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Review

Intrinsic Coupling Modes: Multiscale Interactions in Ongoing Brain Activity

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Intrinsic coupling constitutes a key feature of ongoing brain activity, which exhibits rich spatiotemporal patterning and contains information that influences cognitive processing. We discuss evidence for two distinct types of intrinsic coupling modes which seem to reflect the operation of different coupling mechanisms. One type arises from phase coupling of band-limited oscillatory signals, whereas the other results from coupled aperiodic fluctuations of signal envelopes. The two coupling modes differ in their dynamics, their origins, and their putative functions and with respect to their alteration in neuropsychiatric disorders. We propose that the concept of intrinsic coupling modes can provide a unifying framework for capturing the dynamics of intrinsically generated neuronal interactions at multiple spatial and temporal scales.

Introduction

Ongoing activity has been both nuisance and enigma to neuroscientists for a long time. Early physiological and modeling studies assumed that ongoing neural activity corresponds to noise resulting from random signal fluctuations without any meaningful patterning or computational relevance. In the 1970s and 1980s, this notion was intimately related to another key assumption. It was generally believed that the brain is a passive stimulus-processing device that builds stimulus-driven representations in a bottom-up manner and "idles" when it is not fed with sensory data.

Meanwhile, a new paradigm has emerged that considers the brain as inherently active and constantly creating predictions about upcoming stimuli and events (Engel et al., 2001; Friston, 2005; Arnal and Giraud, 2012). Due to this shift in background assumptions, the intrinsic dynamics of brain circuits, that is, those aspects of dynamics not enforced by a stimulus or task, started to move into the focus and has now become a major research theme in systems neuroscience. Opposing the classical view, it soon became clear that ongoing activity carries information and is endowed with meaningful spatiotemporal structure, which reflects previous learning and can bias the processing of stimuli (Engel et al., 2001; Deco and Corbetta, 2011). The latter was first demonstrated by in vivo studies in cats combining microelectrode recordings with optical imaging (Arieli et al., 1996). These studies showed that low-frequency spatiotemporal fluctuations in ongoing activity could account for most of the trial-to-trial variability in sensory response amplitudes.

Importantly, these fluctuations of ongoing activity were strongly synchronized across spatially distributed neuronal populations (Steriade et al., 1996a; Contreras and Steriade, 1997; Destexhe et al., 1999), suggesting that processing of stimuli is biased not just by fluctuations in a local neuronal population but, actually, by the dynamics of coherently active networks. These coupling patterns in ongoing activity did not only involve low-frequency fluctuations in the delta-band (1–4 Hz) or below (Steriade et al., 1993; Contreras and Steriade, 1997; Destexhe et al., 1999), but also faster frequencies in the theta- (5–8 Hz), alpha- (9–12 Hz), beta- (13–30 Hz), and gamma-frequency range (>30 Hz) (Steriade et al., 1996a; Destexhe et al., 1999). Oscillations in these frequency bands are well known to be involved in a broad variety of cognitive processes (Singer, 1999; Fries, 2009; Engel and Fries, 2010; Siegel et al., 2012).

Oscillatory ongoing activity had also long been known from electroencephalography (EEG) studies of the human brain. However, the first demonstrations of spatially organized networks in ongoing activity were achieved using neuroimaging approaches such as fMRI (Biswal et al., 1995) and positron-emission tomography (PET) (Raichle et al., 2001). These studies established what became known as "resting state networks," that is, networks of brain areas that show correlated fluctuations in the absence of a stimulus or task that the subject is engaged in (Fox and Raichle, 2007; Raichle, 2010; Deco and Corbetta, 2011; Corbetta, 2012). In the past decade, a number of resting state networks have been extensively characterized using fMRI-based approaches. These include the default-mode and the dorsal attention network, as well as executive control, visual, auditory, and sensorimotor networks (Figure 1). Classically, the concept of resting state networks has been understood mainly in functional-anatomical terms, and it has been employed as a tool to map the structural organization and parcellation of brain systems (Yeo et al., 2011; Buckner et al., 2013).

As measured by fMRI, such networks show very slow (<0.1 Hz) temporal fluctuations that are coupled across different brain regions. An important shortcoming of fMRI approaches is that fluctuations on faster timescales (that is, timescales commonly analyzed in neurophysiological data) are not captured. For this reason, analysis of fast dynamics has largely been missing in

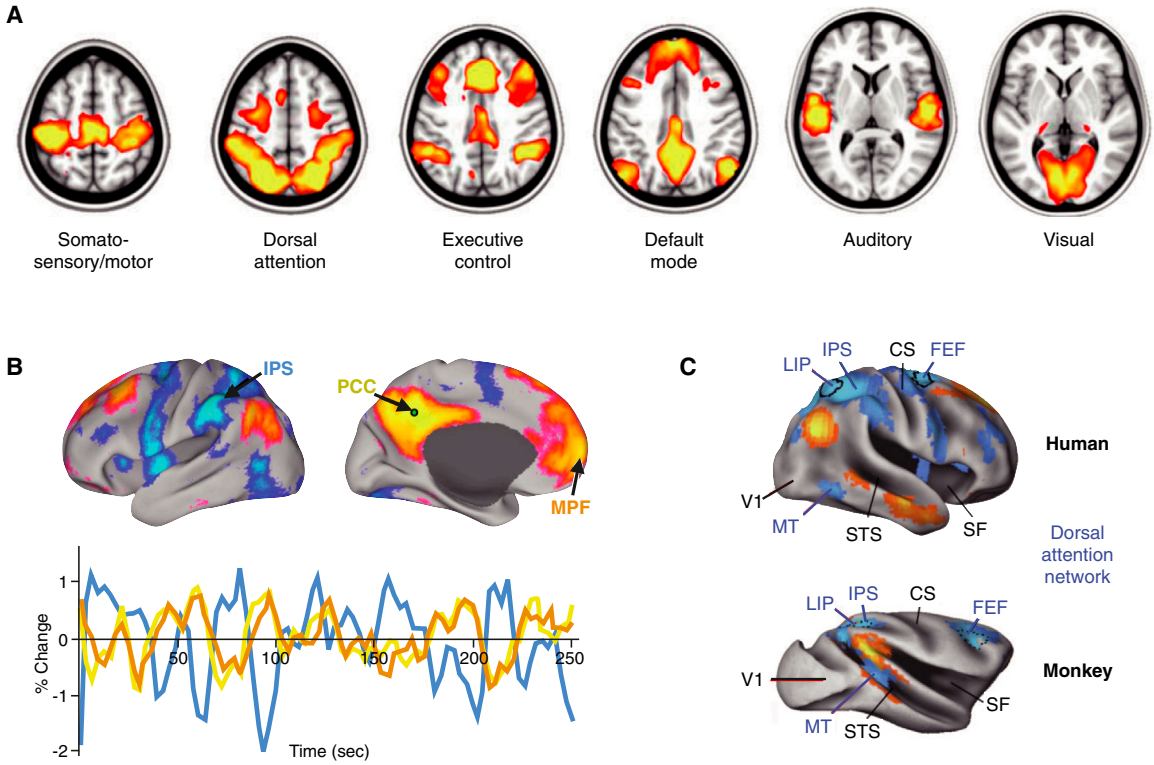

Figure 1. fMRI-Based Approaches for Analysis of ICMs

(A) Resting-state networks revealed by analysis of fMRI signals. Seed-based analysis of BOLD signal correlation across different regions gives rise to typical network patterns in resting activity. Modified from Raichle (2010).

(B) Functional connectivity can be detected by correlating the BOLD signal across different regions. In this example, the posterior cingulate cortex (PCC) was taken as a seed region. Top: maps of positive (warm colors) and negative (cool colors) correlations with the seed region. Bottom: single run BOLD time courses for PCC (yellow), medial prefrontal cortex (MPF, orange), and intraparietal sulcus (IPS, blue). Positive correlations with the seed region identify the default mode network, which includes midline regions such as PCC and MPF, as well as regions in angular gyrus and superior frontal sulcus regions. Modified from Fox et al. (2005). Copyright National Academy of Sciences, USA.

(C) Similarities between BOLD correlation patterns in the human and monkey brain. Maps of the dorsal attention network (blue regions) generated by seeding the lateral intraparietal area (LIP) in humans (top) and macaque monkeys (bottom). In both species, the network is distinguished by correlated activity between LIP and other regions of IPS, the frontal eye field (FEF), and visual motion areas (MT). Note that the network is identical to the one appearing in blue color in (B). Modified from Corbetta (2012).

studies of resting state networks (Deco et al., 2011), and it is only recently that novel methods have become available allowing for better characterization of frequency-specific coupling in ongoing activity using EEG or magnetoencephalography (MEG) (Hipp et al., 2012; Hillebrand et al., 2012; Marzetti et al., 2013).

In this Review, we specifically focus on the large-scale dynamics of ongoing activity and on the investigation of coupling using neurophysiological methods such as EEG, MEG, or in vivo animal recordings. As we will argue, oscillatory dynamics and frequency-specific coupling across brain regions are particularly important for the characterization of functional networks in ongoing activity. In the following, we will use the concept of "intrinsic coupling modes" (ICMs) to denote coupling that is not imposed by the current stimulus or action context. As will be discussed below, ICMs exhibit characteristic spectral and spatial signatures, which can be complex in nature and are likely to change dynamically over time. We hypothesize that ICMs do not represent context-invariant networks but spatiotemporal coupling patterns that are modified in a context- and learning-dependent manner. For example, the same network might exhibit different ICMs at different levels of vigilance; similarly, one particular cortical region could engage in different ICMs, possibly even in the same epoch. Furthermore, we assume that ICMs do not only emerge during rest but in fact also occur during processing of stimuli or execution of a task, since there is always substantial "background" ongoing activity unrelated to the particular "foreground" context.

In the following sections, we will discuss evidence suggesting that ICMs, as emergent features of network dynamics, are particularly important in shaping neural and cognitive processing. It will become evident that two types of ICMs can be distinguished that differ in their dynamics, the underlying coupling mechanisms and their putative functions. One type arises from phase coupling of band-limited oscillatory signals, whereas the other results from coupled aperiodic fluctuations of signal envelopes. In the following, we will designate these two types of coupling as "phase ICMs" and "envelope ICMs," respectively (Table 1). As we will propose, the concept of ICMs might provide a framework for describing the dynamics of ongoing activity at multiple spatial and temporal scales. We suggest that

Table 1. Features of Envelope and Phase ICMs

Feature	Envelope ICMs	Phase ICMs
Recording method	fMRI, MEG, EEG, LFP, spike activity	MEG, EEG, LFP, spike activity
Coupling measure	Envelope correlation (amplitude or power correlation, correlation of BOLD signals)	Phase coupling (coherence, imaginary coherence)
Typical frequency range	Below 0.1 Hz	1–150 Hz
Dynamics	Scale-free (aperiodic)	Band-limited oscillations (slow-wave, delta, theta, alpha, beta, gamma oscillations)
Spatial range	From local (within regions) to large-scale (cross-regional) coupling	From local (within regions) to large-scale (cross-regional) coupling
Relation to structural connectivity	Close	Variable
State dependence	Low	High
Relation to learning and plasticity[a]	Might modulate plasticity on slow timescales	Trigger spike-timing-dependent plasticity
Cognitive and computational significance[a]	Modulate performance in sensory and cognitive tasks	Encode priors for processing of perceptual/cognitive contents
Association with disorders[a]	Might be most severely affected if structural network alteration predominates	Changed in disorders with structural or functional network alteration
Putative function[a]	Regulate the activation of neural populations or brain regions	Regulate the integration and flow of cognitive contents

[a]Entries largely represent hypotheses requiring further testing.

characterizing ICMs may substantially advance our understanding of the mechanisms underlying cognition and neuropsychiatric disorders.

