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Neuronal Oscillations Scale Up and Scale Down the Brain Dynamics

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8.1 Introduction

Understanding the complexity of the global dynamics of the nervous system poses an enormous challenge for modern neurosciences [1]. Very large sets of data can now be obtained from all organization levels by the explosive growth of new physiological recording techniques and functional neuroimaging. Nevertheless, gathering the data is only the first step toward a fully integrated approach. Understanding of the interdependency between microscopic function of individual neurons, their mesoscopic interrelation, and the resulting macroscopic organization is also crucial [2]. In the mammalian cerebral cortex, these large-scale dynamics are produced by a complex architecture characterized by multiple spatial scales – ranging from neurons, to local networks (of thousands of neurons) and to entire brain regions (of millions of neurons). Churchland and Sejnowski called these scales “levels of organization” [3]. As a result of the pioneering anatomical studies of Ramón y Cajal [4], it became clear that the microscopic scale consists of different types of neurons with axons and dendritic arbors. At a scale of approximately 100 μm, the fine structure of the nervous system is composed of small clusters of neurons that are synaptically connected to form basic cortical microcircuits [5]. At a mesoscopic scale, groups of ~10,000 neurons with similar response properties, and internal connectivity, tend to be vertically arrayed into columnar arrangements of approximately 0.4–0.5 mm in diameter [6,7]. Finally, at macroscopic scales, the brain has been partitioned into regions, and delineated according to functional and anatomical criteria [8]. The different parts of the brain typically include the interactions of tens, perhaps hundreds, of these brain regions that are reciprocally interconnected by a dense network of corticocortical axonal pathways [9]. Recorded at different spatial scales, neuronal activities take the form of rhythmical cellular discharges at the scale of individual neurons, high-frequency oscillatory activity in the local field potentials (LFPs), or intermittent synchronization in the electroencephalogram (EEG) at the large scale. On each spatial scale, these characteristic processes run at various timescales: the scale of the spike (or other intrinsic cellular rhythms) is on the order of milliseconds, the scale of local synchronization of small
networks is on the order of 10 ms, and finally, the large-scale integration occurs on the order of 100 ms. In accordance with these different temporal and spatial scales, multiple neuronal oscillations (i.e., rhythmic neural activity) are recorded, covering a remarkably wide frequency range from very fast oscillations with frequencies exceeding 400 Hz to very slow oscillations under 0.1 Hz [10]. Fast oscillations reflect the local synchrony of small neuronal ensembles whereas slow oscillations can recruit neuronal populations of several brain structures [11].

How can these complex multiscale dynamics be understood? Largely pioneered by Skarda and Freeman [12], the general theoretical framework that explicitly considers nonlinear, nonequilibrium, open, and strongly coupled systems has provided important insights into global brain dynamics [13]. Typically, complex systems possess a large number of elements or variables interacting in a nonlinear way, and thus have very large state spaces. However, for a broad range of initial conditions, some systems tend to converge to small areas of the state space (attractors) – a fact that can be interpreted as a spontaneous emergence of long-range correlations. In neurosciences, the growing need for a better understanding of these types of collective behaviors led to a general description of brain activities based on dynamic system theory [14–18]. Employing principles based on dynamical systems has advanced our understanding of the interplay between micro- and macroscopic scales [15,19]. In particular, in addition to experimental works, the plausibility of this view has been demonstrated by large-scale simulations showing dynamical regimes that were not explicitly built-in, but emerged spontaneously as the result of interactions among thalamocortical networks [20]. Nevertheless, a gap still exists between these formal descriptions and physiology. Indeed, many observations generated by this dynamical approach are still waiting for a clear biological interpretation.

Given that the global brain dynamics comprises multiscaled patterns and processes, the main purpose of this chapter is to address the following two questions: (1) Are there general rules for scaling up and scaling down brain dynamics? (2) Is it possible to characterize the physiological processes underlying these rules?

