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Linking Band-Limited Cortical Activity to fMRI and Behavior

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This chapter addresses the relationship of band-limited electrophysiological mass activity to behavior on the one hand, and to the BOLD fMRI signal on the other. Electrophysiological mass activity generally reflects several different components of neuronal activity, which are generated by distinct neural mechanisms and expressed in different frequency ranges. The relative strengths of these components thus determine a so-called specific spectral fingerprint of a perceptual or cognitive process. A striking discrepancy between the spectral fingerprint of stimulus-driven responses in sensory cortices and the fingerprints of intrinsic processes (such as top-down attention or switches between perceptual states) within the same cortical areas is highlighted. It is proposed that this dissociation reflects recurrent interactions between distant cortical areas and/or neuromodulation of cortical activity patterns by ascending systems, which are both thought to play an important role in such processes.

Introduction

Since the discovery of the electroencephalographam (EEG), it has been possible to measure neural mass activity with millisecond temporal resolution (Nunez and Srinivasan, 2006). Nowadays, neural population signals can be recorded at various spatial scales, using microelectrodes (measuring the local field potential, LFP), subdural surface electrodes (electrocorticography, ECoG), extracranial scalp electrodes (EEG), or magnetic field sensors (magnetoencephalography, MEG). Spectral analysis uncovers components of such population signals, which are "induced" by, but not necessarily "phase-locked" to, external events, such as stimulus onsets or motor responses (Pfurtscheller and Lopes da Silva, 1999; Tallon-Baudry and Bertrand, 1999).

Spectral analysis has primarily been used to characterize oscillatory patterns in the ongoing EEG (Dietsch, 1932; Grass and Gibbs, 1938). By contrast, studies of stimulus- and task-related EEG responses have long been dominated by the event-related potential (ERP) technique (Luck, 2005). This technique is based on averaging signal waveforms in the time domain across repeats of an external event, thereby isolating neural response components *phase-locked* to the event of interest. These response components are typically transient, lasting a few hundred milliseconds from the event. The rationale is to isolate the "signal" of interest from the "noise." However, neural responses to external stimulus and task events also reflect more sustained components.

We argue that, because the spectral analysis approach also captures sustained, non-phase-locked signal components, it is ideally suited for relating stimulus- and task-related neural mass activity to perception and cognition. First, many perceptual and cognitive processes (e.g., attention, short-term memory, and decision-making) unfold over time scales longer than the event-related potential. Second, these processes are not directly driven by external events, but emerge from recurrent network interactions within the brain. Such processes are thus likely to manifest themselves in the non-phase-locked neural response components. Third, investigating neural activity in the frequency domain may provide critical insights into the *mechanisms* underlying cognitive processes: Different mechanisms are often accompanied by different patterns of oscillatory neural activity (Buzsaki and Draguhn, 2004; Sejnowski and Paulsen, 2006; Steriade, 2000; Wang, 2003). For these reasons, we have recently witnessed an increasing use of spectral analysis in LFP studies in animals and in EEG and MEG studies in humans. This trend has led to an encouraging degree of convergence between these different levels of observation.

For the same reasons, we argue that spectral analysis is the prime approach for relating electrophysiological mass activity to the blood oxygenation level dependent (BOLD) contrast signal (Ogawa et al., 1990), the current mainstay of functional magnetic resonance imaging (fMRI). fMRI has proven to be an extraordinarily useful tool for identifying

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the large-scale cortical networks engaged in a variety of higher brain functions, including such seemingly elusive ones as attention, awareness, and decision-making (Corbetta and Shulman, 2002; Haynes and Rees, 2006; Heekeren et al., 2008; Kanwisher and Wojciulik, 2000; Kastner and Ungerleider, 2000). Cognitive neuroscience could make a major step forward if we knew how to link electrophysiological and fMRI signals measured during perception and cognition.

In this chapter, we will first address the question of how electrophysiological population signals are linked to sensory and cognitive processing. We review a wide range of studies all suggesting that such links are typically frequency-specific. We will refer to these links as the "spectral fingerprints" of the functional processes in a given brain region. We highlight that different classes of processes (and maybe even different classes of brain regions) seem to have remarkably different spectral fingerprints, a fact that is often overlooked. For example, stimulus-driven activity in sensory cortices generally seems to have a simple spectral fingerprint, the network mechanisms of which are becoming increasingly clear. By contrast, the spectral fingerprints of *intrinsic*, cognitive processes (such as "top-down" attention or switches between different perceptual states) in the same sensory regions appear to be more complex, and their underlying mechanisms are as yet elusive. We speculate that the reason for this discrepancy is that the latter kind of processes involve stronger recurrent network interactions between distant brain areas and/or neuromodulation[1] of cortical processing by ascending brainstem systems.

Second, we will discuss how the electrophysiological population signals relate to the fMRI signal. Many previous discussions of the relationship between invasive electrophysiology and the fMRI signal (e.g., Heeger and Ress, 2002; Lauritzen, 2005; Logothetis, 2008; Logothetis and Wandell, 2004) have focused on the question which aspect of neuronal activity (spiking vs. synaptic) drives the fMRI signal. We will not address this question here. Instead, we ask whether we can identify simple, general rules that govern the relationship between electrophysiological population activity and the fMRI signal at a macroscopic level. Based on the evidence reviewed below, a simple answer to this question appears to be "no." The relationship between these signals seems to depend on the specific *functional process* and, perhaps, even the *brain area* under study. While, again, a relatively simple relationship is beginning to emerge for stimulus-driven responses in sensory cortex, this relationship appears more complex, and as yet elusive, for higher cognitive processes. Thus, we propose that a fruitful approach toward integrating electrophysiology and fMRI may be an indirect one, that is, via the processes under study. We conclude with a list of open questions, answers to which might fundamentally advance our understanding of the issues addressed here.

A Brief Primer on Band-Limited Neural Activity

Electrophysiological Population Signals

Current electrophysiological techniques provide measures of neuronal population activity across a broad range of spatial scales. Intracortical microelectrode-recordings allow for directly measuring the spike output (action potentials) of individual (single-unit activity or SUA) or multiple (multi-unit activity or MUA) neurons. While spike signals are mostly confined to signal components above 500 Hz, the low-frequency signal (approx. <250 Hz) recorded from intracortical microelectrodes constitutes the local field potential (LFP), which reflects summed dendro-somatic currents surrounding the electrode tip (approx. <1 mm) (Juergens et al., 1999; Logothetis and Wandell, 2004; Mitzdorf, 1987). The LFP averages over several hundreds of neurons, and its amplitude is thus thought to reflect predominantly *synchronized* synaptic events and other slow nonsynaptic potentials (e.g., spike afterpotentials). The electromagnetic fields corresponding to these synchronized dendritic currents can also be recorded from outside of the cortex. The ECoG measures these fields with sub- or epidurally placed electrodes, often referred to as intracranial EEG (Lachaux et al., 2003). At the most macroscopic level, scalp EEG and MEG measure the corresponding electric/magnetic fields using scalp electrodes (Nunez and Srinivasan, 2006) or magnetic field sensors (Hamalainen et al., 1993). While the intracortical LFP depends on the laminar placement of the electrode tip, the ECoG, EEG, or MEG do not provide such laminar specificity. The ECoG, EEG, or MEG mainly reflect the electromagnetic fields generated by the large dendrites of pyramidal neurons, which are arranged in parallel to one another and which are oriented perpendicular to the cortical surface.

"Frequency Bands" and Neural Oscillations

These electrophysiological signals comprise activity over a broad frequency range. Their power roughly follows a power-law decay (1/frequencyn) (Bedard et al., 2006; Buzsaki and Draguhn, 2004; Freeman et al., 2000). Thus, at higher frequencies, modulations of the spectral power are typically small in absolute magnitude and, without normalization, often masked by strong low-frequency components. Therefore, it is useful to calculate electrophysiological responses as power changes relative to a "baseline" (e.g., prestimulus interval) spectrum for visualizing the effects of a particular experimental manipulation, and for comparing them across different frequency ranges. Figure 4.1.1 illustrates this for MEG responses to a visual grating stimulus.

The different frequency ranges of these electrophysiological measures are commonly referred to as "bands,"

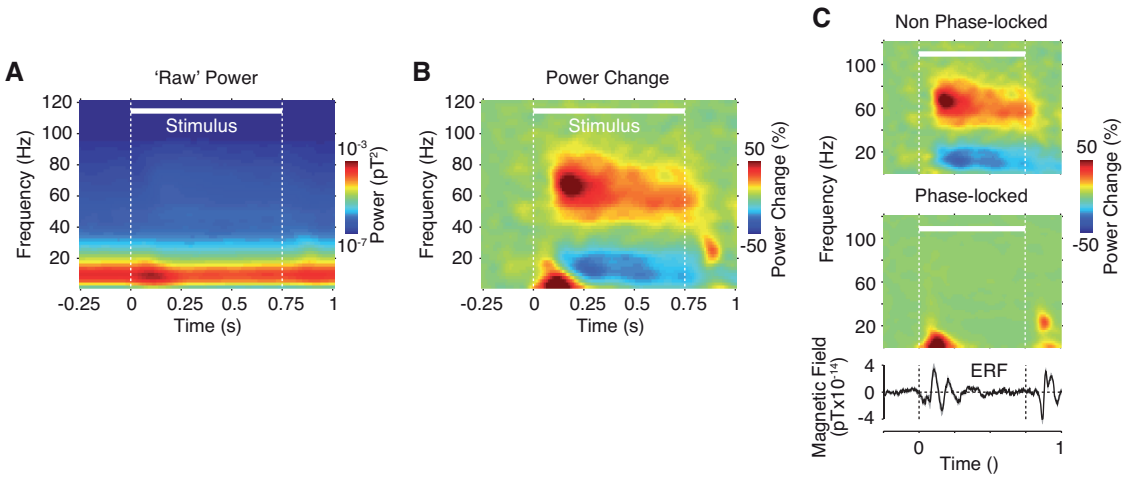

Figure 4.1.1. Illustration of the spectral analysis of human MEG responses (one occipital sensor) to a full-contrast drifting sine-wave grating presented for 750 ms. (**A**) Time-frequency representation of the *raw* MEG power, which exhibits the typical power law decay toward higher frequencies (1/frequency^n), masking the responses at high frequencies. (**B**) *Normalized* MEG response (percent power change relative to prestimulus baseline). By compensating for the power decay, this normalization reveals the high-frequency component of the stimulus response. (**C**) Dissociation of the response components phase-locked and non-phase-locked to stimulus onset. The stimulus-locked components correspond to the time-domain average of the MEG-signal that is displayed in the lower panel along with its time-frequency representation. The time-domain average only captures the transient phase-locked responses to stimulus on- and offset below 30 Hz. By contrast, the non-phase-locked components (upper panel) capture the prominent sustained responses induced by the stimulus: A power reduction in the 10–30 Hz range and a power enhancement in the 40–90 Hz range. The non-phase-locked response was isolated by subtracting the time-domain average from each trial before transforming the data into the frequency domain.

whose definition typically follows clinical EEG conventions: "delta" (2–4 Hz), "theta" (4–8 Hz), "alpha" (8–12 Hz), "beta" (12–30 Hz), and "gamma" (30–80 Hz). This taxonomy is derived from the logarithmically scaled peaks of spectral power that are often superimposed onto the overall power decay, and it appeals to the notion of distinct oscillators producing these spectral peaks. There are considerable inconsistencies in the exact definition of frequency bands across studies. Therefore, we will state the exact frequency ranges along with the band names used by the authors in our literature review below.

