Flexible information routing by transient synchrony

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Perception, cognition and behavior rely on flexible communication between microcircuits in distinct cortical regions. The mechanisms underlying rapid information rerouting between such microcircuits are still unknown. It has been proposed that changing patterns of coherence between local gamma rhythms support flexible information rerouting. The stochastic and transient nature of gamma oscillations in vivo, however, is hard to reconcile with such a function. Here we show that models of cortical circuits near the onset of oscillatory synchrony selectively route input signals despite the short duration of gamma bursts and the irregularity of neuronal firing. In canonical multiarea circuits, we find that gamma bursts spontaneously arise with matched timing and frequency and that they organize information flow by large-scale routing states. Specific self-organized routing states can be induced by minor modulations of background activity.

Here we investigate a class of circuit models that naturally exhibits extensive power, frequency and timing variability and that contains key types of heterogeneity, including heterogeneous transmission delays. In these models, below the onset of developing oscillatory synchrony, collective oscillations are short-lived, with durations on the order of a few cycles, are weakly synchronized and exhibit stochastically drifting frequencies. When multiple circuits with these characteristics are coupled by long-range excitatory connections, the resulting large-scale dynamics spontaneously generates temporally co-occurring bursts of synchrony. We find that the drifting frequencies of each region track each other, giving rise to transient phase-locking within the gamma bursts. Through state-resolved information-theoretical analyses, we assessed whether these transient patterns of coherence can gate information flow. We further examined the propagation of external input signals relayed from different source regions, as well as under which conditions these signals can be decoded from the activity of a downstream target region. We find that the transient coherence between the activities of the local circuits dynamically shapes the flow of information between them: information transfer is either selectively boosted or suppressed along different routes according to the transient phase pattern. These distinctive routing states have a direction set by the transient phase-relations and are modulated by the fluctuating level of synchrony. We find that the propagation of externally supplied information can be selectively gated on or off along different pathways depending on the routing state. Unexpectedly, the stochastic and fleeting nature of ongoing oscillations more effectively modulates information flow than stronger and more coherent forms of synchronized circuit activity.

RESULTS

The transient synchrony regime

Oscillatory neuronal activity in vivo is comprised of epochs of synchronous activity arising from an overall poorly synchronized state.

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We identified and characterized a regime of local circuit dynamics, below the onset of oscillatory synchrony, that mimics this fundamental feature and reproduces the substantial fluctuations in both frequency and power seen experimentally in local field potential (LFP) recordings.12,13

The dynamics of a local circuit (or region) with transient synchrony is characterized in Figure 1. A circuit is modeled as a large network of excitatory and inhibitory spiking neurons with heterogeneous local connectivity (Fig. 1a), synaptic conductances and latencies (Online Methods; parameters summarized in Table 1). Figure 1b depicts the evolution over time of the average membrane potential in the local circuit, together with the spiking patterns of individual neurons and a histogram of the multiunit activity rate (Online Methods). In the following we call the population-averaged membrane potential, a convenient descriptor of the collective neuronal activity, an LFP-like signal.18 As indicated in Figure 1b, the amplitude of the LFP trace exhibits transient epochs of increased oscillatory amplitude. These oscillatory events are more difficult to detect when inspecting the spiking patterns of a few single units whose firing is always stochastic.19,20 Individual neurons can fire at every phase of the ongoing oscillation, as revealed by an average circular variance of ~0.6 of the overall distribution of the phases of firing.

In our local circuit, as in experimental observations,21 the generation of oscillatory activity relies on delayed, recurrent interactions, either occurring through direct delayed connections or mediated by inhibitory–excitatory–inhibitory loops.20 The level of recurrent inhibition controls the overall level of synchrony of the network. Enhancing recurrent inhibition induces a graded transition toward higher synchrony. In Figure 1c this is shown via an increase of the probability $P_I$ of establishing local inhibitory connections (see Supplementary Fig. 1c for single-neuron firing rates). Dashed circles in c and d highlight two working points, with similar collective oscillation frequencies in the gamma range but very different synchronization levels. Upper (black) dashed circle (transient synchrony): $P_I = -0.25$ and $\nu_{in} = -2.5$ kHz. Central (gray) dashed circle (high synchrony): $P_I = -0.55$ and $\nu_{in} = -5.5$ kHz. (e) Transient gamma bursts are evident in the spectrogram of LFP activity at the transient synchrony working point. (f) Joint distribution of the frequencies and durations of these gamma bursts. Note the predominance of short-lived variable-frequency bursts.

Figure 1 The transient synchrony regime. (a) Scheme of the local connectivity of a brain region or area (inhibitory and excitatory neurons in blue and red, respectively). (b) Simulated activity in the transient synchrony regime. Transient oscillatory bursts in LFP time-series (bottom) and multiunit activity (middle, measured as percentage of active neurons). Individual neurons fire irregularly and not at every oscillation cycle, as indicated by the raster.

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and a short mean duration close to 100 ms (i.e., four to six oscillation cycles). We call this the ‘transient synchrony regime’. It represents a multidimensional range of parameters (cf. Supplementary Figs. 1–3) leading to a qualitatively similar mixed dynamic in which asynchronous and synchronous epochs both stochastically occur. Its properties are in good agreement with in vivo LFP recordings. In the following we consider model networks with transient synchronies, representing multiple brain regions and linked into simple structural-connectivity motifs, and analyze their emergent dynamics. In particular, we study their coordinated oscillatory bursting dynamics and their phase locking properties and, finally, test whether these features can subserve the selective and flexible routing of information.

Simultaneous emergence of phase-locked gamma bursts
We first treated the simplest case of two local circuits (corresponding to two generic areas or regions X and Y), coupled by long-range excitatory projections (Fig. 2a) established with equal probability ($E_L^R$) and strength in both directions (i.e., X-to-Y and Y-to-X). If the duration and the frequency of oscillatory epochs fluctuate independently in each brain region, it would be extremely unlikely to observe simultaneous oscillatory bursts in a source and a target region aligned in a well-defined phase relation. To analyze the inter-regional coordination (or lack of thereof) we examined the relative timing, frequencies and phase relationships of gamma bursts in the two connected regions.

