CHAPTER 6

The Infrastructure of Brain Rhythms and Its Disruption in Pain

Alexis T. Baria

Take a look at any fMRI BOLD signal in the brain, and the most prominent feature is its rhythmic activity—it periodically fluctuates between high and low values. Unlike the common depiction of a single neuron that fires action potentials in the event of some stimulus and remains silent otherwise, you will never see a *silent* BOLD signal in a living brain. The fact is that rhythmic activity is ubiquitous in the brain and the rhythms can be measured when recording from vast populations of cells (as with fMRI, EEG, and local field potential [LFP]) all the way down to the single cell. These rhythms have been studied for a very long time, beginning with the discovery that rhythmic behaviour (such as breathing and locomotion) could exist without descending input from the brain. The idea that rhythms play a role in more complex operations such as cognition and perception, however, is relatively new, and somewhat more controversial. This chapter will thus go over some of the basic concepts behind the orchestrated rhythms in the brain, their relation to mental activity, and how they can be studied in *frequency space*. In particular, it will discuss the special properties of the brain's frequency spectrum that allow the many systems in the brain to communicate, and will go over how pain can be examined from this viewpoint.

BRAIN RHYTHMS AND NETWORK COMMUNICATION

The prevalent view of how the brain works suggests it is a reflexive system. That is, when it is perturbed by some outside force, different elements within the brain send messages back and forth to plan a response, and then it generates an output response signal. This is similar to the many spinal reflexes, like the knee jerk reflex one might experience at the doctor's office, as is with single neurons, which are often depicted as being mostly silent until perturbation from some external stimulus. This view illustrates the brain's default activity as quiet unless driven to react. This is only a half-truth, however, because while brain activity *is* influenced by exogenous forces, the vast majority of its energy is spent intrinsically, and in fact is never silent. Brain activity continuously ebbs and flows, periodically changing the distribution of its energy, whether you are thinking or not, dreaming or entirely unconscious, until you are no longer living. Thus, the brain is restless, and a growing number of scientists and clinicians are using this fact to understand the brain in new ways.

The most famous depiction of this view is probably that of the α wave, the most prominent EEG signal localized in the occipital cortex. This wave was discovered to constantly oscillate at about 10 Hz (the wave fluctuates 10 times/second), peaking around 150 μV, and change in amplitude when a subject kept their eyes closed [33]. From a certain standpoint,

however, it is difficult to intuit what ongoing oscillations have to do with actions and mental processes that seemingly do not oscillate. Certainly, there do not appear to be any 10 Hz oscillations when closing one's eyes. To put it in the perspective of fMRI, a brain region may "activate" with a specific stimulus, but it never flat lines. The fact is that region is continuously "activating" (fluctuating between high and low blood oxygenation) regardless of whether the stimulus is there or not. Band-limited power of EEG signals behaves in the same manner, chugging along peaks and valleys in a way that is seemingly independent of behaviour or environmental stimuli. So what exactly is going on? The question has challenged neuroscientists for many decades, but the emerging answer is that oscillations reflect widespread modulation of activity that is driven by the system itself [26]. In other words, oscillations signify that certain groups of cells are working together to influence the activity of other groups of cells, which ultimately influences behaviour and perception. Such groups of cells (commonly referred to as systems or networks) are able to influence the actions of the others across long distances and at different temporal scales. The intricate interactions of the many brain rhythms play an important role in maintaining and interpreting information, and predicting environmental demands. The details of how this works is beyond the limited space allotted to this chapter, but we briefly describe it below.

The following is a simple illustration of how brain oscillations are defined by the communication of many networks. In actuality, the interactions are far more complex than described below, but hopefully this, and the corresponding Fig. 6-1, provides a good starting point to understand the concept. Imagine a small group of close, interconnected neurons that we will call "network A." Let us say the cells within it are *synchronized*, that is, they all fire together within a certain time window. The network is able to do this because (1) each neuron by itself exhibits phase-dependent excitability (there are periods of time when a perturbation is more likely to cause it to fire than others, due to the arrangement of channels along its membrane [26]), and (2) these periods of excitability can be shifted