In this chapter, we will use the descriptive term "band-limited" activity to refer to neural activity in specific frequency ranges. The often-used term "oscillatory" activity implies that the measured signal is generated by a single oscillator, or by a system of coupled oscillators. Indeed, (see below, "Why do different frequency bands exhibit different functional properties?"), experimental evidence suggests that the brain contains specific neural mechanisms (cellular and circuit-based) that produce oscillatory behavior in neural networks. Nevertheless, the presence of band-limited modulations in the measured signals does not necessarily imply the presence of an underlying neural oscillation, for several reasons. First, population activity in a given frequency band may simply reflect the summation of relatively transient, nonperiodic signals with a specific spectral signature. For example, band-limited LFP power may reflect the summation of slow spike afterpotentials with dominant power in a specific frequency range (Buzsaki and Kandel, 1998). Second, apparently "band-limited" activity may also result from the superposition of broadband signals with band-limited effects specific to neighboring frequency ranges. For example, limb movements are typically associated with a high-frequency enhancement (50–200 Hz) and a low-frequency suppression (10–50 Hz) of the ECoG recorded over motor cortex (Crone et al., 1998a; Crone et al., 1998b; Miller et al., 2007). The high-frequency enhancement has commonly been interpreted as an induced gamma-band oscillation. However, principle component analysis (PCA) of movement-related ECoG activity revealed that the high-frequency enhancement in fact reflects a broadband (i.e., non-oscillatory) increase of 1/frequencyn activity, superimposed onto a movement-related decrease of low-frequency oscillations in the 10–50 Hz band (Miller et al., 2009). Analogous analyses will help to distinguish between oscillatory and non-oscillatory signals associated with other processes.

Phase-locked Versus Non-Phase-Locked Responses

Modulations of population signals correlated with external events can be classified according to the phase relationship between these events and neural activity (see Figure 4.1.1) (Pfurtscheller and Lopes da Silva, 1999; Tallon-Baudry and Bertrand, 1999). For example, the onset of a sensory stimulus leads to transient amplitude changes of neural activity that show a constant phase-relationship to stimulus onset across several repeats. However, sensory stimulation and cognitive tasks also induce sustained neural responses, which are not phase-locked to external events. Because of

their variable phase-relation to external events, time-domain averaging removes these response components. Thus, they are not reflected in the ERP. By contrast, spectral analysis allows for investigating non-phase-locked responses: First, the signal is transformed to the frequency- or time-frequency-domain on a single-trial basis. Then, the resulting complex spectrum is squared, which extracts the signal's power (i.e., variance) at a particular frequency, and discards its phase (Figure 4.1.1A). Eventually, power can be averaged across trials and normalized by a baseline-spectrum to account for the power decay toward high frequencies (Figure 4.1.1B).

For several reasons, the frequency domain is ideally suited for analyzing responses of electrophysiological population signals: First, cognitive processes often evolve over extended time periods (e.g., attention, short-term memory, decision-processes) and are thus often better reflected in sustained non-phase-locked response components than in transient phase-locked responses. Second, such cognitive processes are often not directly driven by external events (such as stimulus presentation). The corresponding neural responses are thus often not precisely aligned to external events and again better captured by sustained non-phase-locked responses. The analysis of ongoing activity unrelated to external events presents a special, and the most extreme, case for which, again, spectral analysis is ideally suited, but the ERP approach is, by definition, impossible.[2] We will here focus on task-related activity and thus not discuss studies of ongoing activity (reviewed by Laufs, 2008). Third, cognitive processes commonly display characteristic "spectral fingerprints" that presumably reflect the specific neural mechanisms and networks involved (see below, "Linking band-limited neural activity to behavior"). These fingerprints can be directly visualized in the frequency domain, which thus may provide a window into the neural mechanisms underlying the cognitive process under study.

When interpreting responses in the frequency domain, one needs to keep in mind that these reflect neural activity, which is both phase-locked and non-phase-locked to external events. Signals with sharp transients contain energy across a wide range of frequencies. Thus, ERPs are often reflected by transient broadband responses in the time-frequency domain, with significant power in the high frequency range, in the absence of a high-frequency oscillation. In other words, simply detecting significant power in any frequency band of the spectrum (e.g., "gamma") does not imply that the signal contains a neuronal oscillation in that frequency range. Furthermore, one needs to be cautious about electromagnetic activity from non-neuronal sources such as muscles that may be picked up by extracortical EEG/MEG sensors. For example, Yuval-Greenberg et al. (2008) demonstrated that the transient enhancement of spontaneous microsaccades, typically occurring around 200 ms after the onset of visual stimuli, causes a transient broadband increase of high-frequency power in the scalp EEG that is likely generated by ocular muscles. Fortunately, such artifacts have distinct spectral and temporal profiles that allow for dissociating them from the more sustained stimulus driven gamma-band responses (see Figures 4.1.1–4.1.3 and 4.1.5) (Fries et al., 2008a). This highlights the advantage of sustained stimulation protocols (stimulus durations of several seconds) as commonly used in single-unit physiology and fMRI. Furthermore, source-reconstruction or localization techniques and high-resolution eye-movement recordings will help rule out such artifacts.

Possible Functional Roles of Neuronal Phase Coherence

The band-limited power of population signals like LFP, EEG, or MEG primarily reflects neural activity that is locally synchronized across the spatial integration scale of the respective signal. More long-range synchronization of neural populations, e.g., between different brain regions, can be assessed by computing the phase consistency ("coherence") between pairs of simultaneously recorded signals (see also below, "Different windows into interactions between brain areas").

Dynamic adjustments of neuronal coherence may provide flexible mechanisms for regulating neuronal communication (Engel et al., 2001; Fries, 2005; Salinas and Sejnowski, 2001). First, synchronization of *presynaptic* spikes may enhance their functional impact on postsynaptic processing stages, and thus the effective connectivity between pre- and postsynaptic stages (König et al., 1996; Salinas and Sejnowski, 2001; Usrey and Reid, 1999). Theoretical (König et al., 1996; Salinas and Sejnowski, 2000; Shelley et al., 2002; Tiesinga et al., 2004) and experimental (Alonso et al., 1996; Azouz and Gray, 2000; Azouz and Gray, 2003; Bruno and Sakmann, 2006; Usrey et al., 1998) evidence suggests that cortical neurons act as "coincidence detectors": Presynaptic spikes that arrive synchronously on a millisecond time scale are more effective in driving a postsynaptic response than nonsynchronized inputs. In fact, neurons may be particularly sensitive to such synchronized synaptic input in regimens of high-conductance (Shelley et al., 2002) or balanced excitation and inhibition (Salinas and Sejnowski, 2000; Salinas and Sejnowski, 2001). Second, the phase alignment between *pre- and postsynaptic* processing stages in the cortex may also dynamically regulate their effective connectivity (Buzsaki and Draguhn, 2004; Fries, 2005; Womelsdorf et al., 2007): Subthreshold membrane potential oscillations induce rhythmic changes in neural excitability, and presynaptic spikes that are aligned to the excitable phase of such postsynaptic oscillations are more likely to drive spiking activity at the postsynaptic stage. In light of these biophysical considerations, it is of great interest to investigate whether the cortex in fact dynamically adjusts the local or long-range coherence of

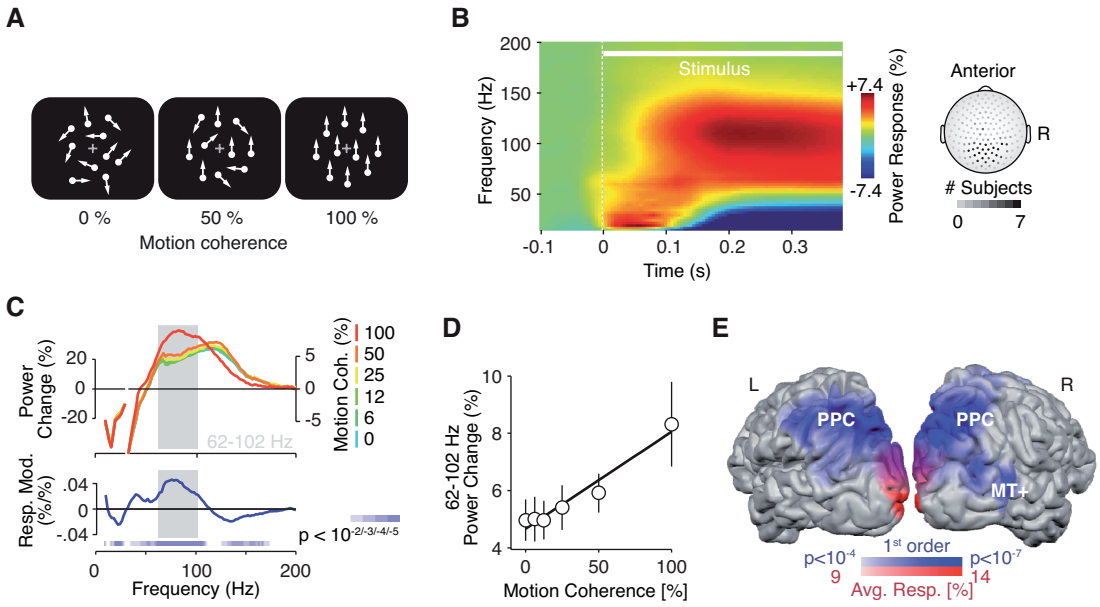

Figure 4.1.2. Modulation of band-limited MEG-activity by visual motion strength. Subjects viewed dynamic random dot patterns of different levels of motion strength. (**A**) "Motion coherence" (fraction of coherently moving dots) determines the strength of the visual motion signal. (**B**) Time-frequency response (percent power change relative to prestimulus baseline) across 30 MEG–sensors (indicated on the scalp projection). Stimuli induced a sustained broadband power enhancement in the gamma band (50–150 Hz) and a suppression below 50 Hz. Note the higher and broader gamma response as compared to moving gratings (Figure 4.1.1B). (**C**) Top panel: Spectral distribution of responses (100–500 ms past stimulus onset) for each level of motion coherence. Responses are scaled separately for frequencies below and above 30 Hz. Lower panel: Linear modulation of the response by motion coherence (percent response per percent motion coherence). The gray band (62–102 Hz) marks the strongest modulation. (**D**) 62–102 Hz responses as a function of motion coherence, evaluated with a linear fit. (**E**) Cortical distribution of the average 62–102 Hz response across all levels of motion coherence (red overlay) and of its linear modulation by visual motion strength (blue overlay). While the strongest average response was located around the calcarine, the linear modulation was maximally expressed in posterior parietal cortex (PPC) and the human motion-sensitive area MT+.(Reprinted and modified with permission from Siegel et al. (2007).)

neural oscillations for regulating information flow, for example during selective attention or decision-making.