We found that our model spontaneously generates correlated episodes of matched timing and with tracking frequencies between stochastically emitted gamma bursts in the two connected regions. This is depicted in the spectrograms in Figure 2b. The burst-tracking phenomenon can be quantified by the normalized overlap between the occurrence times of oscillatory bursts in distinct regions as a function of their instantaneous frequency (Online Methods). Figures 2c,d reveal that, for frequencies in the gamma band, the overlap between the timing of bursts with matching frequencies can reach relatively high values, peaking at ~0.5 for nearby collective oscillation frequencies of 60 Hz. A similar frequency-tracking behavior has been observed experimentally. We find that coordination between oscillatory episodes occurs not only between bursts with an exactly matching main frequency (Fig. 2c) but also in a cross-frequency manner (Fig. 2d).

Beyond time and frequency coordination, we find that oscillatory bursts also exhibit transient phase synchronization (Fig. 3). We performed a time-resolved cross-covariance (XC) analysis of the LFP signals from the two coupled regions of the structural motif in Figure 2a (Online Methods). Transiently rising values of XC denote the onset of epochs of increased inter-region oscillatory coherence (Fig. 3a). The time dependent maximum of XC (denoted $XC^*(t)$) occurs at a fluctuating time-lag $\tau^*(t)$, generally different from zero (in-phase) and from the average half-period (antiphase), indicating out-of-phase locking, as observed empirically. The relative phase of the rhythms of the regions, $\Delta\Phi$ (Online Methods), is a strongly fluctuating quantity whose distribution, $p(\Delta\Phi)$, is broad (Fig. 3b).

The precision of phase-locking markedly increases with the instantaneous level of cross-covariance (Fig. 3c). As shown by the joint distribution of $\Delta\Phi$ and $XC^*(t)$ (Fig. 3c), events of higher-value $XC^*$ are less frequent than those with lower values, but they tend to occur at specific relative phases. Conditioning the joint distribution on the values of $XC^*$ better reveals this phenomenon (Fig. 3c). For low values, corresponding to a poorly synchronized baseline activity, the distribution of the relative phase $\Delta\Phi$ remains broad (Fig. 3d). During epochs of strong cross-covariance, however, it becomes prominently bimodal (Fig. 3d).

A similar preference for out-of-phase interareal phase-locking is observed at the higher-synchrony working point of our system.
Figure 3 Transient phase-locking. (a) Time-resolved cross-covariance (XC) between simulated LFPs of the two coupled brain regions of Figure 2a. Circuits are set at the same working point. Horizontal dotted lines mark $\tau^* = 0$ ms (white) and $\tau^* = \pm T / 2$ (black) with $T$ equal to the length of the average period. The positions of the highest XC maxima, displaced with respect to these guiding lines, reveal the occurrence of transient episodes of interareal phase-locking with out-of-phase relations. (b) Distribution of instantaneous interareal phase-differences between simulated LFPs, in polar (left) and linearly unwrapped (right) histogram forms. Note the two peaks at relative phases $\Delta \Phi^{*+} > 0.5$ and $\Delta \Phi^{*-} < 0.5$. (c) Left: joint probability distribution of the relative phase $\Delta \Phi$ and the time-dependent maximum XC of the cross-covariance XC. Right: the joint distribution is conditioned on the value of XC*. Note the enhanced peaks associated with the high-synchrony events. (d) Polar (left) and linearly unwrapped (right) histograms of relative phase, conditioned on XC* being lower (top) or higher (bottom) than threshold levels (Online Methods). Relative phases close to $\Delta \Phi^{*+}$ or $\Delta \Phi^{*-}$ dominate when XC* is high.

(Supplementary Fig. 4). In this case, the simulated LFPs persistently oscillate and the two phase-locking configurations are stable attractors (Supplementary Fig. 4c), giving rise to a prominently bimodal $\Delta \Phi$ distribution (Supplementary Fig. 4d). The gamma-bursting dynamics can be viewed as transiently replicating oscillatory modes that would be stable in the high-synchrony regime (Supplementary Fig. 5).

Spiking activity is only weakly modulated by oscillations on average. Nevertheless, we found that the phase-concentration of neuronal firing transiently rises to higher values during high XC* transients (Supplementary Fig. 6). The instantaneous circular variances of the distribution of firing phases drops to $\sim 0.3$ during the strongest coherence oscillatory bursts and rises as high as $\sim 0.8$ during interburst periods.

Emergent routing states

The canonic two-regions motif of Figure 2a can be used as a model of two interconnected brain regions at two different levels in the cortical structural hierarchy, such as, for example, a sensory region and a prefrontal cortical (cf. the scheme in Fig. 4a) interacting in an attention-modulated manner on or a frontal and parietal pair of regions during different stages of motor planning.7,24 Others have observed that the direction of influence between such region pairs can change depending on task and behavioral stage.0,25 We thus examined how the transient dynamics of gamma bursts emerging in our models (Fig. 3) modulate the direction and strength of information flow. We quantify the efficiency and direction of inter-region information exchange of spontaneous activity depending on the system’s states by means of information theoretical analyses.

A useful measure is provided by transfer entropy (TE)26,27, here computed based on LFPs from different regions (see Supplementary Fig. 7 for an equivalent analysis based on multiunit activity). TE, in a model-free fashion, quantifies how much the knowledge of the past activity of a putative source region improves the prediction of the future activity of a target system; in this sense it constitutes a generalization of the Granger causality approach (exactly as mutual information (MI) generalizes linear correlation). The information-theoretical setting naturally allows conditioning the estimation of TE or MI on an arbitrary set of constraints. We designed state-selecting filters that condition information measures on transient dynamical features (for example, on specific relative phase conditions to be fulfilled) and so define a state-specific directed functional connectivity (or, in short, a routing state). As summarized in Figure 4b, transients of a system’s activity fulfilling specific state-filtering conditions are pooled, through time and trials, into separate statistical samples. Different distributions of activity were obtained from these separate samples and quantified information-theoretically (Online Methods). Using this approach we probed information transfer specifically within state-filter-selected epochs.

Using a TE analysis in which the relative phase is constrained to a narrow band, we study state-specific directed functional connectivity between the collective neuronal activity of the regions X and Y (Fig. 4c).

