

The connectome

Discovering oscillatory interaction networks with M/EEG: challenges and breakthroughs

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The systems-level neuronal mechanisms that coordinate temporally, anatomically and functionally distributed neuronal activity into coherent cognitive operations in the human brain have remained poorly understood. Synchronization of neuronal oscillations may regulate network communication and could thus serve as such a mechanism. Evidence for this hypothesis, however, was until recently sparse, as methodological challenges limit the investigation of interareal interactions with non-invasive magneto- and electroencephalography (M/EEG) recordings. Nevertheless, recent advances in M/EEG source reconstruction and clustering methods support complete phase-interaction mappings that are essential for uncovering the large-scale neuronal assemblies and their functional roles. These data show that synchronization is a robust and behaviorally significant phenomenon in task-relevant cortical networks and could hence bind distributed neuronal processing to coherent cognitive states.

Interareal synchronization coordinates anatomically distributed processing

Psychophysical data suggest that perception and cognition operate with integrated object representations and yet, at the neuronal level, these objects are represented by neurons signaling only the objects' constituent features. Neuronal feature representations are constructed from peripheral sensory information in a simple to complex manner [1] in the cortical hierarchy from primary sensory cortices to higher-level sensory and associative cortices, where the identities and higher-level abstractions of objects are represented [2–5]. This anatomical distribution of functionally specialized neuronal feature processing is the basis for a 'perceptual binding problem' [6]: what mechanisms integrate the scattered neuronal feature representations into a coherent perceptual object representation?

Higher-level functions, such as attention, working memory (WM) and sensory awareness, also arise from neuronal activity that is distributed both anatomically and temporally in widespread cortical networks. The neuronal substrates of these functions involve the posterior parietal (PPC), temporal and prefrontal cortices (PFC) [7–10].

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Thus, perception and cognition emerge through cooperation of numerous distinct brain regions, which, like the 'perceptual binding problem', poses a generic binding problem: what are the mechanisms that coordinate the communication and integration in the network of task-relevant brain structures [11,12]?

Rhythmic millisecond-range spike–time correlations (i.e. spike synchronization) may be one mechanism for feature integration because neurons effectively detect and respond to temporally coincident spikes and synchronization thus boosts the impact of neuronal signals on downstream neurons [6,13]. Synchronization thus confers on a neuronal assembly an advantage over less coherent neurons in the competition of engaging their target neurons [14,15].

Several early studies from cat and monkey visual cortices showed that stimulus-related neuronal activity becomes transiently synchronized and entrained into gamma-frequency band (30–80 Hz) oscillations if the stimulus features are in line with Gestalt binding criteria, such as continuity, similarity, colinearity and common motion, and hence were likely to represent a common physical object (Figure 1a; for reviews, see [6,14], but see [16]). Importantly, spike synchronization was also associated with sensory

Glossary

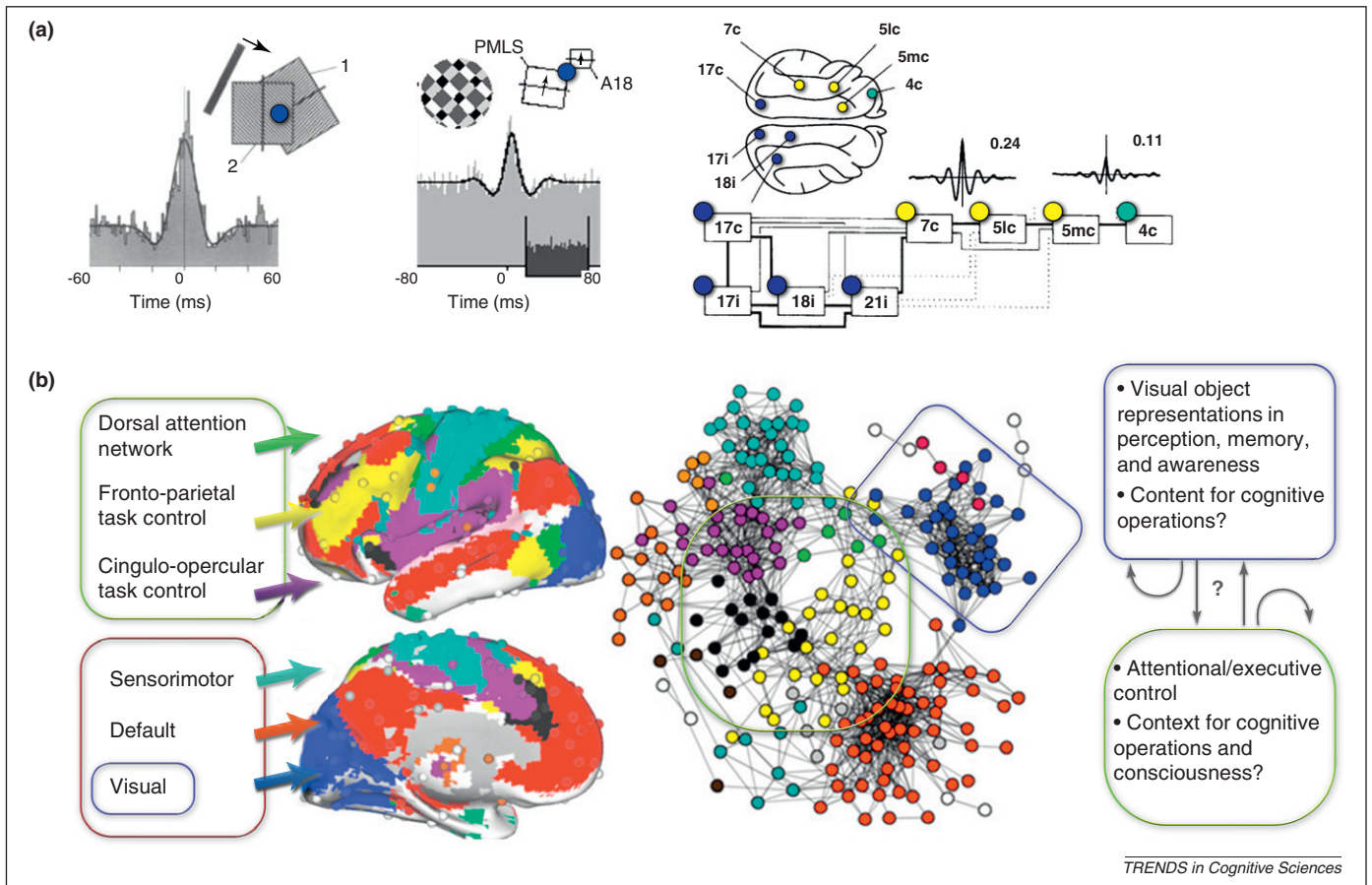
Hub: a brain region that has high centrality in a network. Hubs can be identified by many different centrality metrics such as degree or betweenness centrality. Degree is the number of edges that connect the vertex with other vertices. Betweenness centrality quantifies the fraction of the shortest paths in the graph that pass through the vertex [51].

Graph: a mathematical description of network data, which is defined by a set of nodes or 'vertices' and by connections or 'edges' that link the vertices. In brain networks, brain areas constitute the vertices and the edges are defined by structural, functional or effective connectivity.

Magneto- and electroencephalography (M/EEG): techniques that measure non-invasively at the scalp level the magnetic and electric fields, respectively, produced by coherent neuronal activity. The macroscopic magnetic fields are thought to emerge from summation of ionic currents in cell bodies of thousands of coaligned pyramidal neurons whereas the electric potential differences are associated with the corresponding volume-conducted currents in the extracellular space.