Phase coherence may not only regulate neural communication, but also play an important role for neural coding of information. Evidence suggests that the phase of neural oscillations may provide scaffolding for information coding by the spikes of individual neurons (Kayser et al., 2009; Lee H et al., 2005; Montemurro et al., 2008; Siegel et al., 2009). For example, while monkeys remembered complex visual objects over a brief delay, spikes were synchronized to prominent theta-band (4–8 Hz) oscillations of the LFP in extrastriate visual area V4 (Lee H et al., 2005), i.e., spikes preferentially occurred at a specific theta-phase. Notably, not all spikes were equally informative about memory content, but those at the preferred theta-phase of spiking conveyed most information about the remembered objects. In monkey prefrontal cortex, spikes conveyed most information about two objects simultaneously held in short-term memory at specific phases of the mid-frequency (20–50 Hz, beta and gamma) LFP (Siegel et al., 2009). Notably, the most informative phases differed between the two remembered objects. Finally, stimulus-driven spiking activity in sensory cortices also conveys more information when its timing relative to slow (<8 Hz) LFP fluctuations is taken into account (Kayser et al., 2009; Montemurro et al., 2008). In sum, the information conveyed by individual cortical neurons seems to depend critically on their spike timing, relative to coherent activity of the surrounding neural population. It is an exciting question for future research to which extent, and in which systems, the brain utilizes such a "phase-dependent coding" scheme.

Source Reconstruction of Band-Limited EEG/MEG Activity

A major challenge for understanding the functional role of band-limited population activity and relating it to fMRI responses is the comparison of results across species and spatial scales. At the sensor-level, EEG and MEG signals reflect a coarse summation of cortical activity and thus provide only limited information about the exact cortical regions involved. Reconstruction of cortical source-level activity from the sensor-level data is a critical step in relating EEG/MEG to intracortical electrophysiological or fMRI signals. Recent methodological advances yielded tools that are particularly well suited to estimate source-level activity from EEG or MEG data in the frequency domain. Specifically, adaptive linear spatial filtering techniques based on

the "beamforming" approach allow for estimating the power and coherence of cortical population activity across the brain (Gross et al., 2001; Liljestrom et al., 2005; Van Veen et al., 1997). The spatial resolution of these techniques depends on the number of MEG/EEG sensors, the signal-to-noise ratio of the recorded signals, and the number of underlying cortical sources. Estimates of the spatial resolution are on the order of a few centimeters, or below for currently available recording techniques (Gross et al., 2003).

Linking Band-Limited Neural Activity to Behavior

In this section, we will review studies relating band-limited cortical population activity to specific sensory and cognitive processes, focusing on visual tasks and the primate brain. Rather than providing a comprehensive review, we will try to identify general principles underlying the spectral fingerprints of specific functional processes. To this end, we will contrast stimulus-driven signals in sensory cortex with intrinsically generated activity produced by recurrent cortical interactions and ascending neuromodulators during higher-level cognitive processing. This distinction is certainly an oversimplification, but it constitutes a very useful heuristic for sorting recent results.

Stimulus-Driven Activity in Visual Cortex

Several studies have identified the frequency ranges of cortical mass activity that exhibit, first, selectivity for visual features (such as contour orientation or motion direction), and second, dependence on feature strength (such as luminance contrast or motion coherence).[3] These studies suggest that neural gamma-band activity reflects visual features.

Neural population responses in early visual cortex induced by visual stimuli exhibit a characteristic spectral signature. Activity is enhanced in a broad gamma band from about 30 Hz to well above 100 Hz and suppressed below 30 Hz (e.g., in the alpha and beta band, 8–30 Hz; see Figures 4.1.1, 4.1.2, 4.1.3, and 4.1.5). In particular the stimulus-driven gamma-band enhancement is consistently measured in early visual areas ranging from LFPs in cats (Brosch et al., 1995; Eckhorn et al., 1988; Gray et al., 1989; Gray and Singer, 1989; Kayser and König, 2004; Siegel and König, 2003) and monkeys (Belitski et al., 2008; Berens et al., 2008; Frien and Eckhorn, 2000; Frien et al., 2000; Henrie and Shapley, 2005; Liu and Newsome, 2006; Logothetis et al., 2001) to human EEG or MEG (Donner et al., 2007; Fries et al., 2008a; Gruber et al., 1999; Hall et al., 2005; Hoogenboom et al., 2005; Siegel et al., 2007; Siegel et al., 2008; Van Der Werf et al., 2008; Wyart and Tallon-Baudry, 2008). By comparison, in invasive recordings the low-frequency suppression is found less consistently than in non-invasive recordings. Microelectrode recordings suggest that the gamma-band response reflects synchronized oscillations of local neuronal ensembles. The strength of synchronization between neurons correlates with the similarity of their receptive fields and tuning properties (Brosch et al., 1995; Eckhorn et al., 1988; Frien and Eckhorn, 2000; Frien et al., 2000; Gray et al., 1989; Gray and Singer, 1989; Nir et al., 2007; Siegel and König, 2003). Hence, the amplitude of the local gamma-band LFP is tuned for specific sensory features and its tuning preference corresponds to the averaged selectivity of the neural population contributing to the gamma-band LFP. In primary visual cortex, the gamma-band LFP is selective for stimulus orientation (Berens et al., 2008a; Frien et al., 2000; Gray and Singer, 1989; Kayser and König, 2004; Siegel and König, 2003), spatial and temporal frequency (Kayser and König, 2004), and ocular dominance (Berens et al., 2008a). In monkey area MT, the gamma-band LFP is selective for motion direction and speed (Liu and Newsome, 2006). This selectivity is typically confined to a frequency range from about 50 to 100 Hz. In addition to the gamma band, several studies reported a second, weaker feature-selective frequency range from about 8 to 25 Hz. (Berens et al., 2008a; Kayser and König, 2004; Liu and Newsome, 2006; Siegel and König, 2003).

Comparison of LFP-selectivity across different kinds of visual features provides insight into the spatial integration properties of the LFP. Liu and Newsome (2006) observed that LFP responses to moving stimuli in area MT were selective for speed at higher frequencies (> 80 Hz) than for direction (> 40 Hz). Neurons with the same speed preference cluster in small groups of 500 m diameter, whereas neuronal clusters ("columns") of the same direction preference span up to 2000 m perpendicular to the cortical surface. The authors concluded that lower LFP frequencies reflect neuronal activity integrated across a broader spatial scale, explaining the loss of speed information, but the persistence of direction information. This is consistent with findings from monkey V1, where ocular dominance is organized on a broader spatial scale than orientation tuning: The LFP reflects ocular dominance at frequencies above 30 Hz, but preferred orientations only at above 80 Hz (Berens et al., 2008a). These findings suggest that the high-frequency LFP (>80 Hz) reflects more local activity as compared to the more widespread activity reflected at gamma frequencies from about 30 to 80 Hz.

The EEG and MEG do not provide sufficient spatial resolution to delineate feature selectivity *within* a given cortical region (e.g., orientation columns in V1 or direction columns in MT). Thus, electrophysiological studies in humans have focused on how population responses are modulated by the *strength* of sensory features. Consistent with the above data on feature-selectivity, these demonstrate enhanced gamma-band activity with increasing strength of

visual features. Combining human MEG and source-reconstruction, Hall et al. (2005) found robust visual responses in the gamma band (30–70 Hz), localized around the calcarine sulcus (i.e., area V1), and increasing monotonically with stimulus contrast, consistent with LFPs in monkey V1 (Henrie and Shapley, 2005; Logothetis et al., 2001). These findings accord well with a human MEG study that characterized the modulation of neural activity by strength of visual motion (Figure 4.1.2) (Siegel et al., 2007). The strongest increase of neural activity with strength of motion occurred in the gamma band (60 to 100 Hz). Lower frequencies (10–30 Hz) showed a slightly weaker opposite relationship. The strongest mean gamma-band response was located in area V1, but the *modulation* of the response by motion strength prevailed in motion-sensitive areas in extrastriate cortex, such as area MT+ and the intraparietal sulcus (Figure 4.1.2). Thus gamma-band activity is specifically modulated in the cortical systems processing a specific visual feature.

In sum, a highly consistent picture emerges: In early visual areas, visual stimuli enhance population activity in the gamma band (30–150 Hz) and suppress population activity in the alpha and beta bands (8–30 Hz). The stimulus-driven gamma-band activity is tuned for specific sensory features and increases monotonically with feature intensity. The neural mechanisms underlying this spectral fingerprint of stimulus driven activity are becoming increasingly clear (see also "Types of Neural Networks" below). The low-frequency suppression may reflect the disruption of widespread ongoing activity involving reverberation in cortico-thalamic loops (Pfurtscheller and Lopes da Silva, 1999; Steriade 2000). By contrast, local gamma-band activity involves fast recurrent interactions between excitation and inhibition within local, activated cortical networks (Bartos et al., 2007; Cardin et al., 2009; Hasenstaub et al., 2005; Sohal et al., 2009). This mechanistic understanding of the spectral fingerprint of stimulus-driven activity stands in contrast to the comparatively poor understanding of the spectral fingerprints of more intrinsic functional processes that we will discuss in the following sections.

Perception-Related Activity in Visual Cortex

We will now discuss modulations of neural activity in visual cortex that are correlated with perception rather than with changes of the sensory input. We focus on two prime examples of such perception-related activity: First, activity correlated with spontaneous fluctuations of conscious perception, and second, the modulation of neuronal responses by selective attention. The spectral fingerprints of these processes are more complex than the stimulus-driven responses discussed above.

Perceptual phenomena, which evoke fluctuating perceptual experience in the face of constant sensory stimuli, provide ideal tools for isolating patterns of neural activity that are specifically associated with conscious visual perception (Kim and Blake, 2005). For example, during prolonged viewing of bistable stimuli (such as the "vase-face" illusion), our perception switches spontaneously between two distinctly different states (Blake and Logothetis, 2002). Similarly, stimuli near the psychophysical detection threshold are sometimes seen and sometimes not (Green and Swets, 1966). A number of electrophysiological studies in monkeys and humans have used such psychophysical tools to establish links between band-limited cortical population activity and perception. Monkey LFP studies suggest that gamma-band (about 50–100 Hz) responses in extrastriate visual cortical areas (such as MT and V4) correlate with conscious perceptual reports; this holds for both bistable and near-threshold stimuli (Liu and Newsome, 2006; Wilke et al., 2006). Thus, the gamma-band LFP is not only stimulus-selective, but also seems to reflect subjects' conscious perception of these stimuli.