For both directions of interaction, TE exhibits a broad peak centered on a specific combination of the state delay $\tau$ and $\Delta \Phi$ (Fig. 4d and Online Methods). In both panels, the state delay, $\tau$, that maximizes information transfer corresponds to a lag of $\sim 4$ ms, at which $\text{XC}(t)$ peaks during coordinated bursting events (Fig. 3a). This optimal state delay $\tau$ depends on the metastable phase locking ($\Delta \Phi^{*+}$) and therefore differs from the mean interareal transmission delay $\delta$ of 1.5 ms (Supplementary Figs. 5 and 18 and “Discussion” section). For longer state delays, TE does not rise significantly above chance level ($P < 0.05$, bootstrap confidence interval (c.i.) comparison over the whole white-colored range in Supplementary Fig. 8a). Optimal functional coupling occurs at different relative phases for different directions of influence. This phenomenon is quantified by the functional anisotropy index, $\Delta \text{TE}$, proportional to $\langle \text{TE}_{Y \rightarrow X} \rangle - \langle \text{TE}_{X \rightarrow Y} \rangle$ (Fig. 4c and Online Methods). Two patches with equal absolute values, $\Delta \text{TE}$, but different signs correspond to effectively unidirectional configurations with opposite directions (Fig. 4f), supported by the same fixed bidirectional structural connectivity. We refer to the states corresponding to these two configurations, filtered by the $\Delta \Phi^{*}$ ($Y$ leading, $X < \Delta \Phi < 0.5$) and $\Delta \Phi^{*}$ ($X$ leads $Y$ and $0.5 < \Delta \Phi < 1$) conditions, as the Top and Bottom routing states, respectively. Information transfer proceeds from the region leading in phase to the region lagging in phase, as if long-range synaptic connections from the laggard to the leader region were effectively nonfunctional.

Based on analysis of the relative phase-dependency of TE in Figure 4d,e we adopted coarser state-filtering criteria, using solely the $\Delta \Phi^{*}$ and $\Delta \Phi^{*}$ conditions. Figure 4g,h shows the net directed information transfer in the Top (Fig. 4g) or Bottom routing states (Fig. 4h) compared to chance-level expectations (Online Methods). Information transfer in the opposite laggard-to-leader direction falls below chance level, thus actively quenching information transfer.

Information transfer in the leader-to-laggard direction was highly significant despite the coarseness of the $\Delta \Phi^{*}$ and $\Delta \Phi^{*}$ conditions ($P < 0.0001$, bootstrap c.i. comparison). This indicates that the emergence of information transfer anisotropy requires just a weak degree...
of phase-locking. In fact, we find unidirectional transfer of information during Top and Bottom transients to be robust, persisting within extended ranges of local synaptic strength (Supplementary Fig. 9), interareal coupling (Supplementary Figs. 9 and 11a) and synchronization levels (Supplementary Figs. 10 and 11b), and we find that such information transfer emerges for distinct mechanisms for the generation of oscillations (Supplementary Fig. 12) or indicators of the population’s activity (Supplementary Fig. 7). We further restricted the analyses in Figure 4g,h to transients with peak $\Delta \Phi$ rising above (Supplementary Fig. 8c,d) or dropping below (Supplementary Fig. 8e) different threshold levels (Online Methods). We found that information is transmitted primarily inside the bursts. The interareal synchrony thus works as a gain control that boosts information transfer in one of the two directions when synchronization is high and limits it during asynchronous epochs.

Flexible routing of information streams

The existence of a phase-gated dynamic switching between Top and Bottom routing states only starts to address the question of routing. In particular, it is not obvious that streams of external information entering the circuits are routed in a fashion similar to the spontaneous activity analyzed so far. To examine this aspect in our models, we introduce external streams of input currents, $S_{X}$ and $S_{Y}$, modeling incoming activity from surrounding areas or direct sensory stimulation (for a characterization of this state, see Supplementary Fig. 13). We then studied how these input streams propagate through the interconnected regions conditional on the current routing state (Fig. 4i, and Online Methods). The addition of external input did not modify the system’s states as defined by TE, which remain markedly unidirectional (Fig. 4j,k). State-resolved information theoretical analysis between the input streams $S_{X}$ (or $S_{Y}$) to the source region $Y$ (or $X$) and the neuronal activity of the target region $X$ (or $Y$) revealed that the information supplied to a source region propagated toward an interconnected distant target, following the path imposed by the routing states, defined by the state-specific TE analysis. The phase-relations between the neuronal rhythms define the direction of information flow of input signals, as revealed by the MI analysis of Figure 4l,m and the TE analysis of Supplementary Figure 14.
Next, we further extended the model to include three interconnected regions, X, Y and Z. As shown in Figure 5a, the state-selection procedure can be extended straightforwardly to this case. In this system, six different conditions can arise, denoted by the state-selecting filters $ΔΦ_{12}$ to $ΔΦ_{6}$ (where $ΔΦ_{i}$ indicates a first-phase configuration in which X leads Z or Y within a cycle; Supplementary Fig. 15 and Online Methods). Depending on parameters and inputs, a multitude of possible functional motifs can arise.

This three-region architecture enabled us to study a setting typical of visual selective-attention experiments\textsuperscript{1,12,29}. For instance, one can consider a situation in which two distinct visual stimuli are processed by distinct populations X and Z in lower-order areas such as parts of V1, whose distinct receptive fields both fall within the larger field of a third population, Y, in a higher-order area such as V4 (Fig. 5b). In such an experiment, the attentional effect may be alternatively directed to one stimulus or the other, defining an information-routing problem in which the transmission toward Y of the input stream entering X (or Z) and associated with the attended stimulus must be enhanced, while the other, unattended, stream entering Z (or X) should be gated off.

A routing-state analysis of the three-region system (Fig. 5c) is shown in Figure 5d and Supplementary Figure 15. In this setting, X and Z send convergent projections toward a third higher-order region, Y, which, in its turn, sends weaker feedback projections to X and Z (for a system with equally strong back-projections see Supplementary Fig. 15). TE analysis of the LFP signals of the three coupled regions shows that multiple routing states can arise, depending on the phase pattern. In particular, in the routing states defined by the phase configurations $ΔΦ_{31}$ and $ΔΦ_{42}$, information transfer along one of the possible feedforward pathways is completely blocked.