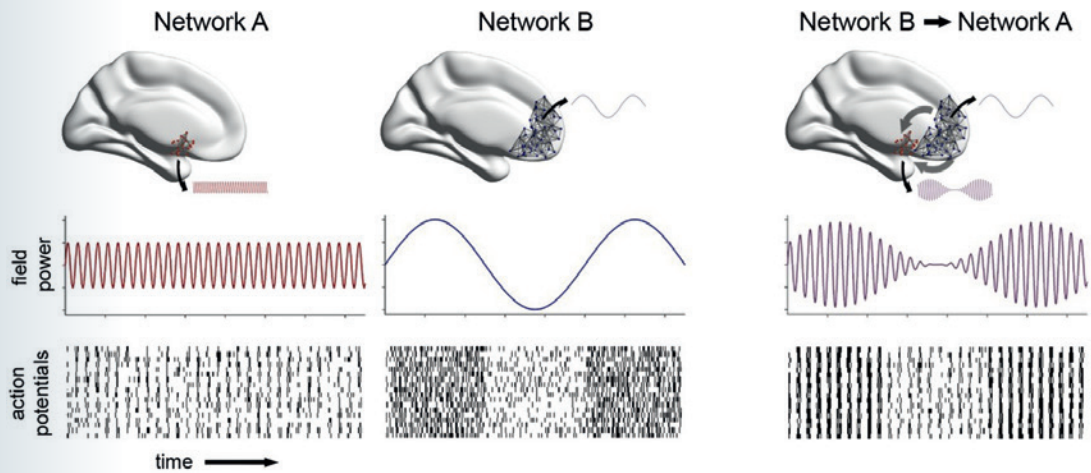

FIGURE 6-1 Brain rhythms indicate network synchrony. Left: Network A is small; thus, synchrony occurs within short time windows. The arrow points to an example of oscillatory behaviour that arises from network A. The waveform below is an enlarged view, demonstrating the rhythmic behaviour of the voltage field power generated by synchrony within the network. The raster plot on the bottom is temporally aligned to the field power wave. Each black mark indicates the firing of an action potential from a single unit (each row in the raster plot) from within the network. Notice, most action potentials occur around the peak of the waveform. Middle: Network B is much larger; thus, the field power generated by synchrony within it is much larger. Notice, the temporal windows by which single units within the network synchronize are much longer. Right: The influence of network B on A (cross-frequency coupling) results in increased high-frequency synchrony appearing periodically in long time windows.

by perturbations, for example, by an action potential transmitted from another physically connected cell. In general, the neurons within network A are able to synchronize because each cell can adjust to the intrinsic oscillatory behaviour of the others through their physical connections. Synchronization within network A can occur within very small time windows, or high frequencies, because the cells are close together and the transmission of action potentials along their axons is very fast. This synchronization generates a mean voltage field that fluctuates up and down—when the synchronization of the cells is tighter, the mean field generated by the network is higher. Because there are only a few cells generating the voltage field, the mean field oscillates around a relatively small value—on the scale of microvolts. Keep in mind this is far below the voltage needed to cause an action potential in a hyperpolarized cell, but it may be just enough to push a cell (or network of cells) near firing threshold to depolarize.

Now suppose there is a much bigger group of neurons, network B. Their mean distance is further from each other and thus they cannot synchronize within short time windows due to synaptic delays and limitations of axon conductance; their synchronization is defined by longer temporal windows (low frequencies). Because there are so many cells synchronizing within these longer time windows, their integrated activity generates bigger, slower fluctuations in the mean voltage field, which has some important implications. First, the stronger voltage field means it can have greater influence on the firing of other cells. This voltage field is still in microvolts, but it is much larger than that of network A, and thus it can push a cell (or network of cells) into firing that is even further from threshold. Second, the slow fluctuations of the field put it at higher strengths for longer periods of time; thus, its ability to push other cells into firing is temporally extended, compared with network A. Finally, both the larger strength and the lower frequency fluctuation of the field allow it to influence the behaviour of many more cells (or networks of cells), compared with network A. Overall, this means that these big, slow fluctuations can influence the behaviour of many cells, which may fire and fluctuate at much higher frequencies. This interaction is called "cross-frequency coupling" [10], and it is how networks communicate across different spatial and temporal scales. It is an important mechanism that enables parallel processing in the brain, and is the putative link between perception and behaviour occurring on relatively slow timescales to neural activity that is magnitudes faster. The short punch line of all this is that the larger, slower fluctuating networks have the power to influence the behaviour of the smaller, faster networks. But it does not stop there. In fact, there is some reciprocity of influence between smaller and bigger networks, and the intricate orchestration of this communication is a very important part of what allows us to perceive our environment, to learn, to make decisions—virtually everything we do. For more detailed and excellent reviews on the topic, see the following [8, 10, 14, 17].