But two further observations suggest that the picture is more complex than the one for stimulus-driven activity. First, in V1, modulations of the low frequency (<30 Hz) activity exhibit a *positive* correlation with visual awareness during bistable perceptual suppression phenomena (Gail et al., 2004; Wilke et al., 2006). This contrasts sharply with the typical stimulus-induced suppression of low-frequency activity; it might reflect feedback from extrastriate areas (Gail et al., 2004; Wilke et al., 2006). Second, in extrastriate areas, the low frequency LFP was negatively correlated with visual motion perception in a fine discrimination task (Liu and Newsome, 2006), but positively correlated with the perceptual suppression of a salient visual target (Wilke et al., 2006). Such differences between visual phenomena might provide hints to the specific mechanisms mediating the fluctuations of perception under the different conditions. Further studies are required to gain more insights into the significance of such perception-related LFP modulations.

Another important step in this field of research will be the regular use of protocols designed for isolating conscious perception from attention (Huk et al., 2001; Koch and Tsuchiya, 2007; Lamme, 2003), which have often been conflated. A recent MEG study provides an excellent example for such a successful dissociation (Wyart and Tallon-Baudry, 2008), suggesting that spatial attention and conscious perception have distinct spectral fingerprints within the gamma band (Figure 4.1.3). MEG activity in the range from 54 to 64 Hz was larger over visual cortex when subjects detected a faint visual target stimulus than when they did not, irrespective of the locus of attention. By contrast, the spatially specific effect of an endogenous cue (directing subjects' attention to the left or right visual hemifield) was expressed in a higher frequency range (76–90 Hz). Interestingly, these two dissociated, and relatively narrow band

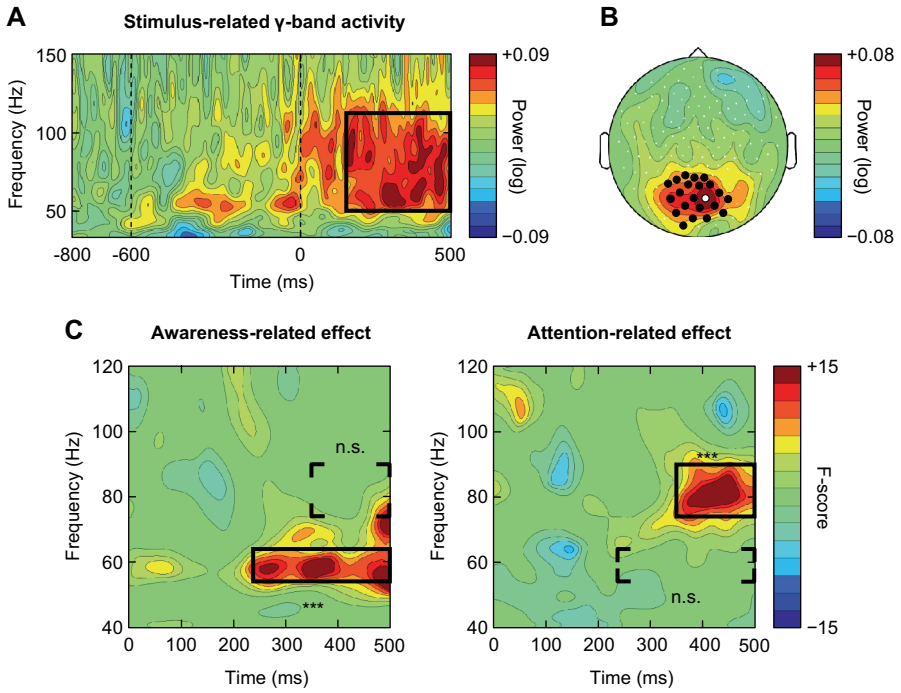

Figure 4.1.3. Dissociated spectral fingerprints of spatial attention and visual contrast detection. (**A**) Time-frequency representation of the high-frequency MEG response (in log power) of one occipital MEG sensor to low contrast gratings near psychophysical detection threshold. Following a central cue to the left or right, a grating was presented for 0.4 s in either the left or right hemifield, or no stimulus was presented at all. The first vertical line indicates cue onset, stimulus onset is at 0 ms. Subjects reported the presence/absence of the target stimulus after a variable delay. The faint grating stimuli induced an MEG response in the high gamma (50–110 Hz) range. Note the similarity to the gamma-band responses shown in Figure 4.1.1B. (**B**) Scalp topography of the high gamma-band response (50–110 Hz, 50–110 ms after stimulus onset, black box in A), averaged across left and right hemifield stimuli. Gamma-band responses were expressed over posterior sensors overlying visual and parietal cortex. The sensors marked with the peak response in black constitute the ROI for averaging responses in C. (**C**) Effects of target detection ("awareness-related") and of spatial cue ("attention-related") on the high-frequency MEG-response (statistical F-maps; ***$p < 0.001$ corrected: n.s., nonsignificant effect).(Reprinted with permission from Wyart and Tallon-Baudry (2008).)

effects of detection and cue were superimposed onto the typical broadband, stimulus-driven gamma-band response from about 50 to above 100 Hz, suggesting distinct underlying mechanisms. The detection-related modulation in the 54–64 Hz range predicted subjects' "target present" reports even on "target absent" trials (that is, when their perceptual reports were inaccurate). This further suggests that this modulation did not simply reflect attention. Since, the authors focused their analyses on the gamma band (30–150 Hz), it is unknown whether the lower frequency activity also correlated with subjects' perceptual reports, in a similar way as in monkey V1 (see above).

Neuronal responses in visual cortex to constant sensory input can also be affected by instructing subjects to shift attention from one location or stimulus feature to another (Desimone and Duncan, 1995). Several monkey LFP studies and human EEG/MEG studies have characterized the spectral signature of the "top-down" modulation of neural activity in visual cortex by selective attention. During stimulus processing, spatially selective and feature-based attention enhance gamma-band activity (30–100 Hz) in the human MEG and EEG (Gruber et al., 1999; Muller and Keil, 2004; Siegel et al., 2008; Wyart and Tallon-Baudry, 2008) and macaque area V4 (Bichot et al., 2005; Fries et al., 2001; Fries et al., 2008; Taylor et al., 2005). By contrast, before presentation of a visual stimulus, spatial attention induces a widespread suppression of alpha-band activity across visual cortex, demonstrated again in both human EEG/MEG (Siegel et al., 2008; Thut et al., 2006; Worden et al., 2000; Wyart and Tallon-Baudry, 2008) and macaque area V4 (Fries et al., 2001; Fries et al., 2008b). Before and during stimulus presentation, the strength of these attentional modulations predicts the accuracy (Siegel et al., 2008; Taylor et al., 2005) and speed (Thut et al., 2006; Womelsdorf et al., 2006) of behavioral reports. Thus, rather than being constant or stimulus-independent, the spectral fingerprint of selective attention in visual cortex seems to depend strongly on the presence of a visual input. This suggests that band-limited activity in these regions reflects the result of a complex interaction between "bottom-up" and "top-down" signals.

The spectral fingerprint may also differ substantially between different processing stages within visual cortex (Siegel et al., 2008). By means of MEG source-reconstruction, Siegel et al. (2008) were able to separate attentional modulations in visual cortical areas V1/V2 and

MT+. Area MT+ showed attentional effects in accordance with the findings from sensor-level EEG/MEG and monkey V4 studies discussed above: Prestimulus activity was strongly suppressed in the alpha (5–15 Hz) and beta (15–35 Hz) band, while attention enhanced broadband gamma-band activity (35–100 Hz) during stimulation. By contrast, in V1/V2 attention selectively *enhanced* activity in the beta band (15–35 Hz) during stimulation and, *surprisingly*, suppressed high gamma-band activity (60–100 Hz) before stimulus onset. Thus, the spectral fingerprint of attentional modulation does not only depend on the presence of sensory input, but may also vary qualitatively between cortical processing stages. Further studies are needed to compare attentional modulations between processing stages, and to characterize their interaction with bottom-up signals. Further, a closer integration of findings between monkey and human studies is needed, which can be accomplished by the use of common experimental protocols and source-reconstruction of non-invasively recorded data.

Integrative Processes in Frontal and Parietal Association Cortex

We now turn to processes at the interface between perception and action: The control of attentional selection and the flexible mapping of perceptual representations onto voluntary actions (sensorimotor integration and decision-making). These processes are related at a functional level, and they seem to engage an overlapping network of regions in prefrontal and posterior parietal association cortex (Corbetta and Shulman, 2002; Desimone and Duncan, 1995; Gold and Shadlen, 2007; Kastner and Ungerleider, 2000; Miller and Cohen, 2001; Schall, 2001). In particular, a large number of neuroimaging studies have implicated two cortical association regions in the control of attention: the intraparietal sulcus in posterior parietal cortex, and the frontal eye fields in prefrontal cortex (Corbetta and Shulman, 2002; Donner et al., 2000; Kastner and Ungerleider, 2000; Moore et al., 2003; Serences and Yantis, 2006). Several recent studies have demonstrated that attention modulates band-limited activity within these regions, as well as their long-range coherence. However, the spectral profile of these effects differed markedly between studies. It remains to be clarified by future studies whether these discrepancies reflect differences in behavioral tasks, analysis methods, or the cortical regions under study.

In the macaque lateral intraparietal area (LIP), attention enhances population activity in the beta and low gamma band (25–45 Hz), while boosting coherence between areas MT and LIP in a broad alpha and beta frequency range (10–35 Hz) (Saalmann et al., 2007). This dissociation between effects of attention on local processing and on inter-regional coherence is consistent with the MEG results from Siegel et al. (2008) discussed above (see "Perception-related activity in visual cortex"). In this study, attention enhanced gamma-band coherence (35–100 Hz) and suppressed alpha- and beta-band coherence (5–35 Hz) between the intraparietal sulcus, frontal eye fields, and MT+ independent of visual input. This stimulus independent spectral profile stands in sharp contrast to strongly stimulus dependent modulation of local band-limited activity in MT+ and the intraparietal sulcus. Further, these modulations of inter-regional coherence contrast with an attentional suppression of beta-band (15–35 Hz) activity in the frontal eye fields. The latter results underline the regional specificity of attentional modulation in cortex.