Revealing ICMs

A number of different approaches can be used for revealing ICMs, which differ in terms of the signals acquired, the spatial scale of the measurements, and the invasiveness of the technique. The most widely used noninvasive approach is the fMRI-based analysis of ongoing fluctuations of blood oxygen level-dependent (BOLD) signals that has been applied in both humans and in animals (Fox and Raichle, 2007; van den Heuvel and Hulshoff Pol, 2010; Corbetta, 2012; Hutchison and Everling, 2012). A straightforward approach consists in the extraction of the BOLD signal time course from a region of interest and computation of its correlation with that of other regions (Figure 1B). This correlation provides a measure of "functional connectivity" (van den Heuvel and Hulshoff Pol, 2010; Corbetta, 2012) between the "seed" region and other brain areas (Figures 1B and 1C). As an alternative, model-free methods can be applied that do not require the a priori definition of a seed region. Numerous studies have used independent component analysis, which represents a data-driven approach that yields a set of spatially independent networks, each with associated time course of BOLD fluctuations (Cole et al., 2010). The results obtained with these methods yield a rather consistent picture of networks distinguished by correlated slow BOLD fluctuations.

Using MEG and EEG, it becomes possible to study ICMs across a broad range of timescales and in a spectrally resolved manner. This can also be achieved by invasive recording of local field potentials (LFPs) or spike activity. Due to their millisecond time resolution, the information captured by these neurophysiological recordings is considerably more complex than what can be obtained from fMRI measures. In particular, coupling across different neural populations or brain regions can be quantified in a frequency-specific manner. For the study of ICMs, functional connectivity in MEG, EEG, or LFP data can be quantified by a number of different correlation measures that are similar to those used in fMRI data analysis (Lachaux et al., 1999; Nolte et al., 2004; Hipp et al., 2012). A widely used approach is coherence, which is a normalized measure of the linear relationship between oscillatory waves that adopts a high value if the signals are similar in amplitudes and aligned in their phases. Coupling measures reflecting primarily the latter are phase coherence or the phase locking value (Lachaux et al., 1999). Therefore, these are well suited to quantify what we call phase ICMs (Table 1). Several recent studies have applied correlation measures to the amplitude or power envelopes of the recorded signals, rather than to the phase of the underlying oscillations (de Pasquale et al., 2010; Brookes et al., 2011, 2012; Hipp et al., 2012). Analysis of such signal envelopes can be used to capture slow fluctuations similar to what is provided by the BOLD imaging (Laufs et al., 2003; Tagliazucchi et al., 2012a). Both the analysis of envelope correlations in electrophysiological signals and of correlated BOLD fluctuations yields what we designate as envelope ICMs (Table 1).

An important caveat in the study of ICMs by EEG or MEG is that, due to their limited spatial resolution, these methods are prone to signal mixing artifacts, which are especially severe for estimates of brain interactions (Nolte et al., 2004; Stam et al., 2007a). Through volume spread, any active source contributes, in weighted manner, to the signals at all sensors (Figure 2A). This can give rise to spurious signal correlations and, thus, distort connectivity measures. Several methods have been suggested to address this problem, which are based on the notion that volume spread contributes to apparent coupling with negligible delay, whereas true neuronal communication also occurs at other delays. One possibility is to analyze the imaginary part of coherence, which, if significant, cannot be explained by volume spread (Nolte et al., 2004). Subsequent studies have introduced related measures such as the phase lag index (Stam et al.,

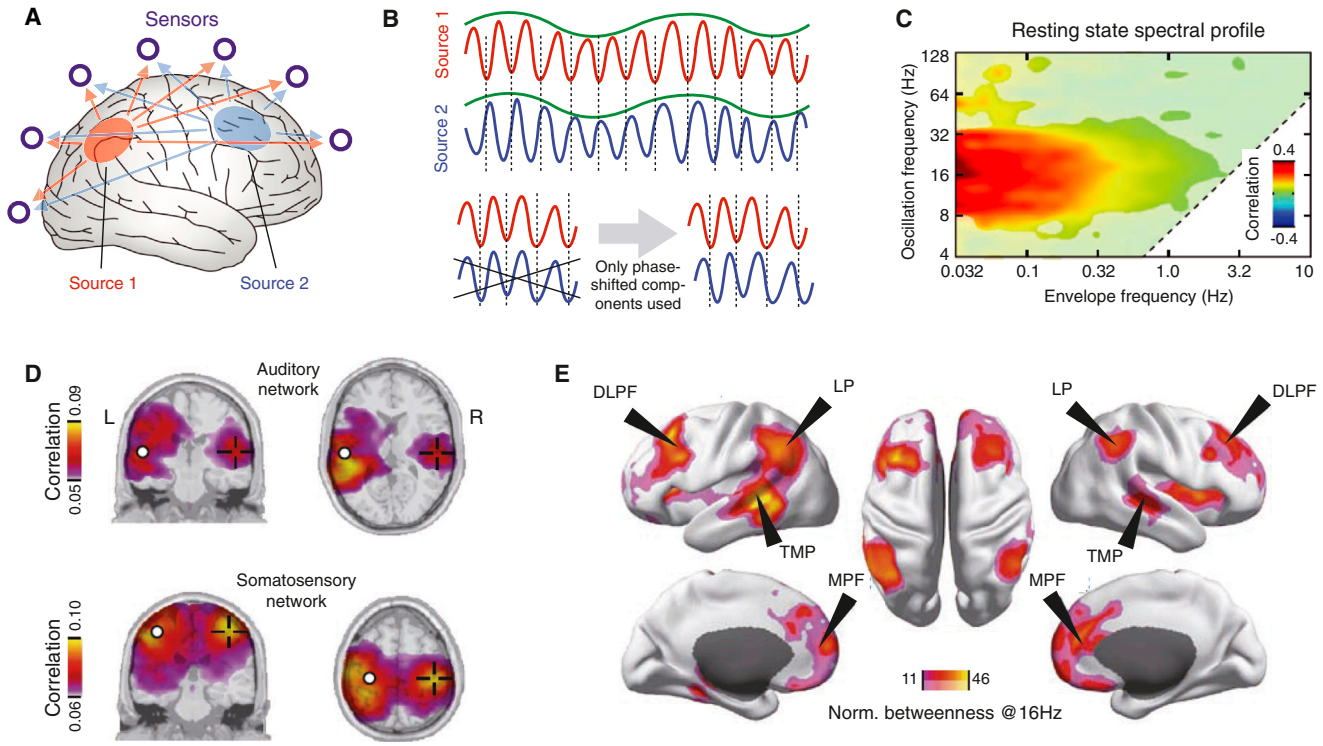

Figure 2. Neurophysiological Investigation of ICMs

(A) Volume spread leads to source mixing, because each sensor measures signal contributions from different sources.

(B) Analysis of coupling can be based on using amplitude envelopes (green) or (if squared) power envelopes. Bottom: preprocessing of recorded signals by phase orthogonalization eliminates phase-aligned signal components.

(C) Resting state coupling patterns revealed by correlation of power envelopes have a specific spectral profile, characterized by the frequencies of the underlying neuronal oscillations (mainly in the alpha and beta band) and the frequencies at which signal envelopes are correlated (mostly below 0.1 Hz).

(D) Envelope correlation reveals spatially specific coupling between homologous sensory areas in both hemispheres.

(E) Graph-theoretical analysis reveals specific coupling patterns. Analysis of betweenness (reflecting the number of shortest paths through each node) in the beta band reveals a bilateral network involving dorsolateral (DLPF) and medial prefrontal (MPF), lateral parietal (LP), and temporal (TMP) regions. (C), (D), and (E) are modified from Hipp et al. (2012).

2007a). Another approach that has recently been introduced has used phase orthogonalization of oscillatory signals from different sources before analyzing power envelope correlations (Figure 2B) (Hipp et al., 2012). This is equivalent to removing, after Fourier transformation, those components that have the same phase for the two signals. This method is insensitive to trivial correlations arising from two sensors seeing the identical signal component and enables the selective study of true neuronal interactions from MEG or EEG recordings (Figures 2D and 2E) (Hipp et al., 2012; Brookes et al., 2012). It should be noted, however, that this comes at the cost of also discarding true zero-phase synchrony, which is known from microelectrode recordings to be abundant in the brain (Singer, 1999; Engel et al., 2001). For studying ICMs, it is also highly interesting to quantify functional relationships between waves of different frequencies (Jensen and Colgin, 2007; Palva and Palva, 2011). Measures such as n:m phase locking for $n \neq m$, phase-amplitude coupling, or amplitude-amplitude coupling can reveal nonlinear coupling across different frequencies, which is also less susceptible to volume spread artifacts.

Functional connectivity, in whatever form, can in principle be estimated between all pairs of voxels specified on a grid or surface. It is essentially impossible to visualize such a connectivity matrix in its complete form and hence approaches using graph-theoretical measures (Bullmore and Sporns, 2009) have become popular to characterize ICMs with a small set of parameters for each voxel. Beyond data compression, this representation may indicate general properties of brain connections having, for instance, small world topology, in which there are many local but few remote connections, such that the neural nodes are generally connected by short paths (Bullmore and Sporns, 2012).

Neurophysiology of ICMs

Correlation patterns in ongoing activity were first described in animal studies. Early investigations in the cortex of cats reported phase ICMs at various timescales, ranging from coupled "slow-wave" oscillations in the range of 1 Hz to coupling of oscillations in the gamma band (Amzica and Steriade, 1995; Steriade et al., 1996a, 1996b; Contreras and Steriade, 1997; Destexhe et al., 1999). Coupling of slow-wave oscillations was found to occur over large distances, even between widely separate cortical areas, and to involve subcortical regions such as thalamus or striatum (Amzica and Steriade, 1995; Contreras and Steriade, 1997; Destexhe et al., 1999; Volgushev et al., 2011). Faster

cortical oscillations were spatially much more restricted in their coherence (Steriade et al., 1996b; Destexhe et al., 1999), but they were also coupled with ongoing fast rhythms in the thalamus (Steriade et al., 1996a). Interestingly, coherence of slow rhythms was temporally sustained, while coupling of beta and gamma activity strongly fluctuated over time (Destexhe et al., 1999). Importantly, coupling in all frequency bands could occur with phase lags close to zero (Steriade et al., 1996b; Contreras and Steriade, 1997). Optical imaging studies using voltage-sensitive dyes produced similar results, revealing large-scale spatial coupling of ongoing oscillations that was particularly widespread for low frequencies (Arieli et al., 1996).