Phase synchrony: a consistent, non-random phase difference between two signals. Phase correlations of neuronal oscillations may be tightly associated with millisecond-range temporal correlations in neuronal firing (spike synchrony), but phase correlations may also be observed between oscillations in much longer time scales, up to hundreds of seconds.

Source modeling: a family of methods to reconstruct from M/EEG signals the time series of the underlying cortical sources.



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Figure 1. (a) Interareal synchronization among visual cortical regions is observed in cat field potential recordings for perceptually coherent objects that share related features. Left panel: interareal synchronization among cell groups with overlapping receptive fields in area 17 when activated by single light bar. Adapted from [87]. Synchronization is also observed for superimposed gratings between areas A18 and posteromedial lateral suprasylvian (PMLS) sulcus (middle panel, adapted from [88]), and for patch gratings among visual, parietal and motor cortical regions (right panel, adapted from [89]). **(b)** Blood oxygenation level-dependent (BOLD) signal correlations in functional magnetic resonance imaging (fMRI) are correlated with oscillation amplitude–amplitude correlations in electrophysiological recordings and define stable patterns of interareal functional connectivity. This network has a salient community structure and can be divided into dorsal attention, frontoparietal task control, cingulo-opercular task control, sensori-, sensorimotor, default and visual systems. Adapted from [27].

awareness of the presented stimuli, demonstrating that synchrony is functionally relevant at the systems level [17]. Later field potential and multiunit recordings have shown that gamma-band synchronization is also strengthened by attention (for review, see [18,19], but see [20]), which suggests that interareal spike synchronization may contribute mechanistically to the coordination of attentional signals across brain regions [21].

In addition to spike synchronization, correlations between neuronal oscillations *per se* may also have a functional role. Oscillations are directly associated with rhythmic membrane potential fluctuations [22,23] so that neuronal excitability is stronger in one phase than in the opposite. Hence, oscillations impose excitability windows that regulate neuronal activity in local networks and thereby both facilitate interactions between areas having an appropriate phase difference and suppress inputs arriving at the inhibitory phase. Phase correlations of neuronal oscillations could thus play a key mechanistic role in coordinating interareal communication [24] and collective neuronal dynamics, and could thereby underlie the coordination of anatomically distributed neuronal activity into coherent cognitive states [12,14,25].

In time scales much longer than those of spike synchronization and phase correlations, oscillations are also

coupled through amplitude–amplitude correlations. In humans, these correlations characterize spontaneous resting-state activity and are closely associated with interareal correlations of slow fluctuations in the blood oxygenation level-dependent (BOLD) signals recorded with functional magnetic resonance imaging (fMRI) [26]. Graphs of such slow functional connectivity can be partitioned into several distinct modules, or ‘subgraphs’, that constitute functionally distinct task-positive and -negative systems such as sensory, dorsal and ventral attention, cingulo-opercular, as well as default mode networks (Figure 1b) [27].

Although the human functional connectome, as defined by fMRI, has been studied intensively over the past decade, much less is known about spike synchronization and phase correlations of fast neuronal oscillations in the human cortex. Non-invasive recordings of spike synchrony appear impossible at the moment, but phase correlations can be investigated non-invasively with M/EEG (see Glossary). We review here the brief history of M/EEG studies that have used source modeling in investigations of interareal phase synchronization and its role in human perception and cognition. We also outline the principal methodological challenges in analyses of neuronal interactions in non-invasive M/EEG data.

Signal- and source-space views on synchronized oscillations and their attentional and perceptual correlates in the human brain

If interareal interactions contributed mechanistically to the binding of scattered neuronal activities into cognitive functions, they should be observed among the task-relevant cortical regions and be correlated with behavioral measures. MEG and EEG can be used to probe non-invasively the phase and amplitude dynamics of ongoing activity of local neuronal assemblies in human cortex and are thus the primary experimental tools for addressing the functional significance of interareal phase and amplitude interactions in human cognitive operations.

Analyses of phase synchrony between MEG-sensor or EEG-electrode signals have shown that the strength of synchronization in the alpha (8–14 Hz), beta (14–30 Hz) and gamma (30–120 Hz) frequency bands is indeed correlated positively with sensory awareness [28,29], complex cognitive task performance [30], attention [31] and working memory [32–34]. These and many other signal-space studies thus strongly suggest that task demands for cognitive integration are associated with long-range synchronization of cortical oscillations. However, sensor-to-sensor interaction analyses can be confounded by signal mixing, source amplitude changes, and other issues [35] (see Boxes 1 and 2). Most importantly, signal-space data shed little light on the underlying synchronized anatomical structures. Identification of the anatomical sources is crucial for appropriate interpretations of the results because even nearby cortical regions (see, for example, the ‘default’ and ‘task control’ systems in Figure 1b) may play very different functional roles. For instance, the functional implications of ‘frontoposterior’ M/EEG synchronization would be different if the underlying (undiscovered) sources were in the default-mode network than if they were in the dorsal attention network.

Source reconstruction approaches hold great promise for solving these problems but although source modeling methods have been available for nearly two decades, technical and computational challenges have hindered cartographic mapping of interareal interactions in source space.

Nevertheless, in the past decade, a growing number of studies on interareal synchronization have used M/EEG data and various source modeling methods. Most studies have considered interactions among ~2–9 cortical regions of interest (ROIs) and successfully revealed modulations of interareal synchrony pertaining to perceptual or attentional task performance [36–40]. Gross *et al.* [36] investigated the role of interareal synchronization in attention with an attention–blink paradigm, where visual stimuli were presented at a rapid stimulus presentation rate and the subjects’ task was to detect target letters presented randomly in the stimulus stream. In this paradigm, target letters preceded by another target shortly before are difficult to detect. Beta (14–30 Hz) frequency band synchronization between PFC, PPC, temporal and cingulate regions was stronger when the target stimulus was detected than when it was not (Figure 2a), indicating a role for this interaction in attention. In another study, spatial attention was found to enhance gamma-band synchronization between ROIs in the middle temporal (MT) area, intraparietal sulcus (IPS) and frontal eye fields (FEF) when visual stimuli were in the attended compared to the ignored hemifield [38]. This study was among the first demonstrations of similarity in attention-related interareal synchronization in humans and monkeys. Kveraga *et al.* [40] investigated interareal synchronization in the contextual association network by minimum–norm–estimate (MNE)-based source modeling and ROIs in visual, parahippocampal and medial prefrontal regions, and observed that transient synchronization in high alpha- and beta-frequency bands in this network was correlated with behavioral contextual associations (Figure 2b). These data together suggest that synchrony among task-relevant structures is indeed strengthened in experimental conditions where successful task performance dictates a joint operation of many distinct cortical areas.

Comparable results have been obtained with intracranial EEG recordings, which yield much more sharply localized signals with less mixing than M/EEG (see Box 1) but, on the contrary, allow only sparse sampling. The interareal synchronization in these direct cortical recordings has been

Box 1. A paradigm for non-invasive interaction mapping with M/EEG

Coherent postsynaptic currents in a sufficiently large sheet of colinearly oriented pyramidal neurons produce a macroscopic electromagnetic field that can be recorded by measuring electric potential differences with EEG and magnetic fields or field gradients with MEG. Although these fields can be estimated accurately from known current sources through ‘forward’ modeling, the reconstruction of unknown sources from measured fields (i.e. ‘inverse’ modeling) is an ill-posed problem with no unique solutions. Nevertheless, constraints, such as minimization of total current and modeling of sources on individual cortical surfaces, can be exploited to obtain good estimates of the neuronal sources underlying M/EEG signals.

