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Ongoing physiological processes in the cerebral cortex

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Abstract

Functional magnetic resonance imaging (fMRI) has revealed that the human brain undergoes prominent, regional hemodynamic fluctuations when a subject is at rest. These ongoing fluctuations exhibit distinct patterns of spatiotemporal synchronization that have been dubbed "resting state functional connectivity", and which currently serve as a principal tool to investigate neural networks in the normal and pathological human brain. Despite the wide application of this approach in human neuroscience, the neural mechanisms that give rise to spontaneous fMRI correlations are largely unknown. Here we review results of recent electrophysiological studies in the cerebral cortex of humans and nonhuman primates that link neural activity to ongoing fMRI fluctuations. We begin by describing results obtained with simultaneous fMRI and electrophysiological measurements that allow for the identification of direct neural correlates of resting state functional connectivity. We next highlight experiments that investigate the correlational structure of spontaneous neural signals, including the spatial variation of signal coherence over the cortical surface, across cortical laminae, and between the two hemispheres. In the final section we speculate on the origins and potential consequences of ongoing signals for normal brain function, and point out inherent limitations of the fMRI correlation approach.

Introduction

In 1936 the New York Times ran an article entitled "*Inside telephones in the brain*." The title referred to the brain's intrinsic connectivity, and specifically to the experiments of J. G. Dusser de Barenne, the father of chemical neuronography. Barenne and colleagues for the first time used neural activity to infer large-scale connections between brain areas. They placed a minute amount of the excitatory agent strychnine on the cortex of experimental animals and then measured the resulting spatial pattern of electrical responses over the cortical surface. This approach revealed, in their words, "the directed functional (and anatomical) relations between the various cortical areas" (Hogenhuis, 2002; Dusser de Barenne and McCulloch, 1938). A decade and a half later Pribram and MacClean used the

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same method to study the organization of the limbic cortex (MacLean and Pribram, 1953; Pribram and MacLean, 1953). They reported five distinct zones of reciprocal excitation, which we would now call networks, that appeared strikingly similar in cats and monkeys (**Figure 1**). Prior to these experiments, the large-scale organization of the mammalian brain had been a topic reserved for anatomists working with fixed tissue or for neuropsychologists applying surgical ablation. Now for the first time neurophysiologists were able to weigh in on this issue by charting “functional networks” in the brain of live animals. Nonetheless, the application of chemical neuronography was short-lived, perhaps due to technical hurdles or perhaps because it was ahead of its time. Shortly after the experiments of Pribram and MacLean, most electrophysiologists abandoned questions of large-scale brain organization and focused instead on cataloging and describing the response patterns of isolated cells.

Only in the last decade has neural activity again taken center stage in the study of the brain's large-scale architecture. Functional MRI is now routinely used to identify and characterize networks in the human brain. Unlike neuronography, which involved excitation of brain tissue, the modern field of functional network mapping in the human brain is noninvasive, and relies exclusively on the brain's endogenous (spontaneous, or “ongoing”) hemodynamic fluctuations. Based on first principles, there is no reason to suspect that these signals should yield much useful information. Until recently, most neurophysiological studies have considered spontaneous neural activity to be an irrelevant or even nuisance signal, representing “noise” in the system that might interfere with sensory encoding or motor responses. According to this theoretical framework, ongoing fMRI fluctuations might be, at best, a sluggish and imprecise approximation of this undesirable neural activity. However, a wide range of studies have now demonstrated that spontaneously occurring fMRI fluctuations are not random, but instead have a high degree of spatiotemporal organization. In fact, patterns of temporal correlation measured between distant voxels, dubbed “functional connectivity”, exhibits consistent spatial patterns that find striking agreement across experiment, laboratories, and subject groups. As a result, functional connectivity, measured in subjects at rest, has become the principal means to investigate the integrity of large-scale functional networks in the human brain. Thus while structured fMRI fluctuations could not have been anticipated, and are in many respects still mysterious, they have come to provide a new window on brain neurophysiology that simply cannot be ignored.

The modern field of functional connectivity began in 1995. In that year, Biswal and colleagues discovered that slow fMRI fluctuations in the sensorimotor strip and several other regions of a resting subject's brain showed a pattern of temporal coordination that closely resembled the pattern of functional activation found during a more conventional behavioral task (Biswal et al., 1995). The authors suggested that the spontaneously occurring correlations reflected the inherent functional organization of the neural network itself, at the same time briefly reporting similar observations in auditory and visual networks. The immediate implication of this finding was that the basic properties of large-scale neural networks could be probed by simply analyzing the correlational structure of spontaneous hemodynamic signals in the absence of a task. Biswal's seminal study launched a field of study which, sixteen years later, has produced thousands of publications, and appears to be growing at an exponential rate (Friston, 2011). Analysis of ongoing fMRI signals in resting subjects consistently differentiates several distinct cortical and subcortical functional “networks”, or regions exhibiting high temporal covariation (Tomasi and Volkow, 2011). Such networks are often compared across individuals (Biswal et al., 2010), tracked through the course of development (Power et al., 2010), and evaluated in patients with neuropsychiatric and neurodegenerative disease (Greicius, 2008; Andrews-Hanna et al., 2007). Moreover, functionally derived networks show a significant, though imprecise, correspondence with structurally derived networks based on fiber pathways revealed by diffusion tensor imaging (DTI) (Honey et al., 2009). At present, resting state functional

connectivity figures prominently into the neuroscience community's ambitious effort to assemble a comprehensive network map of the human brain, or “connectome” (Sporns, 2011).

In this article, we review electrophysiological characteristics of the brain's spontaneous activity, focusing on features that are most pertinent to resting state functional connectivity measured with fMRI. We focus on the cerebral cortex because both its resting state fMRI signals and its spontaneous neural activity have been studied in greatest detail. In the first section, we describe neural correlates of spontaneous fMRI that have been established during simultaneous electrophysiological and fMRI recordings. In the second section, we describe the spatial organization of the candidate electrophysiological signals gauged by the pattern of interelectrode correlation over the cortical surface and across cortical laminae. In the third section, we speculate on potential generative mechanisms for slow electrophysiological fluctuations that might underlie hemodynamic functional connectivity, and we also offer important caveats concerning the inherent limitations of inferring neural activity based on fMRI correlation. We will not discuss methodological issues related to functional connectivity analysis, nor survey specific functional networks, as these topics have been reviewed elsewhere (e.g. Cole et al., 2010; Deco and Corbetta, 2011; Bullmore and Sporns, 2009; Power et al., 2010). We will also leave aside semantic issues, such as the inherent imprecision of the terms “functional connectivity”, “network” and “resting state”, and mention only that the growing terminology in this field needs to be matched by well-defined and measureable features of the brain if it is to be useful in the long term.