A study of ICMs in the visual cortex of awake monkeys (Leopold et al., 2003) investigated coupling both for the phase of ongoing oscillations and for their amplitude envelopes (cf. Figure 2B). Across the array of implanted electrodes, phase coupling decreased with increasing spatial separation and was inversely related to the frequency. Interestingly, a different pattern was revealed for the amplitude envelope correlations. Envelopes showed predominantly slow correlations (<0.1 Hz), which achieved very high values even over large distances (Leopold et al., 2003). This was particularly true for the amplitude envelopes of gamma-band oscillations that, in terms of their phase, showed much weaker coupling across distance. This seems interesting because states of global synchronization in the brain are typically associated with lower frequencies such as slow-wave oscillations or delta or alpha waves (Destexhe et al., 1999; Supp et al., 2011).

In the human brain, resting state dynamics has been explored using EEG or MEG mainly in the context of neuropsychiatric disorders (see below) and studies focusing on phase or envelope ICMs using these methods in the healthy brain have remained scarce. Envelope ICMs have been studied using intracranial recordings during presurgical clinical testing in epilepsy patients (Nir et al., 2008; He et al., 2008; Jerbi et al., 2010; Keller et al., 2013). Simultaneous recordings of unit activity and LFPs from left and right auditory cortex revealed strongly correlated fluctuations of firing rate and LFP power envelopes across the hemispheres (Nir et al., 2008). Similarly to what has been reported in monkeys (Leopold et al., 2003), signal envelope correlations were particularly robust for high-frequency activity. Gamma-band power envelope correlations have also been reported for sensorimotor networks (He et al., 2008), which were low for slow-wave sleep but high for REM sleep and awake state. Task-related decreases in gamma-band power have been demonstrated in the default-mode network (Jerbi et al., 2010). In addition, anticorrelated gamma-band power fluctuations for different networks have been observed in invasive human recordings (Keller et al., 2013). Several EEG studies have suggested that the dynamics of the slow fluctuations giving rise to envelope ICMs may be scale-free, that is, not characterized by defined peaks in the power spectrum (Linkenkaer-Hansen et al., 2001; He et al., 2010; Palva and Palva, 2011).

Only recently, a number of studies have aimed to investigate the neurophysiology of ICMs by combining noninvasive MEG recordings with source space analyses. Several of these studies used amplitude or power envelope correlations (de Pasquale et al., 2010; Brookes et al., 2011, 2012; Hipp et al., 2012; de Pasquale et al., 2012), while others employed phase coherence (Hipp et al., 2011; Bardouille and Boe, 2012), phase lag index (Hillebrand et al., 2012), or imaginary coherence (Marzetti et al., 2013). An interesting result is that plain correlation of signal envelopes yields spatially unspecific correlation patterns characterized by high correlation of the seed with neighboring voxels and a monotonic drop off to more distant sites (Hipp et al., 2012). While also comprising true interactions, such patterns are likely to reflect, to a substantial amount, spurious correlations arising from volume spread (Nolte et al., 2004; Hipp et al., 2012). However, ICM dynamics can be recovered if correlation patterns resulting from volume conduction are suppressed before analyzing functional connectivity (Hipp et al., 2012; Brookes et al., 2012; Hillebrand et al., 2012; Marzetti et al., 2013).

A recent study that successfully employed this approach for investigation of envelope ICMs has used phase orthogonalization (Figure 2B) to remove zero-phase coupling (Hipp et al., 2012). Analysis of correlations among power envelopes revealed spatially specific coupling patterns. For instance, signal power was correlated between homologous sensory areas of the two hemispheres (Figure 2D), which matches similar patterns observed in BOLD signals (Figure 1A). Overall, ICMs were most prominent in the alpha and beta band. The power envelope fluctuations were coupled at very slow frequencies below 0.1 Hz (Figure 2C), suggesting a close correspondence to correlated BOLD activity fluctuations (Fox and Raichle, 2007; Deco and Corbetta, 2011; Raichle, 2010). The data indicate that this approach can reveal a rich set of spectral signatures for functional networks. Analysis of coupling in different frequency ranges exposes distinct sets of hubs. For interactions in the beta band, these are located in dorsolateral prefrontal, lateral parietal, and temporal cortex (Figure 2E). In contrast, theta-band interactions involve major hubs in the medial temporal lobe, and gamma-band hubs can be observed in sensorimotor cortex (Hipp et al., 2012). An important finding is that coupling, as revealed by envelope correlations, can dissociate from the spatial distribution of local signal power. Another MEG study employing a related approach has provided similar results (Brookes et al., 2012).

A recent study of phase ICMs employing the phase lag index has revealed somewhat different patterns of highly connected regions that differ across frequency bands (Hillebrand et al., 2012). In the alpha band, the most strongly connected regions were visual and posterior cingulate cortex. In the beta band, this involved sensorimotor and parietal cortex, and in the gamma band, temporal and parietal areas showed high functional connectivity. Phase ICMs have also been mapped in a recent study that focused on coupling in the dorsal attention network (Marzetti et al., 2013). Significant delta- and alpha-band interactions were observed between homologous regions of the attention network in the left and right hemisphere. Moreover, this network showed coupling in the alpha band to visual regions, as well as beta-band interactions with sensorimotor regions. Taken together, these studies seem to provide evidence that phase ICMs can dissociate from envelope ICMs, but further studies will be required to elaborate this in greater detail.

An important question is to what extent the neurophysiological signatures of ICMs match their MRI-based characterization. The

relation between LFP and BOLD signals has been the subject of a number of studies. BOLD fluctuations seem to correlate best with the slow power envelope fluctuations observed for LFPs and MEG or EEG signals (Logothetis et al., 2001; Leopold et al., 2003; Nir et al., 2007; He et al., 2008). In particular, this holds for the gamma band, but lower frequencies have also been found to be related to the BOLD signal (He et al., 2008; Magri et al., 2012; Keller et al., 2013). This is supported by studies that have employed direct coregistration of ongoing EEG or LFPs with BOLD activity (Shmuel and Leopold, 2008; Schölvinck et al., 2010; Tagliazucchi et al., 2012a). It has been suggested that slow changes in both BOLD signal and power envelopes of oscillatory signals, may reflect endogenous fluctuations of neuronal excitability, which occur in a coupled manner across different cortical and subcortical regions (Leopold et al., 2003; Deco and Corbetta, 2011). Taken together, these studies provide evidence that BOLD coupling analyses primarily reveal envelope ICMs, thus converging with neurophysiological analyses of envelope correlations.

The studies discussed above suggest that spectrally and temporally resolved analyses of ICMs can provide important information, beyond what can be revealed by BOLD connectivity (Laufs, 2008; Deco et al., 2011). First, this concerns the fast dynamics of ongoing activity. At present, phase ICMs cannot be revealed by fMRI-based investigations. Spectral signatures can differ substantially across networks and hubs, which are not captured by the BOLD dynamics (Laufs, 2008; Jann et al., 2010; Hipp et al., 2012). Second, frequency-specific analyses are likely able to reveal a richer dynamics of interactions than reflected by BOLD connectivity. Thus, for instance, coupling has been shown to be highly variable across epochs (de Pasquale et al., 2012) and to occur across different subnetworks defined by BOLD correlations (Marzetti et al., 2013). Third, connectivity patterns revealed by BOLD seem to be quite stable across brain states and are observed even under deep anesthesia (Vincent et al., 2007). However, temporal and spectral characteristics of ongoing activity can change profoundly in anesthesia or deep sleep compared to the waking state (Destexhe et al., 1999; van der Togt et al., 2005; He et al., 2008; Supp et al., 2011). Fourth, there is substantial evidence for cross-frequency coupling (Steriade et al., 1996b; Monto et al., 2008; Schroeder and Lakatos, 2009; Palva and Palva, 2011) in ongoing activity that cannot be captured by fMRI-based analyses.

Taken together, the studies discussed above demonstrate a close correspondence between the results obtained in animals and in humans. The data suggest that ICMs occur on a broad range of spatial and temporal scales, involving two distinct types of dynamics that rise to phase ICMs and envelope ICMs, respectively (Table 1). Phase ICMs are defined by phase coupling and involve oscillatory signals with band-limited dynamics, which occur at frequencies between 1 Hz (slow-wave oscillations) to about 150 Hz (fast gamma-band oscillations). Envelope ICMs can be uncovered by correlation of signal envelopes or BOLD time courses. They comprise presumably aperiodic (scale-free) activity fluctuations that typically show most of their energy at frequencies below 0.1 Hz. Thus, they may reflect the coactivation of neuronal populations on slow timescales ranging from several seconds to minutes.

Origins of ICMs

Key questions are how ICMs arise, which factors modulate their expression, and whether these differ in their relevance for the emergence of envelope and phase ICMs. Considering these issues, it is important to distinguish the mechanisms giving rise to local activity fluctuations from those that mediate the coupling across spatially separate neuronal populations. In the following, we focus on the latter.

A straightforward hypothesis is that ICMs may be determined by the underlying structural connectivity. Evidence is available that this may hold, at least in part, for envelope ICMs. Studies in monkeys have shown that BOLD correlation patterns match with known anatomical connectivity (Vincent et al., 2007; Wang et al., 2013). Studies in humans have also related functional BOLD coupling to structural connectivity data. Several investigations reported consistent identification of fiber tracts linking regions within networks defined by BOLD correlation (Hagmann et al., 2008; Greicius et al., 2009). However, structural connectivity seems to account only for about half of the variance in BOLD functional connectivity (Skudlarski et al., 2008; Honey et al., 2009). Indeed, BOLD coupling is not only mediated through direct connections but can also occur through polysynaptic connections (Vincent et al., 2007; Damoiseaux and Greicius, 2009) and, conversely, functional coupling can be absent despite the presence of structural connections (Honey et al., 2009). Taken together, the available data show that envelope ICM dynamics is only partially, but not completely, determined by structural connectivity (Damoiseaux and Greicius, 2009; Deco and Corbetta, 2011).

Very likely, the same holds true for phase ICMs, but quantitative studies relating phase ICM dynamics to structural connectivity are lacking. It has been shown that phase coupling of cortical oscillations requires corticocortical connections (Engel et al., 1991; Singer, 1999), but there is abundant evidence that structural connectivity does not strictly determine phase ICMs. Rather, factors relating to stimulus context, task, or cognitive setting strongly modulate the coupling of neuronal oscillations (reviewed in Singer, 1999; Engel et al., 2001; Fries, 2009; Engel and Fries, 2010; Siegel et al., 2012). The notion that phase ICMs may be less determined by structural connectivity than envelope ICMs is also supported by modeling studies exploiting the monkey connectome (Honey et al., 2007).

An additional important factor determining functional connectivity are conduction delays, particularly in long-range pathways, which have been shown to directly influence the coherence of neuronal oscillations (König and Schillen, 1991). Interestingly, delays seem not only relevant for phase ICMs but also for envelope ICMs. This has been addressed in models that investigated the dynamics of the monkey connectome, showing that nonvanishing delays can be critical for the emergence of spatially coordinated slow fluctuations (Ghosh et al., 2008; Deco et al., 2009, 2011).