Figure 1a displays matrices of interaction strengths as quantified with phase-locking values (PLVs, z-axis, see Box 3) between every cortical patch in a whole-cortex parcellation of 150 patches. In the ‘control condition’ (C), the simulated patch time series are uncorrelated and have equal mean amplitudes whereas in the ‘task condition’ (T), 10 out of 150 cortical patches are mutually phase synchronized as depicted in the graph with small phase lags but without a change in mean amplitude. Forward modeling yields a virtual M/EEG recording of these synthetic cortical data and subsequent phase synchrony analyses (Figure 1b) between all pairs of 204 planar gradiometers reveal

considerable artificial synchrony that is caused by the mixing of cortical signals at the scalp level. Task condition synchronization can be estimated roughly by subtracting the control condition (‘T–C’) or by using an interaction metric that is insensitive to linear signal mixing (such as the imaginary part of PLV, ‘Im(T)’, see Box 2), but in either case, the resulting sensor-level connectivity is not anatomically informative.

Cortically constrained minimum–norm–estimates (MNE) can be used to reconstruct cortical phase and amplitude dynamics (Figure 1c,d). The matrices in Figure 1c show the pairwise synchronization among cortical patches (same as in (a)) obtained by MNE inverse modeling of the M/EEG sensor signals (see (b)). Importantly, although there is a considerable amount of artificial synchronization in inverse modeled data even in the absence of any true correlations (Figure 1c, left panel), the inverse transform successfully reduces the fraction of corrupted signal pairs compared to the sensor level (Figure 1e; p-gr., planar gradiometers; mag., magnetometers). The source reconstruction also recovers relatively well the simulated time series (see Figure 1d) and reveals the original simulated phase correlation network (see Figure 1c, right panels, color scale as in (b)), albeit with residual spurious correlations (see Box 2). Advanced inverse methods and cortical parcellations can further improve the source separability.

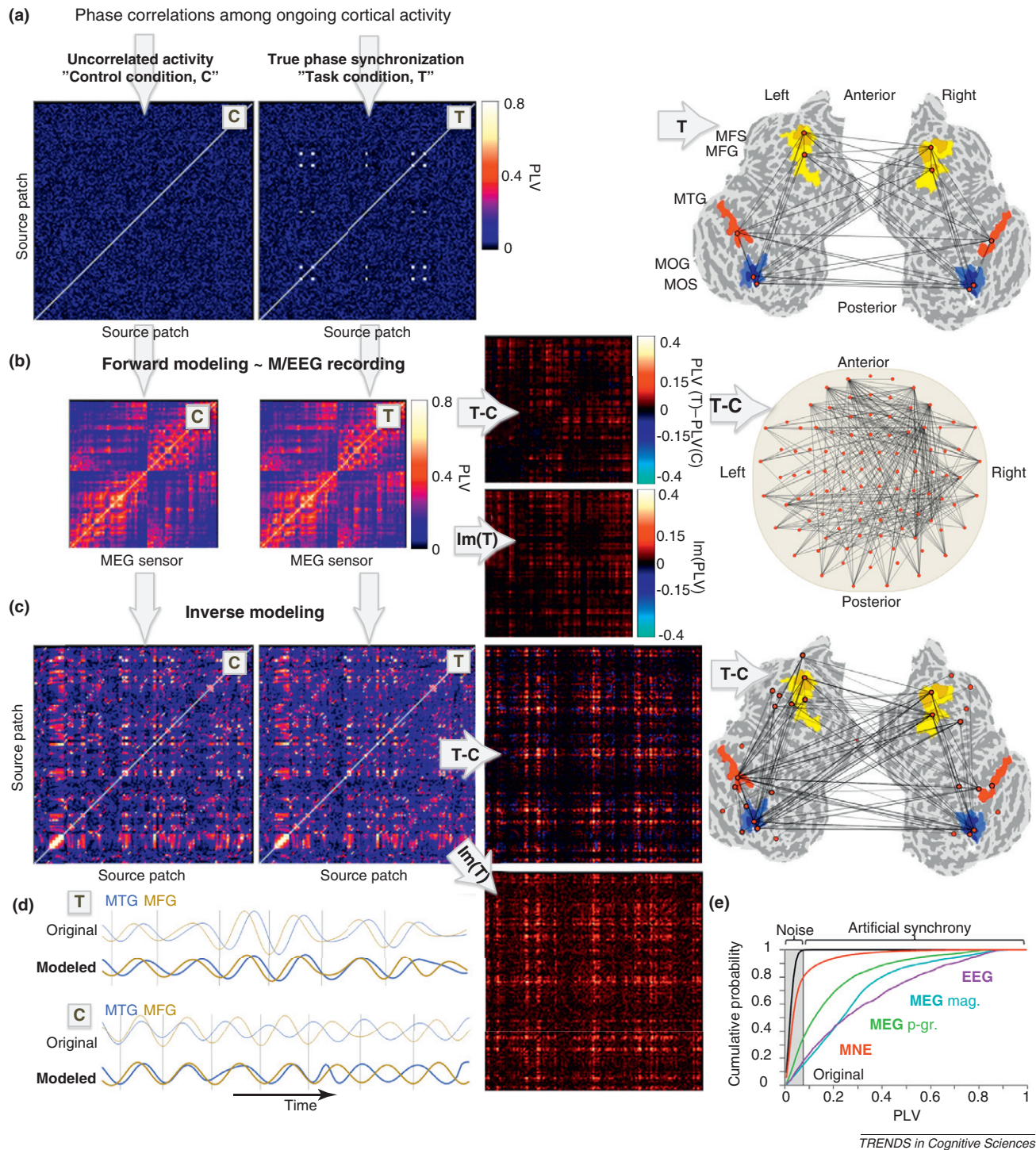


Figure 1. A schematic illustration of the signal mixing problem in M/EEG recordings and source reconstructed data. **(a)** The matrices show all-to-all pair-wise phase synchrony, as indexed by a phase locking value (PLV), in a simulation of uncorrelated cortical patches (left panel, control condition, C) and in a simulation of a set of correlated patches with an amplitude equal to the uncorrelated ones (middle panel, task condition, T). The anatomical background (right panel) shows the left and right, respectively, flattened cortical surfaces with colored patches indicating the correlated sources in T and the black connections indicating the correlations per se (M, middle; F, frontal; T, temporal; O, occipital; S, sulcus; G, gyrus). **(b)** All-to-all pair-wise phase synchrony matrices for MEG planar gradiometers can be obtained by forward modeling the data in (a) in conditions C and T (left panels). Subtraction of the control from the task condition (T-C, middle up) or a usage of a signal-mixing-insensitive interaction metric (here the imaginary part of PLV, $\text{Im}(T)$, middle down) can be used to compensate for artificial synchrony. The interactions in MEG sensor layout (right panel) are not very informative about the underlying anatomy [see (a)]. **(c,d)** Inverse modeling can be used to estimate with acceptable fidelity the source patch time series (d) from the measured M/EEG time series, which thereafter can be used to obtain an all-to-all pair-wise phase synchrony matrix for patches covering the complete cortical surface (c) and to estimate task-condition networks [see (b)], albeit with residual spurious interactions (see Box 2). **(e)** Cumulative probability distributions of C condition matrices in a (original, black), b (MEG planar gradiometers, green; MEG magnetometers, cyan; EEG, purple), and c (source reconstruction, red). The distributions show that source reconstruction alleviates signal mixing but does not remove it completely.

Box 2. Challenges in electrophysiological connectivity analyses

We summarize here the central confounders and pitfalls in M/EEG-based interaction analyses as well as possible strategies for addressing them in empirical work.