This allows selection of only one of the two possible information sources when external input streams are supplied to the system (Fig. 5e). We focus here on routing of the signals $X_{1}$ and $X_{2}$ coding for different stimuli (for more routing examples see Supplementary Fig. 16). In a phase configuration in which X leads Y leads Z, only information about the input stream $X_{1}$ is present in the downstream region Y (Fig. 5f), although no other mechanism besides an unsuitable phase relation prevents information about $X_{2}$ from arriving at Y. Switching between the routing states detected by the $ΔΦ_{31}$ and $ΔΦ_{42}$ conditions thus produces rerouting effects analogous...
to those that would be associated with a reorientation of the attentional spotlight.

Steering information routes
In the examples of Figs. 4 and 5, transients of the different routing states (Top and Bottom for the two-regions model and ΔΦXY to ΔΦXY (or the three-regions model) arise spontaneously, with similar probabilities of occurrence. We found that applying a weak bias, making the bursts of a given type more likely to occur, can enforce a dominant direction of information transfer (Fig. 6).

Figure 6a–c refers to routing-state control in the two-regions model (Fig. 4), and Figure 6d refers to one in the three-regions model (Fig. 5). Raising the baseline input to either one of the two possible source regions by ΔV increases the probability that the biased region will transiently become a phase leader, favoring the occurrence of specific routing states. As indicated by the pie charts in Figure 6c, a bias to circuit X (or Y) increases the probability of occurrence of a Bottom (or Top) state, as seen in the rightmost (or leftmost) columns. Equivalently for the three-regions model, a bias to the region X increases the probability of X leading Y and, simultaneously, of Y leading Z (Fig. 6d). Similarly, a bias to the region Z increases the probability of Z leading Y and, simultaneously, of Y leading X (right columns). As the relative phase-distributions (Fig. 6b and Supplementary Fig. 17) take on more asymmetric shapes, maps of the functional anisotropy index reveal a strong asymmetry in the direction of information transmission, showing that information flows preferentially from the biased region toward the target one. This is detailed in Figure 6b for the two-regions model in and in Supplementary Figure 17 for the three-regions model.

DISCUSSION
Our results demonstrate that, in coupled circuits with transient synchrony, frequency tracking and out-of-phase locking of oscillatory bursts are emergent features of the large-scale circuit’s collective dynamics. Bursts are generated in coordinated sets of near-simultaneous onset and mediate transient phase-locking between the regions’ activities. The transient patterns of inter-regional coherence define flexible routing states that determine the direction of information flow of both endogenously generated rate fluctuations and externally supplied signals.

While the mechanisms of transient interareal frequency tracking and phase-locking in biologically plausible models were largely unexplored, evidence for such patterns of coherence has been reported experimentally but questioned elsewhere. Distinct from the typical behavior of chains of weakly coupled oscillators, burst coordination in our model is fast enough to conciliate transient phase-locking with a rapid dissolution of oscillatory synchrony after a few cycles. This intrinsic and spontaneous coordination is achieved despite the sparseness of interareal connections and the heterogeneity of conduction delays. Our work demonstrates that fast dynamic frequency-matching is a robust emergent feature of interacting neuronal populations with transient synchrony and does not require an external controller.

Our study of the dynamics of a general regime of neuronal network activity with transient synchrony sheds a new light on longstanding arguments against coherence-mediated communication.
A first widespread concern has been the low and inconsistent power of gamma oscillations in vivo\textsuperscript{12,13}. In our models, LFP oscillations show inconsistent power and fluctuate stochastically between 40 and 70 Hz, and their time-averaged LFP spectrum presents broadband gamma modulation (Supplementary Fig. 6f), consistent with other models of transiently synchronous neuronal activity\textsuperscript{31}. Despite the weak average gamma power, TE analyses revealed that the transient power rise during oscillatory bursts is sufficient to impact on information transfer between areas and on the propagation of externally supplied information. A second concern relates to the low level of spiking correlations. While several studies identify marked and context-dependent oscillatory synchrony\textsuperscript{32}, others find only weaker spiking correlations\textsuperscript{33}. In our simulations, spiking activity always remained highly irregular. In particular, neuronal firing was poorly phase-concentrated, with the exception of burst events (Supplementary Fig. 6). These short epochs nevertheless convey the largest net contribution to directed information transfer (Supplementary Fig. 8c,d). A third concern is raised by the large variability of interareal conduction delays, impeding the phase-matched arrival of presynaptic spikes with respect to the oscillation in the target region. The regulation of information transfer, however, is the outcome of collective emergent states and not just of direct monosynaptic interactions. In fact, observed interareal phase relations are largely independent of the distance between the interacting sites\textsuperscript{34}. The average interareal cross-correlation lag is not determined solely by the neuronal conduction delay but also depends on the phase response properties of the coupled populations\textsuperscript{35,36}, which in turn reflect local circuit parameters\textsuperscript{37}. As shown in Supplementary Figure 5, different interareal phase-locking relations can be implemented with a fixed interareal delay just by changing the level of local inhibition. It is thus conceivable that the fine control of local inhibition exerted by specialized interneuron types\textsuperscript{38} might play an active role in setting interareal phase relationships.

Our model predicts that transitions between alternative routing states, multiplexed within a fixed structural circuit\textsuperscript{39}, are reflected by switching patterns of interareal phase differences\textsuperscript{40}. Such a routing mechanism would be compatible with both rate coding and more-complex representations relying on finer organization of the spiking patterns\textsuperscript{41,42}. Given the irregular spiking in our models, coordinated excitability fluctuations may gate the transmission of complex spike patterns. Future studies could, for instance, explore whether the simultaneous emergence of synchronized bursts can modulate information propagation through embedded systems of interacting synfire chains\textsuperscript{5,6} or whether stimulus-dependent cell assemblies\textsuperscript{43,44} could be selectively gated by interareal phase coordination.