Evidently, some of the early research on envelope ICMs started out with the assumption that some of these were related to particular brain states (e.g., the default mode network being related to a "resting state"). However, envelope ICMs actually seem to be relatively robust against global state changes. As shown by studies in monkeys, BOLD correlation patterns

observed in the awake state are largely unchanged in sleep (Larson-Prior et al., 2011) or under anesthesia (Vincent et al., 2007). This might relate to the observation that BOLD fluctuations correlate with power envelopes of neural signals in multiple frequency ranges (Schölvinck et al., 2010; Magri et al., 2012). Phase ICM dynamics, in contrast, seems strongly susceptible to state changes. Both the spectral characteristics and the strength of coupling in phase ICMs change profoundly in anesthesia or deep sleep compared to the waking state. Indeed, changes in arousal were shown to shift the predominant frequency band and the spatial ranges at which coupling of ongoing oscillations occurs (Destexhe et al., 1999; van der Togt et al., 2005; He et al., 2008; Supp et al., 2011). Phase ICMs have long been known to be critically influenced by neuromodulators involved in the regulation of global brain states (Deco and Thiele, 2009). For instance, activation of cholinergic brain stem nuclei enhances gamma-band coherence in cortical networks (Munk et al., 1996). As a possible mechanism, modeling studies suggest that acetylcholine modulates the efficacy of intracortical connections through changes in local neuronal excitability (Verschure and König, 1999).

It is highly likely that ICMs are strongly influenced by the history of ongoing or task-related network dynamics. Substantial evidence suggests that both envelope and phase ICMs are sculptured by experience-dependent plasticity, reflecting a history of coactivation during previous tasks (Singer, 1999; Izhikevich et al., 2004; Corbetta, 2012). Indeed, ongoing activity patterns resembling preceding task- or stimulus-related activation have been reported in studies on rat hippocampus (Foster and Wilson, 2006) and sensory cortex (Luczak et al., 2009; Xu et al., 2012). Shaping of envelope ICMs by history of coupling during preceding tasks has been shown in several studies involving sensorimotor learning (Albert et al., 2009; Lewis et al., 2009) or memory encoding (Tambini et al., 2010). Moreover, a number of studies have demonstrated that spatial patterns in ongoing activity can resemble functional topographies in visual and auditory cortex, which are molded by experience-dependent plasticity (Kenet et al., 2003; Fukushima et al., 2012). Phase ICMs are also likely to be shaped through learning and spike-timing-dependent plasticity (Singer, 1999; Uhlhaas et al., 2010). This has been shown, for instance, in studies in amblyopic cats in which experience-dependent network changes lead to altered coherence of oscillations in visual cortex (Roelfsema et al., 1994).

Taken together, the available evidence suggests that ICMs are determined by a number of factors including structural connectivity, conduction delays, level of neuromodulators, global network states, as well as previous task-related activation or coupling. This suggests that ICMs are not reflecting highly invariant networks but coupling patterns that adapt through use-dependent plasticity and are modified in a context-dependent manner.

Functional Significance

A huge body of evidence is available regarding putative functions of stimulus-induced or task-related coupling (Singer, 1999; Engel et al., 2001; Jensen and Colgin, 2007; Fries, 2009; Schroeder and Lakatos, 2009; Engel and Fries, 2010). The computational and cognitive significance of coupling in ongoing activity is not yet resolved, but a number of putative functions have been suggested.

An obvious possibility is that ICMs provide coordinated windows of enhanced or decreased excitability for spatially separate neuronal populations (Schroeder et al., 2008; Schroeder and Lakatos, 2009; Fries, 2009; Deco and Corbetta, 2011). This might then modulate local dynamics either on slow or faster timescales, depending on whether envelope or phase ICMs predominate. Moreover, this might regulate plasticity within and among the populations involved in the ICM and, thus, contribute to shaping the network structure and to consolidating patterns of synaptic changes. In addition to regulating local excitability and plasticity, ICMs might bias the functional connectivity across neuronal populations during upcoming stimuli or tasks (Engel et al., 2001; Fox and Raichle, 2007; Deco and Corbetta, 2011; Corbetta, 2012). Shaped by previous learning, ICMs might encode predictions about expected correlations between regions that might be cooperating in the future. ICMs might embody dispositions for expression of dynamic coupling patterns underlying cognitive processing and, thus, act as priors for the processing of upcoming stimuli. These priors might take effect by constraining task-related dynamics and by facilitating certain coupling patterns during stimulation.

A number of studies suggest that envelope ICMs can modulate perception and cognitive processing. It has been shown that variability of both a behavioral response and BOLD signals in sensorimotor cortex was influenced, on a trial-by-trial basis, by an ICM involving left and right sensorimotor areas (Fox et al., 2006, 2007). BOLD fluctuations across visual areas were shown to modulate the dynamics of spontaneous perceptual changes in a bistable perception task (Donner et al., 2013). Interestingly, the perceptual changes were related to retinotopically specific coupling modes, suggesting that envelope ICMs can encode predictions in a spatially specific way (Figure 3A). In studies involving continued detection of somatosensory stimuli, the amplitude (Linkenkaer-Hansen et al., 2004) or the phase (Monto et al., 2008) of slow envelope fluctuations was found to modulate the subjects' detection performance.

An important question is whether ICMs occurring during rest are similar to coupling patterns observed during a task. ICMs might persist as "background" coupling patterns during task performance or stimulus processing. Studies in both monkeys and humans suggest that envelope ICMs indeed may be similar in ongoing activity and during tasks (Leopold et al., 2003; Vincent et al., 2007; Smith et al., 2009). In the study on BOLD fluctuations and bistable perception mentioned above (Donner et al., 2013), the coupling patterns investigated actually represent envelope ICMs present during the task.

While a substantial number of studies have looked at predictive effects of local oscillatory activity, studies on predictive effects of phase coupling on perception or task performance are relatively rare. Based on studies of auditory and language processing, delta- and theta-band ICMs have been associated with predictive timing ("predicting when"). Beta- and gamma-band ICMs, in contrast, may be relevant for encoding predictions about the nature of upcoming stimuli ("predicting what") (Arnal and Giraud, 2012). It has been postulated that beta-band ICMs

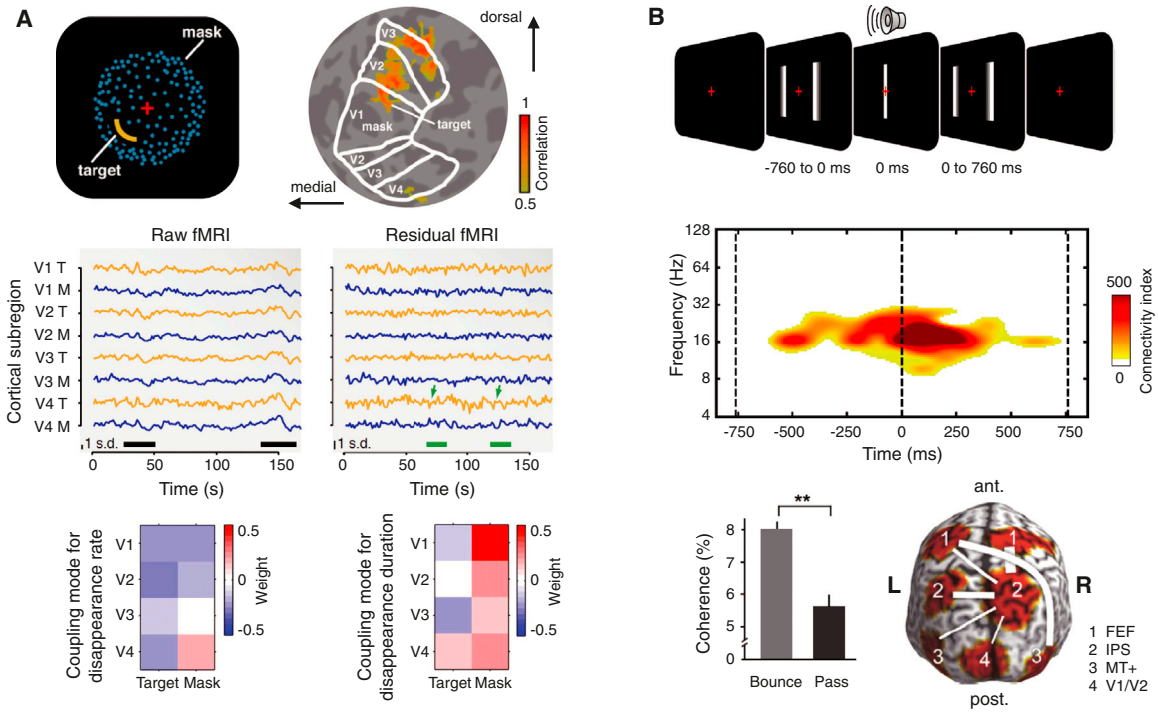

Figure 3. ICMs Can Bias Cognitive Processing

(A) Fluctuations of an envelope ICM shaping perceptual dynamics during motion-induced blindness. Top left: a yellow target was surrounded by a moving dot pattern (blue), which appeared as a rotating sphere. While viewing this stimulus, participants repeatedly experienced the spontaneous disappearance and reappearance of the target. Top right: retinotopic subregions activated by target and mask in visual areas V1–V4. Colors represent correlation between measured activity and stimulus alternations. Middle left: example of a raw fMRI time series for the cortical subregions activated by targets (T, orange) and by the mask (M, blue). Black bars at the bottom indicate epochs of strong global fluctuations across all subregions, which were unrelated to the perceptual dynamics. Middle right: residual time series after removing the global mean across all subregions. Green bars and arrows mark epochs of anticorrelated fluctuations in the target and mask subregions of V4. Coupling of fluctuations in the residual BOLD signals predicted the subjects' perceptual dynamics. Bottom left: coupling mode correlating with the rate of target disappearance. Colors represent weights that quantify the contribution of each retinotopic subregion to the fluctuation. Bottom right: coupling mode related to the duration of target disappearance. Modified from Donner et al. (2013).

(B) Phase ICM biases perception in the bounce-pass paradigm. Top: while EEG was recorded, participants watched a screen on which two bars approached, briefly overlapped, and moved apart again. At the time of overlap of the bars, a brief click sound was played. Participants perceived this stimulus either as two bouncing or passing bars, with the percept spontaneously changing across trials. Middle: around the time when the stimulus became perceptually ambiguous, beta-band coherence (15–30 Hz) was enhanced. Bottom left: the strength of beta-band coupling predicted the subjects' percept: stronger beta-band coherence predicted perceiving the bars as bouncing, whereas weaker coherence predicted the percept of passing bars. Bottom right: this beta-band ICM (white lines indicate coherence strength) occurred in a large-scale cortical network including bilateral frontal eye fields (FEFs), posterior parietal cortex (IPS), visual areas involved in motion processing (MT+), as well as early visual cortex (V1/V2). Modified from Hipp et al. (2011).

may specifically be involved in predicting a maintenance of the current sensorimotor setting, while gamma-band ICMs may encode the prediction of a change in stimulation or cognitive set (Engel and Fries, 2010). Alpha-band ICMs have been implicated in the inhibition and disconnection of task-irrelevant areas (Jensen et al., 2012).