The spectral fingerprints of attention also vary between different modes of attentional control. Buschman et al. (2007) compared the spectral profile of frontal-parietal coherence in macaques between visual search guided by "top-down" information (a target held in working memory)

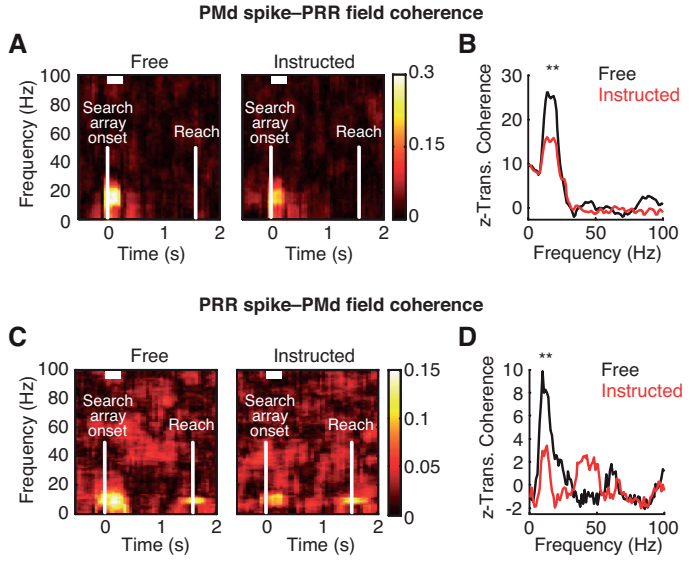

Figure 4.1.4. Frontal-parietal coherence around 15 Hz reflects decision-making during motor planning. (**A**) Time-frequency representation of coherence between spikes in the dorsal premotor area (PMd) and the LFP in the parietal reach region (PRR) during free (left panel) and instructed (right panel) search. See main text for details of the task. Neuronal activity is aligned to search array onset. The second vertical bar marks the average time of the first reach. The horizontal bar at the top shows the analysis window for panel B. (**B**) Spectra of z-transformed coherence between PMd spikes and the PRR LFP directly after search array onset. (**C**) and (**D**) display the same analyses as panels (A) and (B) but for spikes in PRR and the LFP in PMd. (**; $p < 0.05$).(Reprinted by permission from Pesaran B, Nelson MJ, Andersen RA (2008) Free choice activates a decision circuit between frontal and parietal cortex. Nature 453:406–409. Copyright Macmillan Publishers Ltd. (2008).)

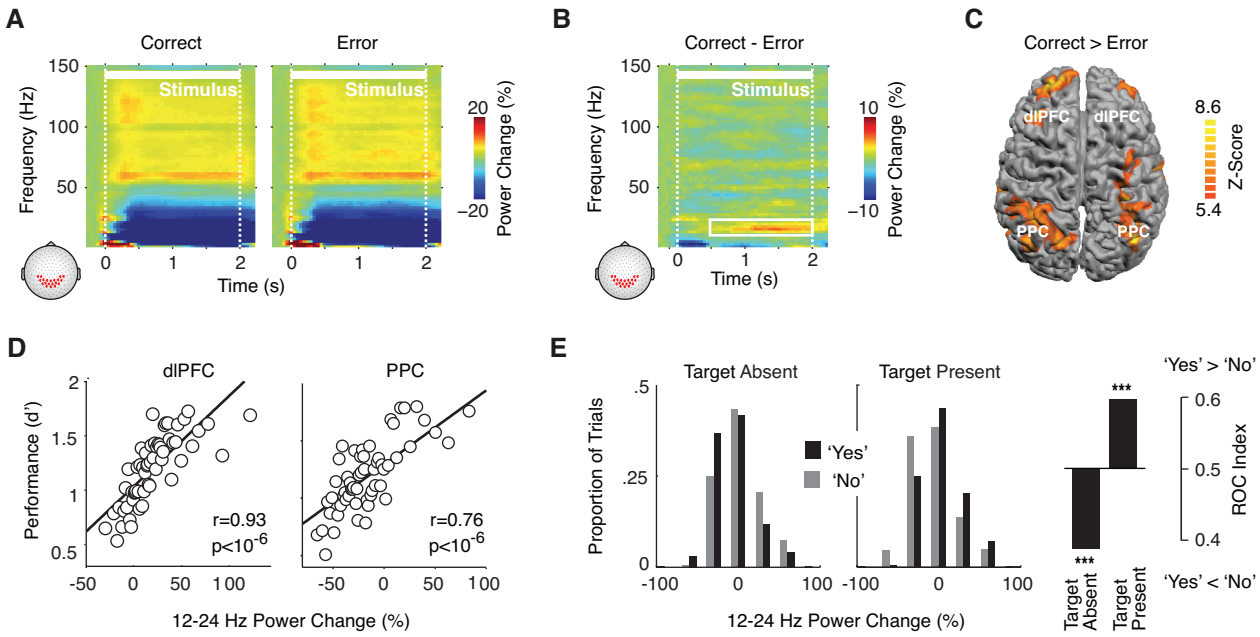

Figure 4.1.5. Frontal-parietal 12–24 Hz activity predicts correct perceptual decisions. (**A**) Time-frequency representations of MEG responses (percent power change relative to baseline) to moving random dot patterns (average across 20 sensors marked in red). Stimuli were presented for 2 s while subjects judged the presence of a weak coherent motion target signal embedded in dynamic noise. They indicated their "yes/no" decision by button press after a variable delay (0.5–1 s). The steady-state response at 60 Hz was phase-locked and driven by the large fraction of "noise" dots flickering at that frequency. The moving dot patterns induced a sustained enhancement of MEG power in the high gamma range (50–150 Hz) and suppression in the low frequency range (8–50 Hz) before both correct and incorrect decisions. (**B**) Difference between correct and incorrect decisions. 12–24 Hz (beta) range activity (white box) was enhanced before correct decisions, specifically during stimulus viewing; this effect was superimposed onto the more broadband stimulus-induced suppression. (**C**) Cortical distribution of performance-predictive 12–24 Hz activity during stimulus viewing, based on beamforming (statistical Z-map). (**D**) Trial-to-trial fluctuations of 12–24 Hz activity during stimulus viewing in dlPFC and PPC were tightly correlated with detection performance (d'). Trials are binned by response magnitude (200 trials per bin). (**E**) Left. Single-trial 12–24 Hz response distributions for the dlPFC of an example subject, sorted according to perceptual report and target absent/present conditions. Right. ROC-indices quantifying the overlap between response distributions. An index of 0.5 indicates perfect overlap, larger than 0.5 indicate "yes" > "no," and smaller than 0.5 indicate "yes" < "no" (***$p < 0.001$, permutation test).(Reprinted and modified with permission from Donner et al. (2007).)

and attention guided by "bottom-up" stimulus saliency. In general, attention broadly enhanced coherence from about 15 to 70 Hz, but coherence was higher in the beta range (22–34 Hz) for "top-down" attention and higher in the low gamma range (35–55 Hz) for "bottom-up" attention. Thus, different modes of attentional control entail different modes of frontal-parietal communication, with distinct spectral fingerprints. These differences might reflect different directions of information flow (i.e., frontal to parietal in "top-down" mode and vice versa in "bottom-up" mode) or different neuronal subpopulations engaged in the two modes.

Large-scale electrophysiological recordings have also characterized the neural basis of sensorimotor integration and decision-making. These processes seem to involve frontal-parietal activity in lower and intermediate (alpha and beta) frequency ranges (Brovelli et al., 2004; Buschman and Miller, 2007; Donner et al., 2007; Gross et al., 2004; Pesaran et al., 2008; Rubino et al., 2006). This line of evidence is well illustrated by a study (Pesaran et al., 2008) correlating neural activity between posterior parietal and dorsal premotor cortex while monkeys planned of a series of reach movements (Figure 4.1.4). In the condition of interest ("free search"), the animals were free to choose the sequence of movements. In the control condition ("instructed search"), a stimulus array instructed a particular sequence of movements. Coherence between spikes in premotor cortex and LFPs in the parietal reach region, and vice versa, increased transiently after the onset of the stimulus array (i.e., in the period of the trial in which monkeys formed their decision about the sequence of reaches). This effect occurred in the low frequency range (peaking at around 15 Hz) and was stronger during "free" than "instructed" search. Thus, decision-making seems to activate long-range coupling between the nodes of a large-scale frontal-parietal network. Further, the latency difference between the responses of each area (about 30 ms), as well as the spike-LFP coherence in both directions, further suggested that premotor cortex was influencing parietal cortex and the decision process in a feedback fashion.

Further support for the relevance of beta-band activity in decision-making comes from human MEG studies of different visual detection processes (Donner et al., 2007; Gross et al., 2004). During a motion detection task, trial-to-trial fluctuations of MEG activity in the 12–24 Hz range

predicted correct perceptual choices of the subjects (Figure 4.1.5). This predictive activity was expressed in a widespread cortical network comprising frontal, parietal, and visual cortex. It did not just reflect slow fluctuations of subjects' arousal state, but was specifically expressed during the stimulus interval. Similarly, during the "attentional blink" phenomenon[4], 13–18 Hz MEG activity in frontal, parietal, and visual cortex, as well as their coherence, predicted successful target detection (Gross et al., 2004).

Importantly, the 12–24 Hz activity predicted the accuracy of subjects' "yes/no" detection decisions, irrespective of their content ("yes/no"): On target-present trials, the activity tended to be higher before "yes" than before "no" choices (i.e., "hits" > "misses"), whereas, on motion-absent trials, it showed the opposite relation to the "yes/no" choice (i.e. "correct rejects" > "misses"). Thus, the 12–24 Hz activity does not reflect a cortical *representation* (of the target or of an abstract decision variable), but the *mechanism* transforming this representation into a motor plan (deCharms and Zador, 2000).

What might be this mechanism? In many cases, perceptual decision-making involves the accumulation of "sensory evidence" over time, which in turn seems to be mediated by persistent neuronal activity (Gold and Shadlen, 2007). As originally suggested by Hebb (1949), persistent neural activity in cortex might be established by reverberant activity within local and long-range networks. Reverberant activity can be reflected in oscillations as measured by neural population signals (Wang, 2001). Indeed, several studies explicitly probing the neural correlates of short-term memory in frontal, parietal, and visual cortex found these to be specifically expressed in similar beta frequency ranges (Tallon-Baudry et al., 2001; Tallon-Baudry et al., 1998; Tallon-Baudry et al., 2004).

To sum up, the most consistent spectral fingerprints of population activity are observed for stimulus-driven activity in sensory cortex. Sensory stimulation generally induces stimulus-specific increases of gamma-band power and (less specific) decreases in low-frequency power. Similar principles seem to apply to movement-selective activity in motor cortex (Crone et al., 1998a; Crone et al., 1998b; Miller et al., 2007; Rickert et al., 2005; Spinks et al., 2008). By contrast the spectral fingerprints of higher cognitive processes (such as attention or decision-making) appear more complex. We suggest that one reason for this discrepancy might be that the latter processes involve strong recurrent interactions, within and between distant cortical networks, and various neuromodulators interacting with these cortical processes. In addition, the spectral fingerprints might also differ systematically between sensory cortex on the one hand and association cortices on the other hand, perhaps reflecting distinct network properties. In light of present evidence these ideas remain largely speculative, but we can address the more general question of what can be inferred from neural population activity in the different frequency bands.

Why Do Frequency Bands Exhibit Specific Functional Properties?

Several previous accounts of cortical frequency bands have mapped coarsely defined psychological concepts (e.g. "cognitive binding") onto specific frequency bands (such as the "gamma-band"). This approach bears some similarity to the "neo-phrenological" approach in functional neuroimaging, which aims at labeling each region of the cerebral cortex with a specific cognitive process (Friston, 2002; Nichols and Newsome, 1999). We think that it will be more fruitful to approach the question at a basic neurophysiological level (i.e., the properties of individual neurons and neuronal circuits). Do the spectral fingerprints of functional processes provide hints toward the specific neural computations underlying these processes?