The phase relations we find may be potentially useful in establishing dynamic functional hierarchies of interareal communication\textsuperscript{23}, with information flowing preferentially from phase-leading toward phase-lagging regions. Since the structures of these phase patterns are not solely prescribed by connectivity, different regions can compete flexibly, assuming the functional roles of sender or receiver of information, depending on the specific context and modulatory signals (Fig. 6 and Supplementary Fig. 17). Interareal interactions may be mediated not only by coherence in the gamma band but also by that in the beta band\textsuperscript{46} or by coordinated faster and slower oscillations, as in the hippocampus\textsuperscript{46,47}. For simplicity, our model was designed to generate transient oscillations within a single gamma band. This specification, however, is not inherent to our approach and can be relaxed to reproduce multifrequency oscillations\textsuperscript{48}. At a brain-wide scale, functional networks associated with multifrequency spectral fingerprints may be actively generated\textsuperscript{49,50}. Future studies could thus also examine more complex models, including multifrequency interactions or multiareal networks of greater complexity. Our study lays out a methodology that can be used to assess the dynamic routing properties of such models stringently and critically and can guide the design of future experimental studies. Features that at first sight appear to be noncompliant with information routing may actually provide the brain with a particularly flexible routing mechanism.

METHODS

Methods, including statements of data availability and any associated accession codes and references, are available in the online version of the paper.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

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AUTHOR CONTRIBUTIONS

A.P. performed the simulations of the models and analyzed the results; A.P., F.W. and D.B. conceived the study, designed models and developed analysis pipelines; A.P., T.G., F.W. and D.B. wrote the paper. All authors discussed the results and implications.

COMPETING FINANCIAL INTERESTS

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Online Methods

Network models. The networks used to model local brain regions consisted of 1,000 excitatory and 250 inhibitory conductance-based Wang-Buzsáki neurons with random connectivity. Synaptic conductances had a difference of exponentials time-course, proportional to a postsynaptic channel open probability

\[
\tau = B \left[ \frac{t - t_0 - d}{\tau_1} - \frac{t - t_0 - d}{\tau_2} \right]
\]

where \(t_0\) is the time of the presynaptic spike, \(d\) is a combined axonal and synaptic transmission delay, \(\tau_1\) and \(\tau_2\) define the rise and decay synaptic time-constants ([\(\tau_{\text{rise}} = \tau_1, \tau_{\text{fall}} = \tau_2\)]), respectively, and \(B\) is a normalization factor. Excitatory (E) or inhibitory (I) synaptic currents were then given by \(E_{(E,I)} = g_{(E,I)}^{(E,I)} v^{(E)}(t)\) for \(v^{(E)} \rightarrow V_x\), where \(g_{(E,I)}^{(E,I)}\) is the peak conductance of the considered synapse and \(V^{(E)}\) is the synaptic reversal potential. We used \(V_E = 0 \) mV and \(V_I = -80 \) mV for excitatory and inhibitory synapses, respectively.

Both peak synaptic conductances and synaptic delays were Gaussian-distributed random variables with prescribed means \(g_{(E,I)}^{(E,I)}\) and \(\tau\) and standard deviations \(\sigma_{(E,I)}\). The probability of establishing an excitatory (or inhibitory) connection within each modeled brain region is denoted by \(P_E\) (or \(P_I\)). The background drive to each neuron in the network was provided by external excitatory inputs, modeled as Poisson processes with rate \(\lambda_{E}\) and statistically independent for different neurons. Each spike injected by this external driving source induced in the target neuron a synaptic current as in equation (1). Peak conductances of the external drive were also heterogeneous and assumed values sampled from a truncated Gaussian distribution with mean \(g_{(E,I)}^{(E,I)}\) and s.d. \(\sigma_{(E,I)}\). Long-range synaptic connectivity between two or three brain regions was purely excitatory, targeting both excitatory and inhibitory neurons in the target region. In the two-regions network architecture, the probability of having a long-range excitatory projection, \(P_{EL}\), was held equal between regions. In the three-regions network architecture, the region \(Y\) (at the highest hierarchical level) received feedforward connections from \(X\) and \(Z\) with a probability \(P_{EL}\) that was stronger than or equal to probability \(P_{EL}\) of feedback connections from \(Y\) to both \(X\) and \(Z\). Both feedforward (and feedback) connections had equal conductance strength. No connection was present between \(X\) and \(Z\). Long-range excitatory synaptic conductance values were drawn from the same distribution as for recurrent excitation within each local region.

The default set of default network parameters is summarized in Table 1. These default values were used, unless specified otherwise (specific parameter variations are listed in the following). Simulations were performed with \(P_{EL} = 0.3\) in Figures 1, 2 and 6 and Supplementary Figures 17, \(P_{EL} = 0.6\) in Supplementary Figures 4 and 14, and \(P_{EL} = 0.1\) in Supplementary Figures 12 and 14f-h. The probability of establishing a local excitatory connection deviated from default values in Figures 4 and 5 and Supplementary Figures 15-17, where \(P_{EL} = 0.35\); in Supplementary Figures 7 and 14 with \(P_{EL} = 0.25\); and in Supplementary Figure 12 with \(P_{EL} = 0\). In Figure 6, we also adopted a smaller degree of input conductance heterogeneity, \(\sigma_{V_x} = 0.1\) nS in Supplementary Figures 9, 10, 13 and 16 we adopted \(\sigma_{V_x} = 0.5\) nS; and in Supplementary Figures 15 and 17 we adopted \(\sigma_{V_x} = 0\) nS. Large values of \(\sigma_{V_x}\) might lead to symmetry-breaking network instances, in which one specific phase-locking configuration is favored over the other even when there is no bias applied. For clarity of illustration, these symmetry-breaking instances were excluded from all analyses. Typical simulation runs were performed with a fourth-order Runge-Kutta method when the input was a smooth random field (fixed time-step \(\Delta t = 0.05\) ms or simple Poisson spike-trains (fixed time-step \(\Delta t = 0.1\) ms), and lasted 10 min unless otherwise indicated (details found in the corresponding section). When the input was modeled as an Ornstein-Uhlenbeck process, an Euler-Maruyama integration scheme with \(\Delta t = 0.01\) ms was used instead. To sample neuronal activity distributions, we combined multiple simulations with quenched heterogeneity and connectivity and different initializations of the stochastic drive to the system. Generally, no statistical methods were used to predetermine sample sizes, but our sample sizes are similar to those reported in previous publications.