A number of animal studies demonstrate predictive or modulatory effects of phase ICMs. Spike synchronization in monkey motor cortex was observed to reflect the animal's expectancy of an upcoming stimulus (Riehle et al., 1997). Similarly, beta-band ICMs were found to occur in cat visual and parietal cortex during expectation of a task-relevant stimulus (Roelfsema et al., 1997). In cat visual cortex, gamma-band coupling in prestimulus epochs was shown to predict first-spike synchrony during stimulation (Fries et al., 2001). Studies of monkey visual cortex indicate that fluctuations in gamma-band ICMs modulate the speed at which animals can detect a behaviorally relevant stimulus change (Womelsdorf et al., 2006). EEG studies in humans provide convergent evidence that prestimulus fluctuations in phase ICMs can modulate target detection (Hanslmayr et al., 2007; Kranczioch et al., 2007), suggesting that perception of a task-relevant stimulus is hampered by alpha-band but facilitated by beta- and gamma-band ICMs. Furthermore, intrinsic fluctuations of phase ICMs are associated with fluctuations in perceptual states in ambiguous stimulus settings. Fluctuations in a beta-band ICM have been shown to predict the perceptual state in an ambiguous audio-visual paradigm (Hipp et al., 2011) (Figure 3B). Intrinsically generated fluctuations in a gamma-band ICM seem responsible for perceptual changes in a dynamic apparent motion stimulus (Rose and Büchel, 2005). Both studies demonstrate the relevance of intrinsically generated fluctuations in coupling that are present during the task and interact with the stimuli such that one perceptual interpretation is favored.

Importantly, phase ICMs also closely relate to plasticity. In addition to being enabled by preceding learning and plasticity

(see preceding section) phase ICMs are, in turn, important in triggering synaptic changes. During development, phase ICMs are involved in shaping the network structure (Weliky, 2000; Uhlhaas et al., 2010). Synchronized ongoing activity is present in the nervous system already early in development and has been shown to be important, by triggering spike-timing-dependent plasticity, for normal development of topographic maps, connection topologies, and neuronal response properties (Weliky, 2000; Feldman, 2012). In the adult brain, phase ICMs are known to play a role in both working memory and long-term memory. Well-established examples are theta-band ICMs linking the hippocampus to frontal regions and beta-band ICMs coupling frontal and parietal areas during working memory (Fell and Axmacher, 2011). In sleep, slow-wave oscillations are thought to have a role in memory consolidation, enabling transition of memories from a labile state into a stable state that is hippocampus independent (Diekelmann and Born, 2010). During the slow oscillations, replay of previously processed signals seems to occur (Luczak et al., 2009), suggesting that phase ICMs can also serve to revisit and consolidate activity patterns that have been learnt during stimulation.

An important, but unresolved, question is how envelope and phase ICMs might interact. Between phase ICMs in different frequency bands, cross-frequency coupling seems abundant. For instance, in auditory cortex, delta-band ICMs modulate the amplitude of theta-band ICMs, whose phase in turn modulates the amplitude of gamma-band ICMs (Schroeder et al., 2008). During sleep, slow oscillations also seem to orchestrate fast oscillations (Diekelmann and Born, 2010). It has been suggested that cross-frequency coupling may also occur between envelope and phase ICMs (Palva and Palva, 2011). Indeed, the phase of envelope ICMs has been shown to modulate the amplitude of faster ongoing oscillations (Monto et al., 2008). Thus, envelope and phase ICMs might interact to organize hierarchies of dynamic patterns by cross-frequency coupling (Schroeder et al., 2008). Envelope ICMs might facilitate phase ICMs by changing effective coupling at faster frequencies through excitability modulation (Palva and Palva, 2011). Conversely, hypercoherent low-frequency ICMs may also impair communication through phase ICMs at higher frequencies. For instance, during anesthesia ongoing low-frequency coupling seems to block specific processing at faster coupling modes (Supp et al., 2011).

Taken together, the available data seem to support the following set of hypotheses on the putative function of ICMs (Table 1). Envelope ICMs might primarily be involved in regulating the activation of particular networks that might be relevant for an upcoming task. They seem to represent coherent excitability fluctuations that lead to coordinated changes in the activation of brain areas. Phase ICMs, in contrast, seem to facilitate communication between separate neuronal populations during stimulus or cognitive processing (Fries, 2009; Corbetta, 2012), which may be relevant for regulating the integration and flow of cognitive contents. Another important function of phase ICMs is that they enable spike-timing-dependent plasticity and are related to encoding of memories and to the stabilization of circuitry during development. It is currently unclear whether envelope ICMs might also have a function in gating plasticity on slower timescales, possibly through neuromodulation (Pawlak et al., 2010). At present, little experimental evidence is available to support this, but studies in sleep suggest a role for slow ongoing oscillations in regulating plasticity (Marshall et al., 2006).

Changes in Neuropsychiatric Disorders

A large number of neurological and psychiatric disorders involve malfunctions in distributed brain networks mediating perceptual and cognitive processes. Available evidence suggests that this holds for disorders such as schizophrenia, depression, autism, Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), or stroke. Therefore, it is hardly surprising that there is a steadily growing interest in how coupling patterns change in these and other disorders, both in task-related (Schnitzler and Gross, 2005; Gerloff et al., 2006; Uhlhaas and Singer, 2012) and in ongoing activity (Fox and Greicius, 2010; Gerloff and Hallett, 2010). It has been hypothesized that the spatiotemporal dynamics of distributed networks may provide a key to understanding the pathophysiology of these neuropsychiatric disorders (Schnitzler and Gross, 2005; Uhlhaas and Singer, 2012). In this context, ICMs seem particularly relevant because they might reflect the underlying type of network malfunction, may constitute intermediate phenotypes linking risk gene variants to behavior and clinical symptoms (Fornito and Bullmore, 2012), and can possibly serve as markers for diagnostic and therapeutic interventions (Bullmore and Sporns, 2009; Carter et al., 2012). In this section, we discuss several examples of disorders in which substantial research on changes in ICMs has been carried out, namely, AD, MS, stroke, PD, and schizophrenia. Comparing network dynamics across these disorders seems highly interesting, as they represent different types of network disturbances, such as large-scale neurodegeneration (AD), focal (stroke) or multifocal (MS) lesions, regional neurodegeneration with loss of a modulatory transmitter system (PD), and late developmental network modifications (schizophrenia).

A wealth of studies on AD has addressed altered functional connectivity in ongoing activity, suggesting profound changes in envelope ICMs in this neurodegenerative disorder (Filippi and Agosta, 2011). Consistently, a disruption of envelope ICMs in the default-mode network and a decrease of coupling between default-mode network and hippocampus has been described (Broyd et al., 2009), which has been linked to the memory dysfunction occurring in this disorder. More recent studies have reported decreases of envelope ICMs also for other BOLD-defined networks (Brier et al., 2012) (Figures 4A and 4B). Graph-theoretical analyses revealed that brains of AD patients show a reduction of long-distance connections, increased path length between nodes, and reduced local clustering (Supekar et al., 2008; Sanz-Arigita et al., 2010), indicating a loss of small-world network properties. Changes in phase ICMs have been reported by neurophysiological studies in AD, showing reduced long-range synchrony in the alpha and beta band (Babiloni et al., 2004; Koenig et al., 2005; Stam et al., 2006). These reports did not address potential confounds by volume spread, but similar results were obtained in studies using coupling analyses avoiding this problem (Stam et al., 2007a; Dubovik et al., 2013). Graph theoretical analysis has also been applied to EEG and MEG data in AD, confirming the loss of network complexity reported in fMRI studies (Stam et al., 2007b; de Haan et al., 2012).

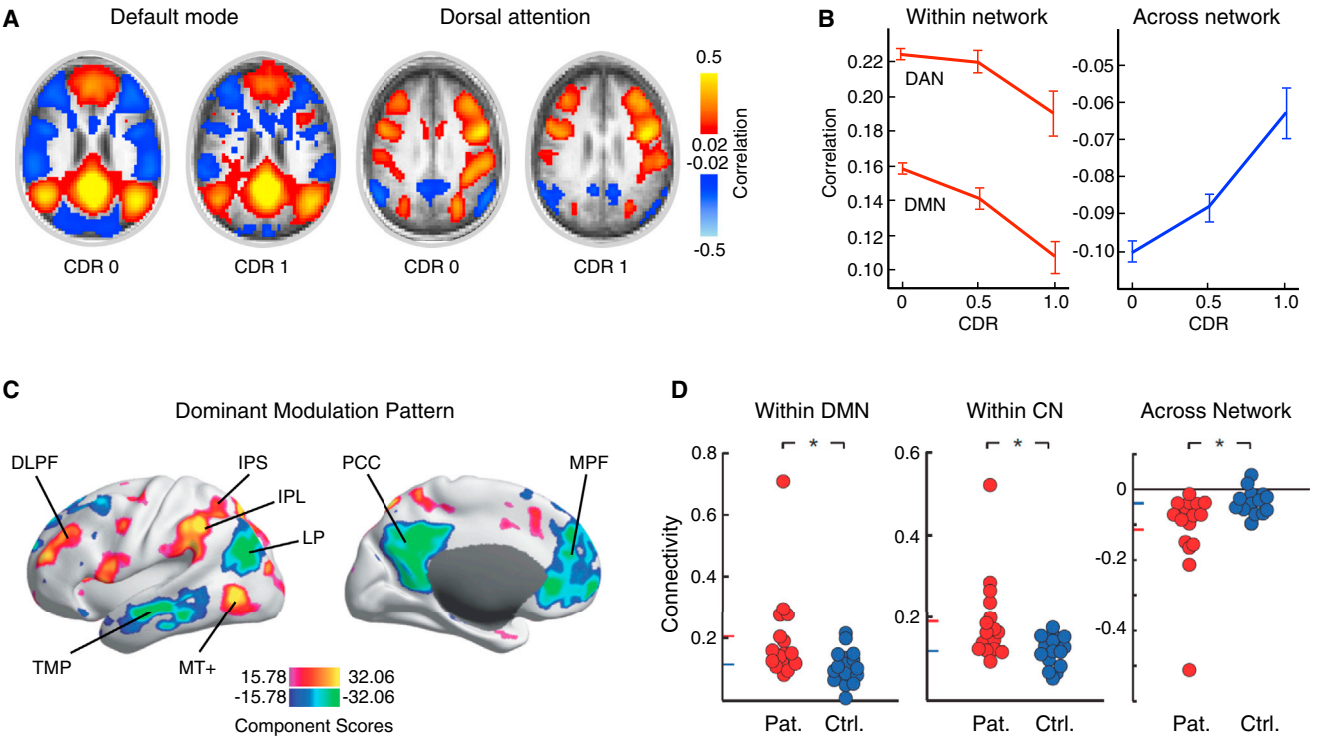

Figure 4. Alteration of Envelope ICMs in AD and MS

(A and B) In AD, BOLD functional connectivity decreases within the default mode network (DMN) and the dorsal attention network (DAN) as well as between networks. These alterations are correlated with a change in clinical dementia rating (CDR), reflecting no (CDR 0), very mild (CDR 0.5), or mild (CDR 1) dementia. (A) Seed-based connectivity maps for DMN and DAN at CDR 0 and CDR 1. For DMN, the posterior cingulate cortex and, for DAN, MT+ were chosen as seed region, respectively. Red, positive correlation; blue, anticorrelation. (B) Within network correlation and between network anticorrelation as a function of CDR. Note that both are reduced with increasing disease severity. (A) and (B) are modified from Brier et al. (2012).