The 1/*f* Frequency Power Spectrum

What is the infrastructure of rhythms that allows for the coordinated transfer of information, and thus communication, to occur across different systems in our brains? The question is easier to answer if one views brain activity in frequency space using a Fourier transform. This tool allows one to decompose fluctuating signals into components of sine waves with different frequencies (wavelengths, or time between peaks) and amplitudes (height of the wave). The amplitude of each sine wave can then be plotted as a function of its frequency, and the resulting plot is the *power spectrum* for the original signal. The power spectrum shown in Fig. 6-2 is typical of a BOLD signal in the brain, demonstrating the

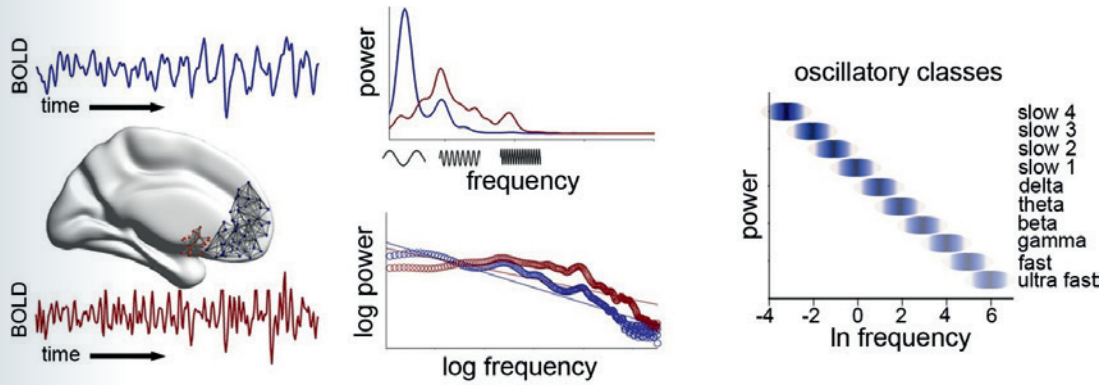

FIGURE 6-2 Brain rhythms can be examined in frequency space. Left: Typical fMRI BOLD signals are shown for different regions of the brain. Notice, the biggest fluctuations in the blue signal are slow relative to the big fluctuations in the red signal. Middle: These can be transformed into frequency space, where the signal is decomposed into sine waves with different wavelengths **(top middle)**. Bottom middle: Neural frequency spectra are characterized by the 1/*f* distribution of power. The frequency spectrum shown on the top is log-transformed, and can be described by the linear fit, where a steeper slope in the line indicates a greater distribution of power towards lower-frequency activity. Right: Oscillatory classes within the neural frequency spectra are defined by the natural log of their mean frequency. Demarcations between classes are fuzzy, indicated by the overlaps in the plot. In general, the slower frequencies exhibit higher power, or greater amplitude, in their fluctuations.

highest power at the low frequencies. In other words, the biggest variance, or largest fluctuations in the signal, occur over longer periods of time, whereas smaller fluctuations occur relatively quickly. This relationship is presumed to exist at all spatial scales, and essentially is identical whether measured through LFPs that track activity in the micrometre range [24] or through EEG and fMRI [17] that track collective activity from many thousands to millions of cells across millimetres to centimetres of tissue. Interestingly, when plotted on the log scale, the power spectrum is roughly linear, and this distribution is referred to as "1/*f*," which has special implications for transfer of information within the brain, and will be discussed further below. But first let us quickly go over the rhythms within the distribution.

Typically, the power spectrum is divided up into different frequency bands, or boundaries demarcating specific rhythms that are associated with different functions and mechanisms, or drivers (Fig. 6-2). Examples of such mechanisms could be a network of cells, a specific part of the brain, or networks of cells across multiple brain structures. There are at least 10 frequency bands that make up the entire range of neural activity from <0.01 to >500 Hz, each one putatively generated by at least one distinct driver. However, the boundaries are not entirely clear-cut, as most frequencies of the brain power spectrum have been associated with an extensive number of behaviours and functions. Therefore, assigning a single driver to a specific rhythm is likely impossible. Attempts to localize drivers to frequency-specific rhythms show that the distribution is widespread, but anatomically distinct [1, 4, 5, 42]. The fact that many drivers can be linked to a single rhythm, and vice versa, is not a mistake. There is a specific order by which these 10 frequency bands (and thus mechanisms driving the activity within the bands) interact, allowing the brain to synchronize many of its systems at different timescales. If one divvies the power spectrum according to the mean frequency at each band, one will find the ratio between adjacent bands is *e*, or the base of the natural logarithm. Because *e* is an irrational number (roughly 2.17), this guarantees that the phase of the oscillators at each band will never overlap, resulting in fluctuating signals that are nonrepeating and weakly chaotic. In other words, adjacent frequency bands do not lock-step with each other, but constantly transition between