Volume conduction and linear signal mixing: ‘artificial’ synchrony

As illustrated in [Box 1](#), the mixing of neuronal signals is inevitable in M/EEG recordings. This problem influences, albeit to a lesser extent, the invasive electrophysiological recordings with depth and subdural electrodes. In coherence and phase synchrony estimates, linear mixing of signals causes artificial synchrony between nearby sources. Nevertheless, artificial synchrony can be attenuated or removed by several measures. (1) Baseline compensation or control conditions can be used to identify non-artificial changes in phase synchrony when using interaction metrics such as the phase-locking value (PLV), pairwise phase consistency or mutual information. This approach is, however, sensitive to concurrent changes in source amplitudes [35,50]. (2) Because linear mixing is always instantaneous, interaction metrics that detect exclusively lagged interactions and suppress zero-phase lag synchrony, such as the imaginary coherence, imaginary part of the phase locking value, phase-slope index and the (weighted) phase-lag index, are immune to artificial synchrony but at the cost of an inability to detect true zero-phase lag interactions [80]. (3) Directed interactions such as those revealed by transfer entropy and partial directed coherence [37,43] may be robust against linear mixing. (4) CF phase interaction analyses are nonlinear and (see [Box 3](#)) are not contaminated by artificial synchrony although local CF interactions are sensitive to broadband artifacts.

‘Spurious’ synchrony

Spurious interactions ([Figure 1a,b](#)) persist even after artificial interactions are removed in one way or another and thus constitute a profound problem. The spurious interactions can be suppressed by minimizing the effects of linear mixing in the first place, for instance with source reconstruction and efficient cortical parcellation approaches [48–50]. At present, however, there are no established effective strategies or unique solutions for removing residual spurious interactions.

Stimulus-evoked responses

Additive neuronal activity and also phase resetting of ongoing activity caused by exogenous events bias all interaction estimates directly. If the evoked components did not have intertrial latency variability, their effect could be estimated and compensated by surrogate data obtained with trial shuffling, but because such latency variability is a well-known phenomenon [81], the true efficiency of trial shuffling remains unclear. The ultimate solution is thus to use experimental designs where the time window of interest is not contaminated by evoked responses at all.

Signal-to-noise ratio dynamics

Spontaneous and stimulus-induced changes in the amplitudes of ongoing activity change (i) the signal-to-noise ratio of signals from a given source in relation to environmental and sensor noise and (ii) the

balance in the mixing of signals from multiple concurrent sources. Both effects influence the accuracy of phase (and amplitude) estimates of the signal from the source of interest and thereby bias the interaction estimates. Although the effects of the signal-to-noise ratio changes on interaction estimates can be estimated with simulations [49], they remain a significant putative confounder.

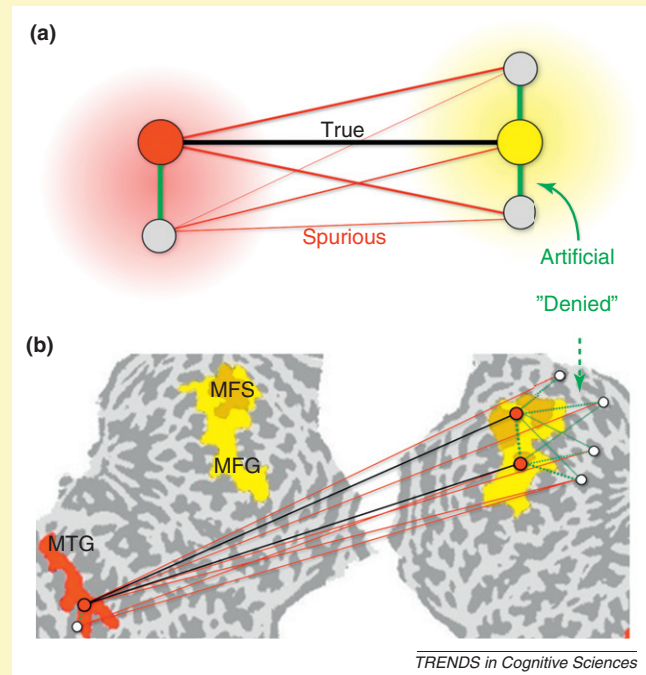
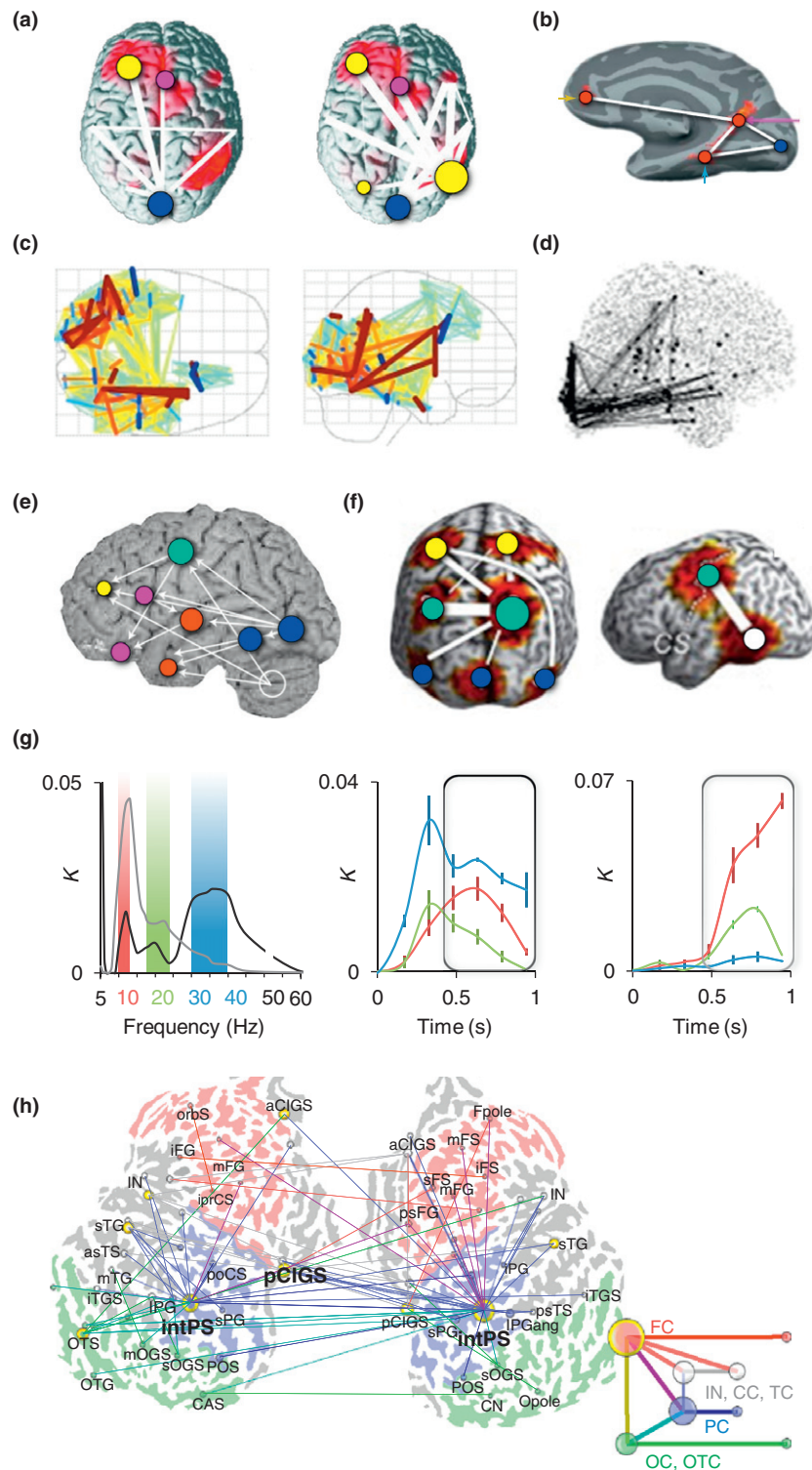


