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The contribution of electrophysiology to functional connectivity mapping

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ABSTRACT

A powerful way to probe brain function is to assess the relationship between simultaneous changes in activity across different parts of the brain. In recent years, the temporal activity correlation between brain areas has frequently been taken as a measure of their functional connections. Evaluating 'functional connectivity' in this way is particularly popular in the fMRI community, but has also drawn interest among electrophysiologists. Like hemodynamic fluctuations observed with fMRI, electrophysiological signals display significant temporal fluctuations, even in the absence of a stimulus. These neural fluctuations exhibit a correlational structure over a wide range of spatial and temporal scales. Initial evidence suggests that certain aspects of this correlational structure bear a high correspondence to so-called functional networks defined using fMRI. The growing family of methods to study activity covariation, combined with the diverse neural mechanisms that contribute to the spontaneous fluctuations, has somewhat blurred the operational concept of functional connectivity. What is clear is that spontaneous activity is a conspicuous, energy-consuming feature of the brain. Given its prominence and its practical applications for the functional connectivity mapping of brain networks, it is of increasing importance that we understand its neural origins as well as its contribution to normal brain function.

Introduction

Using fMRI to study processes in the brain requires the interpretation of hemodynamic activity time courses. Traditionally, fMRI studies have mapped the physiology of the brain by measuring how such time courses change as a result of stimuli or actions occurring at definable points in time (Kwong et al., 1992). Researchers can map the mean fMRI response to a given type of stimulus by comparing the measured time courses of voxels throughout the brain to model time courses derived from the dynamical structure of the task design. This powerful approach has certain limitations. First, its success relies heavily on the capacity to construct a sensible model time course, which is often difficult (Aguirre et al., 1998; Handwerker et al., 2004). Second, it is insensitive to brain activity that is not time-locked to the task, such as spontaneous activity. For these reasons, and based on initial findings that spontaneous fMRI signals are not only prominent but also highly organized (Biswal et al., 1995), a second principal mode of fMRI investigation has emerged. This new set of methods, generally falling under the term 'functional connectivity', represents a fundamental shift in the strategy towards decoding fMRI time courses. Rather than linking fluctuations to external task design, this approach asks how voxel time courses throughout the brain relate to one another. In most cases, there is no task at all, and subjects simply lie in the scanner with their eyes closed.

Analysis of fMRI time courses in the absence of a task, also called 'resting-state' data, has led to the discovery of a relatively small number of stable, spatially organized patterns of correlated activity. The robustness and reproducibility of such 'resting-state networks' over time and laboratories (Braun et al., 2012; Zuo et al., 2010), as well as the spatial correspondence between resting-state and task-driven data (Smith et al., 2009), have led to an explosion of interest in spontaneous activity among fMRI researchers. An interesting aspect of this new trend is that, in contrast to conventional fMRI design, functional connectivity analysis is almost entirely data driven (Van den Heuvel and Hulshoff Pol, 2010). When a priori hypotheses are applied, they usually come into play at a later stage, as in comparing between different patient groups, rather than during the mapping process itself (Sorg et al., 2009; Zhang and Raichle, 2010). As such, this new mode of fMRI investigation is more exploratory than its predecessor, and the two approaches are often applied together. As a measure of functional anatomy, this approach

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is also playing a particularly prominent role in the human connectome project.

Despite the success of fMRI in mapping brain-wide spatial patterns in spontaneous activity, the link between the measured hemodynamic signals and the underlying neural signals is only indirect (Logothetis, 2003). Direct electrophysiological measures are required to study neurophysiological processes that underlie these hemodynamic networks. In that vein, several recent studies have attempted to specify the relationship between spontaneous electrical and hemodynamic signals in the brain (Laufs, 2008; Shmuel and Leopold, 2008). These studies have revealed clear neural correlates of spontaneous fMRI activity, with hemodynamic fluctuations following shortly after, and presumably caused by, local neural events. Importantly, however, identification of a correlate is not a demonstration of causality, nor is it equivalent to understanding the physiological origin of spontaneous activity. These neural correlates merely indicate that the fMRI signal is a reliable indicator of local spontaneous neural activity. It is thus worth noting that the electrophysiological signal has been shown to correlate with hemodynamic fluctuations even centimeters away (Schölvinck et al., 2010), drawing attention to the shortcomings of purely correlative approaches. Why does the brain show widespread fluctuations in the first place? If the spatial pattern of these fluctuations cannot be attributed entirely to anatomical connectivity, as considerable evidence suggests (Damoiseaux and Greicius, 2009; Honey et al., 2009), then what other factors are at play in shaping BOLD activity correlations? Despite the intense interest in spontaneous brain signals that has emerged in the past decade, relatively little attention has been paid to these important questions. In the era of the human connectome project, the utility of functional connectivity maps derived from an enormous amount of resting-state fMRI data may ultimately be determined by our understanding of brain's endogenous processes. Moreover, as terms such as *functional connectivity* and *functional network* have proven to be highly adaptable in the face of new methods and observations, they no longer signify unique or precise quantities. While these diverse measures of "connectivity" reflect genuine scientific advances, they pose distinct challenges to the connectome project, which aims to compile results across studies in order to build a comprehensive description of the brain's functional connections.

The present article explores the neurophysiology of spontaneous brain activity in an effort to link fMRI functional connectivity to electrical signals. We review the spatiotemporal organization of a range of electrophysiological measurements, including the local field (LFP) and electrocorticographic (ECoG) potentials in experimental animals and human patients, as well as electroencephalographic (EEG) and magnetoencephalographic (MEG) recordings in human research subjects. After introducing concepts related to correlational methods for investigating brain function, we describe the spatial and temporal scales of electrophysiological brain signals. Next, we review a small number of studies directly comparing large-scale electrophysiological correlation with fMRI functional connectivity-defined networks, and outline some of the theoretical and practical issues with measuring and defining functional connectivity in electrophysiology. Finally, we speculate on the origins and purpose of spontaneous brain activity as well as its bearing on the human connectome project.