unsynchronized and transiently synchronized states; the transient synchronization provides windows by which temporally independent mechanisms can communicate with each other. This is important because behaviour occurs across a range of timescales, from fractions of a second to several seconds, and precise timing of these behaviours is needed to successfully predict changes in the environment and navigate accordingly.

Now, back to the 1/*f* distribution of power that spans these frequency bands. The distribution arises from the intricate architecture of physical connections between cells and transmission delays that occur as action potentials travel longer distances [9]. The implication of the 1/*f* distribution of power is that a perturbation to low-frequency activity involving the synchrony of many cells (and thus high mean field power) will modify the activity in adjacent, higher frequency bands associated with fewer cells (which possess less mean field power). The low-frequency oscillations bias the extracellular membrane potential in local cortical regions, making it more likely that those local cells will fire synchronously [14]. Again, large brain networks with lots of energy influence local, small groups of networks over long expanses of space and time—low-frequency oscillating systems modulate high-frequency systems. And because the division of frequency bands in the power spectrum promotes quasistable interactions between systems (as mentioned above), this bouncing of interactions allows for parallel processing and cross-network communication. The main point of all of this is that the 1/*f* power distribution in the brain establishes a link between slow observable behaviour and fast neural activity [10].

Linking Slow Activity to Behaviour

Students are often introduced to neuroscience by demonstrating how single cells are related to behaviour—shine a light within the receptive field of a recorded neuron in the primary visual cortex, and one can hear a burst of sound from the recording equipment, representing an increase in the firing rate of action potentials. It is natural for students, then, to understand the brain–behaviour relationship within the context of single cells and fast, spiking activity. Establishing a causal link between slow, spontaneous oscillations and behaviour does not come so naturally, however. Yet, the evidence linking the two is quite strong, as human performance actually fluctuates at very low frequencies [35]. Another way to think about it is that performance is autocorrelated—how one performs in any one trial is similar to the recent preceding trials. Fluctuations in such behaviour can occur at roughly the same rate as infra-slow fluctuations (ISFs, 0.01–0.1 Hz) in the brain, and this property is preserved across a number of tasks [7, 22, 30]. For example, the phase (or the position along a waveform such as a *peak* or a *valley*) of EEG ISFs is highly correlated with the ability of subjects to perceive barely detectable visual stimuli, and detection is more reliable when ISFs are around the peak of their waveforms [31]. To bring back the 1/*f* distribution, this implies that when large groups of cells are synchronized, performance in this task is at a peak, presumably owing to enhanced communication between local visual networks and global cognitive networks.

RHYTHMS IN FMRI BOLD SIGNAL

Note, ISFs are just within the bandwidth of fMRI BOLD, suggesting perhaps that BOLD is more suitably illustrated as reflecting modulations to local neuronal activity rather than simply responding to local activity (as it is more commonly depicted). In fMRI research,

we often model brain representations of behaviour according to the latter by employing a general linear model convolved with a hemodynamic response at a 6- to 12-second lag following a stimulus. This type of analysis implies one is interested in how the BOLD signal *responds* to the environment. Once again, from such a perspective we view the brain only as a *reflexive* system. Certainly, studying fMRI in this manner has provided much valuable information about brain function, and the evidence that BOLD signal does change in response to fast neuronal events is strong [23, 25]. But there is growing evidence that BOLD more accurately reflects a mixture of ongoing brain rhythms, as evidenced by simultaneous fMRI–LFP/EEG recordings [27, 28, 32, 37, 40]. Given this, it seems at least equally appropriate to examine fMRI signals from the viewpoint of their rhythmic behaviour, in frequency space.