Neural correlates of resting-state fMRI

The simultaneous acquisition of electrophysiological and hemodynamic signals provides the most direct assessment of neural processes that underlie resting state fMRI. This approach has been conducted in both humans and laboratory animals. In humans, the noninvasive scalp electroencephalogram (EEG) exhibits significant temporal correlation with resting fMRI fluctuations (Ritter and Villringer, 2006; Laufs et al., 2003; Picchioni et al., 2011). Likewise, in animals, direct measures of intracranial neural activity covaries with hemodynamic signals (Lu et al., 2007; Leopold et al., 2003; Huttunen et al., 2008; Pan et al., 2010; Shmuel and Leopold, 2008; Schölvinck et al., 2010). Here we focus on experiments from the nonhuman primate that establish specific neural correlates with spontaneous cortical fMRI signals. Because resting state functional connectivity draws upon very slow fMRI fluctuations, we begin with a brief digression in order to describe the derivation of electrophysiological signals whose time course can evolve over similar time scales.

Types of slow electrophysiological signals—Electrical signals in the brain vary over behaviorally relevant timescales ranging from milliseconds to minutes. Neural activity involves the dynamic redistribution of electrically charged ions across cellular membranes, which can be measured with an electrode as time-varying potentials. The fastest changing electric potentials in the brain are millisecond-duration impulses, or spikes. Spikes represent the direct, digital communication between neurons, often transmitting information between brain areas over long axonal projections. Slower “field” potentials arise from a superposition of heterogeneous neural processes and are most closely associated with synaptic activity (Buchwald et al., 1966). These field potentials include the EEG, the electrocorticogram (ECoG) and the local field potential (LFP), measured from the scalp, pial surface, and neuropil, respectively (**Figure 2a**). Importantly, because they are shaped by spatial and temporal summation of microscopic currents, field potentials are strongly influenced by both the geometric arrangement and temporal synchronization of the cellular structures that give rise to them.

In considering potential correlates of resting state fMRI activity, it is necessary to identify neural processes that vary over the same time scales as empirically observed slow hemodynamic fluctuations. Some field potential components, such as the so-called slow cortical potential, evolve over many seconds or longer (Birbaumer et al., 1990), and might thus might serve as a direct correlate for spontaneous fMRI fluctuations (He and Raichle, 2009), although this hypothesis has not been directly tested. Other field potential components, such as the gamma-range (50-100 Hz) activity are too fast to compare directly to the fMRI signal but exhibit slow changes in their power. Thus a particularly important family of electrophysiological signals is derived from computing the band-limited power (BLP), which allows for the evaluation of slow changes produced by fast components of the LFP. This somewhat counterintuitive notion is explained in **Figure 2b**. Briefly, the *raw LFP* is first filtered into a particular frequency band in order to isolate a physiologically meaningful signal component. The resulting *band-limited LFP* is then rectified in order to create a time-varying estimate of the signal power within that frequency range, or BLP. Rectification is the important step for understanding the apparent contradiction of slow variation in a fast signal: because rectification is a nonlinear operation, the frequency spectrum of the rectified BLP differs entirely from that of the raw LFP signal. In fact, the BLP signal can change arbitrarily slowly. Based on a single raw LFP signal, the BLP can be computed for multiple passbands, resulting in a family of slowly varying time signals derived from a single measurement of the time-varying field potential that bear different relationships to the underlying physiologically processes and to the spontaneous fMRI signal.

It bears mentioning that despite the frequent use of the term “oscillation” in the literature describing field potentials and fMRI signals, most spontaneous neural signals are aperiodic rather than oscillatory. In the frequency domain, that means that the signals are composed of a broad range of frequencies rather than a narrow band of energy around a single frequency, which would indicate an oscillatory signal. (There are some obvious exceptions, such as the prominent alpha rhythm measured from the occipital cortex (Berger, 1929)). In general, spontaneous brain signals obey a $1/f^{\beta}$ spectral distribution, where β is the exponent of a power law. This relationship, which results in a linear function on a double logarithmic plot of power or magnitude versus frequency, indicates that lower frequency components have proportionally larger amplitudes than higher frequency components, but that no particular frequency dominates the spectrum. The $1/f^{\beta}$ spectral distribution characterizes spontaneous signals measured with fMRI, LFP, ECoG, EEG, and magnetoencephalographic (MEG) recordings as well as the BLP derived from these raw signals (Leopold et al., 2003; Leopold and Logothetis, 2003; Nir et al., 2008; He et al., 2010; Dehghani et al., 2010; de Pasquale et al., 2010). Interestingly, it also characterizes the spectrum of slow performance variation in a repeated behavioral task (Gilden et al., 1995), suggesting that slow, intrinsic activity variation may impact the brains interaction with the environment.

Simultaneous fMRI and electrophysiology—Combined fMRI and electrophysiological measurements have revealed multiple neural correlates of resting state hemodynamic responses. In a pair of recent studies combining functional echoplanar imaging and intracranial recordings in the nonhuman primate, the electrophysiological signals showing the strongest and most consistent correlations with spontaneous fMRI fluctuations were neural spiking activity and gamma-range BLP. In one study, Shmuel and Leopold acutely recorded from area V1 in monkeys that were scanned under general anesthesia (Shmuel and Leopold, 2008). They found that the blood oxygen level-dependent (BOLD) signal in V1 was coupled to changes in both spiking rate and gamma-range BLP. Schölvinck et al. subsequently recorded from multiple cortical areas in the awake monkey during “resting-state” MRI scans using chronically implanted electrode arrays (Schölvinck et al., 2010). Instead of the BOLD signal, they measured changes in regional cerebral blood

volume (CBV) following the intravascular injection of monocrystalline iron oxide nanoparticles (MION). Like Shmuel and Leopold, they found that the spontaneous fMRI signal closely followed fluctuations in the gamma-range BLP. They also reported correlation with the BLP derived from other, lower frequency LFP components, though these correlations were less consistent than that derived from the gamma-range. In that study, spiking activity was not measured.

In both studies, cross-correlation analysis between neural and fMRI fluctuations near the recording electrode produced prominent peaks, indicating that the spontaneous fluctuation of the neural and fMRI signals were tightly coupled. The correlation peaks were not centered at zero, but were instead offset by a few seconds, with fMRI signal lagging the spiking and gamma-range BLP. Though this measure only indicates a correlation rather than a causal relationship, such lags would be expected if the hemodynamic fluctuations were a direct consequence of the neural activity. By contrast, such a pattern of correlation between the two signals would not be expected to arise from chance fluctuations of either signal alone or by artifacts that simultaneously affect both signals. It also is important to point out that the *highest* correlation coefficients observed were approximately 0.5, which corresponds to less than 25% of the total variance. Thus while a significant fraction of the resting state fMRI signal variance can be attributed to a single measure of spontaneous neural activity, the majority of its variance remains to be explained.

To summarize recent findings on the neural correlates of spontaneous fMRI fluctuations, simultaneous electrophysiological and fMRI measurements in primates point to spiking and gamma-range BLP signals as being the most reliable correlates of resting state fMRI activity, though other potential candidates, such as slow cortical potentials, have not yet been explored.