(C and D) Alteration of BOLD-derived coupling in MS patients with early MS. (C) Dominant spatial pattern of connectivity modulations explaining about 40% of the overall connectivity modulation variance. This pattern comprised areas of the default mode network (DMN) and areas implicated in the deployment of attention and cognitive control (control network [CN]). (D) In both DMN and CN, connectivity was increased in patients compared to controls. Patients showed slightly stronger anticorrelation between the two networks. Note that the increase of within network coupling was associated with a decrease in cognitive efficiency that was observed using a neuropsychological test battery. Abbreviations: DLPF, dorsolateral prefrontal cortex; TMP, temporal cortex; IPL, inferior parietal lobule; IPS, intraparietal sulcus; LP, lateral parietal cortex; MT+, middle temporal region; PCC, posterior cingulate cortex; MPF, medial prefrontal cortex. (C) and (D) are modified from Hawellek et al. (2011).

Studies on ICMs in MS patients are currently relatively scarce, presumably due to the heterogeneity in symptoms and individual course of the disease. A number of recent fMRI studies have demonstrated changes of envelope ICMs in networks related to cognitive and sensorimotor functions (Filippi et al., 2013). Patients at the earliest stage of MS show increased BOLD connectivity in the default-mode network and other networks (Roosendaal et al., 2010; Hawellek et al., 2011; Faivre et al., 2012). The increase in envelope ICMs can occur despite significant cognitive decline and beginning structural disintegration of cortical networks (Hawellek et al., 2011) (Figures 4C and 4D). This suggests that, at an early stage of the disease, increased envelope ICMs might reflect a compensatory effort of brain networks to maintain appropriate function. However, at later stages of MS, functional disconnection seems to prevail, correlating closely with cognitive decline (Rocca et al., 2012). Hitherto, only very few studies are available on changes of fast neural dynamics in MS and, thus, almost nothing is known about alterations of phase ICMs in this disorder. By affecting conduction delays, demyelination and axonal damage are likely to cause changes in local carrier oscillations as well as functional disconnection of brain regions even before massive structural lesions occur. In agreement with this hypothesis, altered functional interaction across distant brain regions has been observed in MEG studies (Cover et al., 2006; Schoonheim et al., 2013; Hardmeier et al., 2012). While showing decreases of phase ICMs in the alpha and beta band, these studies also provide evidence for partially increased connectivity in parietal hubs (Hardmeier et al., 2012). Clearly, more studies are required to provide a comprehensive picture of phase ICM changes in MS and their sensitivity to disease progression.

Research on ICMs is also becoming increasingly important in stroke because even in case of focal damage communication is altered with regions outside the lesion focus (Gerloff and Hallett, 2010; Carter et al., 2012). Therefore, behavioral deficits do not reflect local network lesions alone but imbalance and disturbance of communication in a large-scale network. Furthermore, recovery after stroke will, in most cases, imply compensatory shifts in cross-regional interactions (Gerloff et al., 2006; van Meer et al., 2010; Carter et al., 2012). Envelope ICMs involving

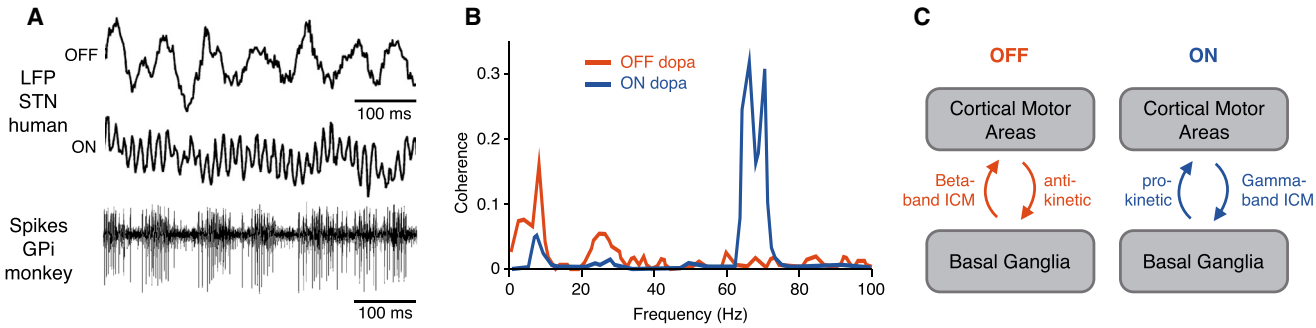

Figure 5. Alteration of Phase ICMs in Parkinson's Disease

(A) Top: example LFP recording from the STN in a PD patient. The top trace shows an epoch of data in the state after overnight withdrawal of medication (OFF) and the bottom trace a recording from the same patient after levodopa administration (ON). Note the slow oscillatory pattern in the OFF, which is replaced by much faster gamma-band oscillations in the ON state. Bottom: spike activity recorded from the internal segment of the globus pallidus (GPi) in a monkey rendered parkinsonian by application of MPTP, a neurotoxin that induces degeneration of dopaminergic neurons. The spikes are grouped in bursts that appear at beta-band frequency. Top traces are modified from Brown and Williams (2005); bottom panel is adapted from Stein and Bar-Gad (2013).

(B) Coherence of oscillatory signals between cortex and basal ganglia in a PD patient off medication (OFF, red trace) and after reinstitution of levodopa (ON, blue trace). In the OFF, coupling is dominated by tremor-related frequencies below 10 Hz and by a beta-band ICM. In the ON state, strong coupling in the gamma-band appears. Modified from Brown (2003).

(C) Schematic summary of the interactions between cortex and basal ganglia observed in PD patients.

somatomotor, executive, and attention networks are well investigated in stroke and during recovery and have been shown to be predictive for both behavioral deficits and adaptive reorganization after stroke (Carter et al., 2010; Wang et al., 2010). This holds, in particular, for interhemispheric coupling in these networks (Carter et al., 2012). In contrast, evidence regarding changes in phase ICMs is limited to a few recent studies. Alpha-band ICMs have been observed to be decreased in perilesional and increased in contralesional regions, and this interhemispheric difference has been found to predict cognitive and motor performance as well as aspects of poststroke recovery (Westlake et al., 2012; Dubovik et al., 2012). Moreover, ongoing beta-band interhemispheric coupling was found to change under the influence of rehabilitation training (Pellegrino et al., 2012).

In PD, numerous studies have addressed changes in ICMs. Substantial evidence has accumulated demonstrating that phase ICMs are altered in specific ways in PD and that they correlate with clinical symptoms and behavior. Many of the studies in PD patients involve recordings from basal ganglia structures during stereotactic surgery for deep brain stimulation. These provide clear evidence for abnormal beta-band ICMs in corticobasal ganglia loops (Figure 5A), which correlate with severity of bradykinesia and rigidity, the key clinical symptoms in PD (Brown, 2003; Stein and Bar-Gad, 2013). Accordingly, their suppression by dopaminergic medication or deep brain stimulation ameliorates the patient's condition. These findings have also been confirmed by MEG studies of phase ICMs in PD (Stoffers et al., 2008; Litvak et al., 2011). Interestingly, dopaminergic therapy and reduction of motor impairment are associated with the emergence of a gamma-band ICM between cortex and basal ganglia (Brown, 2003; Jenkinson et al., 2013) (Figure 5B). Overall, these studies have led to the notion of movement-permissive (gamma-band) versus movement-prohibitive (beta-band) ICMs (Brown, 2003) (Figure 5C). More generally, it has been suggested that these ICMs permit or prohibit a change in the sensorimotor or cognitive set (Engel and Fries, 2010). Studies on envelope ICMs using fMRI have observed increased coupling between cortex and basal ganglia in PD that is attenuated by dopamine (Kwak et al., 2010; Baudrexel et al., 2011). Whether this might relate to power envelope correlations of the abundant beta-band activity has apparently not yet been tested.

In schizophrenia, functional disconnection in brain networks has been considered an important pathophysiological mechanism already early on (Friston and Frith, 1995). Impaired functional coupling has been implicated in the generation of cognitive deficits that are typically found in the domains of working memory and attention and perceptual organization (Uhlhaas and Singer, 2012; Fornito et al., 2012). Envelope ICMs have been addressed in numerous fMRI studies, often using graph-theoretical approaches (Lynall et al., 2010; Alexander-Bloch et al., 2010). These studies suggest that there is a reduction in functional connectivity that particularly concerns interactions between frontal and posterior regions (Fornito et al., 2012). Graph-theoretical analyses reveal decreased local clustering and decreased modularity, indicating less effective local communication (Alexander-Bloch et al., 2010; Fornito et al., 2012). However, there are also indications of reorganization at a global level toward higher efficiency (decreased path length) and increased robustness (resistance to fragmentation after removal of nodes) (Alexander-Bloch et al., 2010). Phase coupling has often been studied in task-related activity patterns (Uhlhaas and Singer, 2012; Gandal et al., 2012) but less extensively in ongoing activity. Available studies on phase ICMs seem to support the hypothesis of regionally decreased functional connectivity in the alpha (Hinkley et al., 2011) and gamma band (Kikuchi et al., 2011). Overall, a complex pattern of developmentally reorganized coupling is present where connectivity is not generally reduced but may also involve abnormal increases and, in this sense, schizophrenia may represent a dysconnection, rather than a disconnection, syndrome (Uhlhaas, 2013).

Taken together, the studies reviewed above suggest that alterations in envelope or phase ICMs correlate with behavioral or cognitive alterations in the respective disorder. The changes in

ICMs seem to differ considerably across disorders, suggesting progressive disconnection in AD and MS, dysconnectivity in schizophrenia, the predominance of an abnormal phase ICM in PD, and altered functional balance across different subnetworks in stroke. The studies clearly demonstrate that investigation of ICMs can add significantly to our understanding of specific network pathologies and that they can broaden our view on the physiological relevance of network stability, for example, by assessing parameters like robustness as available from graph theoretical analyses (Bullmore and Sporns, 2009, 2012). In several disorders, clear and testable hypotheses on causal relations between changes in ICMs and clinical phenotype have been formulated. A highly relevant insight is that changes in functional connectivity observed in several of these disorders cannot be predicted in a straightforward manner from structural alterations.