Figure 1. ‘Artificial’, ‘spurious’ and ‘denied’ interactions in networks influenced by signal mixing. **(a)** The schematic graph shows two brain regions (red and yellow nodes) that are coupled by an interaction (black line). After M/EEG data acquisition and inverse modeling, signals from these regions are mixed with signals from nearby regions (grey nodes, blurry background indicates significant mixing). The mixing results in artificial linear correlations including artificial phase synchronization with a 0- or 180-degree phase difference between the affected signals (green lines). This mixing also results in the mirroring of the true interaction into spurious interactions (red lines) that at least partially maintain the characteristics of the true interaction such as a phase difference or directionality. **(b)** A subset of the task-control network from [Box 1, Figure 1c](#). The black lines indicate the true phase interaction and red lines the spurious interactions. Using a control condition (as here), or an interaction metric that is insensitive to artificial synchrony, does not abolish the spurious interactions. Artificial connections in the graph, however, become ‘denied’ (dashed green lines) in the sense that because of associated strong signal mixing, it is impossible to observe true interactions between these nodes (e.g. here the connection between the MFS and MFG, cf. [Box 1, Figure 1a, right panel](#)).

found to be correlated with sensory awareness [41], top-down attentional control [42] and working memory [43,44]. The study of Gaillard *et al.* [41] investigated differences in the conscious and non-conscious processing of words by using a masking procedure and intracerebral EEG. In the conscious condition, causality analysis revealed an information flow among the occipital and occipitotemporal cortices as well as from occipital to frontal electrodes ([Figure 2c](#)). In the non-conscious condition, no causal interactions were observed.

Observations made with source-localized M/EEG data and with invasive intracranial recordings from humans are thus in line with findings from invasive animal recordings and show that interareal synchronization among the

task-relevant sensory and executive regions (see [Figure 1b, right panel](#)) is correlated with behavior and modulated by attentional and perceptual loads. Importantly, these studies support the hypothesis that, in the human brain, interareal synchronization mechanistically underlies the coordination of neuronal communication and integration of anatomically distributed processing. Insight into large-scale brain dynamics obtained by ROI-based M/EEG analysis approaches is, nevertheless, limited by two factors. First, the selection of ROIs is sparse and might not yield an accurate or adequate selection of the brain structures that contribute to the experimental task performance. Second, the leakage of spurious interactions (see [Boxes 1c and 2](#)) from regions outside the ROIs is a confounder that is



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Figure 2. Synchronization among task-relevant cortical regions is observed in several different cognitive tasks. **(a)** Frontoparietal beta-band synchronization is correlated with the success of allocating attention towards a stimulus in an attention-blink paradigm. Adapted from [36]. **(b)** Representation of contextual information is associated with beta-band synchronization among medial frontal, parahippocampal and visual regions. Adapted from [40]. **(c)** Granger causality analysis shows that visual awareness is correlated with directed beta-band interaction from occipital to frontal cortex. Adapted from [41]. **(d)** The first all-to-all mapping of interareal phase correlations reveals visual stimulus-induced network synchrony occipital, temporal and parietal regions. Adapted from [45]. **(e)** Attentive, visually paced reading is associated with both coherence and directed interactions in the alpha band in a network of occipitotemporal, temporal, orbital and motor areas. Adapted from [37]. **(f)** Perceptual binding of ambiguous audiovisual stimuli is correlated with beta-band synchronization among frontocentral and occipitotemporal regions. Adapted from [48]. **(g)** Alpha-, beta- and gamma-band phase synchrony is sustained and load dependent during the visual working memory (VWM) retention period. Left panel: The black line shows the fraction of interactions (connection density, K , y-axis) that were strengthened by the VWM as a function of frequency (x-axis). The gray line shows the fraction of interaction that was positively correlated with memory load. Middle panel: Connection densities of task performance-related networks in the alpha (red), beta (green) and gamma (blue) frequency bands as a function of time. The rectangle denotes the memory retention period. Right panel: Connection densities of load-dependent networks. Adapted from [49]. **(h)** In the same task, intraparietal sulcus (intPS) is the principal hub in the alpha- and beta- (not shown) band phase interactions that predicted the individual VWM capacity. Adapted from [49].

difficult to control. These limitations can be avoided by an 'all-to-all' mapping of interactions between pairs of sources throughout the cortical surface, which reveals the dominant connections in the entire network.

All-to-all mapping of phase correlations in cortical networks

One of the first mappings of all-to-all interareal synchrony was made by David *et al.* [45], who used MNE-based source modeling and observed that occipital and occipitotemporal large-scale networks became synchronized during a visual task (Figure 2d). Later studies have used, for example, source clustering- and beamforming-based approaches to investigate the functional significance of interareal coherence across the whole brain. Pollok and colleagues showed that sensorimotor integration was correlated with interareal alpha-band coherence among cerebellum, thalamus and premotor cortex [46,47]. Kujala *et al.* [37] studied large-scale cortical networks during reading, and recorded MEG during fast, intermediate and slow presentation rates of words that comprised a meaningful story that was comprehended only at the slow presentation rates. Reading was associated with enhanced alpha-band coherence in a network comprising the cerebellum, PFC, temporal cortical regions and orbital structures, whereas comprehension strengthened synchrony among cerebellar and temporal regions (Figure 2e). In addition, this study addressed causal interactions among these regions, and found that the cerebellum and inferior temporal regions were the nodes driving the information flow in a posterior to anterior direction. A study by Hipp *et al.* [48] used EEG recordings to investigate the functional significance of interareal synchrony in an audiovisual task. The strength of beta- and gamma-band phase synchrony among central and temporal brain regions was correlated with the perception of ambiguous audiovisual stimuli (Figure 2g), which is in line with prior studies in cats and monkeys on the role of beta- and gamma-band synchrony in perceptual binding.

A similar approach was used by Palva and colleagues [49,50], who performed a complete cortical mapping of dynamic 3–90-Hz phase interactions during visual working memory (VWM) encoding and retention by using MNE-based M/EEG source reconstruction and a cortical parcellation that minimizes spurious interactions. In these data, interareal synchronization concurrently in the alpha (8–14 Hz), beta (14–30 Hz) and gamma bands was sustained and load dependent during the VWM retention period (Figures 2g and 3) [49]. Interareal synchronization in alpha- and beta-frequency bands also predicted the individual VWM capacity, which indicates the functional significance of interareal synchronization in supporting human VWM (Figure 2h).

Taken together, these data suggest a mechanistic role for phase correlations in large-scale cortical networks in perceptual, attentional and WM processing. These studies also demonstrate that all-to-all analysis approaches are feasible, informative, and may reveal as complete as possible networks of interareal interactions in a hypothesis-free manner and hence support unbiased investigations on the functional significance of neuronal synchrony. Further insight into the topological significance of these connections, and also into

the connected brain regions and the whole network, can be obtained by depicting the interaction data as graphs where the brain regions are the vertices and the interactions the connecting edges.