Investigating functional interactions in the brain

The study of functional connectivity taps into the interaction between brain regions. Historically, neuroscientists have employed a wide range of approaches to study how two or more brain areas interact. For example, early electrophysiological studies in animals examined the effects of chemically evoked activity at one cortical site on the neural activity measured elsewhere in the same hemisphere (Dusser de Barenne, 1924; Pribram and Maclean, 1953). Other types of studies probed the behavioral effects of 'disconnecting' two areas by ablating one of the areas in each of the hemispheres (Mishkin, 1972). In the last decades, the capacity to simultaneously record activity from multiple isolated neurons has pushed correlative approaches to the forefront of studying neural interaction. The correlated activity between neurons, measured within the same area or between areas, has contributed to theories of stimulus processing (Eckhorn et al., 1988; Gray et al., 1989) and other aspects of cognition (Murthy and Fetz, 1996).

Early single-unit work considered the possibility that the spontaneous spiking of neural pairs might provide an indication of their anatomical connectivity (Aertsen and Gerstein, 1985), and this method was applied to study, for example, the pattern of horizontal connections in the cerebral cortex (Ts'o et al., 1986). Such shared electrical activity is often spatially localized; for instance, millisecond-precise synchronization between nearby neurons in primary visual cortex of macaques is most frequently observed when these neurons share similar orientation preferences (Frien and Eckhorn, 2000; Kohn and Smith, 2005), an effect that has been attributed to horizontal connections linking regions of similar stimulus preference (Smith and Kohn, 2008). Other work has revealed spiking correlations between neurons over longer time scales, with simultaneously measured neurons exhibiting shared trial-to-trial variability upon repeated presentation of the same stimulus (Shadlen and Newsome, 1998). Such correlations in activity that are not determined by a stimulus are often called *noise correlations*. In general, single unit spiking, even that of nearby neurons, shows levels of spontaneous correlation that rarely exceed 0.05–0.1 over either short or long time scales (Ecker et al., 2010; Gawne and Richmond, 1993).

A typical measure of local neuronal activity, other than spiking, is the local field potential (LFP). The LFP is a complex measure of neuroelectric activity that contains within it the aggregate membrane potential fluctuations of a local ensemble of neurons (Buzsáki et al., 2012). In contrast to spiking activity, correlation in the spontaneous LFP measured over similar distances is typically much higher, ranging from ~0.2 for LFP in the gamma (30–100 Hz) frequency range to ~0.7 for LFP in the delta (1–4 Hz) frequency range (Leopold et al., 2003). Comparable values have in fact been found in fMRI resting-state correlations over much larger distances (Fox and Raichle, 2007). How is it possible that the noise correlations in spiking activity are so low, but that the spontaneous LFP correlation and BOLD correlation are so high? A potential reason for this discrepancy might be found in the spike threshold; when the mean membrane potential of neurons is far below threshold, firing rates are low and many of the shared membrane potential fluctuations will be visible in the LFP but are unobservable in spiking responses (Dorn and Ringach, 2003).

It is important to note that temporal correlation as a measure of neural interactions can be distorted by any factor that affects either one or both of the signals being compared. One example of this is common input resulting from sensory stimulation. Common input will trivially increase the measured correlation whenever two neurons, sites, or voxels are driven by the same external stimulus. To contend with this issue, neurophysiologists have established methods to eliminate shared variance caused by predictable external events in order to focus on the so-called noise correlation described above (Perkel et al., 1967). A growing number of fMRI functional connectivity studies capitalize on these methods, trying to capture noise correlations in BOLD activity measured during a task (Arfanakis et al., 2000; Fair et al., 2007). Unpredictable or immeasurable external sources of sensory input, such as the occurrence of eye movements, pose a greater challenge and often cannot be entirely discounted (Fig. 1; Ramot et al., 2011). Small residual correlations must thus be interpreted with great caution, particularly if they show patterns similar to those evoked by the task design.

In the case of spontaneous activity examined during rest, it is more reasonable to assume that endogenous processes shape measured time courses and thus are the primary determinants of functional connectivity. However, there are still several significant problems if one wants to interpret this measure as reflecting the interaction between

areas. First, as described above, it is impossible to entirely eliminate the contribution of external sensory events to correlational measures. Second, certain categories of internal activity, such as changes in arousal, will cause large-scale changes that synchronize a broad range of areas (Tagliazucchi et al., 2013). These sources of variance are difficult to remove or minimize, and attempts to do so with various types of global signal regression are controversial (Murphy et al., 2009). Third, even for the endogenous processes that serve as the basis for functional connectivity measures, there is no way to discern direct interaction from common anatomical input. For example, brain structures that are not anatomically connected, such as the left and right caudate nucleus, can still exhibit strong functional connectivity, which is likely caused by some form of common input from a third structure (Di Martino et al., 2008). Fourth, it is not only sources of common input that shape measured correlation but also patterns of *exclusive* input. For example, a decrease in the measured correlation between two areas may not reflect a decrease in their coupling, but could equally reflect the addition of a new, unshared process to only one of the areas. All these problems pose significant interpretive challenges for the functional connectivity method.

Finally, a tacit assumption in most correlational measures is that of temporal stationarity, meaning that the signals maintain their statistical characteristics within the time window over which their correlation is computed. Given the 1/f power spectrum of most neurophysiological signals, meaning that the slowest fluctuations have the highest amplitude, it seems impossible to determine a single window size in which all frequency components of the signal are stationary. Recent work in resting-state fMRI has therefore begun to investigate how temporal correlations themselves evolve over time (Chang and Glover, 2010; Handwerker et al., 2012; Hutchison et al., 2010; Keilholz et al., 2012), all concluding that the assumption of temporal stationarity is a poor one. This implies that different functional networks measured over short time windows might be integrated into the same fMRI network measured over longer time scales, and that transient functional networks might not even be visible in fMRI. Though usually interpreted as evidence for 'dynamic functional connectivity', these findings raise questions about the nature of the observed correlations, the methodologies currently used to elucidate them, and the interpretation of functional connectivity maps more generally.