Spatial Scales of Measurements and Neural Networks

To understand the significance of LFP or EEG signals in particular frequency bands, we need to consider how these signals emerge from the activity of individual neurons and their interactions. In particular, what is the relationship between signals measured at different spatial scales?

The phase-coherence of simultaneously recorded LFPs decreases with cortical distance, and coherence declines faster for higher as for lower frequencies (Frien and Eckhorn, 2000; Leopold et al., 2003). Further, feature selectivity of the LFP is confined to higher frequencies for sensory features that are represented in more local cortical clusters (Berens et al., 2008a; Liu and Newsome, 2006). These results could either reflect broader spatial scales of neural interaction at lower frequencies (i.e., an *active* process) or simply the biophysical principles governing *passive* signal propagation in the cortex. In other words, the effect could simply be caused by a stronger attenuation of high-frequency signals in the cortex, which would result in the LFP reflecting activity over a broader spatial scale at lower frequencies. Measurements of the frequency dependent cortical impedance argue against the latter explanation (Logothetis et al., 2007). Over the relevant frequency range, the impedance-spectrum along the cortical surface is largely flat within each cortical layer. This implies that the LFP propagates equally well across different spectral components, which, in turn, suggests that the frequency dependent decay of LFP coherence and feature selectivity indeed reflect more local synchronization at higher frequencies compared to more widespread synchrony at lower frequencies.

This relation between spatial scale and frequency is also supported by theoretical studies. It has been suggested that, for spatially more separate neural ensembles, longer conduction delays may constrain oscillatory interactions to lower frequencies (König and Schillen, 1991; Kopell et al., 2000), consistent with several invasive animal studies and non-invasive studies in humans: Long-range, inter-regional synchronization is typically expressed at frequencies below 40 Hz (Brovelli et al., 2004; Gross et al., 2004; Pesaran et al., 2008; Roelfsema et al., 1997; Saalmann et al., 2007; Sarnthein et al., 1998). However, some studies found also synchronization between distant brain areas well above 40 Hz (Buschman and Miller, 2007; Engel et al., 1991; Siegel et al., 2008).

Considering the spatial scale (or spatial resolution) of measured signals is also particularly important for the interpretation of the MEG and EEG. Despite the application of advanced source-reconstruction techniques, the spatial resolution of EEG/MEG is likely one order of magnitude coarser than the resolution of the LFP. Thus, changes in the spatial structure of synchronized population activity can lead to different effects for LFP signals on the one hand and EEG/MEG signals on the other hand. Suppose a visual stimulus reduces frequency specific synchronization on a broader spatial scale of a few millimeters along the cortical surface, but has little effect on synchrony on a more local scale of less than one millimeter. Then, the power of the LFP will show little decrease. By contrast, the coarser spatial resolution of the non-invasive recordings will lead to a more prominent power reduction for EEG/MEG signals. Such an effect could explain an apparent discrepancy between LFP and MEG/EEG studies of visual stimulus responses: For the EEG or MEG visual stimulation induce a strong suppression of low-frequency activity over wide, posterior brain regions (Donner et al., 2007; Hoogenboom et al., 2005; Siegel et al., 2007; Siegel et al., 2008; Tallon-Baudry et al., 1998), whereas this suppression is typically weaker, or even absent, for the LFP (Belitski et al., 2008; Berens et al., 2008a; Henrie and Shapley, 2005; Lee H et al., 2005; Liu and Newsome, 2006; Siegel and König, 2003).

Types of Neural Networks

It becomes increasingly clear that the spectral profile of neural population activity is critically determined by biophysical properties on the cellular and network level. An intensely investigated example is the mechanism underlying the cortical spindle activity (8–14 Hz) observed during slow-wave sleep (Destexhe and Sejnowski, 2003; Llinas and Steriade, 2006). Detailed in vivo and in vitro studies at the cellular and network level, combined with numerous modeling studies, underline the importance of intrinsic cellular properties of thalamic neurons for the generation of these rhythms. Thalamocortical (TC) relay cells and thalamic reticular (RE) neurons are equipped with voltage-dependent conductances that support intrinsically oscillating firing patterns. However, the spindle-activity observed in vivo does not only depend on these intrinsic cellular properties. Instead, such activity results from the interactions between these thalamic cell types as well as between thalamic and cortical neurons within large-scale cortico-thalamic loops (reviewed in Destexhe and Sejnowski, 2003).

Local, synchronized gamma-band activity in the cortex provides another prime example: Inhibitory interneurons play a key role for this type of activity. Networks of synaptically and electrically (gap-junctions) coupled interneurons engage in rhythmic gamma-band activity (Bartos et al., 2007; Whittington et al., 1995). Throughout the cortex, inhibitory neurons interact with excitatory cells in local excitatory-inhibitory loops, in which they entrain and synchronize excitatory cells in a rhythmic fashion. Within each oscillatory cycle, excitatory neurons spike with a sufficient decline of network inhibition during the depolarizing phase of the LFP. This triggers the firing of inhibitory neurons, which, in turn, shuts down excitatory neurons in a synchronized fashion until inhibition decays and the next cycle begins. Strong evidence for this mechanism has been obtained from the rodent hippocampus (Csicsvari et al., 2003) and the prefrontal cortex of anesthetized ferrets (Hasenstaub et al., 2005). Furthermore, two recent studies provided direct causal evidence for this mechanism by optogenetic manipulation of fast-spiking interneurons (Cardin et al., 2009; Sohal et al., 2009). The peak frequency and bandwidth of these local gamma-band processes seem critically determined by the cellular properties of the participating neurons (Bartos et al., 2007). It remains open to which extent this also holds for other types of neural oscillations.

Gieselmann and Thiele (2008) provided indirect evidence that gamma-band activity of the LFP indeed reflects the underlying inhibitory activity. The authors recorded spiking activity and LFPs in V1 of behaving monkeys presented with visual gratings of variable size. Gratings extending beyond the summation area of receptive fields inhibited spiking activity (presumably due to lateral inhibition), while the LFP gamma-band activity increased monotonically for all grating sizes. Thus, rather than reflecting only excitatory drive, the gamma-band LFP seems to reflect the oscillatory interaction between local excitation and inhibition. The fact that band-limited population activity reflects excitatory-inhibitory interactions, and active processing within specific functional networks, rather than mere average levels of excitation seems particularly important if one aims to link band-limited cortical population activity to the fMRI signal.

Linking Band-Limited Neural Activity to fMRI

We will now discuss attempts to uncover the relationship between band-limited neural activity (as measured by the LFP, EEG, or MEG) on the one hand and the BOLD fMRI signal on the other hand. We will adopt a descriptive perspective, searching for simple rules that may govern this relationship at the macroscopic level. In principle, we might be able to identify such rules despite our present lack of a detailed understanding of each of the signals' generation from the activity of individual neurons and neuronal circuits. As in the previous section, we will contrast stimulus-driven responses with neural activity reflecting higher-order cognitive processes. The relationship between band-limited activity and fMRI seems relatively simple and reasonably well understood for the former, but more complex, and as yet elusive, for the latter.

Simultaneous Versus Nonsimultaneous Measurements

Electrophysiological and fMRI recordings can be integrated based on either simultaneous or nonsimultaneous measurements. Nonsimultaneous recordings are technically less intricate, provide optimal signal quality in both recording modalities, and allow for optimizing the experimental design within each modality. By contrast, simultaneous recordings ensure that the data in both modalities have been obtained under exactly identical conditions and are particularly well suited for studies of dynamic changes, such as learning.

One general important issue in this context is that different sources of variance can drive correlations between the signals measured with both modalities: variance across different experimental conditions and variance across time or trials within conditions. Nonsimultaneously recorded signals can only be linked based on the covariance controlled by experimental conditions (e.g., stimulus contrast, cognitive task, or behavioral report). Simultaneously recorded signals, however, can also be linked based on the covariance of their trial-to-trial fluctuations, which are not controlled by the experimenter. Such intrinsic, stimulus-independent fluctuations are a pervasive feature of neural activity (Ermentrout et al., 2008; Faisal et al., 2008; Fox and Raichle, 2007; Leopold et al., 2003). One might obtain different correlations between electrophysiology and fMRI, depending on the source of variance (experimental conditions vs. trial-to-trial) used for the analysis. This has immediate consequences for the question of whether one should perform simultaneous or nonsimultaneous recordings: The nonsimultaneous approach seems sufficient for identifying the relationship between stimulus-driven responses in the different modalities; the same holds for cognitive processes well controlled by the task at hand. By contrast, the simultaneous approach is preferable for determining the relationship between intrinsic signal fluctuations, whether measured in the "resting state" or in the presence of a stimulus or task.

For the EEG, it is also important to consider that correlations with local fMRI signals do not necessarily identify electrophysiological activity from that same region. For example, several studies have identified a correlation between widespread alpha-band EEG activity on the human scalp and simultaneously recorded fMRI signals in the thalamus. Does this imply that the scalp-EEG alpha-band activity directly reflects the electrical fields generated by a thalamic source? Certainly not. Rather, this correlation is likely to be caused by a modulation of *cortical sources* of alpha-band EEG activity by thalamic input (Feige et al., 2005; Goldman et al., 2002; Mantini et al., 2007; Moosmann et al., 2003; Steriade, 2000). Such indirect correlations can be exploited for investigating which brain structures modulate band-limited population activity in other cortical areas. However, if one aims at identifying correlations driven by identical structures for the EEG and fMRI signal, source-reconstruction techniques (see above) should be used to project the EEG data into a common source-space where they can be more directly correlated with the fMRI data.

Different Windows into Interactions Between Brain Areas

Analyses of "functional connectivity" (i.e., correlations between remote fMRI time-series) are a common motif in fMRI research (Friston, 2002). In particular, studies of coherent resting-state fluctuations across large-scale cortical and subcortical networks are increasing in popularity (Fox and Raichle, 2007). It is by no means straightforward to establish a direct correspondence between the phase coherence of electrophysiological signals at a fine temporal scale and the temporal correlations of sluggish fMRI signals. The fMRI signal is likely to be blind to the phase coherence between cortical responses, at least in intermediate- and high-frequency (beta and gamma) ranges. Instead, experimental evidence suggests that correlations between the *amplitude envelopes* of band-limited cortical responses may be the source of the correlations between distant fMRI time-series (Leopold et al., 2003; Nir et al., 2008). However, it is important to note that the phase coherence and the correlation between the amplitude envelopes of two signals are independent of one another. For example, the amplitude envelopes (i.e., power) of the gamma-band responses of two regions can covary strongly, despite their phases' being randomly distributed. The reverse can be true as well. Slow covariations between amplitude envelopes are typically as slow as the resting-state fluctuations of the fMRI signal, in that they have a 1/f spectrum with dominant frequencies at 0.1 Hz and below (Fox and Raichle, 2007). Such slow covariations may not play a direct role in neural coding. It has

been speculated that they reflect common input from neuromodulatory projections ascending from the brainstem (Leopold et al., 2003). If so, such slow intrinsic signal fluctuations may generally have strong links to cognition and behavioral performance across a large variety of tasks (see below, "Questions for future research").