It must be mentioned that the nonneural factors associated with BOLD fluctuations are quite extensive and include changes in oxygen consumption, microvascular architecture, blood flow, and movement artefact [6, 19]. The temporal fidelity of the hemodynamic response, which exhibits different waveforms in different brain areas [15], may also be a confounding factor when determining neural contribution to the signal. Regardless of how much neural activity is represented in BOLD, overwhelming evidence suggests that fMRI activity is of great functional relevance, and is sufficient for furthering our understanding about how the brain works. Interestingly, recent studies have shown that astrocyte networks are synchronized within the ISF frequency band [21, 38], and thus fluctuate at about the same frequency as BOLD. Up until recently, the function of these cells has largely been interpreted as supporting the physical structure of the brain, but perhaps large astrocyte networks are also granted the power to modulate activity of dispersed networks of neurons.

BRAIN RHYTHMS AND PAIN

So how do we relate all of this to pain? Chronic pain is characterized by its spontaneous onset and seemingly unexplainable persistence. Its qualities and descriptions vary from patient to patient, and the dynamics of its intensity are independent from the behaviour of the patient. For some reason, long after injuries have healed, this unpleasant experience sticks with some patients, and for them the gears of pain machinery continue to turn. As perception is a cortical phenomenon, chronic pain must be related to the mechanisms that drive the ongoing rhythms of the brain. Because of its complex nature, attempts to localize pain perception to a unitary brain region have failed. Although visual, somatosensory, and motor systems exhibit modality-specific and frequency-specific reactivity to stimuli, pain causes widespread modulations in power with acute stimulation [13, 36]. Gamma band oscillations in the primary somatosensory cortex are known to covary with acute pain perception [39, 41], and a multitude of studies have localized a "pain matrix" consisting mainly of the thalamus, primary somatosensory cortex, insula, anterior cingulate cortex, and periaqueductal gray that activates with painful stimuli. However, whether these changes in brain activity purely correspond to pain perception or are merely correlates of salience [41] presents a major challenge in pain research.

An emerging hypothesis suggests pain arises from the dynamic integration of information across many parts of the brain, which are embedded in its ongoing fluctuations [2, 11]. A recent study in our laboratory demonstrates this, showing that chronic pain changes oscillatory activity in the default mode network (DMN), and these disrupted oscillations are correlated with real-time spontaneous pain perception [3]. We divvied the power–frequency