A continuum of scales

Given the potential value of correlation methods, as well as the caveats described above, we next survey a number of relevant properties of electrophysiological signals measured across the brain over a range of scales. As mentioned above, the spiking times of individual neurons can be coupled at timescales as short as several milliseconds, with correlations highest among neighboring neurons (Maffei and Galli-Resta, 1990; Pillow et al., 2008). However, it is clear that for the brain to create a unified sequence of actions based on multimodal sensing of the environment, neural activity must be coordinated over much larger scales as well. Indeed, simultaneous EEG-fMRI resting-state measurements have shown increased functional integration between brain areas as subjects transcended from deep sleep to wakefulness (Tagliazucchi et al., 2013). In contrast to fMRI, electrophysiological methods are well-suited to reveal structure in spontaneous activity over this entire range of spatial, temporal, and spectral scales (Fig. 2).

Slow electrophysiological activity changes are of great interest for two reasons. First, they occupy similar time scales as the sluggish hemodynamic signal. Second, their pattern of spatial correlation in some cases bears resemblance to fMRI functional connectivity, as we will see in the next section. Fluctuations in electrophysiological signals in the 0.01–0.1 Hz range have been termed slow cortical potentials (SCPs) (Birbaumer et al., 1990; McCallum and Curry, 1993). They are thought to be caused by long-lasting excitatory postsynaptic potentials (EPSPs) at apical dendrites in superficial layers (Speckmann and Elger, 1993). Since a predominance of EPSPs results in a negative shift in scalp-recorded EEG, a negative shift in SCPs is typically interpreted as increased cortical excitability (Birbaumer et al., 1990). This assumption is further substantiated by the finding that negative SCP amplitude is correlated with the amount of task-related cognitive effort (Khader et al., 2007) and with the positive fMRI BOLD response (He and Raichle, 2009; Hinterberger et al., 2003; Jost et al., 2011, 2012).

A second category of slow electrophysiological fluctuations is, in fact, derived from faster signals. The Band Limited Power (BLP) corresponds to the *power* or envelope modulations of a relatively narrow range of LFP frequencies, for instance the alpha (8–13 Hz) band. BLP modulations, like the SCP modulations, show temporal variation over time scales of seconds and even minutes. Like fMRI correlations, correlations in the BLP fall off with distance, yet much more gradually than the correlations in the raw high-frequency LFP from which it is derived (Leopold et al., 2003). Spontaneous gamma BLP fluctuations recorded from depth electrodes in epileptic patients (Nir et al., 2008) and MEG sensors in healthy subjects (Liu et al., 2010) revealed correlations between bilateral homotopic brain regions, which is consistent with numerous fMRI functional connectivity studies. This work is supported by further studies using MEG source space localization to show long range temporal correlation between spontaneous BLP signals in, for example, left and right primary motor cortices (Brookes et al., 2011a; Hall et al., 2012; Hipp et al., 2012).

Closer examination of the wide spatial and temporal spectrum over which neural correlations are observed suggests that the two scales are inextricably linked; the slower the electric potentials, the larger the area over which they can be correlated (Frien and Eckhorn, 2000; Leopold et al., 2003; Von Stein and Sarnthein, 2000). There are several biophysical properties of oscillations that could

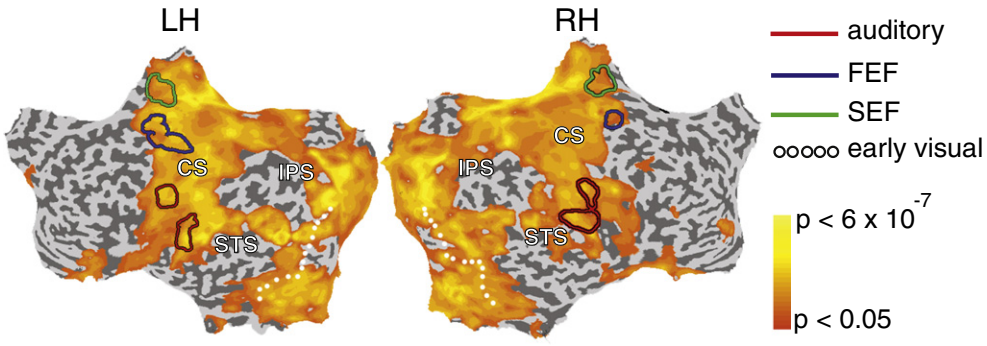

Fig. 1. An example of uncontrolled common input during the resting state. The flatmaps show the widespread correlation of spontaneous eye movement amplitude with the BOLD fMRI signal recorded during the resting state, averaged over 30 subjects. Contours show auditory cortex (red), the frontal and supplementary eye fields (blue and green respectively), and the early visual areas (dotted white line). CS, central sulcus; STS, superior temporal sulcus; IPS, intraparietal sulcus; LH, left hemisphere; RH, right hemisphere. Adapted with permission from Ramot et al., 2011.

