting from supragranular layers) [38<sup>••</sup>]. This correlation between anatomical and functional asymmetry was significantly positive in the theta- and gamma-band and significantly negative in the beta-band, indicating that theta and gamma frequencies contribute to feedforward communication and beta frequencies to feedback communication. Thus, long-distance communication channels in the feedforward and feedback directions are separated not only anatomically but also spectrally. While such a spectral segregation of the counter-streams solves the problem of bi-directional communication with nonzero phase lags, it raises the question of how the segregated streams are integrated where they meet in a given area. This might be achieved through cross-frequency coupling [49,50] or through non-rhythmic coupling [5], which will require further investigation.

We propose that the mechanisms described above operate concurrently to subserve bi-directional cortical communication. Future studies will need to dissect out these possibilities with greater mechanistic detail. We would like to emphasize that existing anatomical studies provide many clues about the functional influences that might be observed. Many other relationships between structure and function are likely to be uncovered as the understanding of widespread cortico-cortical interactions matures [51-53]. In this context, we note that despite the evidence for non-zero phase synchrony reviewed here, cortico-cortical networks also engage in zero-phase synchrony. Long-distance cortico-cortical synchronization in the beta band can exist at zero or near-zero phase lag [6,54,55]. For beta-band influences, long distance zero-phase synchronization is consistent with the original CTC mechanism: input from the sending group can arrive at the receiving group within the same oscillation cycle because the conduction delay is short relative to the cycle length. In fact, in the beta-frequency band, recent studies described the coexistence of long-range synchronization at zero phase and non-zero phase [54,55], and rapid task-dependent switches between stable near-antiphase synchronization and stable near-zero-phase synchronization [54]. These spatially specific and dynamic phase relations might modulate connection strength according to CTC mechanisms.

While anatomical connectivity will shape neuronal communication, it does not fully determine it, because cognitive variables can act as powerful gates to open or close communication links [10,15<sup>••</sup>]. In fact anatomy presents a backbone that can give rise to a diversity of functional interactions [56]. Cortical hierarchy models do not specify a single 'perfect' hierarchy [34<sup>••</sup>,57]. Many pairwise connections do not agree with the global hierarchical model [34<sup>••</sup>], which may be cause and/or consequence of the flexibility in functional interactions, which change the balance between feedforward and feedback signaling depending on the cognitive context [21,38<sup>••</sup>,58]. For example, area FEF can change its directed influence on area V4 dynamically [21], and we found corresponding changes in the pattern of influences between FEF and several other visual areas [38<sup>••</sup>]. These dynamic changes in functional interactions are likely at the heart of our cognitive dynamics, which subserves adaptive behavior.

In summary, we have reviewed evidence showing that there is a diversity of phase relationships between areas and cortical layers at which synchronization can occur. This calls for consideration of non-zero phase relationships as important aspects for theories on the function of oscillations such as BBS and CTC. Non-zero phase synchronization has by now been observed both within and between areas, and therefore likely has a key role in the establishment of communication links. These communication links exist within hierarchically distributed cortical areas with exquisitely structured feedforward and feedback counter-streams which appear ideally suited for segregating the streams either anatomically, spectrally, or by a combination of both mechanisms.

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