Insights from graph theory

Graph theoretical network metrics have been widely used to characterize the properties of cerebral networks defined by structural, functional or effective connectivity in MRI data [51,52]. These metrics yields insight into the network properties at three levels: edges, vertices and the entire graph.

At the graph level, several metrics can be used to characterize specific topological attributes. Brain connectivity graphs have high clustering, short average path lengths, dense intramodular connectivity and sparse intermodular connections [51] that are the hallmarks of a small-world organization [53]. Small-world structures are associated with high local and global efficiency in information transmission as well as facilitated parallel processing within hierarchically organized modules [51].

Several studies have used signal-space M/EEG connectivity analyses to explore the graph properties of interareal networks during task execution [32,54–59]. These data, in summary, show that, at the scalp level, brain graph properties are informative about pathological conditions and modulated by cognitive tasks. Kitzbichler *et al.* [32] showed that even nearby frequency bands can exhibit very different kinds of topologies in task-induced networks.

However, in signal-space data and to a lesser extent in source space (see Figure 1d in Box 1), the signal mixing has dramatic effects on the observed network topology (see Figure 1 in Box 2). Source signals are spread by mixing to produce artificial synchronization and the true interactions are mirrored in several spurious interactions, which artificially increases clustering in the network. On the contrary, the removal of the artificial interactions by using a control condition or a mixing-insensitive interaction metric (see Box 3) does not remove the spurious interactions, and yet, the subset of true interactions that was masked by artificial synchrony remains undetected (see Figure 1 in Box 2), which together decrease clustering below the true value. Thus, the extent to which the present M/EEG literature on connectivity graph metrics relates to the graph properties of the true underlying interaction networks thus remains unclear [60]. Future methodological advancements for eliminating spurious connections in source-modeled M/EEG will play an important role in improving the reliability of graph-property estimates from M/EEG data. Furthermore, millisecond-range temporal precision, which is one of the primary strengths of M/EEG as compared to MRI, remains to be exploited in graph analyses.

The challenges related to mixing effects are less aggravated at the edge and vertex levels, where the network metrics can be very useful in the extraction of physiologically significant topological information as well as in the discovery of most important network components from large amounts of connectivity data. Vertex centrality measures, such as degree and betweenness centrality, reveal which nodes are most important for network integrity in

terms of having many connections or being a waypoint for many of the shortest paths in the graph, respectively. Graph modularity or community structure estimations (see Figure 1b) may further reveal subsets of vertices that are more densely connected to each other than to the rest of the graph and hence uncover functionally specific subsystems.

Localization of hubs in oscillatory communication networks

In a few M/EEG studies, vertex centrality estimates have been used to identify those anatomical structures that are likely to play an important role as hubs in networks of interareal synchronization [37,49,61]. During a continuous reading task [37], occipitotemporal and motor cortices as well as the cerebellum were the strongest hubs in networks of both functional and effective connectivity in the alpha band. Vertex centrality metrics have also been estimated for networks supporting VWM, where alpha-band synchrony was observed in frontoparietal regions, synchronization in the beta band was prominent among the visual regions, and in the gamma band among distributed frontal, parietal and posterior regions [49] (Figure 3a). Degree and betweenness centrality analyses showed that the hubs of alpha-, beta- and gamma-band networks were concentrated in the frontal, occipital and parietal cortices, respectively (Figure 3b). The IPS, a key region mediating visual attention [10,62], was highly central in the gamma-band network, which is in line with the putative role for gamma

activity in the coordination of goal-directed visual attention [18]. Importantly, however, in addition to synchronization among visual regions and the frontoparietal system (i.e. the dorsal and ventral attention networks), the data-driven analysis approach also revealed hubs in the cingulo-opercular system (see Figure 3c and the purple subgraph in Figure 1b) [27,63–65] and thus sheds light on how these regions interact with other task-control systems in sub-second time scales.

Taken together, centrality, coreness and modularity analyses are important tools for grasping essential information from the complex networks yielded by all-to-all interaction mapping. These metrics identify the most important brain regions for communication, the key core structures, and the putative functional divisions among subnetworks. In essence, these three vertex characteristics reveal which brain regions form a ‘global workspace’ [66,67] and which act as peripheral nodes in a specific task-dependent network. Importantly, centrality analyses can also be used to identify the brain regions that exhibit abnormal connectivity patterns in cognitive disorders [61].

Future directions

We highlight here three directions of research for identifying the systems-level mechanisms that bridge the gap from neurophysiology and local neuronal processing to psychological- and cognitive-level phenomena (see also Box 4). These directions are (i) acquisition of causal evidence on the role of specific interactions, (ii) characterization of

Box 3. Quantification and physiological implications of CF interactions

CF phase–phase and phase–amplitude interactions may act as mechanisms for binding and coordinating spectrally distributed processing into coherent cognitive operations [12,22,30,82]. Phase–phase interactions can be quantified as $n:m$ phase synchrony [83], where n and m are small integers that define the frequency equality $nf_x = mf_y$ of the coupled slow and fast oscillations (Figure 1a,b). A direct phase–phase correlation between oscillations in distinct frequency bands has two physiological implications. First, neuronal networks generating the slow oscillation must operate with a temporal reliability in a subcycle time scale of the fast oscillation. Second, because the firing of neurons engaged in the slow oscillation takes place in a specific phase of the fast cycle, $n:m$ phase synchrony is compatible with phase and spike time-based coding schemes [30] similarly to the classical 1:1 within-frequency phase synchrony [24]. Considering a filtered signal $x(t, f) = a_x(t, f) e[i\theta_x(t, f)]$, where i is the imaginary unit, $a_x(t, f) = |x(t, f)|$ denotes the amplitude and $\theta_x(t, f) = \arg(x(t, f))$ the phase, the strength of $n:m$ phase synchrony can be estimated by quantifying the non-uniformity of the generic phase difference ω_{nm} of signals x and y :

$$\omega_{n,m} = n\theta_x - m\theta_y$$

which for all signals $\mathbf{X} = [x]$ in a complex matrix form, $\Phi_{n,m}$, is given by the complex outer product:

$$\Phi_{n,m} = (\mathbf{X}/|\mathbf{X}|)^n \otimes (\mathbf{Y}/|\mathbf{Y}|)^{m*}$$

where the asterisk denotes the complex conjugate. The non-uniformity of $\Phi_{n,m}$ across N samples can be evaluated, for example, with $\text{PLV} = N^{-1} \sum \Phi_{n,m}$.

Palva *et al.* [30] investigated CF interactions in ongoing activity with MEG using a continuous stimulus-free parametric WM task. Transient periods of 1:3 (left) and 1:4 (right) synchrony were visually salient in segments of sensor data (Figure 1c) and statistically robust throughout the frequency spectrum (Figure 1d left). Phase synchrony among