Spatial characteristics of ongoing cortical activity

We next turn to the spatial properties of ongoing electrophysiological signals. As with fMRI, this aspect of spontaneous neural activity relies on the assessing the temporal correlation between sites. An obvious question is whether the spatial pattern of neural correlation bear resemblance to, and perhaps underlie, the fMRI correlations that constitute functional connectivity. While, the answer to this question is still one for future research, a few studies have used cortical recordings from electrode arrays to assess the spatial organization of spontaneous electrophysiological signals over both small and large scales. Here we separately review the surface, laminar, and global features such signals in the cerebral cortex.

Surface correlation patterns—Optical imaging techniques provided the first glimpses of the spatial organization of spontaneous neural activity over the cortical surface. In 1995, the same year that marked the beginnings of fMRI resting state functional connectivity, Arieli and colleagues were able to visualize ongoing signals in the primary visual cortex of anesthetized cats (Arieli et al., 1995). They artificially incorporated a light-absorbing dye molecule into the plasma membrane of cortical neurons whose fluorescence varied linearly with the electric membrane potential. While imaging voltage fluctuations, they also recorded spiking responses from single cells from within the imaged field using a microelectrode. When they compared the voltage changes at each spatial location to the spiking of given cells, they found that action potentials were temporally locked to the membrane voltage fluctuations over a spatially distinct portion of the imaged field (**Figure 3**). In doing so, they created a functional map of membrane voltage fluctuations based on the spontaneous activity of single neurons. They found that two different neurons measured from the same electrode were often coupled with voltage changes in different spatial regions, suggesting

the engagement of the neurons with different components of the local functional architecture (see also Tsodyks et al., 1999). Finally, they demonstrated that the spatial pattern of ongoing cortical activity just prior to visual activation could reliably predict a significant proportion of the natural variability in the stimulus-evoked responses (Arieli et al., 1996), a finding that would later find parallels in human fMRI (Fox et al., 2006). These seminal observations, which have yet to be demonstrated in the awake preparation or in other species, opened the door to the mapping of functional cortical networks using ongoing brain activity.

Subsequent neurophysiological studies examining the correlation of field potentials between pairs of electrodes found that the *average* level of LFP coupling falls off monotonically as a function of distance along the cortical surface (Leopold et al., 2003). In one study, this falloff was so predictable that it was possible to determine the precise position of a sulcus based on the sharply diminished correlation between electrodes positioned on opposite sides of the sulcal opening (Leopold and Logothetis, 2003). The LFP correlation falloff with increasing cortical distance varies as a function of frequency, as evaluated by the frequency-dependent measure of magnitude-squared coherence. Specifically, whereas gamma-range coupling falls off within a few millimeters, lower frequency components fall off more gradually (Leopold et al., 2003). This analysis was extended to examine the spatial correlation of slow BLP fluctuations. Compared to the LFP coherence, the BLP coherence falls off much more gradually with cortical distance, as can be seen in **Figure 4**. The discrepancy is largest between the gamma-range LFP (LFP_{high}) and the gamma-range BLP (BLP_{high}), with the former falling off abruptly and the latter remaining coherent over distances exceeding one centimeter (Leopold et al., 2003).

Measuring electrophysiological coherence over yet larger scales with microelectrode arrays, such as those corresponding to the same spatial scales measured with fMRI, is possible but technically challenging since this approach requires the exposure of large areas of the brain. Noninvasive techniques such as EEG and MEG provide a wider coverage but face severe challenges associated with the so-called inverse problem of source localization. The inverse problem arises because signals measured on each sensor arise from an inherently ambiguous combination of current sources at originating from poses particular multiple locations. This problem difficulties for methods based on the correlation of independent neural signal sources, though there has recently been progress in this field (Ghuman et al., 2011; Brookes et al., 2011).

Subdural ECoG arrays implanted in human epilepsy patients provide an electrophysiological measure similar to the LFP and have allowed for the evaluation of neural correlations over arrays spanning several centimeters. For example, in one study, He et al. investigated spontaneous activity within a large swath of the frontoparietal cortex (He et al., 2008). Electrodes were first conceptually divided into distinct sensorimotor and nonsensorimotor (control) regions based on previous clinical mapping and resting state fMRI correlation patterns. High correlation was found for ongoing activity between electrodes within the sensorimotor region, but not between the sensorimotor and control regions. Furthermore, this region-specific correlation was only present for the lowest frequency range of the raw voltage signal (< 4 Hz), suggesting that the slowest LFP components may be the most specific, and may perhaps contribute to the specificity of fMRI functional connectivity (He et al., 2008). In a different study, Nir et al. used a similar preparation but reached a somewhat different conclusion regarding the frequency range carrying spatially specific information (Nir et al., 2008). They found that spatial specificity of interelectrode correlations was highest in the gamma-range BLP of the ECoG signal. Specifically, they evaluated the correlation of spontaneous signals measured simultaneously from the two hemispheres and found that only the gamma-range BLP showed strong spatial specificity between corresponding homotopic regions of the cortex in the two hemispheres. While

lower frequency signals showed coupling between electrodes, the correlations were unspecific and did not exhibit peaks in symmetrical regions of the two hemispheres.

The finding of homotopic specificity in spontaneous neural activity patterns may be particularly important, since this is a feature common to nearly all resting state fMRI studies (e.g. Smith et al., 2009). The axonal fibers passing through the corpus callosum are likely to support interhemispheric neural correlation to some extent, as supported by decreased symmetry in a patient following a callosotomy (Johnston et al., 2008). However, it is also clear that some parts of the brain showing strong functional connectivity across the two hemispheres are not directly connected by callosal fibers, including both cortical (Vincent et al., 2007) and subcortical (Di Martino et al., 2008) structures. Moreover, a recent study comparing spontaneous activity correlation and microstimulation-evoked responses in anesthetized monkeys (Matsui et al., 2011) found that interhemispheric correlation was not well predicted by the pattern of microstimulation-induced fMRI responses. Thus the basis of the striking hemispheric symmetry commonly observed in studies of fMRI functional connectivity remains somewhat of a mystery.

Laminar organization—The cerebral cortex is a laminar structure whose superficial (layers 1-3), middle (layer 4 with its various sublayers), and deep layers (5&6) are distinct in their anatomical connections and functional responses. To what extent does ongoing neural activity vary as a function of cortical layer? In a third important study from 1995, Snodderly and Gur examined this question by measuring the ongoing spiking rate of neurons in different layers of V1 in the awake macaque (Snodderly and Gur, 1995). They found a striking difference in the spontaneous neural spiking rates measured from different layers of animals sitting in complete darkness. Neurons in layers receiving direct input from the principal layers of the lateral geniculate nucleus (cortical layers 4C, 6, and 4A) showed high spontaneous firing. By contrast, neurons in other layers (cortical layers 2/3, 4B and 5) were nearly silent. While that study did not measure field potentials, a recent study found a similar laminar distribution of gamma-range BLP (Maier et al., 2010). Importantly, most V1 corticocortical projections originate in these layers, with layers 2/3 giving rise to the majority of feedforward connections and layer 4B giving rise to the majority of interhemispheric connections (Kennedy et al., 1986). The lack of spontaneous activity among such neurons is conspicuous, since they would be expected to support most of the direct corticocortical communication within and between cerebral hemispheres during the resting state.