While numerous studies have addressed BOLD envelope ICMs in neuropsychiatric disorders, almost no neurophysiological studies on envelope ICMs and relatively few studies on phase ICMs are available. Partly, this is due to the inherent methodological difficulties of quantifying ICMs with noninvasive neurophysiological methods. Therefore, at present, no firm conclusions seem to be possible on the degree to which envelope ICMs or phase ICMs may differentiate between different disorders. At a very general level, it may be hypothesized that disorders with a high degree of structural alteration may be associated with strong changes in both envelope and phase ICMs (e.g., AD), whereas disorders with less prominent connectomic changes (e.g., PD) may primarily show altered phase ICMs (Table 1). The current data point to a preferential pathophysiological involvement of certain ICMs, which may be altered in specific subnetworks in the respective disorders. However, more neurophysiological investigations of envelope ICMs and phase ICMs are required, which ideally should be combined with source space analyses (Hipp et al., 2012; Brookes et al., 2012; Marzetti et al., 2013). This might allow the identification of ICMs that reflect network pathologies with high specificity and sufficient sensitivity to monitor longitudinal change during disease progression or recovery.

Modeling ICMs

Computational modeling has taken up the challenge of investigating the mechanisms underlying ICMs. One central motivation of such simulations has been to explore the dynamic implications of structural brain connectivity (Bullmore and Sporns, 2012). In addition to incorporating information about anatomical connections (Hagmann et al., 2008), these models also include a generalized description of the dynamics of regional neural populations (Figure 6A). Typically, the models assume largely uniform features for the dynamics of the nodes or the interconnections (Deco and Corbetta, 2011; Deco et al., 2011). The results of several such modeling approaches (Zhou et al., 2006; Honey et al., 2007; Deco et al., 2009; Haimovici et al., 2013) converge on a number of central findings. In particular, the models reproduce empirically observed correspondences between structural connectivity and envelope ICMs (Honey et al., 2009). As a result, envelope ICMs found in the models typically reflect topological features of the underlying connectome, such as modules and hubs (Honey et al., 2007). Models further suggest that structural modularity can endow ICMs with dynamics on different temporal scales (Figure 6B). Intramodular links may provide a substrate for fast interactions, while intermodular connections allow the integration of nodes across modalities at longer timescales (Pan and Sinha, 2009). It is currently unclear to what extent this difference between topological scales may contribute to the physiological distinction between envelope and phase ICMs.

Interestingly, similar results were found in models differing strongly in their local node dynamics (Figure 6A), which may be represented by chaotic oscillators (Honey et al., 2007), phase oscillators (Cabral et al., 2011), neural mass models (Deco et al., 2009), or simple discrete excitable nodes (Haimovici et al., 2013). The essential aspect of these different models is that they are able to explore statistical regularities in network organization, particularly their modularity, through multistable dynamics. The multistability of the global dynamics appears more important than specific model details and can be achieved in various ways. For instance, dynamic node models can be chosen to be intrinsically unstable (Honey et al., 2007) or to become unstable once individual nodes are linked to each other (Deco et al., 2009). The multistability may then be controlled through parameters describing physical network interactions, such as coupling strength, delays, or noise. Noise, in particular, may provide the means for transitions between different multistable cluster synchronization states (Ghosh et al., 2008), shaping the occurrence of ICMs.

The organization of ICMs has been linked to the concept of criticality (Plenz, 2013). Criticality is associated with the phase transition between ordered and chaotic dynamics and characterized by long-range correlations and power-law distributions, for instance, of the amplitude of activity fluctuations. As shown by human and animal studies, the dynamics of envelope ICMs exhibits these characteristic features (Linkenkaer-Hansen et al., 2001; He et al., 2010; Palva and Palva, 2011; Tagliazucchi et al., 2012b). Intuitively, criticality represents a useful operating point between disorder, which provides flexibility but lacks structure, and order, with the opposite features. In this way, critical dynamics may support the multistable exploration of topological features of brain connectivity and enhance information processing capabilities of neuronal networks (Bertschinger and Natschläger, 2004). Indeed, in the critical state, the dynamic range of an excitable network is maximized (Kinouchi and Copelli, 2006) and brain networks optimize their response to inputs as well as their information processing ability (Shew and Plenz, 2013). Computational modeling indicates that envelope ICMs arise in the neural dynamics right at the critical phase transition (Haimovici et al., 2013) or just below it (Deco and Jirsa, 2012), implying an optimal exploration of the structural connectivity by neural dynamics. Conversely, the typical hierarchical modular organization of brain connectivity appears to facilitate critical dynamics (Kaiser and Hilgetag, 2010; Wang et al., 2011a).

Modeling also suggests that, in the case of envelope ICMs, the structural constraints may allow only a small number of dynamic attractors (Deco and Jirsa, 2012). However, the repertoire of envelope ICMs is substantially expanded by phase ICMs that arise at shorter timescales (Figure 6B) (Honey et al., 2007). That is, different frequency-specific networks defined by ICMs

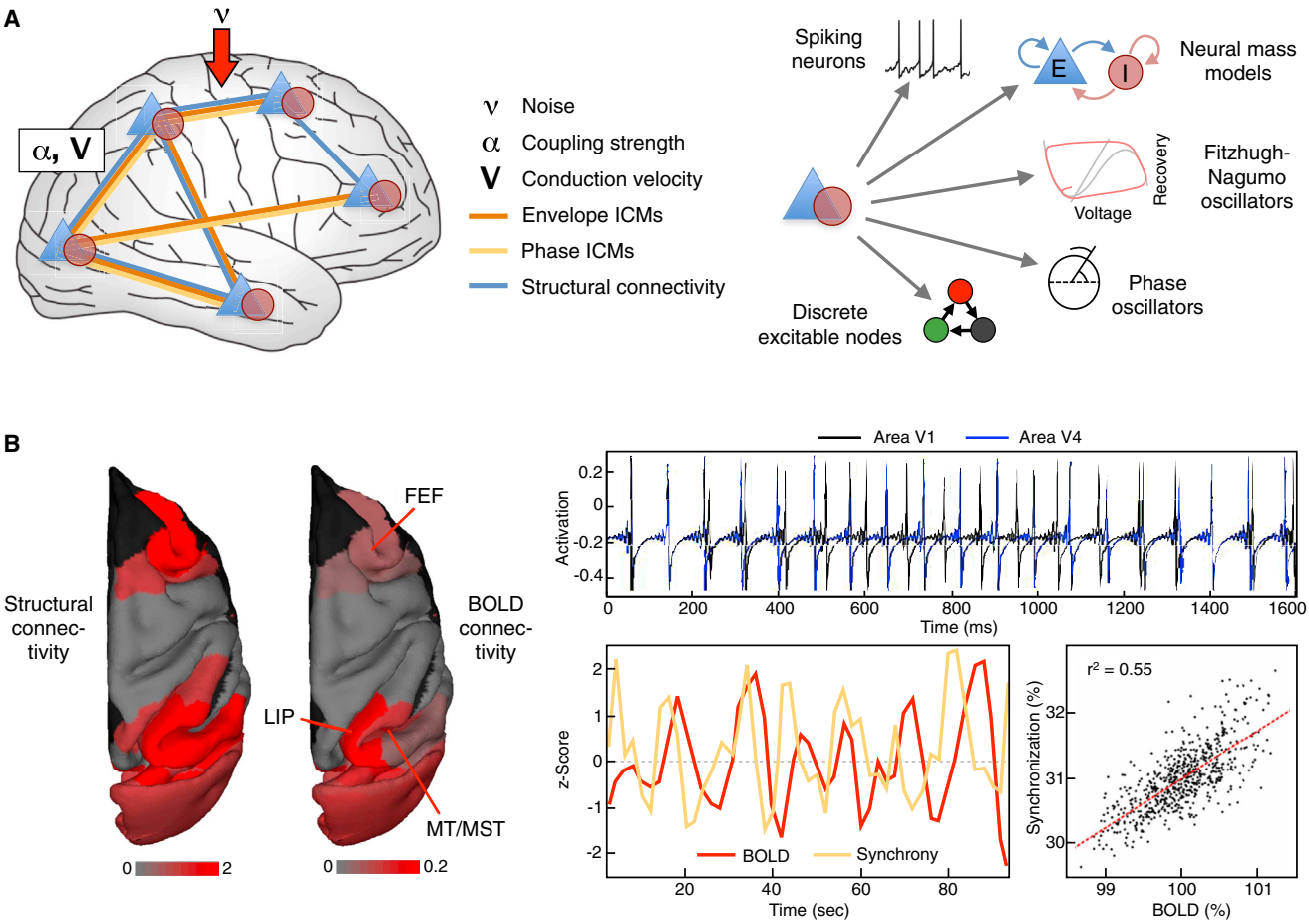

Figure 6. Modeling of ICMs

(A) Models of ICMs combine structural connectivity with local node dynamics. Left: these dynamics are generally thought to arise from balanced interactions of local populations of excitatory neurons (blue triangles) and inhibitory interneurons (red circles). Models may also include the coupling strength (α) and conduction velocity (V) of structural links, as well as externally injected noise (ν). Envelope ICMs (dark orange lines) frequently match the structural connectivity patterns but can also be present in the absence of direct structural coupling. Conversely, they can be absent even when structural links exist. Phase ICMs (light orange lines) may depend on envelope ICMs but may form flexibly within and across topological modules of the structural connectivity. Right: local node dynamics may be represented by diverse models. These include spiking neurons, neural mass models (e.g., Wilson-Cowan oscillators), Fitzhugh-Nagumo oscillators, chaotic or phase oscillators, or even discrete excitable nodes.

(B) Emergence of ICMs at both fast and slow timescales in a large-scale simulation of monkey cortex using a local node mass model. Left: envelope ICMs based on simulated BOLD correlations and structural connection patterns (both using area LIP as seed) show substantial agreements, in line with empirical observations. Right top: at a finer temporal scale, the simulated ongoing activity of two cortical areas (V1, V4) linked by structural connections shows intermittent synchronization and desynchronization. Right bottom: episodes of synchronization are related to slow fluctuations in BOLD amplitude, suggesting a link between phase ICMs operating on a fast timescale (≈10 Hz) and envelope ICMs. (B) is modified from Honey et al. (2007). Copyright National Academy of Sciences, USA.

might form and coexist within the constraints imposed by slower network dynamics. Modeling has also shown that phase ICMs based on synchronization facilitate efficient information transmission (Buehlmann and Deco, 2010). The modeling of phase ICMs has just begun (David and Friston, 2003; Battaglia et al., 2012), and a systematic theoretical analysis of these spectral coupling modes and their interaction with envelope ICMs still presents a challenge.

Another challenge for modeling is to describe the impact of network history on ICMs. Pilot models have demonstrated that mechanisms such as spike-timing-dependent plasticity may contribute to shaping ICMs. For example, in a model of spiking neurons, Izhikevich et al. (2004) found that the interplay between spike-timing-dependent plasticity and conduction delays led to the formation of modules of strongly connected neurons capable of producing time-locked spikes. Alternatively, modular connectivity could be produced from a combination of synchronization-dependent plasticity and growth-dependent plasticity in a neural mass model (Stam et al., 2010). More detailed models will be required to show precisely how previous functional synchronization becomes encoded in patterns of structural connectivity and corresponding ICMs.