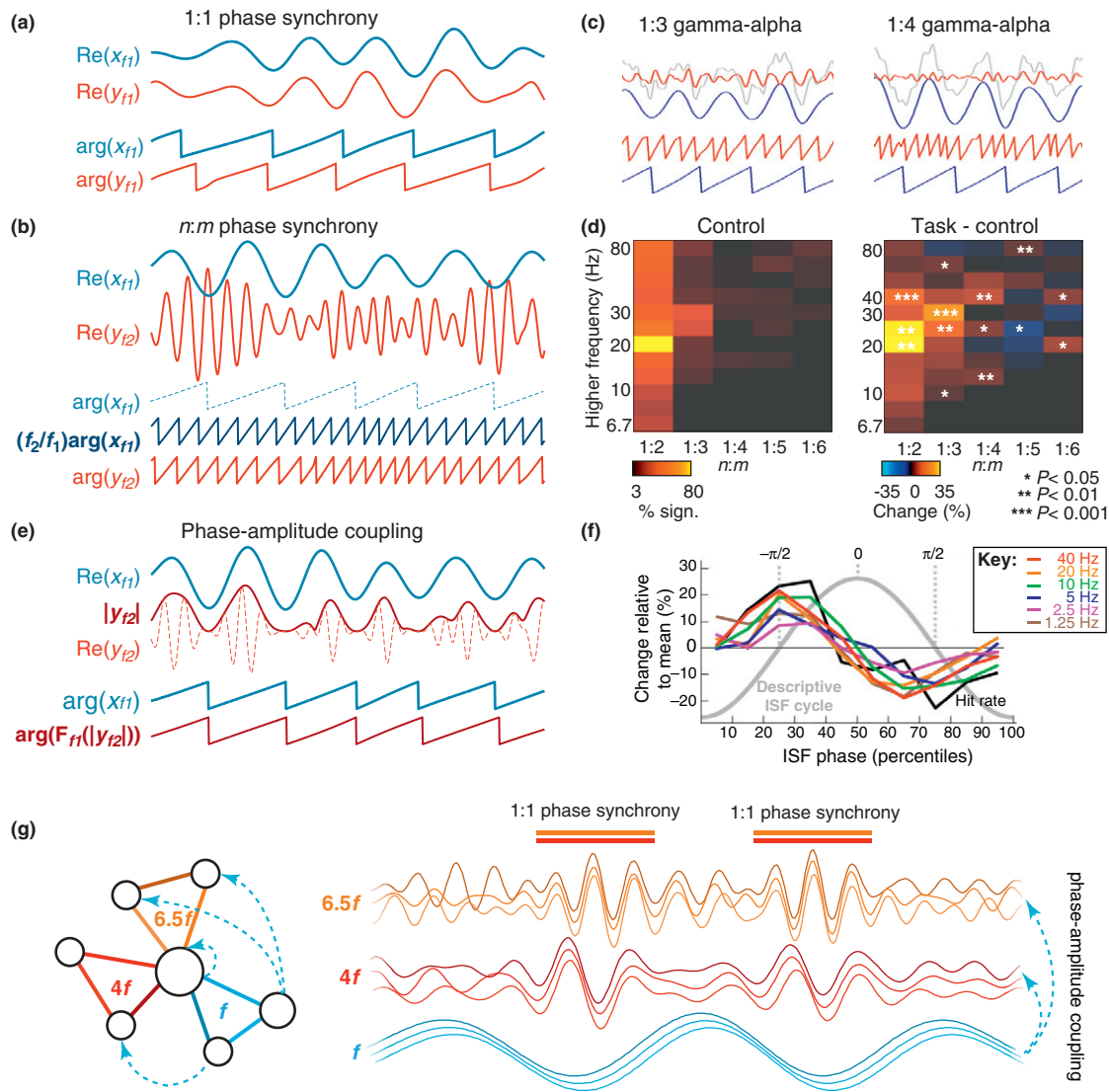
alpha, beta and gamma oscillations was load-dependently enhanced by the WM task (Figure 1d, right).

In CF phase–amplitude interactions, or ‘nested oscillations’, the phase of slow oscillations and the amplitude of fast oscillations are correlated (Figure 1e). The phase difference matrix, Φ_{PA} , for quantifying phase–amplitude coupling can be obtained by filtering the amplitude envelopes \mathbf{A}_x of the faster oscillations at f_x with the filter \mathbf{T}_{fy} that was used to obtain the slower oscillation [84]:

$$\Phi_{PA} = [\mathbf{T}_{fy}(\mathbf{A}_x)/|\mathbf{T}_{fy}(\mathbf{A}_x)|] \otimes (\mathbf{Y}/|\mathbf{Y}|)^*$$

Phase–amplitude correlation is likely to reflect a slow excitability fluctuation in the neuronal circuitry underlying the fast oscillation [22]. For example, amplitudes of fast (> 1 Hz) oscillations are nested in infra-slow oscillations in the 0.01–0.1 Hz band in both sleep [84] and awake conditions [78] (Figure 1f). These correlations are behaviorally significant and reflect the slow intrinsic brain system dynamics [85,86] (see Figure 1b).

It is important to note that the all-to-all mapping approach advocated in this review for 1:1 phase interactions applies to CF phase interactions as well. Anatomically distinct assemblies of slow and fast oscillations may become directly coupled through $n:m$ phase synchrony [30]. Conversely, a slowly oscillating network may modulate local excitability and fast oscillation amplitudes selectively across the network of interacting fast oscillations and thereby also modulate the anatomical structure of these fast 1:1 phase interactions in a task-dependent manner (Figure 1g). This is illustrated schematically in Figure 1g, where a 1:1 synchronized (solid lines in the graph) assembly in frequency band f (blue) modulates the local excitability in some network nodes (dashed lines), which is reflected both in the local amplitudes and transient 1:1 synchronization of assemblies in frequency bands $4f$ (red) and $6.5f$ (yellow). Such network-level nested relationships coordinate the $4f$ and $6.5f$ assemblies to serve modular or functionally specialized processing and yet operate concurrently in the global context.



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Figure 1. Cross-frequency phase-phase and phase-amplitude interactions. **(a)** 1:1 synchrony is a special case of generic $n:m$ -phase synchrony with $n = m = 1$. $\text{Re}(\cdot)$ denotes the real part of a complex filtered signal and $\text{arg}(\cdot)$ its phase. **(b)** A simulated example of 1:4-phase synchrony between a fast and a slow oscillation. **(c)** Transient periods of 1:3 (left) and 1:4 (right) phase synchrony are visually salient in segments of magnetoencephalography sensor data. Adapted from [30], where **(d)** 1:m-phase synchrony is statistically robust throughout the frequency spectrum (d, left panel). In a working memory task, 1:m-phase synchrony among alpha, beta and gamma oscillations is memory load-dependently enhanced (d, right panel). Adapted from [30]. **(e)** An example of a phase-amplitude interaction where the phase of the slow and the amplitude of the fast oscillations are correlated. **(f)** The amplitudes of fast (> 1 Hz) oscillations are phase-amplitude coupled, or 'nested', with infra-slow fluctuations (ISF) in the 0.01–0.1 Hz band during a threshold stimulus detection task (colored lines) and the ISF phase is also correlated with the stimulus-detection performance (black line). Modified from [78]. **(g)** A schematic of how phase-phase and phase-amplitude interactions may be linked. Here, a 1:1-synchronized (solid lines in the graph, left panel) assembly in frequency band f (blue) modulates the local excitability (dashed lines in the graph) in some of the network nodes (black circles in the graph). These modulations are reflected both in the local oscillation amplitudes and in transient 1:1 synchronization within other assemblies in frequency bands $4f$ (red) and $6.5f$ (yellow). The time series (right panel) illustrate these phase-phase and phase-amplitude interactions.

graph dynamics and cross-frequency (CF) interactions, and (iii) dissociation of in-phase and out-of-phase functional connectivity.

First, although several lines of correlative data link synchronization and cognitive performance, and thus support the idea that synchronization in large-scale networks may serve the coordination of scattered neuronal activity into coherent perception and cognition, there is so far little causal evidence to support this hypothesis. In humans, causal-like evidence could be obtained by careful quantification of single-trial brain dynamics and utilization of causal interaction metrics not only to quantify the inter-areal neuronal interactions [37,41] but also to explore

whether a specific set of interactions is necessary and sufficient for a given behavioral outcome. To show that there was a causal link between a neuronal interaction and behavior, this set of interactions needs to be manipulated selectively and the consequences in behavior observed. A step towards this direction has been taken with rhythmic transcranial magnetic stimulation (rTMS), which is able to entrain spontaneous neuronal oscillations at the stimulation frequency [68]. For instance, recent rTMS data have revealed a double dissociation in the effects of 5 and 20 Hz stimulation of the parietal cortex where 5 Hz stimulation facilitates global and 20 Hz stimulation local perceptual processing [69].