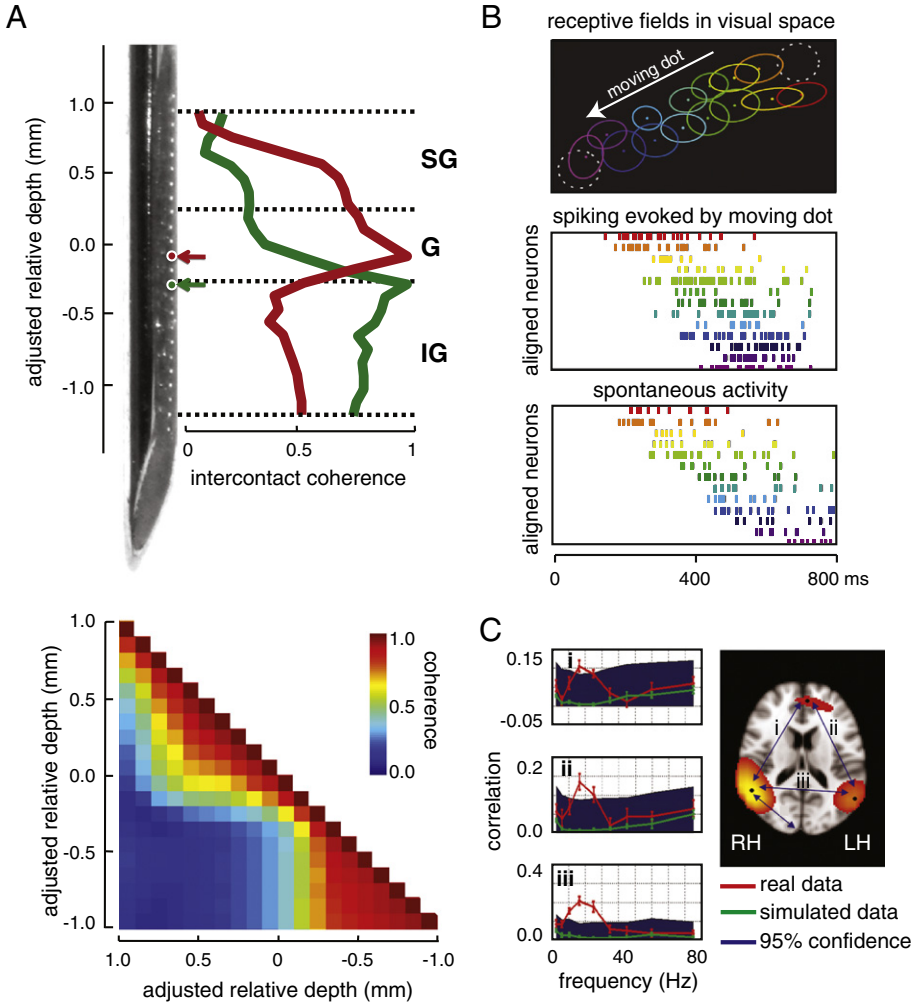

Fig. 2. Detailed spatial, temporal, and spectral patterns observed in spontaneous electrophysiological data. **A** Coherence in the gamma band (30–100 Hz) of spontaneous LFP shows a distinct laminar profile (top). The local LFP measured in the granular layer (red) is highly coherent with other granular (G) and supragranular (SG) sites, whereas the local LFP in the infra-granular layer (green) is only coherent with other infragranular (IG) sites. This division between supra- and infragranular layers is also clearly visible in the cross-correlogram of the spontaneous LFP at all sites (bottom). Adapted with permission from Maier et al. (2010). **B** A neuronal population in rat primary visual cortex shows sequential spiking when a dot moves through its spatially aligned receptive fields; similar spiking sequences are detected in the spontaneous activity after repeated presentation of the moving dot. Adapted with permission from Xu et al. (2012). **C** The correlations (i, ii, and iii) between three nodes of the default mode network (the anterior cingulate and left and right parietal lobules) measured with MEG show spectral differences. Correlations are highest in the beta band (15–25 Hz); compare the real MEG data (red) to simulated data (green). LH, left hemisphere; RH, right hemisphere. Adapted with permission from Brookes et al. (2011b).

account for this finding. It could be simple passive attenuation of higher frequency components due to differences in signal propagation; however, the impedance spectrum of gray matter is the same across different spectral components (Logothetis et al., 2007). Theoretical models (König and Schillen, 1991) and empirical data (Frien and Eckhorn, 2000) suggest that the more distant two neural assemblies are, the longer the signal-conduction delay between them, which biases the maintenance of a phase relationship between the two signals over longer cortical distances towards lower frequencies, with fewer cycles to maintain phase stationarity over. In addition, the spatial superposition of locally generated currents in the extracellular medium is much more likely to be destructive at short wavelengths (i.e. high frequencies), since small time shifts will cause proportionally large phase shifts; this again biases larger spatial correlations towards the lower frequencies. Furthermore, the observed 1/f distribution in frequencies makes coherence in the higher frequencies such as gamma much lower in all cases, although the gamma BLP, which can fluctuate arbitrarily slowly, is again correlated over large spatial scales (Schölvinck et al., 2010). Finally, it is important to point out that the above discussion pertains to the spatial correlation of spontaneous signals. During a task, temporal coupling among electrophysiological signals has been demonstrated repeatedly between distant areas and during specific cognitive states (Buschman and Miller, 2007; Canolty et al., 2010; Gregoriou et al., 2009; Schoffelen et al., 2005). For the present discussion, these effects underscore the fact that activity correlation measured over small or large spatial scales is not, and should not be conceived as, a fixed reflection of underlying anatomical connections and physiological mechanisms.

Functional networks as assessed with electrophysiology

Given the pronounced temporal correlation observed between distant brain sites in ECoG, EEG, and MEG studies, we next consider these results in the context of resting-state 'networks' described using fMRI functional connectivity. Do the spatial patterns found in electrophysiology resemble these networks at all, and if so, to what extent? A functional network is a central concept in fMRI functional connectivity; a set of brain regions whose measured BOLD fluctuations are correlated in time. Typically, regions that are co-activated during certain tasks tend to be correlated in their resting-state activity, and this

might have led to the fact that these resting-state networks are commonly related to a particular cognitive function. Some well-known networks include those associated with perception and action, such as the visual (Wang et al., 2008), auditory (Cordes et al., 2000), and motor (Biswal et al., 1995) networks; and those associated with attention and cognition, for example the fronto-parietal (Fox et al., 2005), and default mode (Greicius et al., 2003) networks.