8.2 The Brain Web of Cross-Scale Interactions

It was recently proposed that fundamental differences between computers and brains might not reside in the particular nature of any of them (artificial/living). Rather, they might consist of different organization principles of interactions between scales [21]. Following this point of view, in computers, microscopic phenomena (like a single electron) are irrelevant for the understanding of more macroscopic phenomena (like the manipulation of bits of memory in software codes). If these microevents interfere with the macroscopic behavior, they are interpreted merely as a kind of “noise”. In contrast, the brain does not shield the macroscopic levels from the microscopic ones in the way that a computer shields bits from electrons (Figure 8.1). In particular, new macroscopic properties can
emerge from microscopic properties and, in turn, these global patterns provide feedback to microscopic activities. In a crude manner, it could be said that the software is acting on the hardware. Two basic types of causalities can be distinguished here. On one hand, small-scale interactions can lead to a large-scale pattern and this feedback can be defined as upward causation. This may lead to an ontologically autonomous, and sometimes unexpected, behavior that cannot be explained by information at the microscopic level alone. Here, a critical mass of spontaneous synchronization may trigger a wave that can propagate across scales of observation. On the other hand, these large-scale patterns can influence the small-scale interactions that generated them. This is often referred to as a downward causation to stress its active efficacy [22,23]. It is important to note that upward and downward causations cannot be defined independently of each other, as they are codetermined. Indeed, due to the strong level entanglement, it is not possible to fully separate these two distinct causal categories, even though we do need to invoke two aspects in causation. Thus, a full account of upward and downward causation depends on (1) local interactions and (2) information about the global context. Typically the latter will enter the solution of the problem in the form of constraints or boundary conditions. Therefore, following Simon [24], upward and downward interplays can be interpreted as a “loose vertical coupling,” allowing the separation between subsystems at each level. While the word “loose” suggests “decomposable,” the word “coupling” implies resistance to decomposition.
8.3 Multiscale Recordings of the Human Brain

Invasive brain recordings in patients with epilepsy constitute an invaluable opportunity for elucidating some properties of the multiscale brain dynamics. This research can be carried out with patients who underwent continuous long-term monitoring for presurgical evaluation of intractable epilepsy. In many cases, scalp-recorded EEG is insufficient to fully characterize epileptic networks due to unavoidable effects of linear summations of current sources over large cortical territories, and the considerable distances from recording sites to deep generators. Determined as a function of the clinical hypotheses, intracranial EEG was recorded from the surface of the cortex (subdurally) or from depth electrodes stereotactically implanted in deeper cortical structures (Figure 8.2a; [25]). Thanks to a relatively broad spatial sampling (with sometimes over 100 electrode sites), such invasive electrodes allow investigation of simultaneously recorded neuronal activity from multiple brain areas, and provide sampling of activities across cortical and subcortical structures that is rarely achieved in animal studies. By recording simultaneously from multiple brain regions, these data have the potential to reveal regional diversity in the properties of local brain activities such as their spatial topography, spectral characteristics, precise timing and propagation, and phase coherence [2,26]. However, recordings of the electrical activity at the large scale do not have sufficient spatiotemporal resolution to distinguish between the local and high-frequency processes whose interactions constitute elementary information processes. A straightforward approach to examine the sources of the EEG events is to simultaneously record small populations of neurons. In this respect, as demonstrated in vivo in animal studies, microelectrode recordings are currently the best technique for monitoring the activity of small networks in the brain [27]. By recording from the electrodes placed near the cells, it is possible to record action potentials – the output of neurons – at a millisecond temporal resolution. By using many electrodes in this manner, it may be possible to record from hundreds of neurons simultaneously in tissue volumes less than 1 mm³. These local field potential measurements or “micro-EEG,” combined with recordings of neuronal discharges, will provide us with information about the cooperating inputs onto the recorded cell population. Nevertheless, with microelectrodes alone, a large number of recording points within a small volume of brain tissue are required for high spatial resolution, and for making interpretation of the underlying cellular events possible. Therefore, the simultaneous recordings of micro- and macroscopic levels are required to provide a high spatial–temporal mapping of network activity. During the last few decades, single and multiple microelectrode techniques have been developed for humans in an attempt to reveal the neuronal and neuronal network processing, occurring within identified cortical functional areas [28,29]. Most of these in vivo microelectrode recordings are microwires attached to standard implanted macroelectrode recordings (Figure 8.2a). The intracranial EEG and microelectrode
recordings present two extreme but complementary views: on one hand, they reveal that complex neuronal processes, such as cognitive or epileptic activities, translate into specific variations of the firing rate of single neurons; on the other hand, they demonstrate that these processes involve widely distributed cortical networks. One may wonder about the optimal level of description of neural activity for human brain dynamics: the single neuron or vast and distributed cell populations? As discussed above, both levels of description seem relevant and complementary, and simultaneous intracranial and microelectrode recordings provide a temporal link between single-neuron electrophysiology and global brain imaging.

Figure 8.2 (a) Multiscale recordings of a macroscopic EEG and local field potentials. Here, in parallel to “clinical” macroelectrodes, microelectrodes emerge at the tip of the dedicated macroelectrode and record the activity of a small group of neurons from a volume around 1 mm$^3$. (b) Display of gamma oscillations (black arrow) appearing simultaneously, in either the raw signals or those filtered between 40 and 120 Hz, in the right and left posterior parahippocampal gyri (PHG) during slow-wave sleep. Note that gamma activities were temporally correlated with positive peaks (i.e., up deviations) of EEG slow waves. (c) Examples of gamma events simultaneously recorded with 30 microelectrodes in the right and left parahippocampal gyri (ant: anterior part and post: posterior part). Note the complex spatiotemporal distribution of these activities, often involving both homotopic sides, the strong variability of involved electrodes, and variable location of the starting site (green triangle).
Physiological Correlates of Cross-Level Interactions