Characterization of network activity. The synchronization index was chosen to be the previously introduced \(\chi^2\), where

\[
\chi^2 = \frac{N \sigma_{V(t)}^2}{\sum_{i=1}^{N} \sigma_{V(t)}^2}
\]

Here is the LFP-like signal. The variables \(\sigma_{V(t)}\) and \(\sigma_{V(t)}\) denote the s.d. of LFP amplitudes over time or, respectively, of the membrane potential traces \(V(t)\) of each individual neuron. The \(\chi^2\) coefficient is bounded to the unit interval, with vanishing values indicating asynchronous dynamics. The frequency of the collective oscillation of a region is calculated as the inverse of the first peak position of the autocorrelation function of a multiunit rate signal, obtained by convolving the raster plot of each local network with a Gaussian kernel of s.d. of 2 ms. The rate signal in Figure 1f was calculated as a histogram with a 1-ms bin width. Single neuron rates were calculated as the inverse of the mean interspike interval. Spectrograms of LFP activity (Figs. 1e and 2c and Supplementary Figs. 4a and 13b) were calculated using a standard time-frequency Fourier analysis with overlapping Hamming windows (300-ms size, 250-ms overlap) and the time-averaged spectra through the multitaper method (16 tapers).

Analyses of gamma-burst properties and coordination. To extract the joint distribution of frequencies and durations of oscillatory burst (Fig. 1f and Supplementary Fig. 4b), we thresholded LFP spectrograms (300-ms size, 280-ms overlap) at the 95th percentile of instantaneous power values. The thresholded spectrograms were then scanned at different frequencies (i.e., line by line) to extract the durations of time intervals over which power at the given frequency was continuously sustained above threshold. We sampled these burst durations by combining 20 trials (overall, 100 min of signal). To study time and frequency coordination between oscillatory bursts occurring in different coupled regions (Fig. 2c–d), LFP spectrograms of each region were thresholded above their 95th percentile and scanned by line, creating a binary string for each population and for each frequency \(\chi_x\). These binary strings were then multiplied against the analogous strings obtained from the other population and normalized by the s.d. of the binary strings to obtain the overlap

\[\phi(f) = \frac{\chi_x(f)}{\sigma_{\chi_x}} \frac{\chi_y(f)}{\sigma_{\chi_y}}\]

The calculation was made using 50 trials for Figure 2c and 10 trials for Supplementary Figures 4 and 13. Significance of the estimated overlap (Fig. 2c) was assessed by comparing 95% c.i. for each overlap value with the associated permutation-based chance levels (2,500 replicas).

Analysis of transient phase-locking. We calculated time-resolved cross-covariance \(\chi(x)\) adopting an overlapping sliding window 50 ms long (roughly two average oscillation periods) and with 0.1-ms steps. Within each time-window, standard cross-covariance was performed between chunks of LFPs of each of the coupled populations:

\[\chi(t, \delta) = \langle \langle V_x(t') - V_x(t) \rangle \langle V_y(t') - V_y(t) \rangle \rangle \]

where \(\langle \rangle\) denotes averaging over a 50-ms time-window \(W(t)\) centered on time \(t\), and \(V_x\) and \(V_y\) are LFP averages over this same window.

The instantaneous phase of each LFP signal \(\Phi_x\) and \(\Phi_y\) was calculated by interpolating a straight line over the unit phase interval \(0 < \Phi < 1\) between consecutive maxima of the population activity of a single repetition. A peak in population activity was considered such if it was the maximum in a neighborhood of a half-period radius of the central oscillation frequency of the population activity. Such a fast approach avoids bandpass-filtering and leads to similar results as a Hilbert transform analysis, as previously shown. The relative phase is then defined by \(\Delta \Phi = (\Phi_y - \Phi_x) \bmod 1\). The joint probability distribution of the time-dependent phase difference \(\Delta \Phi\) and the time dependent peak of \(\chi(x, \Delta \Phi) = \max(t, \delta)\), was obtained from 100 simulated trials (overall, 1,000 min of signal). The conditional probability distributions shown in Figure 3C were obtained by independently normalizing each line of the probability matrix in Figure 3C. The \(\chi^2\) threshold for Figure 3d was the 99th percentile (\(\chi^2 = 0.37\)).

The circular variance of Supplementary Figure 6 was calculated as follows. Given \(\{x_1, x_2, \ldots, x_K\}\) with \(k = 1, \ldots, K\), the set of spike-times within a window of time \(W(t)\) centered at \(t\), emitted by neurons in subset \(X\) of \(K\) neurons belonging to the region \(X\), we define \(\phi^2(t)\) as the phases of the LFP of area \(A\) at spike-times
θX(k) = Φk(xk). The local circular variance of the firing of the subset X, CVX(t), is then the circular variance of the set of phases θX(k). We then average circular variances over the two coupled regions, i.e.,

$$CV(t) = \frac{1}{2}(CV_X(t) + CV_Y(t))$$

We evaluated these circular variances considering two different conditions. In Supplementary Figure 5c–e, the subsets X and Y included all the neurons belonging, respectively, to the regions X and Y. In the right panels of Supplementary Figure 5d,e, these sets were then restricted to just ten randomly chosen neurons within the regions. In both cases, the length of the sliding windows W(t) was equal to that of seven average oscillation periods. We used 200 noise realizations with the same network architecture, lasting 1 min each, to obtain the joint distribution of CV(t) and XC(t). As before, the conditional probability distributions shown in Supplementary Figure 6d,e were obtained by normalizing each line of the probability matrix in Supplementary Figure 6d,e.