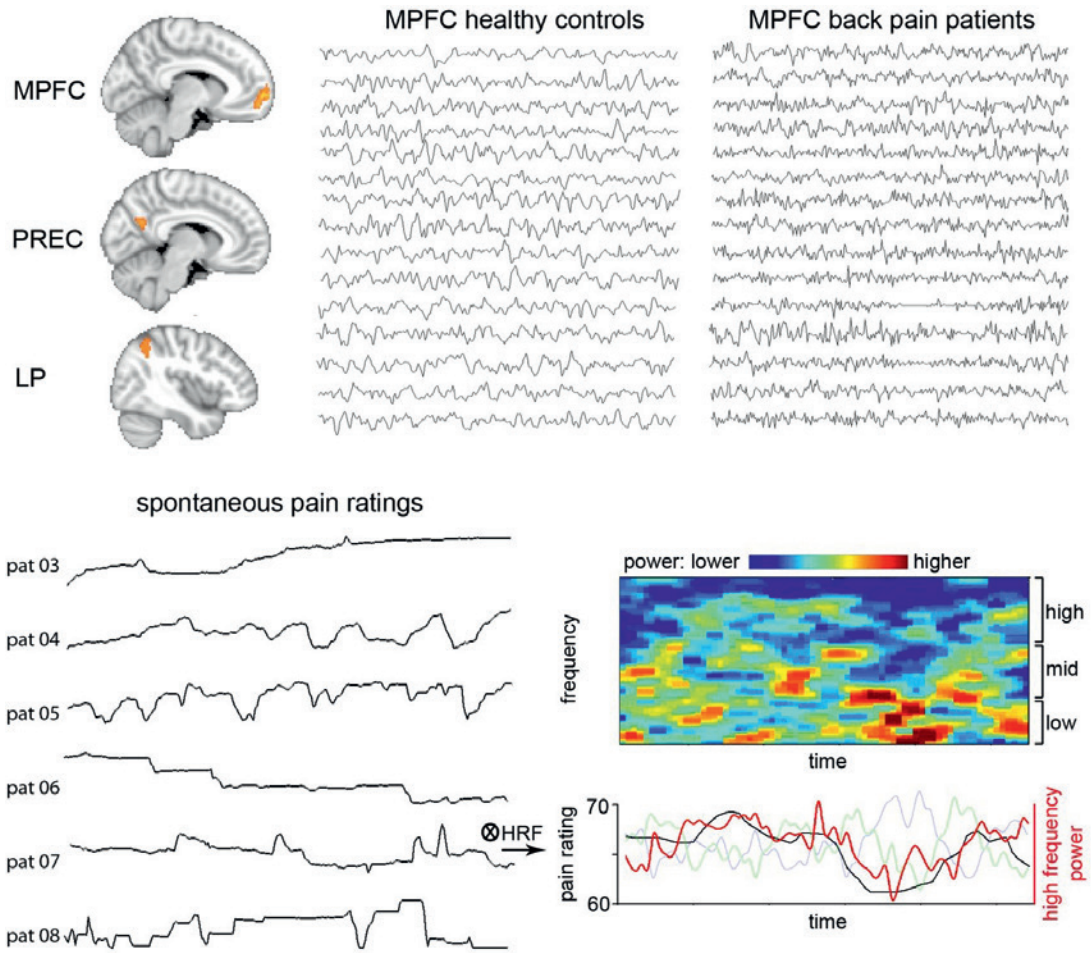

FIGURE 6-3 High-frequency BOLD fluctuations encode spontaneous pain. Top: Coloured regions in the brain indicate where high-frequency BOLD fluctuations are greater in patients with chronic back pain than in control subjects. Time series to the right are BOLD signals from the MPFC for individual subjects. Notice, the pain patients' signals fluctuate at a visibly higher frequency. Bottom: To the left are examples of spontaneous back pain ratings from individual patients. On the top right is the spectrogram of the MPFC BOLD signal for pat 07, demonstrating the progression of the distribution of frequency-specific power across time. The demarcations indicate the boundaries of three frequency bands studied separately: low, mid, and high. The power across time for the high-frequency band (*red line*) is shown in the plot directly below it. Notice, it is highly correlated with the pain rating of pat 07 (after convolving the pain rating with the hemodynamic response function). Power across time is shown for the other two frequency bands with faint lines.

spectrum into relatively low, medium, and high frequencies based off previous delineations of the fMRI BOLD signal [29]. When we compared high-frequency BOLD power in the chronic pain brain with healthy subjects, we found the greatest differences in the medial prefrontal, posterior cingulate, and bilateral parietal cortices (Fig. 6-3)—all major nodes of the DMN. As brain oscillations and network properties are inextricably related, we found these aberrant rhythms were correlated with increased communication between parts of the DMN and the insula and the secondary somatosensory cortex—regions associated with nociceptive processing. This suggests that nociceptive signals from ongoing pain had become integrated with parts of the brain that are responsible for evaluating one's current state of well-being. Finally, we found that the amplitude of high-frequency oscillations in the medial prefrontal cortex (MPFC), from second to second, corresponded to spontaneous

surges in back pain ratings. In other words, when the high-frequency part of the BOLD signal increased from one time point to the next, so did the patient's spontaneous pain. These findings are in line with multiple studies demonstrating a shift in the power spectrum associated with chronic pain in diabetes [12], irritable bowel syndrome [18], multisomatoform disorder [34], fibromyalgia [20], and in multiple other etiologies [29].

More recently, we found predictive power in these brain fluctuations, and were able to identify patients who would respond to a placebo treatment for their back pain [16]. In a 2-week clinical trial of a placebo patch placed on the back of patients who had ongoing pain, we divided patients into placebo responders and nonresponders based off a median decrease in a visual analog scale (VAS) of their pain, ranging from 0 to 100. If a patient had a decrease in pain that was greater than the group absolute median change in pain, they were categorized as a responder. After comparing the frequency spectrum of BOLD signals across the brain for the two groups at baseline, we found that the responder group had bigger fluctuations at high frequencies in the dorsal MPFC. We further found that the frequency content of this region was about 80% accurate in predicting the pain outcome of a separate cohort of patients receiving the same treatment, validating that the findings may be generalized, at least within the chronic back pain population.

It is not surprising that chronic pain modulates the oscillatory activity of endogenous brain networks, which operate together as functionally defined, semi-independent systems. The ongoing and synchronous rhythms generated by these systems are a dynamic sum of the physiological activity giving rise to our subjective current state, or consciousness. Via a quasistable infrastructure, the $1/f$ power spectrum, the systems are orchestrated into playing together across spatial and temporal scales. Pain might be a product of dissonance in the orchestra—an unwanted interference in our consciousness. Here, we have seen how pain influences the rhythms of the brain (and vice versa). These *dissonant ripples* in the pained brain represent a disruption that is widespread across many regions. The growing evidence that pain perception is not localizable suggests, then, that studying network activity captured by the frequency–power spectrum will further our ability to identify how the brain represents pain.