In a rather different exploration of spontaneous activity across cortical laminae, Maier et al. simultaneously measured field potentials within different layers using a multicontact microelectrode (Maier et al., 2010). Parallel recordings allowed for the evaluation of LFP coherence and BLP coherence between different layers. Analysis of pairwise LFP coherence between electrodes revealed two prominent laminar zones, one superficial (layers 1-4) and one deep (layers 5&6). Coherence measured between electrodes situated in the same zone showed high coherence, whereas the coherence measured between electrodes situated on opposite sides of the boundary between the zones (between cortical layers 4C and 5) fell to near zero. Maier et al. speculated that this compartmentalization might reflect a differential engagement of superficial layers with other cortical areas and deeper layers with subcortical areas, which is roughly suggested by the anatomical projection pattern. Importantly, a similar segregation was present in the slow fluctuation of gamma-range BLP signals, which, as described above, is a strong correlate of spontaneous fMRI fluctuations. Taken together, these results suggest that the upper and lower layers contribute differently to measures of resting state fMRI functional connectivity. A recent finding demonstrating layer-specific fMRI coupling between anatomically connected cortical areas in humans supports this possibility (Polimeni et al., 2011).

The "global" resting state signal—Above we described neural correlates of fMRI fluctuations based on simultaneous neural measurements within a delimited cortical region or between interhemispheric homologues. Functional MRI correlations with neural activity have also been observed far away from the recording site. Specifically, in a study by Schölvinck et al., gamma-range BLP fluctuations from recording sites in the occipital, parietal, and frontal cortex of resting monkeys were all correlated with hemodynamic fluctuations over large regions of the cortical mantle (see **Figure 5a**)(Schölvinck et al., 2010). Coupling to the local neural signal was prominent throughout nearly the entire cortex, but was not observed in either subcortical structures or the white matter. While there are man possible interpretations of this result, one obvious one is that global correlations is driven by widespread neural synchrony. Preliminary support for this interpretation comes from paired neural recordings in resting animals in our laboratory. Even electrodes in non-homotopic regions of opposite hemispheres display a strong correlation in the gamma-range BLP, with a prominent zero-lag peak (**Figure 5b**). This observation has important implications for the interpretation of resting state functional connectivity. In particular, the global fMRI signal correlation reported by Schölvinck et al. is commonly observed, yet frequently discarded in functional connectivity analysis, a practice that can introduce artifacts (Murphy et al., 2009; Fox et al., 2009). The fact that this regionally unspecific component of resting state functional connectivity reflects genuine neural activity raises further questions about this practice (Schölvinck et al., 2010).

To summarize this section on the spatial nature of spontaneous neural activity, correlation and coherence measurements in humans and animals demonstrate that neural signals maintain a high level of spatial organization over the cortical surface and across cortical laminae. In addition to the highly organized structure of local neural activity, a significant component of the global fMRI signal appears to be driven by neural activity fluctuations that are themselves coordinated over large regions of the cerebral cortex.

Functional connectivity: speculations and caveats

It is by now well established that spontaneous fMRI activity gives rise to consistent correlational patterns than can be used to study the large-scale organization of the human brain. As reviewed above, while the neural correlates of specific networks may still be out of reach, spontaneous neural activity is organized at multiple spatial scales and is often coupled with resting fMRI signals. In this section we step back from the data to consider fundamental questions about spontaneous brain activity, including its possible physiological origins and limits on the power of correlational methods.

What neural processes give rise to functional connectivity?—Questions surrounding the interpretation of functional connectivity usually focus on whether or not it is an accurate reflection of direct anatomical connections (see, for example, (Fox and Raichle, 2007)). Based on its correspondence with anatomical imaging techniques such as diffusion tensor imaging (DTI) and direct tract tracing, it is reasonable to assume that direct anatomical connections play an important role in shaping functional correlations between distant brain areas (Vincent et al., 2007; Bullmore and Sporns, 2009; Krienen and Buckner, 2009; Heinzle et al., 2011). At the same time, spontaneous activity correlation is frequently observed in areas without direct anatomical connections, emphasizing the dangers in *inferring* anatomical connectivity from mere activity correlation (Zhang et al., 2008; Vincent et al., 2007; Di Martino et al., 2008; Krienen and Buckner, 2009; Margulies et al., 2009) (for a review, see Sporns, 2011). In the monkey, where anatomical connections are known in greater detail, such discrepancies are even more apparent than in humans (Adachi et al., 2011). Activity correlations that arise in the absence of direct anatomical connections are sometime euphemistically termed "network effects".

It is equally straightforward to imagine a system of anatomical interconnections that do not carry slow, coherent hemodynamic fluctuations characterized by $1/f^{\beta}$ spectrum. Based on our current understanding anatomical projections alone do not prescribe any particular pattern of spontaneous activity. In the absence of a solid theoretical framework within which to understand spontaneous activity patterns, the field of resting state functional connectivity is presently retains its original character as a largely empirical science (Biswal et al., 2010). In the long run, determining the origin and significance of spontaneous neural and hemodynamic signals in the brain is likely to prove of greater value for understanding its function than is the purely empirical characterization of hemodynamic correlation patterns.

Early studies were more probing with respect to the physiological origin of resting fMRI correlations, with some investigators questioning whether they may be entirely attributed to spontaneous vasomotor oscillations (Mitra et al., 1997). While vascular effects may contribute to the overall variance, it is now clear that neural processes do play a critical role, not only because of the neural correlates described above, but also because resting state fluctuations are metabolically demanding (Fukunaga et al., 2008). But why should there be any particular spatial organization to spontaneous neural activity, and what might be its consequence for normal brain function? On these points we can only speculate at present.

One possibility is that slow, coordinated activity changes of the brain are related to the establishment or maintenance of synaptic connections between neurons. As during development, spontaneous neural activity could act to stimulate synaptic connections (Katz and Shatz, 1996), or to reinforce them during network formation and homeostasis (Turrigiano and Nelson, 2004; Sur and Rubenstein, 2005). It is known that spontaneous activity influences dendritic spine structure and number in adults (Sur and Rubenstein, 2005; Trachtenberg et al., 2002), and lack of spontaneous activity can lead to cell pathology (Fishbein and Segal, 2007). Over long time scales, such processes could manifest as an ongoing activity correlation between synaptically connected neurons—a slow, continual “handshaking” of sorts between structurally interconnected areas. Synaptic modification made during the day may then be subject to downscaling during a rather different pattern of spontaneous activity associated with sleep (Tononi and Cirelli, 2006).