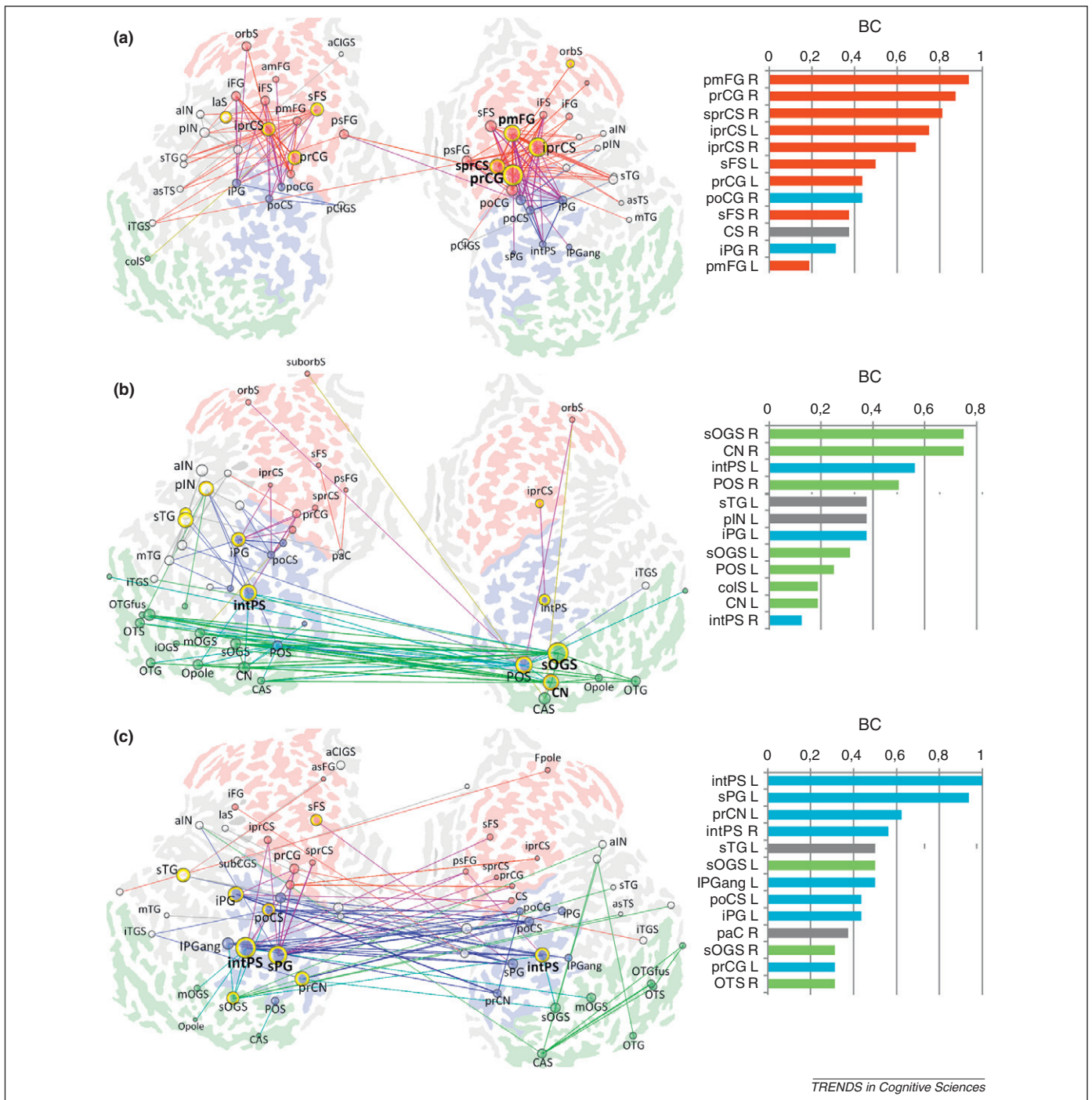


Figure 3. Visual working memory (VWM) retention period is associated with distinct patterns of interareal synchronization in alpha-, beta- and gamma-frequency bands. **(a)** Alpha-band synchronization is observed among frontoparietal regions, **(b)** beta-band correlations among the occipital and occipitotemporal regions, and **(c)** gamma-band synchronization among occipital and parietal regions (left panels). Hubs, that is brain regions with high betweenness centrality (BC, right panels), of these networks are observed in the frontal cortex (red) in the alpha band, in occipital regions (green) in the beta band, and in parietal regions (blue) in the gamma band. Adapted from [49].

Second, although within-frequency phase synchronization may support the binding of anatomically distributed processing, it cannot coordinate neuronal processing distributed into distinct time windows or frequency bands. The binding of anatomically, spectrally and temporally distributed processing could, however, be carried out by CF phase–amplitude interactions (i.e. nested oscillations) or by phase–phase interactions, such as $n:m$ phase synchrony (Box 3). Invasive human [70–72] and animal [73–75] recordings show that nested phase interactions are

observable in human brain dynamics and that they are modulated by cognitive task demands. CF phase interactions have also been investigated with M/EEG recordings, which show that both $n:m$ phase synchrony [30,76,77] and nested oscillations [30,76,78,79] are correlated with VWM performance and sensory awareness. Nevertheless, source reconstruction techniques have not yet been used with CF phase interaction analyses, which leaves the anatomical sources and functional significance of CF phase interactions unclear. The network analyses of CF phase

Box 4. Outstanding questions

- What are the topological, spectral and anatomical similarities of networks supporting cognitive functions of varying scales such as attention, working memory, perceptual awareness and decision making?
- Are there concurrent task-positive and -negative networks of fast phase interactions? Is network modularity and suppression of unwanted communication achieved stochastically by uncorrelatedness or actively coordinated through out-of-phase correlations? Do some of the M/EEG-observed phase correlations underlie such out-of-phase interactions and hence reflect suppressed communication?
- What are the specific subsecond dynamics and mutual interactions of the dorsal and ventral attention, cingulo-opercular, and the default-mode systems in coordinating human cognitive functions?
- What are the roles of phase-phase and phase-amplitude CF interactions in human cognition and perception? Do these CF interactions create transient superstructures that coordinate multiple functionally specialized task-positive subnetworks?
- How are the graph, vertex and edge properties of cortical phase interaction networks altered in brain diseases and are these alterations epiphenomenal or causally related to the cognitive deficits?

interactions in source space will be of great importance in understanding how human cognition and its disorders are formed and caused by hierarchical CF interactions among networks oscillating at distinct frequency bands.

Third, phase-synchrony measures quantify the presence of a phase correlation irrespective of the phase difference between two brain regions. Because oscillations reflect excitability fluctuations, a specific, conduction delay-dependent phase difference ensures that the input signals arrive to the target population at the excitable phase, which conceivably facilitates communication [18,24]. Inputs arriving in the opposite phase, however, are more unlikely to evoke a response and hence a failure in communication between these brain regions. Phase synchrony and coherence measures used at present do not distinguish between these two alternatives. Therefore, interareal phase synchrony does not necessarily reflect only communication networks, but anticorrelations among brain regions as well.

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