REFERENCES

1. Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL. Functional-anatomic fractionation of the brain's default network. Neuron 2010;65(4):550–62.
2. Apkarian AV, Hashmi JA, Baliki MN. Pain and the brain: specificity and plasticity of the brain in clinical chronic pain. Pain 2011;152(3 Suppl):S49–64.
3. Baliki MN, Baria AT, Apkarian AV. The cortical rhythms of chronic back pain. J Neurosci 2011;31(39):13981–90.
4. Baria AT, Baliki MN, Parrish T, Apkarian AV. Anatomical and functional assemblies of brain BOLD oscillations. J Neurosci 2011;31(21):7910–9.
5. Baria AT, Mansour A, Huang L, Baliki MN, Cecchi GA, Mesulam MM, Apkarian AV. Linking human brain local activity fluctuations to structural and functional network architectures. NeuroImage 2013;73:144–55.
6. Birn RM, Diamond JB, Smith MA, Bandettini PA. Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. NeuroImage 2006;31(4):1536–48.
7. Busch NA, Dubois J, VanRullen R. The phase of ongoing EEG oscillations predicts visual perception. J Neurosci 2009;29(24):7869–76.
8. Buzsaki G. Rhythms of the brain. New York, NY: Oxford University Press; 2006.
9. Buzsaki G, Draguhn A. Neuronal oscillations in cortical networks. Science 2004;304(5679):1926–9.
10. Canolty RT, Knight RT. The functional role of cross-frequency coupling. Trends Cogn Sci 2010;14(11):506–15.
11. Cauda F, Sacco K, D'Agata F, Duca S, Cocito D, Geminiani G, Migliorati F, Isoardo G. Low-frequency BOLD fluctuations demonstrate altered thalamocortical connectivity in diabetic neuropathic pain. BMC Neurosci 2009;10:138.