However attractive, models of functional connectivity that rely on direct anatomical connections cannot account for all the data, such as the known functional covariation between anatomically unconnected areas described above. A somewhat different possibility, though not mutually exclusive, is that spontaneous activity correlation reflects ascending neuromodulation or ascending subcortical projections (e.g. from the thalamus). While there is presently not much direct evidence in support of this hypothesis, recent work by Tononi and colleagues emphasizes that sleep, which has traditionally been considered to affect the cortex as a whole, is spatially differentiated over the cerebral cortex (Huber et al., 2006; Nir et al., 2011; Vyazovskiy et al., 2011). Regional sleep is thought to involve local changes in chemical neuromodulators, such as acetylcholine and norepinephrine that originate from central sources in the brainstem and basal forebrain. Moreover, the processes surrounding regional sleep operate over long time scales, and may therefore bear on measurements of fMRI functional connectivity. While activity in sleep is distinct from spontaneous activity in the resting state (Steriade et al., 1993), it is nonetheless interesting to consider that the same or analogous ascending subcortical pathways could provide a cortical mosaic of local, coordinated neuromodulators, which could shape the pattern of temporal correlation observed in functional connectivity (see Drew et al., 2008). In addition, numerous other factors could potentially contribute to specific fMRI correlations measured in functional connectivity, including circulating hormones (Joëls and Baram, 2009), direct innervation of the vasculature (Hamel, 2006), or spatiotemporal waves of cortical activity (Wu et al., 2008;Massimini et al., 2004).

The "inverse problem" of fMRI and its correlations—The multiple candidate neural and vascular contributors to fMRI signal variation described above pose two distinct challenges for interpreting functional connectivity. The first challenge is the degenerate nature of the fMRI signal, whether BOLD or CBV, within a given voxel in the brain. From electrophysiology experiments reviewed here, it is clear that spontaneous neural activity is coordinated at multiple spatial scales, from microscopic to global. It is also clear that the perfusion and oxygenation status of a voxel, which determine the measured "activity" level during fMRI, are can be simultaneously shaped by diverse physiological processes during each time point. Such convergent influences onto a single, unitless scalar intensity value place severe limits on the precision by which one may ascribe an fMRI measurement to any particular neurophysiological process, particularly during the unconstrained conditions of the resting state. In this sense, fMRI has its own type of inverse problem, which pertains not to the *localization* of underlying events (as in EEG and MEG), but to the *decomposition* of its underlying neural events. In other words, a spontaneous rise or fall in the fMRI signal can never be uniquely attributed to a specific type of neural event, since blood flow regulation is the final common pathway of a very large number of heterogeneous physiological mechanisms.

When it comes to interpreting functional connectivity, the situation is yet worse, since the relation between the neural constituents of two hemodynamic signals also tends to vary over time. Computing the correlation between two fMRI signals, in effect, summarizes the temporal covariation between two signals over a window of time and typically assumes stationarity during that period. Increasing evidence suggests that this assumption is ill founded, as it is clear that the correlational structure of resting state networks changes substantially over a period of minutes (Chang and Glover, 2010).

In other words, the fundamental inverse problem of fMRI is compounded when temporal correlations are computed. Now it is not only the neural contribution to each voxel that is ambiguous, but also the relative neural contributions of different signals to the intervoxel correlations over time. The reduction of this information into an r-value ranging from -1 to +1, as is the common practice in functional connectivity analysis, results in an irretrievably ambiguous combination of neural and non-neural signals that is heterogeneous in both space (within each voxel) and time (over the course of a scan). Consider, then, how to interpret a change in functional connectivity, either over time or between groups of individuals. An *increase* in fMRI correlation might occur because there is a subtle but consistent increase in phase locking of the underlying neural signals. Alternatively, it might result from a smaller number of prominent, coincident events, of either neural or non-neural origin, affecting two regions. There are multiple other possibilities.

Likewise, a *decrease* in functional connectivity might stem from an inverse of either of the above mechanisms. Alternatively, it might arise because one region abruptly exhibits an additional, superimposed signal component that is absent in another region. While mathematical methods such as independent component analysis (Beckmann et al., 2005) and multivariate autoregressive models (Rogers et al., 2010) help to disentangle some sources of shared variance, no computational method can precisely separate the physiological contributors to hemodynamic signals, nor isolate elements of shared temporal structure that correspond to distinct neural processes.

The harsh realities described here leave the practitioner of functional connectivity facing a number of problematic questions: Should one regress out the global cortical fMRI signal before evaluating specific correlations, even though a significant portion of the global signal is correlated with neural activity? What is the appropriate duration of a "resting state" fMRI scan, given that the magnitude of functional connectivity varies over time? To what extent

can one reasonably interpret differences in the mean resting state fMRI correlation value between patient groups? Can fMRI correlation values be taken as building blocks upon which to build large-scale network models of the human brain? None of these questions has easy answers, let alone “correct” ones. Researchers must simply be aware of the limitations of their method when designing their experiments, when analyzing their data, and particularly when interpreting their findings. The community must come to accept that the inverse problem of fMRI exists, and that it is particularly devastating for resting state functional connectivity.

Drilling down while building up—Despite the bleak picture painted above, resting state fMRI functional connectivity has proven to be a powerful method and has exhibiting a striking level of consistency between laboratories and studies. Correlational fMRI approaches yield repeatable brain network models and show promise for establishing biomarkers for the diagnosis of neurological and psychiatric disease. Improved spatial resolution and analysis methods promise to deliver further organizational features that will advance our understanding of the human brain. It is vital that during this process we simul taneously dig deeper into the origins of the brain's endogenous physiological processes. What drives spontaneous neural fluctuations during rest? What is the relation between the ongoing neural activity, synaptic function and homeostasis? Is spontaneous neural activity specific to functional networks, as fMRI correlations would suggest? To what extent does spontaneous activity contribute to the brain's enormous energy expenditure? On this last point, it is known that metabolic energy is a costly commodity in evolution, and the brain expends 20% of the body's energy despite accounting for only 2% of the body's mass. Approximately 80% of this expenditure is thought to be related to the maintenance of homeostasis (van Eijsden et al., 2009; Hyder and Rothman, 2010; Raichle, 2006). The contribution of spontaneous activity variation to the brain's resting energy consumption is unknown.

Once regarded as irrelevant “noise”, endogenous neural activity is now respected as a legitimate product of the brain. At present, resting state activity serves as a convenient tool for a new age of neuroscientific empiricism, with the pair-wise correlations of spontaneous activity between fMRI voxels taken as building blocks for constructing elaborate brain networks. However, spontaneous activity must ultimately be understood on its own terms. The consistent patterns observed in functional connectivity suggest that spontaneous activity is fundamental to the functioning of the brain. Whether this role lies in homeostasis, synaptic maintenance, information processing, hormonal regulation, or consciousness (Shulman et al., 2009) are important questions for the future.