One example of interactions between levels is given by the phasic modulation of local high-frequency oscillations by large-scale sleep slow waves. Slow waves constitute the main signature of sleep in the EEG [30], and have a tendency to propagate as large-scale patterns throughout the brain along typical paths, from medial prefrontal cortex to the medial temporal lobe through the cingulate gyrus and neighboring structures [31,32]. Animal studies have established that such waves reflect a bistability of thalamocortical neurons undergoing a slow oscillation (<1 Hz) between active (up) and inactive (down) states [33], and that these waves group and modulate faster than the local brain oscillation like spindles (12–15 Hz) and high-frequency activities in the beta (from 15 to 25 Hz), or gamma range (from 30 to 120 Hz) [34]. Here, the amplitude (or power) of the faster oscillations was systematically modulated by the phase of slow waves, and these cross-frequency couplings (also called phase–amplitude coupling or “nested” oscillations) may be a signature of cross-level interactions. Interestingly, gamma oscillations, usually associated with waking functions such as sensory binding [35], attention [36], or encoding/retrieval of memory traces [37], are therefore strongly expressed during the deepest stages of sleep. It was speculated that cortical gamma patterns briefly restore “microwave” activity and may be implicated in reactivations of memory traces acquired during previous awake periods [38,39]. Until recently, the existence of gamma oscillations during normal sleep had not been reported so far in the human brain. Thus, we explored, with simultaneous micro- and macroelectrodes recordings, the presence of these oscillations in the human cortex during sleep in epileptic patients. Multiple cortical locations were simultaneously recorded with up to 64 microwires, and we confirmed that gamma oscillations are reliably associated with EEG slow waves, and with a marked increase in local cellular discharges [40,41] (Figure 8.2b). By analyzing simultaneous activity across multiple brain regions, we observed that these gamma oscillations form complex spatiotemporal patterns, often involving many different cortical areas at about the same time, including homotopic regions (Figure 8.2c). Similar slow-wave modulations of gamma oscillations were also recently confirmed using intracranial macroelectrodes [42], suggesting a strong local synchronization of the cellular activities. Indeed, coincident firings with millisecond precision between cells within the same cortical area were shown to be strongly enhanced during gamma oscillations [41]. In agreement with old proposals [43], it can be suggested that the slow and global phasic switches between active and inactive states modulate the local neuronal excitability, facilitating the generation of multiple mesoscopic gamma oscillations, and determine whether these oscillations are attenuated or amplified on a large scale (Figure 8.3). Locally, following a similar mechanism of phase–amplitude coupling, gamma oscillations of smaller group of neurons also modulate the probability of spike occurrence [44,45]. Indeed, spikes are mainly generated on a particular high excitability phase of the membrane potential. In particular, gamma-frequency fluctuations in inhibitory and excitatory synaptic potentials have been shown to determine the precise probability and timing of action potential generation, even at the millisecond level [45]. These observations were
reported from experimental cortical preparations (*in vitro* and *in vivo*), but a similar effect is expected to occur under natural conditions when oscillatory fluctuations of the membrane potential are induced by network interactions, leading to fast cyclic alterations of excitatory and inhibitory inputs [39,46]. This suggests that the response properties of a single neuron strongly depend on the ongoing population oscillations of related networks, effectively amplifying cellular activities that occur at particular times of their phases. In this context, as suggested by Fries [47], since network oscillations (in particular in the high-frequency range) impose precise temporal windows for the integration of synaptic input, they also facilitate interactions between different brain areas. Indeed, it was proved that two distinct brain areas exchange spikes when the corresponding field oscillations are in phase [48]. On the contrary, there are no spike exchanges when the field oscillations are out of phase. Therefore, cyclical variations in neuronal excitability generated by synchronous fast oscillations may modulate, and constrain the communications between spatially widespread cellular activities. Prevalent during sleep, macroscopic field potential in the low-frequency range (<4 Hz) may constrain local oscillations in the high-frequency range (40–200 Hz, e.g., gamma oscillations). In turn, these high-frequency oscillations determine, in the millisecond range, the probability of occurrence of spikes and of their temporal coincidences between different brain regions.
identified a spatially distributed phase–amplitude coupling of cortical high-frequency oscillations in the gamma band (40–120 Hz) by theta oscillations (4–8 Hz) [52,53]. These slow field potentials can be recorded during wakefulness in EEG using either depth or surface electrodes [51,54] but are also reflected in the coherent spontaneous fluctuations of the blood-oxygen-level-dependent response (BOLD) observed in functional magnetic resonance imaging [55].