12. Cauda F, Sacco K, Duca S, Cocito D, D'Agata F, Geminiani GC, Canavero S. Altered resting state in diabetic neuropathic pain. PloS One 2009;4(2):e4542.
13. Chen AC, Herrmann CS. Perception of pain coincides with the spatial expansion of electroencephalographic dynamics in human subjects. Neurosci Lett 2001;297(3):183–6.
14. Frohlich F, McCormick DA. Endogenous electric fields may guide neocortical network activity. Neuron 2010;67(1):129–43.
15. Gonzalez-Castillo J, Saad ZS, Handwerker DA, Inati SJ, Brenowitz N, Bandettini PA. Whole-brain, time-locked activation with simple tasks revealed using massive averaging and model-free analysis. Proc Natl Acad Sci USA 2012;109(14):5487–92.
16. Hashmi JA, Baria AT, Baliki MN, Huang L, Schnitzer TJ, Apkarian AV. Brain networks predicting placebo analgesia in a clinical trial for chronic back pain. Pain 2012;153(12):2393–402.
17. He BJ, Zempel JM, Snyder AZ, Raichle ME. The temporal structures and functional significance of scale-free brain activity. Neuron 2010;66(3):353–69.
18. Hong JY, Kilpatrick LA, Labus J, Gupta A, Jiang Z, Ashe-McNalley C, Stains J, Heendeniya N, Ebrat B, Smith S, et al. Patients with chronic visceral pain show sex-related alterations in intrinsic oscillations of the resting brain. J Neurosci 2013;33(29):11994–2002.
AQ1 19. Kim J, Van Dijk KR, Libby A, Napadow V. Frequency-dependent relationship between resting state fMRI signal power and head motion is localized within distributed association networks. Brain Connect 2014;4(1):30–9.
20. Kim JY, Kim SH, Seo J, Han SW, Nam EJ, Kim SK, Lee HJ, Lee SJ, Kim YT, Chang Y. Increased power spectral density in resting-state pain-related brain networks in fibromyalgia. Pain 2013;154(9):1792–7.
21. Kuga N, Sasaki T, Takahara Y, Matsuki N, Ikegaya Y. Large-scale calcium waves traveling through astrocytic networks in vivo. J Neurosci 2011;31(7):2607–14.
22. Lakatos P, Karmos G, Mehta AD, Ulbert I, Schroeder CE. Entrainment of neuronal oscillations as a mechanism of attentional selection. Science 2008;320(5872):110–3.
23. Lee JH, Durand R, Gradinaru V, Zhang F, Goshen I, Kim DS, Fenno LE, Ramakrishnan C, Deisseroth K. Global and local fMRI signals driven by neurons defined optogenetically by type and wiring. Nature 2010;465(7299):788–92.
24. Leopold DA, Murayama Y, Logothetis NK. Very slow activity fluctuations in monkey visual cortex: implications for functional brain imaging. Cereb Cortex 2003;13(4):422–33.
25. Lippert MT, Steudel T, Ohl F, Logothetis NK, Kayser C. Coupling of neural activity and fMRI-BOLD in the motion area MT. Magn Reson Imaging 28(8):1087–94.
26. Llinas RR. The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. Science 1988;242(4886):1654–64.
27. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. Nature 2001;412(6843):150–7.
28. Magri C, Schridde U, Murayama Y, Panzeri S, Logothetis NK. The amplitude and timing of the BOLD signal reflects the relationship between local field potential power at different frequencies. J Neurosci 2012;32(4):1395–407.
29. Malinen S, Vartiainen N, Hlushchuk Y, Koskinen M, Ramkumar P, Forss N, Kalso E, Hari R. Aberrant temporal and spatial brain activity during rest in patients with chronic pain. Proc Natl Acad Sci USA 2010;107(14):6493–7.
30. Mathewson KE, Gratton G, Fabiani M, Beck DM, Ro T. To see or not to see: prestimulus alpha phase predicts visual awareness. J Neurosci 2009;29(9):2725–32.
31. Monto S, Palva S, Voipio J, Palva JM. Very slow EEG fluctuations predict the dynamics of stimulus detection and oscillation amplitudes in humans. J Neurosci 2008;28(33):8268–72.
32. Mukamel R, Gelbard H, Arieli A, Hasson U, Fried I, Malach R. Coupling between neuronal firing, field potentials, and FMRI in human auditory cortex. Science 2005;309(5736):951–4.
33. O'Leary JL. Hans Berger on the electroencephalogram of man: the fourteen original reports on the electroencephalogram, Vol. 168. New York, NY: Elsevier; 1969.
34. Otti A, Guendel H, Wohlschlager A, Zimmer C, Noll-Hussong M. Frequency shifts in the anterior default mode network and the salience network in chronic pain disorder. BMC Psychiatry 2013;13:84.
35. Palva JM, Palva S. Roles of multiscale brain activity fluctuations in shaping the variability and dynamics of psychophysical performance. Prog Brain Res 2011;193:335–50.
36. Ploner M, Gross J, Timmermann L, Pollok B, Schnitzler A. Pain suppresses spontaneous brain rhythms. Cereb Cortex 2006;16(4):537–40.
37. Scheeringa R, Mazaheri A, Bojak I, Norris DG, Kleinschmidt A. Modulation of visually evoked cortical FMRI responses by phase of ongoing occipital alpha oscillations. J Neurosci 2011;31(10):3813–20.

38. Schulz K, Sydekum E, Krueppel R, Engelbrecht CJ, Schlegel F, Schroter A, Rudin M, Helmchen F. Simultaneous BOLD fMRI and fiber-optic calcium recording in rat neocortex. Nat Methods 2012;9:6.
39. Tiemann L, Schulz E, Gross J, Ploner M. Gamma oscillations as a neuronal correlate of the attentional effects of pain. Pain 2010;150(2):302–8.
40. Van de Ville D, Britz J, Michel CM. EEG microstate sequences in healthy humans at rest reveal scale-free dynamics. Proc Natl Acad Sci USA. 2010;107(42):18179–84.
41. Zhang ZG, Hu L, Hung YS, Mouraux A, Iannetti GD. Gamma-band oscillations in the primary somatosensory cortex—a direct and obligatory correlate of subjective pain intensity. J Neurosci 2012;32(22):7429–38.
42. Zuo XN, Di Martino A, Kelly C, Shehzad ZE, Gee DG, Klein DF, Castellanos FX, Biswal BB, Milham MP. The oscillating brain: complex and reliable. Neuroimage 2010;49(2):1432–45.

Query Log

Title: Apkarian

Chapter: 6

Query Nos.	Query	Remarks
AQ1	Please confirm whether the changes made to ref. 19 are fine.	