Conclusions

The fact that the spatial pattern of resting state correlations show such striking consistencies across individuals (Biswal et al., 2010), brain states (Vincent et al., 2007) and even species (Zhang et al., 2010; Moeller et al., 2009) may be seen as a testament to the importance of spontaneous physiological activity. As the field of resting state functional connectivity grows faster than anybody could have possibly imagined only a few years ago, systems neuroscientists must consider their priorities. The existence of functionally connected networks in the mammalian brain has been recognized since even before the work of Pribram and MacClean. Functional MRI allows researchers to noninvasively characterize and track correlational structures that resemble functional networks in humans, which holds great neuroscientific and clinical promise. However, in order to truly understand the meaning of fMRI-based networks, their variability, and their degeneration in disease, human studies must be complemented by invasive studies in animals. We must discover why slow ongoing neural activity exists in the first place, what dictates its spatial organization at

multiple scales, why certain networks are temporally synchronized over long time scales, and how such correlational patterns relate to other aspects of brain physiology such as sleep, learning, and interplay between the hemispheres. Spontaneous activity is in some ways the most ubiquitous and obvious product of the brain; however, despite its recent popularity it remains an aspect of brain function we know very little about.

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Highlights

- We review cortical electrophysiology pertinent to fMRI functional connectivity.
- Early animal studies demonstrated organization in spontaneous neural activity.
- Several neural signals are potentially underlie ongoing fMRI fluctuations.
- We describe the spatial, temporal, and spectral properties of ongoing neural activity.
- We speculate on the neural origins of the intrinsic cortical fluctuations.

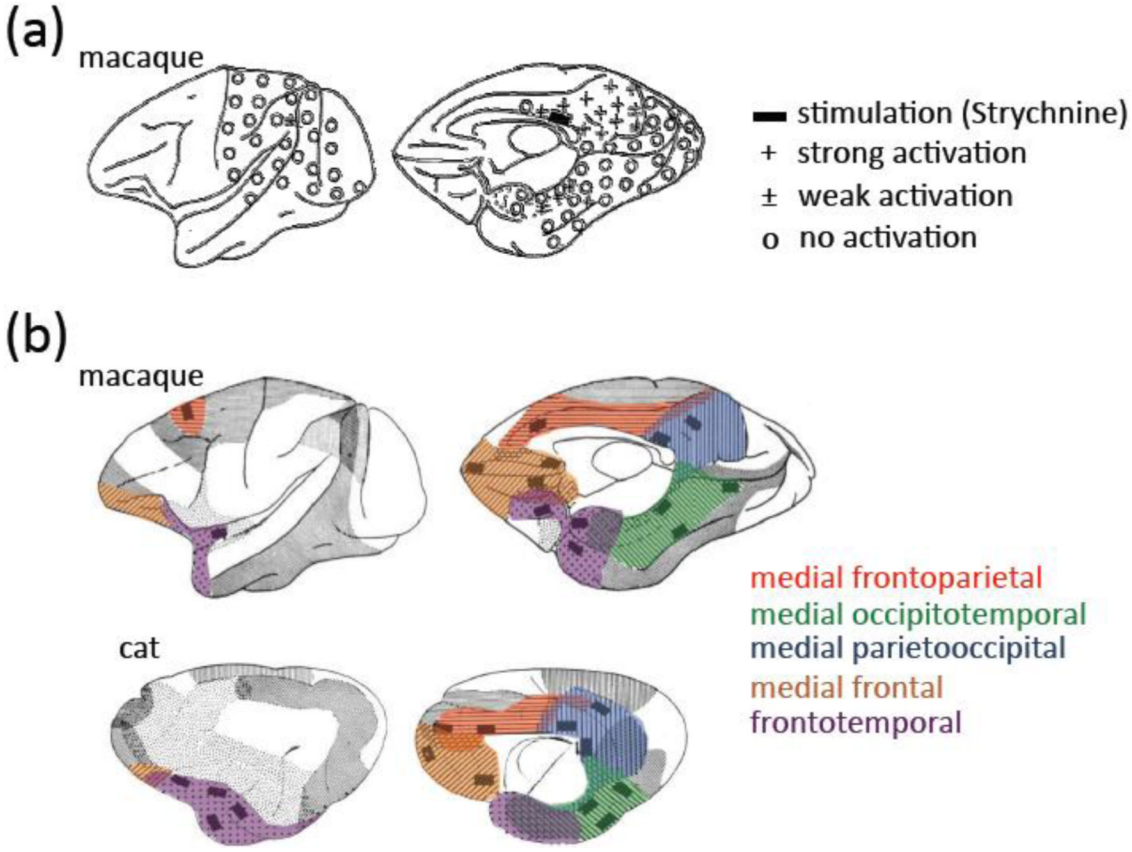

Figure 1.

Strychnine technique for evaluating widespread connectivity in the limbic system. (a) Strychninization of the posterior cingulate (black rectangle) in a macaque led to strong (+) and weak (±) responses on a subset of electrodes placed on the cortical surface whereas others exhibited no (o) responses. (b) Regions of reciprocal connectivity within the limbic cortex of the macaque and the cat brain. Note the five similar limbic networks identified in the two species.