There is also ample evidence that correlations between remote fMRI time series at faster time scales reflect perception, attention, and behavioral performance (Freeman et al., 2008; Friston, 2002; Haynes et al., 2005b; Haynes et al., 2005c). These results strongly suggest that the fMRI signal provides a meaningful measure of the interaction between neuronal populations in cortex. Again, these correlations likely reflect amplitude correlations of band-limited activity, on a faster time scale than during resting state, but measurements to test this hypothesis have not yet been done.

Stimulus-Driven Responses in Sensory Cortex

Electrophysiological and fMRI measurements in primary visual cortex suggest a tight covariation between modulations of the BOLD signal and of gamma-band LFP and MEG activity correlated with stimulus strength. Logothetis et al. (2001) simultaneously recorded BOLD fMRI, spikes, and LFPs in monkey V1. Consistent with other reports (Henrie and Shapley, 2005), they found strong and sustained LFP responses to visual stimulation in the gamma band that peaked around 70 Hz and increased approximately linearly with stimulus contrast. These LFP responses were well correlated with modulations of the BOLD signal that showed a similar linear increase with stimulus contrast. A tight coupling between contrast-dependent modulation of the BOLD signal and gamma-band activity is also supported for human V1 by means of nonsimultaneous noninvasive recordings. A similar linear increase with stimulus contrast is found for the BOLD response (Boynton et al., 1999) and gamma-band activity (30–70 Hz) reconstructed from MEG (Hall et al., 2005) (see also "Linking band-limited neural activity to behavior," above).

A similarly tight relationship between the BOLD signal and gamma-band activity seems to hold for human area MT+ for modulations of visual motion strength. Rees et al. (2000) found a linear increase of the BOLD signal in human area MT+ with motion strength. Siegel et al. (2007) demonstrated a similar linear increase of MEG activity in the gamma band (60–100 Hz) in area MT+ and several other motion responsive regions along the dorsal visual pathway (Figure 4.1.2). Further, albeit weaker and less consistently, low-frequency activity (10–30 Hz) decreased with increasing motion strength.

These findings are consistent with a series of LFP recordings in the auditory cortex of epileptic patients. These exploited "inter-subject correlation"[5] to establish indirect links between the LFP and fMRI activity in normal subjects. Mukamel et al. (2005) recorded LFPs and found a positive correlation of LFP power in the gamma band (40–130 Hz), and a negative correlation of LFP power in the alpha band (5–15 Hz), each with fMRI in auditory cortex. Intermediate bands showed little effect. Nir et al. (2007) further established that this observation also holds for spontaneous activity and that occasional dissociations between SUA and the fMRI response tended to be accompanied by reductions of the correlation between the spiking activity of individual neurons and the gamma-band LFP. In other words, whenever, single neurons activate coherently with the surrounding network, their spiking activity is closely coupled to the fMRI signal; whenever they deviate from the mean of their neighborhood, their spiking activity is a poor predictor of the fMRI signal.

Perception-Related Activity in Visual Cortex

Binocular rivalry has been a major source of apparent discrepancies between electrophysiology in fMRI. In binocular rivalry, a bistable visual illusion, two dissimilar patterns presented to the two eyes cannot be fused, and are consequently perceived in alternation (Blake and Logothetis, 2002). fMRI studies of rivalry consistently found strong response modulations correlated with perception in early visual cortex including V1, and even in the LGN (Haynes et al., 2005a; Lee SH et al., 2005; Lee et al., 2007; Meng et al., 2005; Polonsky et al., 2000; Tong and Engel, 2001; Wunderlich et al., 2005). By contrast, single-unit recordings in awake, behaving monkeys found little modulation in V1 with perception (Blake and Logothetis, 2002; Leopold and Logothetis, 1996). Similarly, the LFP recordings in monkey V1 during binocular rivalry and a related perceptual suppression phenomenon reported little modulation of the gamma-band LFP with visual awareness. However, as discussed above, these studies observed strong perception-related LFP modulations in the low frequency range (< 30 Hz) correlated with perception (Gail et al., 2004; Maier et al., 2008; Wilke et al., 2006), prompting the hypothesis that these may have been the source of the fMRI responses measured in human V1 during binocular rivalry.

Maier et al. (2008) addressed this issue by comparing electrophysiological responses with the fMRI signal in macaque V1, measured within the same animals and experimental protocol. When a salient visual target was physically removed from the screen, responses decreased for all three measures of neural activity, and in particular for a broad frequency range of the LFP, including the gamma band (30–100 Hz). However, when the target was rendered *subjectively* invisible by means of "generalized flash suppression" (a bistable visual illusion analogous to binocular rivalry), these signals diverged: There was a strong reduction of the fMRI response with perceptual suppression, little modulation of the high frequency LFP and MUA spiking

activity, and an intermediate reduction of the low frequency LFP. In other words, virtually identical decreases of the fMRI response during physical removal and subjective disappearance conditions were accompanied by distinctly different spectral fingerprints: The low-frequency suppression was paralleled by an enhancement in an intermediate frequency range (30–40 Hz), and a suppression in the high gamma frequency range (60–80 Hz). The dissociation between the spectral modulations correlated with fMRI responses during physical removal and perceptual suppression demonstrates the context-dependent relationship between these two measures of neural population activity.

A human fMRI study of "motion-induced blindness"[6] (Donner et al., 2008) indicates that the topography of response modulations correlated with perceptual suppression provides clues to the underlying mechanisms, in a similar fashion as the corresponding spectral fingerprints. Also during motion-induced blindness, the fMRI response in V1 modulated strongly with perceptual suppression. However, this modulation was not confined to the cortical representation of the small target stimulus, but expressed throughout the entire visual field representation in V1. Such a "global" modulation can hardly be a specific correlate of the localized target suppression. When this global component was removed from the fMRI signals measured in the retinotopic target subregions of areas V1 through V4, the residual target-specific responses tracked the illusory target suppression strongly only in V4 and showed no modulation in V1. These residual target-specific responses may reflect local modulations of spiking activity and/or the gamma-band LFP (Liu and Newsome, 2006; Logothetis and Wandell, 2004; Nir et al., 2007). By contrast, the "global" response component might reflect widespread modulations of the low frequency LFP, perhaps driven by subcortical inputs. Future studies should characterize the topography of the low-frequency electrophysiological signal components correlated with perceptual suppression. A more general implication may be that, for the fMRI signal, it is the spatial (rather than temporal) pattern that may be used for inferring underlying mechanisms: Stimulus representations are expressed in the spatial fine structure (Donner et al., 2008; Haynes and Rees, 2006), whereas neuromodulatory processes acting on these representations are expressed in the global modulations (Donner et al., 2008; Jack et al., 2006).

Studies of attentional modulation of neural responses in visual cortex are another source of apparent discrepancies between electrophysiology in fMRI. First, spatial attention seems to have little effect on firing rates in monkey V1 (Desimone and Duncan, 1995; Luck et al., 1997; but see Chen et al., 2008; Herrero et al., 2008; Roelfsema et al., 1998), but strong effect on the fMRI signal in human V1 (Brefczynski and DeYoe, 1999; Kastner et al., 1999; Ress et al., 2000; Somers et al., 1999). Second, in the absence of sensory stimulation, attention has only modest effect on baseline firing rates in early visual cortex (V1, V2) (Luck et al., 1997), but again a big effect on the fMRI signal (Kastner et al., 1999; Ress et al., 2000). In principle, these discrepancies could merely be due to the different species, stimuli, and behavioral protocols (e.g. near-threshold vs. suprathreshold stimuli), or they may reflect true differences between the different signals. For example, the effects of attention on the fMRI signal could reflect relatively small modulations of synaptic activity, which are coherent across large populations of neurons, and therefore have a strong impact on population signals, but are weakly reflected by single-unit activity. Alternatively, these dissociations might reflect a primary modulation of the temporal structure of neuronal population activity, which, in turn, might have a particularly strong effect on the fMRI response.

Although there were several differences in terms of behavioral protocols, studies of band-limited population activity are beginning to shed new light on these issues. These studies demonstrated profound attentional modulation of band-limited population activity in the human brain (Doesburg et al., 2008; Fan et al., 2007; Fries et al., 2001; Gruber et al., 1999; Siegel et al., 2008; Taylor et al., 2005; Thut et al., 2006; Worden et al., 2000; Wyart and Tallon-Baudry, 2008). One MEG study (Siegel et al., 2008) compared attentional baseline and stimulus-related effects and characterized modulations in V1 and MT+ at the cortical source-level (see also above, "Linking band-limited neural activity to behavior: perception-related activity in visual cortex"). In accordance with fMRI (Kastner et al., 1999; Sapir et al., 2005) attention modulated population activity in both regions during the baseline and stimulus intervals in a spatially selective fashion. However, the spectral fingerprints of these effects differed strongly between V1 and MT+, and even more surprisingly, between the baseline and stimulation intervals, within each area. Invasive recordings in monkey area V4 also displayed an (albeit weaker) analogous difference in attention effects between baseline and stimulation intervals (Fries et al., 2008b).

In conclusion, attentional effects in visual cortex perhaps do not exhibit a stereotype relation between the BOLD signal and electrophysiological population activity in a single frequency band. However, it remains difficult to assess to which extent the difference between regions found by means of MEG can also be observed on the LFP level. For example, it remains open to which extent extracranially recorded effects are affected by interactions of center-surround type attentional modulations (Silver et al., 2007) with the comparatively low spatial resolution of EEG/MEG (see also above "Spatial Scales of Measurements and Neural Networks").

Integrative Processes in Frontal and Parietal Association Cortex

Numerous fMRI studies have probed the involvement of prefrontal and posterior parietal association cortex in selective attention, sensorimotor integration, and decision-making (Corbetta and Shulman, 2002; Desimone and Duncan, 1995; Gold and Shadlen, 2007; Heekeren et al., 2008; Kanwisher and Wojciulik, 2000; Kastner and Ungerleider, 2000; Miller and Cohen, 2001; Schall, 2001). How closely are the fMRI correlates of these processes related to their electrophysiological correlates discussed in the previous section? Unfortunately, only few electrophysiological studies have used experimental protocols directly comparable to the fMRI studies. Also, few studies have applied source reconstruction techniques to estimate activity specifically in prefrontal and parietal cortex. Both limitations hamper a close comparison between the different measurement modalities.