Analyses of information transfer. We evaluated TE20–27 between discrete time-series of the simulated LFP signals VS(t) and VY(t). These signals are constrained to take values from the set Ξ, and have distributions p(x|y) and p(y|z). The set Ξ corresponds to the set of signal values observed within specific temporal windows in which certain conditions, defining a consistent functional state, are properly fulfilled (state-selecting filter; see below). TE from region X to region Y is defined as a deviation from the Markov condition54,55:

$$P(y_1|y_1^{(k)}) = P(y_1|X_1^{(k)})$$

This reads: the probability of VY at a given value y at time t, given that the k past values of VY were y1(k) = (y1 - t, ..., y1 - t), is independent from the past values of VX given by x1(k). This condition is only fulfilled if there is no influence from the past values of VY on the current values of VX in other words, only if the distributions are conditionally independent. These probabilities are not time dependent; they depend only on the time lags (t1, ..., tk). TE can then be expressed as a measure of the divergence from the above Markov condition:

$$TE_{X \rightarrow Y}(t_1, ..., t_k) = \sum_{y_1(t_1), ..., y_k(t_k)} p(y_1(t_1), ..., y_k(t_k)) \log \frac{p(y_1(t_1), ..., y_k(t_k))}{p(y_1(t_1)|x_1(t_1), ..., x_k(t_k))}$$

(3)

Here we relaxed the Markov condition and adopt a commonly used simplification20,56–62. We replaced the past activity history Ξk and x1(k) in the previous expression with unique observations of past values at a single latency at time y1(k) = y1 - t and x1(k) = x1 - t, and then treated the interaction latency τ as a variable parameter. With this approximation, the TE expression in equation (3) can be simplified as

$$TE_{X \rightarrow Y}(\tau) = H[y_1|y_1 - \tau] - H[y_1|x_1 - \tau, y_1 - \tau]$$

(4)

TE represents the reduction in uncertainty (entropy, H) about the future state of a given region Y when the history of region X is also taken into account. An analogous (but not identical) expression for TE in the opposite Y-to-X direction is obtained by exchanging the indices X and Y. In Supplementary Figure 18, we compared the results obtained with the simplified expression of equation (4) against estimations of TE considering different state-delays for sender and receiver or considering more than a single state-delay.

When more than two regions constitute the interacting system, the above expression for TE must be modified to account for the possibility of indirect functional interactions (for example, transfer from X to Z via Y, etc.). We used partial TE63 to uncover the direct interactions between pairs of populations when embedded in a larger multareal system. Given a set of three populations, X, Y, and Z, partial TE (pTE) with a single state-delay is defined as

$$pTE_{X \rightarrow Y}(\tau) = H[y_1|x_1 - \tau, y_1 - \tau] - H[y_1|x_1 - \tau]$$

(5)

This expression reduces to equation (4) when the activity of Z is statistically independent from that of X and Y.

All the probability densities required for the evaluation of equations (4) and (5) can be straightforwardly derived from the three-term or four-term joint probability distribution p(y1, x1 - t, y1 - t) in the TE case or p(y1, x1 - t, y1 - t, z1 - t) in the partial TE case. These probabilities must be sampled uniquely over the time instants in which specific conditions hold. TE and pTE are then evaluated in a consistent regime, specified by the choice of the filtering conditions, Ξ. Information-theoretical analysis with a specific filtering condition based on the instantaneous interareal phase-difference ΔΦ returns the routing state.

When considering the two-regions model in Figures 4d,e and 6 and Supplementary Figures 8a–c and 17, the ΔΦ range is split into five relative-phase bins of equal size (the TE vs. τ and the ΔΦ surfaces were then smoothed by linear interpolation). Figure 6 and Supplementary Figure 17 show the anisotropy index from single trials. The filtering criteria in just two Top and Bottom routing states (Fig. 4g–m and Supplementary Figures 7, 8d, 9–12, 14 and 17) were selected time instants in which the relative phase fell, respectively, in the coarser ranges ΔΦ5, i.e., 0 < ΔΦ < 0.5, for the Top state or ΔΦ1, i.e., 0.5 < ΔΦ < 1, for the Bottom state.

In Supplementary Figure 8, we adopted a state conditional to the strength of interareal cross-co-variance, in addition to the instantaneous phase relation. Conditions on the instantaneous value of XC were imposed arbitrarily, requiring it to exceed a threshold XC_high = median(XC) + 0.5 (Supplementary Fig. 8b,d) or to be less than XC_low = median(XC) - 0.5 (Supplementary Fig. 8b,e).

In the three-regions model in which a pairwise analysis was devised (Fig. 6 and Supplementary Fig. 17), the procedure was identical to that described above for the two-regions model. More complex state-filtering conditions were devised for complete analysis of the dynamics of the three regions. The six possible hierarchical configurations that the LFP signals can take define six filtering conditions, ΔΦ1,2,3 to ΔΦ2,2,2, giving rise to different (or sometimes the same) routing states, as illustrated in Figure 4d. The conditions can be written in terms of the pairwise phase relations:

$$\Delta \Phi_{12}^{XY} \iff \Delta \Phi_{12}^{XY} > 0.5, \Delta \Phi_{12}^{XZ} > 0.5, \Delta \Phi_{12}^{YX} > \Delta \Phi_{12}^{XY}$$

$$\Delta \Phi_{12}^{XY} \iff \Delta \Phi_{12}^{XZ} < 0.5, \Delta \Phi_{12}^{XY} < 0.5, \Delta \Phi_{12}^{XZ} < \Delta \Phi_{12}^{XY}$$

$$\Delta \Phi_{12}^{XY} \iff \Delta \Phi_{12}^{YX} < 0.5, \Delta \Phi_{12}^{XY} < 0.5, \Delta \Phi_{12}^{YX} < \Delta \Phi_{12}^{XY}$$

$$\Delta \Phi_{12}^{XY} \iff \Delta \Phi_{12}^{XZ} > 0.5, \Delta \Phi_{12}^{XY} < 0.5, \Delta \Phi_{12}^{XZ} > \Delta \Phi_{12}^{XY}$$

$$\Delta \Phi_{12}^{XY} \iff \Delta \Phi_{12}^{YX} > 0.5, \Delta \Phi_{12}^{XY} > 0.5, \Delta \Phi_{12}^{XZ} > \Delta \Phi_{12}^{XY}$$