Large-scale electrophysiological measures have found networks of correlated electrodes or sensors that show some degree of correspondence to the resting-state networks found with BOLD fMRI (Fig. 3). For example, ECoG electrodes implanted over areas of the sensorimotor network in epileptic patients show an activity correlation structure in SCPs similar to that observed in BOLD data (He et al., 2008); similar results have been found in ECoG-recorded gamma power (Nir et al., 2008). Likewise, using spontaneous MEG power reconstructed at each voxel of the brain, De Pasquale et al. (2010) revealed the dorsal attention and the default mode networks well-known to resting-state fMRI researchers; this work was later extended to four additional networks, which showed various degrees of across-network correlations (De Pasquale et al., 2012). Brookes et al. (2011b) also employed spontaneous MEG data to derive the spatial structure of eight MEG networks based on the BLP. In these MEG studies, spectral analysis indicated that the resting-state networks were manifested primarily within the theta, alpha, and beta bands — frequencies lower than those typically associated with the local electrophysiological correlates of BOLD activity, which may reflect the increased signal to noise ratio in these lower frequency bands. Resting-state networks have to our knowledge never been described in BLPs or SCPs of the EEG, but could in principle be found if the spatial resolution of the EEG signal is enhanced by, for example, current source density (CSD) transformation (Hinterberger et al., 2005; Lamm et al., 2005) across the scalp electrodes. Specific spatio-temporal features of the EEG have, however, been used to define so-called EEG microstates; these microstates form spatial maps that are thought to correspond to functionally relevant brain states (Britz et al., 2010; Brodbeck et al., 2012; Musso et al., 2010; Van de Ville et al., 2010).

Recent years have seen a number of emerging clinical applications of these brain-wide electrophysiological networks. For example, differences in MEG functional connectivity compared to healthy controls have been reported for Alzheimer's Disease (Sorg et al., 2009; Stam et al., 2009), Attention-Deficit/Hyperactivity Disorder (Wilson et al., 2013), and epilepsy (Sakurai et al., 2010). Furthermore, acquired brain injury such as a stroke can radically alter functional connectivity patterns (Castellanos et al., 2010, 2011; Gerloff and Hallett, 2010). Knowledge of these alterations in functional connectivity could potentially help optimize rehabilitation strategies (Butz et al., 2009), although any differences in functional connectivity between patients and controls have to be viewed with caution because of the many potential reasons for differences in temporal correlations as discussed above.

The degree of spatial correspondence between electrophysiological and hemodynamic functional networks is still under debate. MEG studies have shown that, if the BLP envelope at a seed location within one node of an fMRI network is taken, one finds that across the whole brain, the highest temporal correlation most often occurs within a separate node of that same fMRI network (Brookes et al., 2011a; Hall et al., 2012; Hipp et al., 2012). The question of spatial correspondence has also been tackled using independent component analysis on BLP signals measured with MEG. Clusters of voxels forming distributed spatial patterns exhibited significantly higher spatial correlation to some BOLD networks than matched surrogate data, implying a degree of spatial concordance (Brookes et al., 2011b). However, it is important to note that despite compelling similarities, clear differences are also observed which are often overlooked. For example, the sensorimotor network includes the supplementary motor area (SMA) in fMRI but this is often lacking in MEG (Brookes et al., 2011a; Hipp et al., 2012). This could reflect a genuine difference between fMRI and MEG networks resulting from the disparate nature of the two signals; however, it could also relate to technical limitations of MEG. Spatial matching of MEG and fMRI networks is inherently confounded because the ill-posed inverse problem (see below) necessarily brings about spatial imprecision in MEG network maps that is not present in fMRI.

In determining the spatial correspondence with functional networks found in fMRI, EEG, and MEG studies have to overcome the fundamental problem that unlike hemodynamic responses, scalp-recorded field potentials are a reflection of neural events happening elsewhere. Technically, this problem is referred to as volume conduction or field spread, meaning that the electric or magnetic field induced by a single source in the brain is recorded at multiple EEG or MEG sensors; likewise a single EEG or MEG sensor will record the activity of multiple sources. As distance from sources to sensors increases, the signal to noise ratio (SNR) drops, and the number of affected sensors grows. This necessarily confounds sensor space connectivity metrics. The problem can, in part, be ameliorated by projection of scalp-based signals to reconstruct time courses of electrical activity at a set of locations in the brain (Schoffelen and Gross, 2009). However, the observed field pattern at the scalp surface could be caused by an infinite number of possible sources in the brain. This makes this so-called MEG/EEG inverse problem mathematically ill-posed, meaning that reconstructed signals will 'leak' between voxels generating spurious connectivity. This leakage changes as a function of the SNR; it is generally more problematic for deeper sources, as has been shown by computing the point spread function of a single dipole at various locations (Hauk et al., 2011), and the leakage is also highly spatially inhomogeneous (Brookes et al., 2011a). In recent years sophisticated methods have been developed to address this problem. For example, a number of studies (Nolte et al., 2004; Guggisberg et al., 2007) have shown that by taking only the imaginary part of the complex coherence, spurious connectivity caused by signal leakage can be eliminated, since leakage is necessarily zero phase lag (i.e. contained wholly within the real part of coherence). These same theories have also been extended for use in BLP correlation estimation, where techniques based on linear regression of projected oscillatory signal, prior to BLP computation, have been used to correct for signal leakage, with some success (Brookes et al., 2012; Hipp et al., 2012). Another approach to combating the inverse problem is to inform the MEG or EEG sources by fMRI scans of the same subject (De Pasquale et al., 2010).

One step further in relating the fMRI resting-state networks to the networks found with electrophysiology is to acquire these signals simultaneously. The correlation between the power of band-passed electrophysiological signals and the fMRI signal in the resting state shows frequency diversity. Lower frequencies such as alpha (Laufs et al., 2003; Mantini et al., 2007; Moosmann et al., 2003) and even SCPs (for a review, see Khader et al., 2008) typically show a negative relationship, although there is also opposing evidence. For example, Niessing et al. (2005) found that delta oscillations in the LFP of anesthetized cats are negatively correlated with the BOLD signal, whereas others showed this relationship to be positive in un-anesthetized, drowsy monkeys (Schölvinck et al., 2010). For the higher frequencies such as gamma, the evidence seems to be unambiguously pointing to a strong, positive relationship between the LFP or EEG power and the fMRI BOLD signal (Niessing et al., 2005; Schölvinck et al., 2010; Shmuel and Leopold, 2008). However, there is certainly no one-to-one correspondence between oscillations in any single frequency band and the BOLD response (Winterer et al., 2007); moreover, these correspondences might change with fluctuations in brain state (Tagliazucchi et al., 2012). It is also important to realize that LFP and EEG signals are merely the reflection of neural processes that may originate elsewhere and that might themselves be correlated to other neural processes leading to the BOLD response. These problems of indirectness and spatial localization are but a few of the many challenges in linking spontaneous electrophysiological and hemodynamic signals.