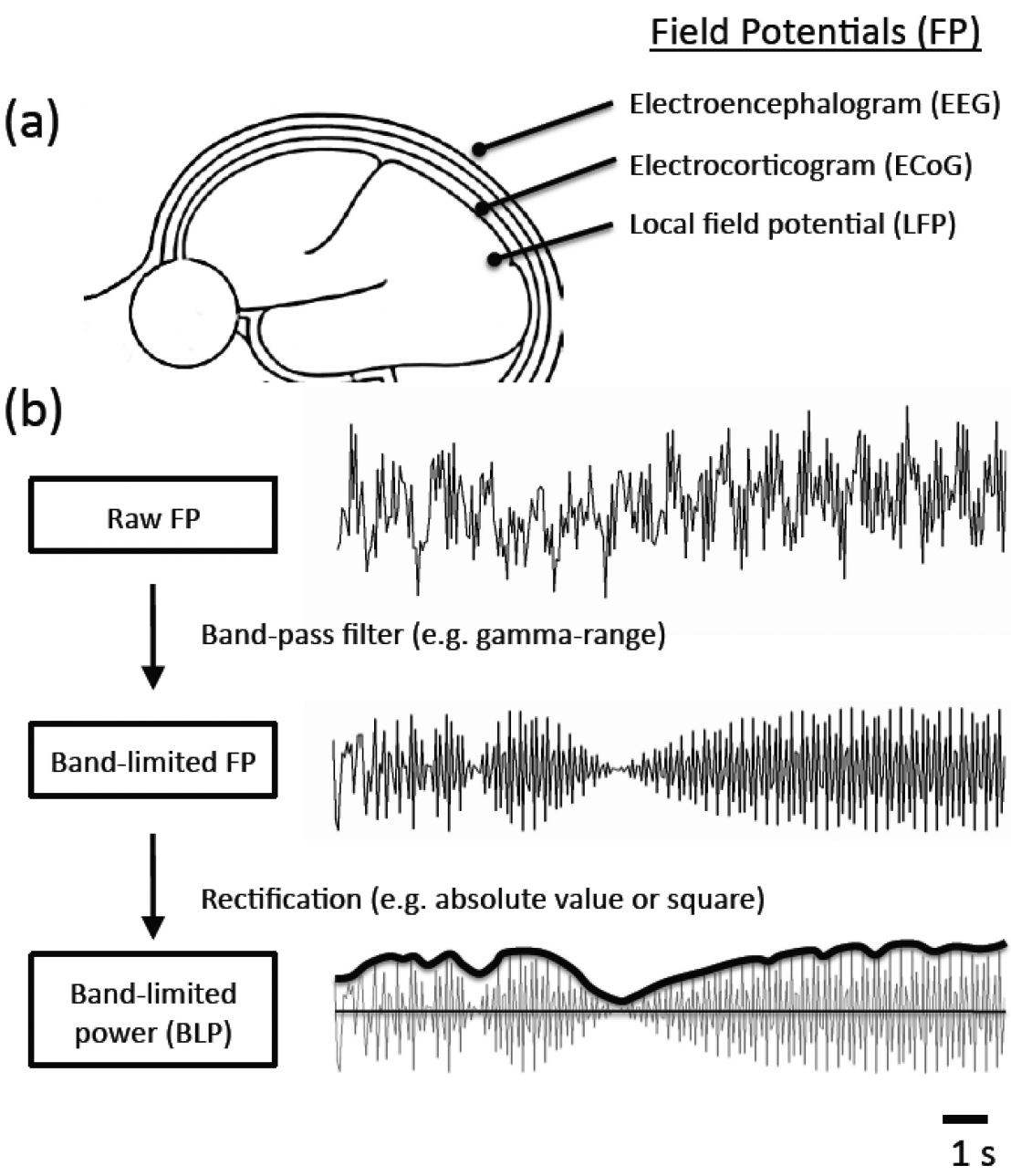

Figure 2.

Derivation of band-limited power (BLP) signal from local field potential (LFP) trace. (a) Using different methodology, Field Potentials (FP) can be recorded from inside the brain, from within the subcranial space or on the intact scalp. (b) A raw FP voltage trace is filtered into a given frequency range using a band-pass filter, typically within a narrow frequency range less than 100 Hz (e.g. gamma range LFP, 50-100 Hz, or multiunit, 500-1500 Hz). The resulting band-limited signal is then rectified by one of a number of methods (e.g. estimating the signal envelope or squaring the band limited signal). The resulting BLP signal is an estimate of the time-varying signal magnitude or signal power. Owing to the non-linear nature of the rectification step, its fluctuations can proceed over time scales that are much slower than the pass band used in the filtering step.

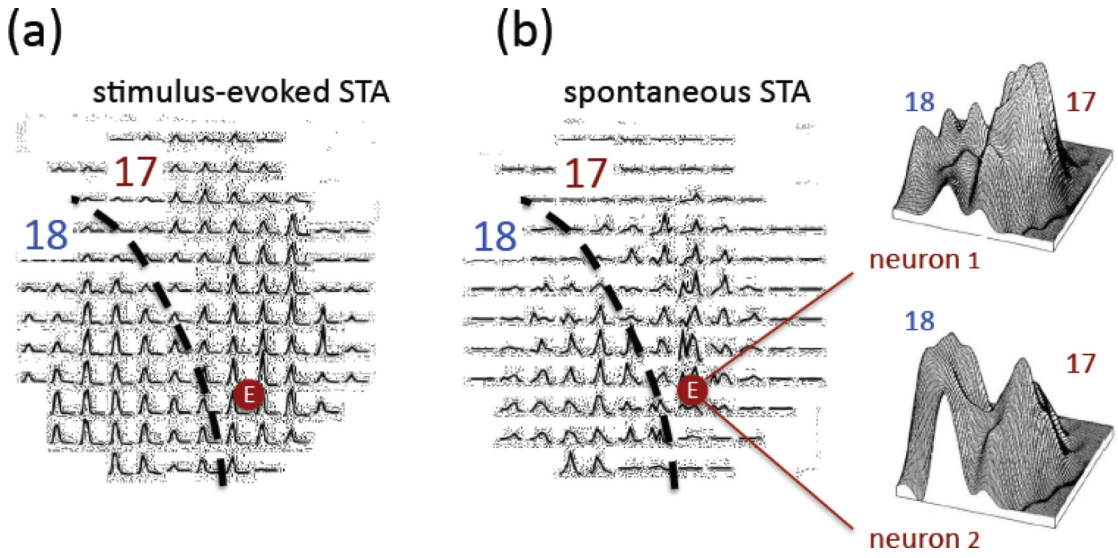

Figure 3.

Spatiotemporal coherence pattern between single neurons and membrane potentials measured with voltage sensitive dye in the visual cortex of an anesthetized cat. (a) Spike triggered average (STA) evoked by a visual stimulus. The STA was evaluated between a cell isolated in area 17 (E = electrode) and the membrane potential over several square millimeters of cortex. The chamber spanned a portion of area 17 and area 18 (see inset). (b) STA evaluated during spontaneous ongoing activity, triggered to the same spike as in (a). This STA showed a pattern of covariation that was restricted to a particular spatial zone within the field of view. (c) Two single neurons measured from the same electrode gave very different spatial patterns in their spike-triggered average, suggesting that they were engaged in different functional networks.

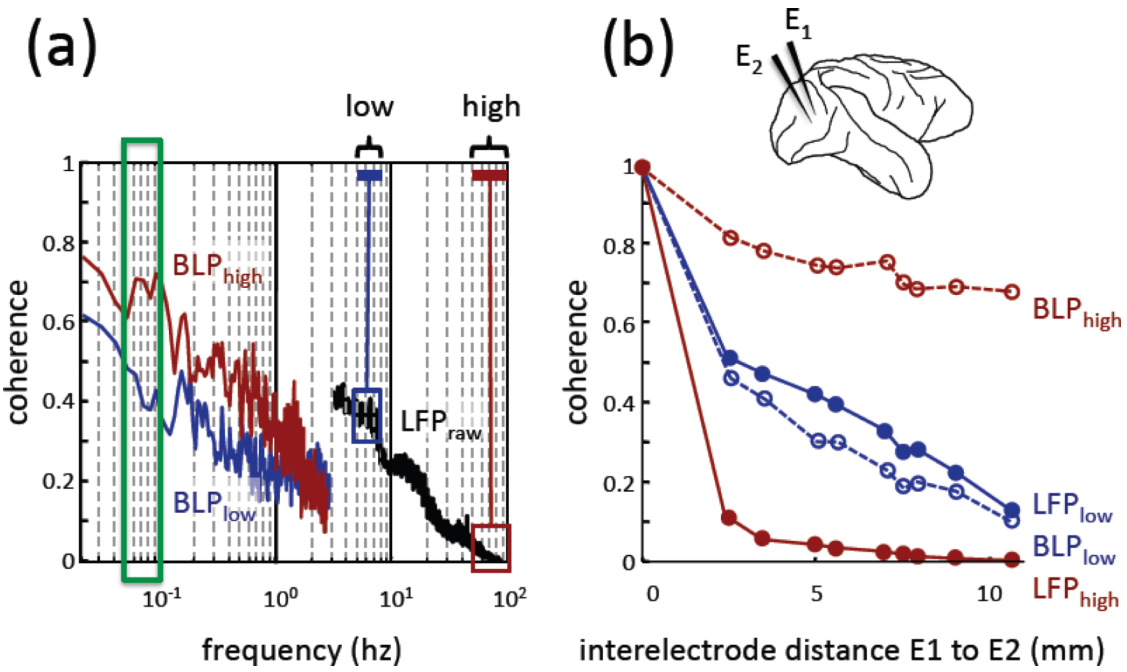

Figure 4.