For the two-regions model, we estimated histograms (within the two possible Top and Bottom routing states) in Figure 4g,h and Supplementary Figure 8d–e based on 500 min of simulated signal from 50 trials of the same network instance; in Figures 4d,e and 6b and Supplementary Figures 8c and 17 based on 10 min of signal from a single network realization (the mean in Supplementary Fig. 8a is based on a total of 150 min from 15 different network instances); for Supplementary Figures 9 and 10 based on single trial simulations, each lasting 10 min; in Supplementary Figure 11 based on 40 different network instances (10 min of LFP signal for each considered parameter configuration); in Supplementary Figure 12 based on 10-min simulations from 50 different network instances (in Supplementary Fig. 7, only 10 network instances were used, with the same simulation time); and in Figure 4j–m and Supplementary Figure 14 based on simulations lasting 50 min each from 40 different network instances (2,000 min of simulation time). In the three-regions model, we estimated histograms (within each of the six state-filtering conditions) in Figure 5d and Supplementary Figure 15 based on simulations lasting 3,600 min each from 12 different network instances; in Figure 5f and Supplementary Figure 16 based on 20 network instances lasting 4,000 min in total; and in Figure 6 and Supplementary Figure 17 based on simulations lasting 10 min each from 25 different network realizations. TE values obtained from the sampled histograms using the definition in equation (4) were then further corrected against finite-size bias by quadratic extrapolation toward infinite sample size64. Given a set of time series of length L, we took three subsets of the same length Lk with Lk = L/k with k = 1, ..., 10. For each trimmed length Lk, TE is calculated from each of the three subsets and then averaged over them to obtain a value TEk. Finally, we evaluated the limit to infinite sample size for TE, extrapolating it as the vertical-axis intercept of a second-order polynomial fit of TEk to k. The 95% c.i. for TE values were approximated as ±2× s.d. above and below the mean, over the considered network instances or trials (95%
Exogenous sources of information. These c.i. were then compared to the null hypothesis (lack of functional coupling), providing a baseline TE range for significance testing. To obtain the null-hypothesis distribution of TE, we relied on resampling techniques and used bootstrapping with replacement to build a distribution of 1,500 surrogates for network realisation, and then collected them. To maintain the oscillatory nature of the analyzed time-series, we built bootstrap surrogates using LFP blocks of a mean length $\Lambda$. This value should be long enough to guarantee that the signal's autocorrelation structure would be preserved when building bootstrap surrogates. To choose $\Lambda$, we analyzed the behavior of the bootstrapped TE versus the chunk length. For oscillatory signals in the transient synchrony regime, the value of the bootstrapped TE initially increases and then saturates at around $\Lambda = 100$ ms. We thus chose $\Lambda = 300$ ms for the TE baseline calculations, and we kept it the same for the MI calculations, although the random inputs are not oscillatory and therefore the values of the bootstrapped MI were independent of $\Lambda$. After building a null-hypothesis histogram of TE values, we determined the range between its 2.5th and 97.5th percentiles and used it as the baseline TE range. TE values whose 95% c.i. was completely disjoint and fell above (or below) this baseline range were indicative of significantly enhanced (or damped) information transfer with respect to chance level.

Finally, we defined the functional anisotropy index:

$$\Delta \text{TE}(t) = \frac{\text{TE}_Y \rightarrow X(\tau) - \text{TE}_X \rightarrow Y(\tau)}{\max(\text{TE}_X \rightarrow Y(\tau), \text{TE}_Y \rightarrow X(\tau))}$$

bounded in the $-1 \leq \Delta \text{TE} \leq 1$ range, as a simpler indicator of the different efficiencies of information transfer in the two possible reciprocal communication directions between a pair of regions.

Modeling of the external input signals. Exogenous sources of information were modeled with two different input models. In the first approach (Fig. 5 and Supplementary Figs. 14 and 16), external inputs were modeled as discrete Gaussian random field (GRF) input currents. GRFs were generated as follows. First, we used an Ornstein-Uhlenbeck process. The input signal was given by a discrete Fourier transformation of a set of $\gamma(t)$, evenly spaced with $\Delta t = 200$ ms for the TE baseline calculations, and we kept it the same for the MI calculations, although the random inputs are not oscillatory and therefore the values of the bootstrapped MI were independent of $\Lambda$. After building a null-hypothesis histogram of TE values, we determined the range between its 2.5th and 97.5th percentiles and used it as the baseline TE range. TE values whose 95% c.i. was completely disjoint and fell above (or below) this baseline range were indicative of significantly enhanced (or damped) information transfer with respect to chance level.

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The currents conveying the externally supplied inputs $I(t) = \psi(t)$ were generated independently for each area. Instances of $I(t)$ were first generated in MATLAB and then fed as input currents to each neuron within the corresponding region. We used the same fourth-order Runge-Kutta integrator ($\Delta t = 0.05$ ms) as described above. The parameters used for the simulations of Figure 5 and Supplementary Figures 14 and 16 were $\tau = 1$ ms, with a gain factor of $\gamma = 2$. Qualitatively similar results were obtained over the entire range $0.5$ ms $\leq \tau \leq 5$ ms.

In Supplementary Figure 14c–h, we used a different noise model, modeling inputs as Ornstein-Uhlenbeck processes. The input signal was given by $dS(t)/dt = -\gamma S(t) + g\eta(t)$, where $\eta$ is a Gaussian white noise with 0 mean and unit variance. In this figure, we used $g = 0.1$ and $\gamma = 1$. An Euler-Mayurama method was used to simulate the input and the network dynamics, with a time step $\Delta t = 0.01$ ms.

Information sharing between the two endpoints of a communication line was assessed via the classical measure MI.$^{25}$ MI between an injected signal $S(t)$ to the source region $X$ and LFP from a target region $Y$ can be state-filtered as TE by pooling only input- and response-value pairs within the epochs fulfilling the filtering criteria specified by the chosen filter, $\Xi$, between the LFP signals $V_X$ and $V_Y$:

$$\text{MI}_X \rightarrow Y(\tau) = \sum_{\tau \in \Xi} p(y_1, s_1 - \tau) \log_2 \left( \frac{p(y_1)p(s_1 - \tau)}{p(y_1, s_1 - \tau)} \right)$$

When analyzing three-region structural motifs in Figure 5 and Supplementary Figure 16, for TE, we computed partial (also called conditional) MI.$^{45,46}$, introducing an additional condition on the third region signal.

Statistics. Generally, we used nonparametric statistical testing procedures based on comparisons between confidence intervals obtained by bootstrapping with replacement (for both the association and the null hypotheses). See details in each specific Online Methods subsection. A Supplementary Methods Checklist is available.

Code availability. Custom-written code for model simulations and their analyses are available on reasonable request to the corresponding authors.

Data availability. All simulations analyzed during the study can be regenerated using the above code.