Diverse correlational measures

The lack of a one-to-one correspondence between spontaneous electrophysiological and hemodynamic measures suggests that electrophysiology might be able to reveal properties of spatial patterns in spontaneous activity that are undetectable with fMRI. For example, the much better temporal resolution of electrophysiology enables researchers to pose questions about networks such as whether one brain area 'leads' while another one in the network 'follows'; despite recent analysis tools such as Granger causality and Dynamic Causal Modeling, such questions remain at best indirectly, and perhaps not at all, answerable with fMRI alone (Smith et al., 2011). In recent years, the complex nature of electrophysiological brain signals combined with increasing focus on spectral differences has led to a combinatorial explosion of measures that bear on the concept of functional connectivity. Whether these new measurements and methods reveal fine-grained functional differences within the resting-state networks that remain invisible to fMRI (Fig. 4), or whether they undermine the concept by blurring its definition, remains to be determined. Here we provide a brief overview of several electrophysiology measures of activity correlation, discussed in the context of functional connectivity mapping.

A commonly computed entity is the magnitude-squared coherence between two signals, which is a measure of correlation between two signals as a function of frequency. Coherence is closely related to the phase-locking value, which also signifies a fixed phase relationship between two neural oscillatory processes at a certain frequency, but which is independent of amplitude (Varela et al., 2001). Coherence and phase-locking have both been computed for spontaneous EEG and MEG activity. For example, Jann et al. (2009) found that EEG electrodes over brain regions that were determined by simultaneous fMRI to form a certain resting-state network, were phase-locked in the alpha band. In MEG there are a number of examples of coherence being used successfully to illustrate long-range connections. Hillebrand et al. (2012), for instance, used phase-locking to investigate the frequency dependence of fixed phase coupling in resting-state networks.

In addition to investigating functional connectivity within certain frequency bands, recent studies have begun to assess cross-frequency effects, such as the amplitude or phase of low-frequency oscillations in one brain region modulating the amplitude or phase of high-frequency oscillations in either the same or a spatially separate brain area (He et al., 2010). For example, the amplitude of the peaks in the oscillatory alpha rhythm in MEG is correlated with the negative amplitude of SCPs (Mazaheri and Jensen, 2008). Coupling between the phase of low frequencies and the amplitude of the gamma frequency has been shown in spontaneous activity in the sensory cortices of monkeys (Lakatos et al., 2005; Spaak et al., 2012) as well as in mouse hippocampus (Buzsáki et al., 2003), and recently, studies have also begun to assess cross-frequency coupling in resting-state activity measured with EEG (Osipova et al., 2008) and intracranial recordings (Foster and Parvizi, 2012) in humans.

A fundamental issue for the connectivity analyses described above and their reliance on various frequency bands is where these different frequency signals are generated. It makes quite a difference for the interpretation of the data if certain rhythms are generated locally (as has been