8.5 Level Entanglement and Cross-Scale Coupling of Neuronal Oscillations

The examples discussed above suggest that brain activities are nested like Russian Matryoshka dolls and are determined by interactions between various scales. In particular, brain oscillations relate to each other in a specific manner to allow neuronal networks of different sizes to cooperate in a coordinated manner [11]. All oscillations are state dependent but numerous oscillation frequency bands are simultaneously present at the different states of the wake–sleep cycle, and can modulate each other. As a general rule, lower frequency oscillations allow for an integration of neuronal effects with longer delays and larger areas of involvement. In contrast, high-frequency oscillations tend to be confined to small ensembles of neurons, and allow for a more precise and spatially limited representation of information with short synaptic delays and low variability. In this context, with other authors [51] (see also Chapter 9), we suggest that a physiological mechanism of multilevel interactions can be based on the phase–amplitude coupling of neuronal oscillations that operate at multiple frequencies and on different spatial scales. Specifically, the amplitude of the oscillations at each characteristic frequency is modulated by phasic variations in neuronal excitability, induced by lower frequency oscillations that emerge simultaneously on a larger spatial scale. Therefore, multiple neuronal oscillations vibrating at various frequencies and on multiple spatial scales may serve as crucial instruments for scaling up or scaling down brain dynamics. Specifically, oscillatory variations in neuronal excitability generate (nonlocal) constraints that lock the many degrees of freedom of a smaller scale together. As the intervals between these activation phases and the temporal window of activation vary in proportion to the length of the oscillation period, lower frequency oscillations allow for an integration of larger brain regions. In this context, although there are numerous open questions, one would expect the large-scale slow cortical oscillations to play an important role in the control of internal cognitive events. In particular, it is well known that animal and human subjects can learn to alter their own brain activity when provided with feedback. This voluntary control of neural activity in the nervous system was demonstrated by multiple studies using operant conditioning of EEG frequency components [56,57], or by brain computer interfaces in which neural activity controls cursors or robotic arms under closed-loop conditions [58,59]. Furthermore, as shown for primates [60,61] or humans [62], conscious control is even possible at the cellular level with an up- and downregulation of the firing activities of specific cellular groups. Following our framework, it can be expected that...
8.6 Conclusions

Over the past decade, the development of new and faster methods of data collection has led to the accumulation of large volumes of data that relate to a variety of scales within the nervous system. However, neuroscientists focus on one level of the nervous system at a time, so there has been very little progress in integrating the observations in order to create a unified understanding of brain dynamics. The main purpose of this chapter is to conjecture physiological principles for scaling up or scaling down the multiscale brain dynamics. Following several observations, we propose that a possible model of multilevel interactions is based on a tight phase–amplitude coupling of neuronal oscillations that operate at multiple frequencies and on different spatial scales. As a general rule, the neuronal excitability is larger during a certain phase of the oscillation period. In particular, downward causations can be seen as cyclical modulations in neuronal excitability that determines whether faster and more local oscillations are attenuated or amplified. Given that the brain dynamics exhibit self-organization and emergent processes at multiple levels, and that emergence involves both upward and downward causation, it also seems legitimate to conjecture that conscious states are correlated with large-scale global activities of the system that governs or constrains local interactions of neurons. Specifically, we propose that a signature of attention and consciousness could be mediated by cortical slow oscillations.

Acknowledgments

This chapter is dedicated to the life and work of Francisco Varela. The idea of exploring cross-scale interactions through brain oscillations emerged from discussions I had in the late 1990s with Francisco and our research team.
References


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Abstract

Progress in understanding the global brain dynamics has remained slow to date in large part because of the highly multiscale nature of brain activity. Indeed, normal brain dynamics is characterized by complex interactions between multiple levels: from the microscopic scale of single neurons to the mesoscopic level of local groups of neurons, and finally to the macroscopic level of the whole brain. Among the most difficult tasks are those of identifying which scales are significant for a given particular function and describing how the scales affect each other. It is important to realize that the scales of time and space are linked together, or even intertwined, and that causal inference is far more ambiguous between than within levels. We approach this problem from the perspective of our recent work on simultaneous recording from micro- and macro-electrodes in the human brain. We propose a physiological description of these multilevel interactions, based on phase–amplitude coupling of neuronal oscillations that operate at multiple frequencies and on different spatial scales. Specifically, the amplitude of the oscillations on a particular spatial scale is modulated by phasic variations in neuronal excitability induced by lower frequency oscillations that emerge on a larger spatial scale. Following this general principle, it is possible to scale up or scale down the multiscale brain dynamics. It is expected that large-scale network oscillations in the low-frequency range, mediating downward effects, may play an important role in attention and consciousness.

Keywords: electroencephalogram (EEG); human brain; intracranial EEG; large-scale brain dynamics; local field potentials (LFPs); microelectrodes.
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