Studies of saccade planning suggest a simple relationship between measurement modalities in parietal association cortex that is largely consistent with the picture emerging for stimulus-driven responses in sensory cortex. Several fMRI studies have demonstrated retinotopically specific fMRI activity in the posterior parietal cortex when human subjects remembered the position of a visual target for a delayed saccade (Hagler and Sereno, 2006; Kastner et al., 2007; Schluppeck et al., 2005; Sereno et al., 2001; Swisher et al., 2007). Converging evidence from monkey and human electrophysiology suggests that such fMRI activity is closely linked to band-limited population activity in the gamma band. Pesaran et al. (2002) demonstrated saccade direction-selective gamma-band activity in monkey area LIP during a delay before saccade execution. Van der Werf et al. (2008) found analogous saccade direction-selective gamma-band activity in the human intraparietal sulcus.

However, the situation appears more complex for studies of attention and decision processes in the same or neighboring cortical networks. There appears to be a positive correlation between electrophysiological activity in the low-beta frequency range (about 12–24 Hz) and fMRI activity in posterior parietal and prefrontal cortex during visual detection tasks. Successful target detection is typically associated with increased fMRI activity in prefrontal and posterior parietal cortex; this is true for motion detection in noise (Shulman et al., 2001), change detection (Beck et al., 2001), flicker detection (Carmel et al., 2006), and target letter detection (Kranczioch et al., 2005; Marois et al., 2004). Recent MEG studies found detection-related enhancements of low beta-band (12–24 Hz) activity in corresponding frontal-parietal regions (Donner et al., 2007; Gross et al., 2004; Linkenkaer-Hansen et al., 2004), suggesting that such performance-related lower frequency activity in frontal-parietal networks correlates positively with the fMRI response in these regions of association cortex, different from the stimulus-induced suppression of low frequency activity in visual cortex. This again suggests that the link between fMRI and electrophysiology may differ substantially between functional processes and cortical regions.

The above studies also illustrate the point that spectral fingerprints of different functional processes may superimpose in a complex fashion, with unknown consequences for the fMRI signal. In particular the performance-related beta activity during motion detection was superimposed onto a more broadband (about 8–50 Hz) stimulus-induced low-frequency suppression (Figure 4.1.5); these two signal components were independent of one another in their trial-to-trial fluctuations and spatial topography (Donner et al., 2007). Both, the stimulus-induced low-frequency *suppression* in visual and parietal cortex and the detection-related beta-band *enhancement* in parietal and prefrontal cortex presumably correlate with increased fMRI responses in different (partially overlapping) cortical regions. Again, this suggests a process- and perhaps area-dependence of the link between fMRI and electrophysiological mass activity.

Questions for Future Research

In the final part of this chapter, we will put forward three questions for future research, the answers to which will be particularly important for understanding the relationship between band-limited neural population activity and both, behavior and the fMRI signal.

What is the Link Between Intracortical and Extracranial Electrophysiology?

Despite the convergence between LFP and EEG/MEG studies that we have highlighted in this chapter, it is still an open question how exactly intracortical LFPs relate to extracranial EEG/MEG signals. For example, which effect does the spatial correlation-structure of neural activity have on invasively and non-invasively recorded signals? The coarser spatial resolution of the latter suggests that they are more sensitive to long-range correlations of neural activity while the LFP primarily reflects synchronized activity on a local spatial scale. Thus, depending on the signal type, the spatial correlation profile of neural activity and its modulation by stimuli or cognitive processes may have profoundly different effects. Similar open questions are to which extent the laminar profile of activity affects different population signals or which role the individual anatomical geometry (gyri, sulci) plays for the relationship between these signals. Quantitative measurements addressing these questions are largely missing (but see Juergens et al., 1999; Mitzdorf, 1987). Addressing them seems crucial for integrating results across different signal scales, and for making infer-

ences between these different levels of observation. Simultaneous LFP and EEG/MEG recordings seem particularly promising for directly elucidating these questions. Furthermore, sub- or epidural surface electrodes (ECoG) constitute an intermediate scale, which might provide a valuable link between intracortical and extracranial signals. Such "intracranial EEG" recordings for research purposes are becoming more frequent, both in human patients (Engel et al., 2005; Lachaux et al., 2003) as well as in non-human primates (Bressler et al., 1993; Tallon-Baudry et al., 2004; Taylor et al., 2005).

How Does Neural Mass Activity Relate to Local Circuit Dynamics?

Attempts to link fMRI and electrophysiological population signals will fall short if these signals are understood as simply reflecting average "activation" levels of cortical regions with different temporal resolution. Both signals are generated by complex interactions between various specialized cell-types within local neuronal circuits (e.g., Heeger and Ress, 2002; Lauritzen, 2005; Logothetis, 2008; Logothetis and Wandell, 2004). We are beginning to understand the principles underlying the processing in such micro-circuits (Douglas and Martin, 2004). It is clear that inhibitory neurons play an integral part in shaping basic tuning properties of individual cortical neurons (Carandini et al., 1997; Heeger et al., 1996; Shapley et al., 2003) as well as generating local network oscillations, e.g., in the gamma band (Bartos et al., 2007). In addition, inhibition might also play a crucial role in high-level cognitive processes such as selective attention (Mitchell et al., 2007). Yet, relatively little is known about how specific cognitive processes affect local network dynamics and how these in turn transfer into modulations of neuronal mass signals as measured with electrophysiology and fMRI. Again, integrated experimental approaches using comparable behavioral protocols and combinations of electrophysiological and functional imaging techniques are required to address these questions. Furthermore, cell-type and layer-specific recordings, as well as genetically targeted manipulations of specific cell classes seem promising techniques to further our understanding of local cortical circuit dynamics and their relation to neural mass signals.

How Does Neuromodulation Shape the Spectral Fingerprints of Cortical Processes?

Several nuclei in the basal forebrain and brainstem send massive, and relatively diffuse neuromodulatory (adrenergic, cholinerig, etc.) projections to wide regions of the cortex. These neuromodulators seem to play an important role in shaping band-limited cortical population activity (Munk et al., 1996; Rodriguez et al., 2004; Steriade, 2000). These ascending systems have traditionally been thought of as merely regulating slow fluctuations of coarse behavioral states, such as vigilance and arousal (Steriade, 2000). However, growing theoretical and empirical evidence suggests that neuromodulators play more specific computational roles in selective attention, short-term memory, and decision-making (Aston-Jones and Cohen, 2005; Hasselmo, 1995; Herrero et al., 2008; Usher et al., 1999; Wang et al., 2007; Yu and Dayan, 2005). Taken together, these lines of evidence suggest that neuromodulators may be an essential factor determining the spectral fingerprints of these cognitive processes. Direct studies of neuromodulator effects on cortical population activity in awake, behaving animals will provide deeper insights into this issue. Such studies could use either local (Herrero et al., 2008) or systemic (Bentley et al., 2003; Coull et al., 1999; Coull et al., 2001; Minzenberg et al., 2008) pharmacological manipulations, or simultaneous measurements of activities in subcortical neuromodulatory centers and in their cortical recipients (Minzenberg et al., 2008). The latter is one area of research for which simultaneous EEG and fMRI recordings might prove to be extremely useful. Simultaneously monitoring subcortical neuromodulatory centers, such as the noradrenergic locus coeruleus with fMRI and widespread band-limited activity patterns in the cortex with EEG during the performance of cognitive tasks could provide deep insights into how the spectral fingerprints of cognitive processes are shaped by subcortical centers.

Conclusion

We have addressed the relationship of band-limited electrophysiological mass activity to behavior on the one hand, and to the BOLD fMRI signal on the other hand. Electrophysiological mass activity generally reflects several different *components* of neuronal activity, which are generated by distinct neural mechanisms and expressed in different frequency ranges. The relative strengths of these components thus determine what we have called the specific *spectral fingerprint* of a perceptual or cognitive process (and perhaps even of a given brain area involved in this process). We have highlighted a striking discrepancy between the spectral fingerprint of stimulus-driven responses in sensory cortices and the fingerprints of intrinsic processes (such as top-down attention or switches between perceptual states) within the same cortical areas. We speculate that this dissociation reflects recurrent interactions between distant cortical areas and/or neuromodulation of cortical activity patterns by ascending systems, which are both thought to play an important role in such processes. If this idea turns out to be correct, we may be able to exploit the spectral fingerprints of functional processes for inferring about the detailed mechanisms underlying these processes.

The fMRI signal, likewise, reflects several different components of neuronal activity. Since the sluggish fMRI signal does not have the temporal fine structure of electrophysiological signals, we cannot use its frequency spectrum to disentangle these different components. However, we may use the scale (local vs. global) of spatial patterns to make inferences about the underlying mechanisms: Neuronal representations are likely to be expressed in the local structure of neural population responses, whereas neuromodulatory processes may be expressed in more global response modulations. Importantly, the multi-component nature of electrophysiological activity and the fMRI signal explains why there does not seem to be a simple, stationary transformation between the two. This important point has often been overlooked in recent discussions. Instead, we suggest that there may exist a cohort of such transformations, one for each class of functional processes and perhaps brain areas. The close coupling between gamma-band activity and the fMRI signal for stimulus-driven responses of sensory cortical regions provides a well established example, the mechanisms of which we are beginning to understand. In this case, identifying the spectral fingerprints of the functional processes would also help define the relation between electrophysiological activity and the fMRI signal. Even if such cohorts of transformations do not exist, characterizing the neural basis of a process under study with both electrophysiology and fMRI will provide more insights than each of these measurements alone.

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Notes

1. The term *neuromodulation* refers to the fact that these respective neurotransmitters (such as norepinephrine or acetylchholine) bind on postsynaptic receptors, which are not directly coupled to ion channels, but instead exert their effects on cortical neurons via second messenger cascades (Hasselmo, 1995).
2. In fact, this is the case, from which the spectral analysis approach to EEG has originally emerged (Mitra and Bokil, 2007).
3. We will not discuss the hypothesis that synchronized population activity serves as a *relational* code that represents which elementary features belong to the same sensory object ("binding by synchrony"). Evidence has been provided in support of (Castelo-Branco et al., 2000; Eckhorn et al., 1988; Gray et al., 1989; Kreiter and Singer, 1996) as well as against (Lamme and Spekreijse, 1998; Palanca and DeAngelis, 2005; Thiele and Stoner, 2003) this specific hypothesis, and it has been intensely debated elsewhere (Riesenhuber and Poggio, 1999; Shadlen and Movshon, 1999; Singer, 1999).
4. When two target objects (e.g., letters) are presented in close temporal succession during rapid serial presentation, subjects frequently miss the second, suggesting that attention (i.e., the mind's eye) "blinks" after detection of the first.
5. "Inter-subject correlation" refers to the phenomenon that, while subjects watch engaging movies, neural population responses tend to become highly correlated across subjects, for multiple areas of the cortical hierarchy (Hasson et al., 2004).
6. Motion-induced blindness is a bistable perceptual suppression phenomenon analogous to binocular rivalry and generalized flash suppression, in which a salient target stimulus disappears spontaneously from conscious perception when surrounded by a moving flow field, only to reappear several seconds later (Bonneh et al., 2001).

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