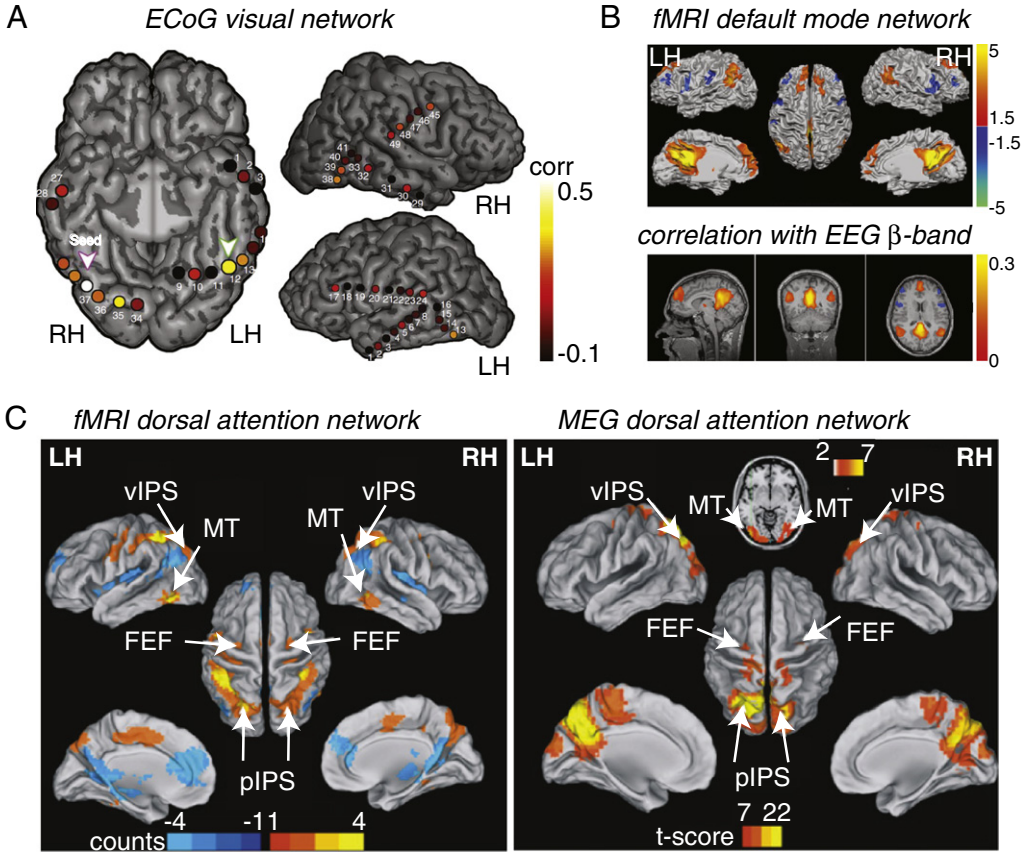

Fig. 3. Functional networks in fMRI and electrophysiology. **A** The visual network as exhibited in intracranial ECoG. Slow spontaneous changes in gamma power of a visual-related electrode in the right hemisphere (seed; pink arrow) correlate strongest with other visual electrodes, especially in a homotopic region in the left hemisphere (green arrow). Adapted with permission from Nir et al. (2008). **B** Regions of the fMRI default mode network (top) are correlated with the beta band power as measured with EEG (bottom). Adapted with permission from Mantini et al. (2007). **C** The dorsal attention network revealed in fMRI (left) and MEG (right). The fMRI map shows voxels with significant temporal correlation in at least three of four predefined seed regions (vIPS, ventral intraparietal sulcus; MT, middle temporal area; FEF, frontal eye field; and pIPS, posterior intraparietal sulcus). The MEG map shows a t-statistic comparing voxel-wise correlation with the seed region versus the mean correlation of the seed region with the rest of the brain. There is rough similarity between the fMRI and MEG network, but also clearly observable differences. LH, left hemisphere; RH, right hemisphere. Adapted with permission from De Pasquale et al. (2010).

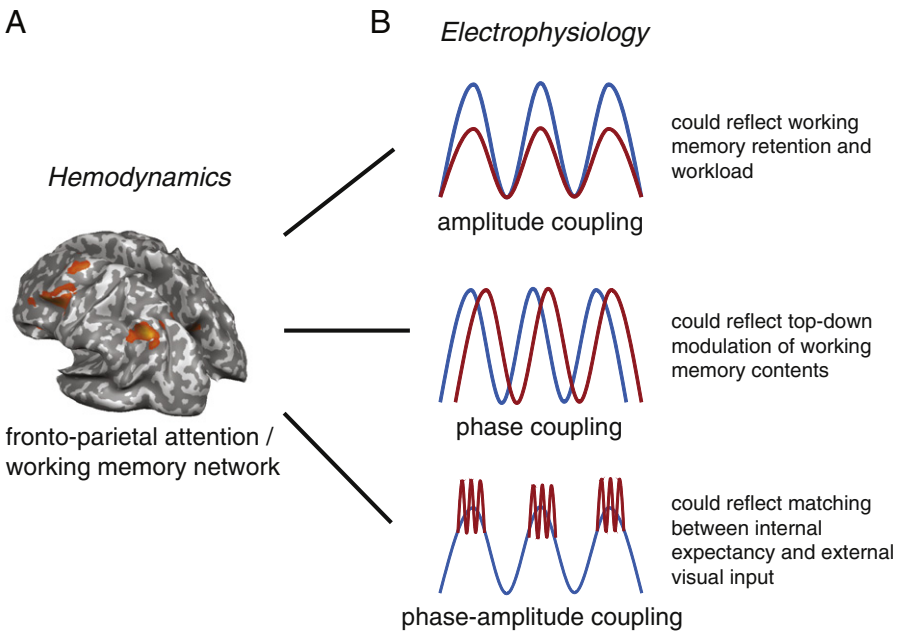

Fig. 4. Electrophysiology might be able to detect fine-grained cognitive differences within functional networks not visible to fMRI. For example, the fronto-parietal attention/working memory network (**A**) that has been found during the resting state (Fox et al., 2005), as well as during task performance (Corbetta and Shulman, 2002), can be reflected on a neurophysiological level by several processes (**B**). Amplitude coupling (top) between frontal and parietal areas has been interpreted as controlling working memory retention and workload (Sammer et al., 2007; Sarnthein et al., 1998). Phase coupling (middle) between these areas could reflect phasic aspects of top-down modulation of working memory contents (Sadaghiani et al., 2012). Lastly, phase–amplitude coupling (bottom) between theta- and gamma-band activity could reflect a memory matching process between internally expected and external visual input (Sauseng et al., 2008).

suggested for gamma activity), or in thalamocortical loops, that then provide modulatory input to cortex (Steriade, 2001); this is analogous to the common input problem described earlier. Even more fundamentally, the multitude of connectivity analyses raises the question of how diversely the term 'functional connectivity' can be defined without losing its usefulness. As described earlier, correlational measures run the danger of capturing heterogeneous processes, only a subset of which reflects an interaction between areas. However, if correlations consistently map onto a specific anatomical connection, then we may be justified in calling it functional connectivity. Even if we accept that in this case, a principle such as 'functional connectivity' exists in the brain, it is highly unlikely that the connectivities one measures in electrophysiology over the entire spatiotemporal scale are subserved by similar physiological mechanisms. Therefore, the concept of functional connectivity is necessarily more vaguely defined in electrophysiology than in fMRI, where we can reasonably assume that the underlying physiological mechanisms generating the BOLD signal are similar over the entire brain.

Role of spontaneous activity

Correlational analysis of spontaneous activity is currently a key component of the human connectome project, serving to provide a comprehensive map of functional connections in the brain. Why spontaneous activity should provide such a reproducible outline of functional brain networks as it does is by no means obvious. Nor is it clear whether the mechanistic basis of activity correlation in different networks is similar. For these and other reasons, it is critical to develop a better understanding of the origins and purposes of the brain's endogenous processes.