A key goal for future modeling approaches will also be to explain the alterations of ICMs in neuropsychiatric disorders. As discussed in the preceding section, even focal stroke typically has a spatially widespread impact on network dynamics and

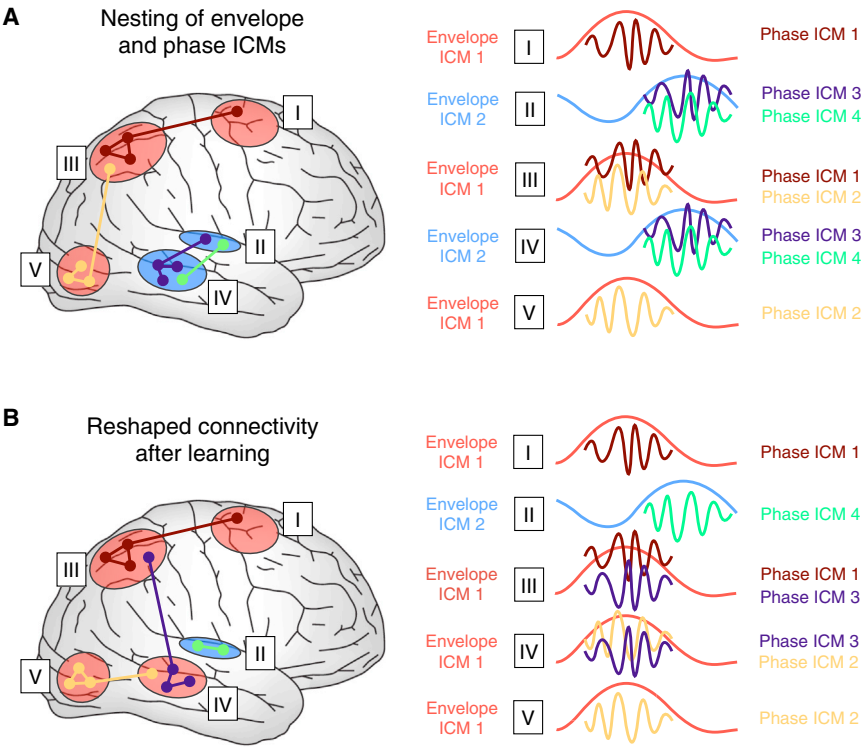

Figure 7. Interaction of Envelope and Phase ICMs

(A) Envelope ICMs may serve for regulating the coactivation of brain regions participating in a functional network. In this example, envelope ICMs 1 and 2 reflect the activation of two distinct networks at different epochs in time. Envelope ICMs possibly modulate the amplitude of oscillatory signals and, thus, gate phase ICMs. Phase ICMs 1–4 (indicated by different colors) represent modes of coherent oscillations that are coupled across subsets of the regions involved. It is hypothesized that, within one envelope ICM, multiple phase ICMs may be nested, which are distinguished by low mutual coherence. Thus, within each envelope-defined network, selective communication can be established between neuronal populations participating in different phase ICMs.

(B) Learning is likely to reshape connectivity, both at the timescale of envelope ICMs and of phase ICMs.

ICMs. This can be modeled by considering the effect of focal lesions of nodes and their connections on envelope ICMs (Alstott et al., 2009). A recent study investigating the impact of moderate, but spatially unspecific, disconnection has demonstrated a decrease in small-world properties and global integration reminiscent of the changes observed in schizophrenia (Cabral et al., 2012). Computational approaches may also become relevant for understanding alterations of ICMs in other network diseases, such as MS. Several computational models suggest that a shift of conduction delays away from the normal set point may lead to suboptimal exploration of the dynamical attractor landscape (Ghosh et al., 2008).

Toward a Unifying Framework

The studies reviewed in the preceding sections comply with the notion that the brain's dynamics are to a large extent determined by its intrinsic communication but much less by interactions with its environment. They demonstrate that intrinsic coupling modes are present in ongoing activity that reflects the sedimented results of previous learning, encodes relevant priors for future processing, and predicts perception and behavior both in the healthy organism and in disorders that affect brain networks.

The available data support a differentiation between two types of ICMs (Table 1) that seem to reflect the operation of distinct coupling mechanisms and have therefore been termed "envelope ICMs" and "phase ICMs." While the latter arise from phase coupling of band-limited oscillatory signals, the former are best described as coupled aperiodic fluctuations of signal envelopes. Both types may be observed at varying spatial scales, ranging from local (within regions) to large-scale (cross-regional) coupling. However, they seem to differ in their typical timescales, their relation to structural connectivity, and their state dependence. Envelope ICMs are observed on slow timescales of several seconds to minutes, are strongly (albeit not completely) reflecting connectomic structure, and appear relatively robust against state changes. Phase ICMs, in contrast, are observed in multiple defined frequency bands between about 1 Hz and 150 Hz, are less constrained by structural coupling, and show strong state dependence. At present, the mutual relations of these two types of ICMs are not yet resolved. On the one hand, it seems likely that envelope ICMs constrain phase ICMs both spatially and temporally. On the other hand, it might be that envelope ICMs emerge, at least in part, from the superposition of multiple phase ICMs.

As we have discussed above, these two types of ICMs may have different but related functions. Envelope ICMs seem to represent coherent excitability fluctuations that lead to coordinated changes in the activation of brain areas. We therefore hypothesize that they might regulate the availability of neuronal populations or regions for participation in an upcoming task. Phase ICMs, in contrast, may facilitate communication between separate neuronal populations during stimulus or cognitive processing, which may serve to regulate the integration and flow of cognitive contents on fast timescales. Another important function of ICMs is that they enable the consolidation of memories and the stabilization of neuronal circuits in development. While gating of spike-timing-dependent plasticity is well established for phase ICMs, the relation of envelope ICMs to plasticity is, at this point, largely hypothetical.

The interaction between both types of ICMs might then enable the following scenario (Figure 7). While envelope ICMs facilitate the participation of certain brain areas in an upcoming task, phase ICMs might prime the activation of particular dynamic links within the respective network. Establishment of such dynamic links just prior to expected events might prime particular

stimulus constellations or movement programs, thus increasing appropriateness and efficiency of the organism's response. Effectively, this interaction between envelope and phase ICMs might establish and coordinate functional hierarchies of dynamic coupling patterns across different spatial and temporal scales. An interesting implication of such a scenario might be that, through the nesting of multiple timescales, global dynamics might influence or bias local dynamics. Evidently, further studies will be needed to investigate the functional interaction between both types of ICMs.

Further research will also be needed to address the relation between ICMs and task-related coupling modes. In natural settings, the operations of the brain will rarely be completely stimulus and task free, except during sleep, anesthesia, or coma. Thus, it may be assumed that ICMs will dominate the dynamics in regions that do not participate in the current task, while they interact or compete with externally triggered coupling modes in other networks involved in the "foreground" process. In the latter, ICMs might interact with task-related coupling modes, resulting in a matching of predictions with incoming signals and a computation of error signals. In the former, in contrast, ICMs might serve to replay and consolidate the results of previous processing and to shield neural populations from getting involved in the task-related coupling modes, thus preventing previous contents from being overwritten. Therefore, it would be interesting to investigate ICMs in subnetworks not engaged in a task, in the presence of task-related coupling modes in other brain networks.

To further corroborate the functional relevance of ICMs, it will be highly relevant to manipulate envelope ICMs or phase ICMs in a specific manner and to test the effects on task- or stimulus-related processing. A number of different approaches may be viable to shape ICMs. One possibility is to modulate ICMs by neuropharmacological intervention, which has been demonstrated for BOLD coupling (Wang et al., 2011b; Cole et al., 2013; Pa et al., 2013) but not yet been applied to modulating phase ICMs in humans. Moreover, training through neurofeedback can be employed to shape ICMs. Several studies have demonstrated effects of neurofeedback on BOLD-defined envelope ICMs (Koush et al., 2013; Haller et al., 2013). A recent MEG study has explored the possibility to shape movement-related cross-hemispheric phase coupling by neurofeedback (Sacchet et al., 2012), suggesting that this might also be possible for ongoing activity.

A third line of approaches is provided by noninvasive neurostimulation techniques, such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), or transcranial alternating current stimulation (tACS), which all have been used to modulate ongoing activity in recent studies (Paulus, 2011; Thut et al., 2012; Grefkes and Fink, 2012; Schulz et al., 2013; Herrmann et al., 2013). Attempts to entrain envelope ICMs have been made using slowly varying tDCS, demonstrating effects on plasticity during sleep (Marshall et al., 2006) and on neuronal excitability during wakefulness (Groppa et al., 2010). Modulation of phase ICMs has been achieved by multifocal TMS in a study demonstrating enhanced alpha- and beta-band coherence following synchronous TMS stimulation over visual and motor cortex (Plewnia et al., 2008). For modulation of phase ICMs, tACS seems particularly promising because it opens up the possibility of entraining ongoing activity in a frequency-specific way (Herrmann et al., 2013). This is suggested by a recent study that has demonstrated an influence of entraining gamma-band ICMs on bistable visual perception (Strüber et al., 2013). A limitation is that effects on phase ICMs have so far only been shown by comparing epochs preceding and following tACS but not yet by directly testing changes in coupling during the stimulation. An interesting possibility is that tACS might also be used to mimic the physiological dynamics of envelope ICMs by entraining with amplitude-modulated oscillatory waveforms. Possible interactions of envelope and phase ICMs might then be tested by varying the coherence of the oscillations independently of the spatial envelope correlation.

Important issues for future studies also arise regarding the clinical implications of ICMs. As discussed above, studies of functional connectivity in neuropsychiatric disorders have most often used BOLD-derived measurements. The novel neurophysiological approaches that have become available (Hipp et al., 2012; Brookes et al., 2012; Hillebrand et al., 2012; Marzetti et al., 2013) show promise to yield a much richer characterization of ICMs. These approaches may help to advance the comparison of ICMs across disorders, to further test their validity as intermediate phenotypes, and to better understand their changes in relation to the progression of the diseases. Furthermore, these approaches may lead to the development of novel network-based markers for monitoring clinical outcomes and for evaluating therapeutic interventions. One of the challenges will consist in extracting robust network markers from sensor-level signals that, in clinical routine, are typically recorded with low electrode numbers. Future research on ICMs is also likely to increase the possibility for therapeutic interventions that target the modulation of functional connectivity, rather than local function, by multisite neurostimulation (Grefkes and Fink, 2012; Schulz et al., 2013). Increasing insight in the pathophysiological relevance of phase ICMs is likely to motivate the usage of frequency-specific entrainment approaches in clinical context. An example is provided by a recent study that has employed tACS at tremor frequencies to suppress the tremor in PD patients (Brittain et al., 2013).

In conclusion, we have discussed ICMs as a key feature of brain dynamics and we have considered their physiological manifestations, putative mechanisms, potential functional roles, as well as their alterations in neuropsychiatric disorders. We propose that the concept of ICMs may provide a unifying framework for capturing the dynamics of ongoing activity at multiple spatial and temporal scales. We have considered envelope ICMs and phase ICMs as two different but interacting coupling modes. Now it is time for studies explicitly addressing both types of ICMs in the same data set and testing possible interactions between these coupling modes. To this end, targeted manipulation of ICMs (e.g., via pharmacology or brain stimulation) holds great potential. Moreover, studies in patients could be very revealing, but they need to start comparing both envelope and phase coupling directly. We believe that the investigation of ICMs will rapidly gain in importance, both for advancing the treatment of network disorders and our understanding of the key role of intrinsic coupling modes in cognition.

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