Spectral and spatial characteristics of low frequency LFP and BLP coherence in monkey visual cortex during rest. (a) The mean pair-wise LFP coherence among an array of electrodes is shown as a function of frequency. Note that the stronger coherence at lower frequencies is dropping off at 1 Hz because that corresponded to the cutoff frequency of a high pass filter used during the recordings. In addition, coherence of the BLP was examined in two frequency ranges (magenta and purple traces indicating low and high frequencies, or 5-8 Hz and 50-100 Hz, respectively). Note that the high frequency BLP showed a strong coherence, even though the underlying fast voltage fluctuations did not. (b) Coherence drop-off as a function of electrode separation. The magnitude-squared coherence of the LFP (closed circles, solid lines) and BLP (open circles, dashed lines) are shown for the frequency ranges highlighted in (a). The coherence of the BLP for the two frequency bands is computed over the frequency range 0.05 – 0.1 Hz, corresponding to the green box in (a). Note that the high frequency BLP hardly falls only very gradually, remaining high at cortical distances exceeding 10 mm. This is in contrast to the coherence of the low frequency BLP and the coherence of the LFP in either frequency range.

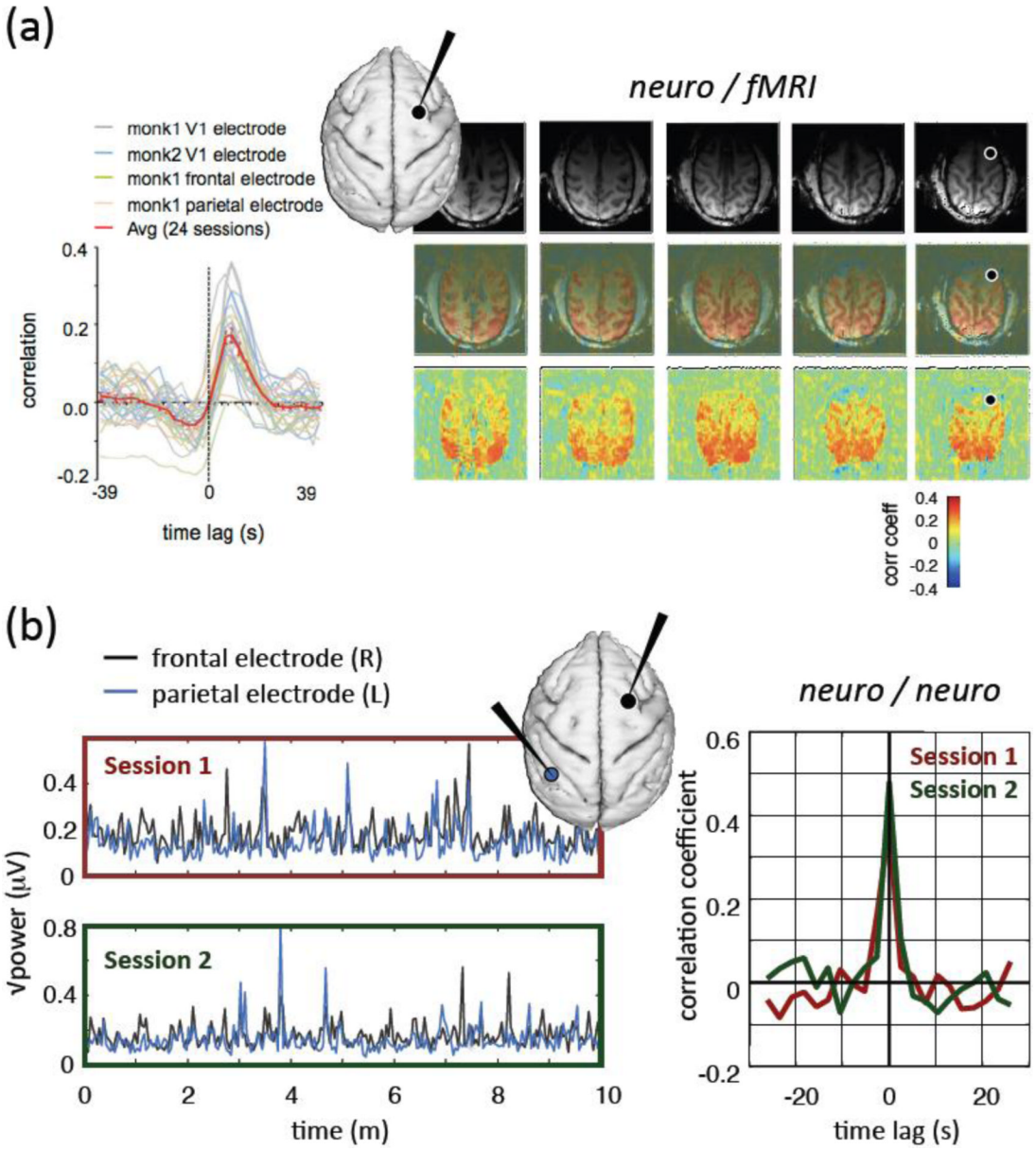

Figure 5.

Widespread correlation of spontaneous activity in the monkey cerebral cortex. (a) Correlation between gamma range LFP power fluctuations measured at an electrode site in the macaque frontal cortex and fMRI signals throughout the brain. Strong correlations were observed in sensory, motor, and associative cortex, but were absent in the white matter and in large subcortical structures such as the thalamus, striatum, and cerebellum (not depicted here). Note that in this example the weaker correlation strength in the anterior cortex is a consequence of a lower signal-to-noise ratio in the MR images resulting from the particular coil used in the fMRI acquisition. (b) Two example sessions demonstrating the correlated spontaneous fluctuations measured in distant cortical electrodes in the macaque brain. The data were collected during whole-brain fMRI data acquisition. Fluctuations in the gamma range LFP power over a 10-minute period are shown from a right frontal electrode and left parietal electrode for each session. Power was estimated each 2.6 s, corresponding to the TR used for the simultaneous fMRI acquisition. Cross correlation between the frontal and

parietal sites revealed a single sharp peak, indicating that the neural activity underlying the global fMRI activity took the form of punctate events rather than slow oscillations.