The brain is, metabolically speaking, an expensive organ (Sokoloff, 2007) and endogenous processes make up the majority of this energy usage (Raichle and Mintun, 2006). Brain metabolism has been studied globally, primarily with the use of positron emission tomography (PET). Elevations in cerebral metabolism induced by a task are relatively small; in fact, local task-induced increases in functional activity, although associated with *regionally* increased blood flow, are too small to induce detectable changes in *global* blood flow or metabolism (Sokoloff et al., 1955). Brain metabolism depends on two factors: oxygen and glucose consumption. During rest, oxygen consumption is much higher than glucose consumption, measured in μmol/min/100 g brain tissue; however, when a strong visual stimulus is presented, oxygen consumption in visual cortex increases only relatively little (5%) compared to glucose consumption (51%). Since the conversion of glucose to energy requires oxygen, this small increase in oxygen consumption implies that much of the glucose taken up is not converted to energy directly, but instead metabolized to lactate (Fox et al., 1988). Therefore the increase in energy consumption during perceptual processing is very small compared to the resting energy consumption (Schölvinck et al., 2008). Since energy is a valuable commodity, these facts point to spontaneous activity as serving a vital function for the brain (Van Eijsden et al., 2009).

It is certainly the case that coordinated spontaneous activity is always present at some level, taking different forms during different states of consciousness. It is striking that even in deeply anesthetized monkeys the familiar fMRI resting-state networks such as the default-mode network have been found (Vincent et al., 2007). It is unknown how these correlated patterns of spontaneous activity relate to the functional networks found in the awake brain. However, we do know that spontaneous activity can display vastly different characteristics, dependent on the internal state of the brain (Harris and Thiele, 2011). During slow-wave sleep and anesthesia, the cortex displays highly synchronized activity with regular 'upstates' of generalized activity and 'downstates' of network silence (Sanchez-Vives and McCormick, 2000; Steriade et al., 1993); during waking or rapid eye-movement sleep, the cortex operates in the desynchronized state, characterized by low-amplitude, high-frequency LFP patterns (Curto et al., 2009). Spontaneous activity in these brain states might serve different functions. A myriad of self-governed oscillations at various spatial and temporal scales can be detected in the sleeping brain, which might temporally link neurons into assemblies (Steriade and Timofeev, 2003; Steriade et al., 1993), and as such, might underlie

memory consolidation (Born and Wilhelm, 2012). In the awake brain, spontaneous activity might be more related to cognitive operations or even day-dreaming (Mason et al., 2007).

One proposed general function of spontaneous activity for the awake brain is that the brain needs to predict external stimuli and events in order to react to them adequately (Engel et al., 2001; Pouget et al., 2003); and to make an accurate prediction of new events, the brain needs to remember past events. Indeed, spontaneous patterns of activity resembling stimulus-evoked responses have been reported in anesthetized (Han et al., 2008; Xu et al., 2012) as well as in awake (Foster and Wilson, 2006) rats immediately following extensive stimulus presentation, reminiscent of a memory trace of the stimulus. Evoked-like patterns in spontaneous activity that are not time-locked to the end of a period of extensive stimulation also seem to occur generally with a likelihood higher than chance (Kenet et al., 2003); this has been taken as evidence for spontaneous activity playing a predictive role for probable upcoming sensory stimuli (Berkes et al., 2011; Fiser et al., 2004). This constant 'remembering' and 'predicting' might require constant cross-talk between areas that are commonly co-activated (Salinas and Sejnowski, 2001). The correlation patterns seen in fMRI resting-state networks might also be viewed in this light; this cross-talk might continue even when the brain is 'at rest'.

Other support for the notion that spontaneous activity resembles dynamic predictions about the environment comes from fMRI studies that show an effect of the spontaneous activity during or just preceding a stimulus on the subsequent perception of that stimulus (Coste et al., 2011; Hesselmann et al., 2008b; Schölvinck et al., 2012). For example, prestimulus activity in the fusiform face area predicts whether the bistable face–vase stimulus will be more likely perceived as a face or a vase (Hesselmann et al., 2008a), and activity in the auditory cortex just prior to a faint auditory stimulus predicts the chance of detecting that stimulus (Sadaghiani et al., 2009). Electrophysiology studies employing the same logic have shown similar effects; for example, for a detected stimulus, the preceding spiking activity in monkey primary visual cortex was stronger than for an undetected stimulus (Supèr et al., 2003), and decreases in EEG alpha power over occipital electrodes ~100 ms before stimulus onset facilitate visual stimulus detection (Romei et al., 2008; Thut et al., 2006). It is possible that predictive activity associated with perception, action planning, and other aspects of behavior not strictly linked to stimulus processing must be continually reinforced with signals transmitted within the circuit. Such activity, thought to occur during sleep, may also have reflections in waking restfulness and may account for certain observed patterns of functional connectivity.

The truth is that, at present, the basis of functional connectivity in the brain is in the realm of speculation. Here we mention but a few candidate processes that have been put forth, most of which link to cognitive operations such as predicting forthcoming sensory stimuli and memory consolidation. Other accounts may take rather different forms related to homeostasis, synaptic reinforcement, or energetics. How the endogenous processes of the brain are conceived and treated in the future remains to be seen, as does their impact on the evolving subfields of functional connectivity that figure so prominently in the human connectome project.

Conclusions

Measuring spontaneous correlations, be it in electrophysiology or in fMRI, has grown to be a much-used way to probe brain function. In some ways this has opened an unexpected chapter in neuroscience; while the prominence of spontaneous activity was always appreciated, no a priori hypothesis of brain structure and function would have led to the prediction of spatially organized patterns of correlated spontaneous activity emerging over timescales much slower than those usually tapped into during conventional paradigms. These so-called resting-state networks commonly found in fMRI seem to possess analogous electrophysiological patterns over the cortical surface. At the same time, the wealth of spectral, spatial, and temporal scales afforded by electrophysiological measurements has begun to put the spotlight on the meaning and value of correlation-based concepts such as functional connectivity and functional networks. Most importantly, the neurobiology underlying the spatially and temporally correlated patterns of spontaneous brain activity is still not understood, and its purpose or role remains in the realm of speculation. As future investigations delve deeper into the origins and possible functions of spontaneous brain activity, we can anticipate gaining deeper insight into the functioning of the brain as a whole, including its comprehensive set of functional connections.

Conflict of interest

The authors declare that they have no competing interests.

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