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Intracellular and computational evidence for a dominant role of internal network activity in cortical computations

Alain Destexhe

The mammalian cerebral cortex is characterized by intense spontaneous activity, depending on brain region, age, and behavioral state. Classically, the cortex is considered as being driven by the senses, a paradigm which corresponds well to experiments in quiescent or deeply anesthetized states. In awake animals, however, the spontaneous activity cannot be considered as 'background noise', but is of comparable — or even higher — amplitude than evoked sensory responses. Recent evidence suggests that this internal activity is not only dominant, but also it shares many properties with the responses to natural sensory inputs, suggesting that the spontaneous activity is not independent of the sensory input. Such evidence is reviewed here, with an emphasis on intracellular and computational aspects. Statistical measures, such as the spike-triggered average of synaptic conductances, show that the impact of internal network state on spiking activity is major in awake animals. Thus, cortical activity cannot be considered as being driven by the senses, but sensory inputs rather seem to modulate and modify the internal dynamics of cerebral cortex. This view offers an attractive interpretation not only of dreaming activity (absence of sensory input), but also of several mental disorders.

Address
Unité de Neurosciences, Information et Complexité (UNIC), CNRS, 91198 Gif-sur-Yvette, France

Corresponding author: Destexhe, Alain (destexhe@unic.cnrs-gif.fr)

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The awake and conscious brain of adult mammals is characterized by ample spontaneous activity. Intracellular recordings of cortical neurons in awake adult cats [1,2•,3•], monkey [4] or mice [5] show that the neurons are always active and rarely exhibit periods of quiescence (reviewed in [6]). Indeed, the resting membrane potential of cortical neurons typically cannot be observed *in vivo*, except in some cases of deep anesthesia or under the action of drugs [7•]. It was shown that in the active regime, cortical neurons are subject to large amounts of fluctuations, often called 'synaptic noise'. This activity is major, as its total conductance can be several-fold larger than the resting membrane conductance, a situation called the 'high-conductance state', which may have many important consequences on the integrative properties of cortical neurons (reviewed in [8,9]).

In awake subjects, the electroencephalogram (EEG) is typically of low amplitude, fast frequency and is very irregular, a pattern which is called 'activated state' or 'desynchronized EEG'. Multiple unit recordings in the aroused brain display irregular firing with very low levels of synchrony, which contrasts with the synchronized and slow oscillatory activities seen during slow-wave sleep [6,10–13]. Because it is during this apparently noisy regime that the main computational tasks are performed, understanding this type of stochastic network state is crucial [14].

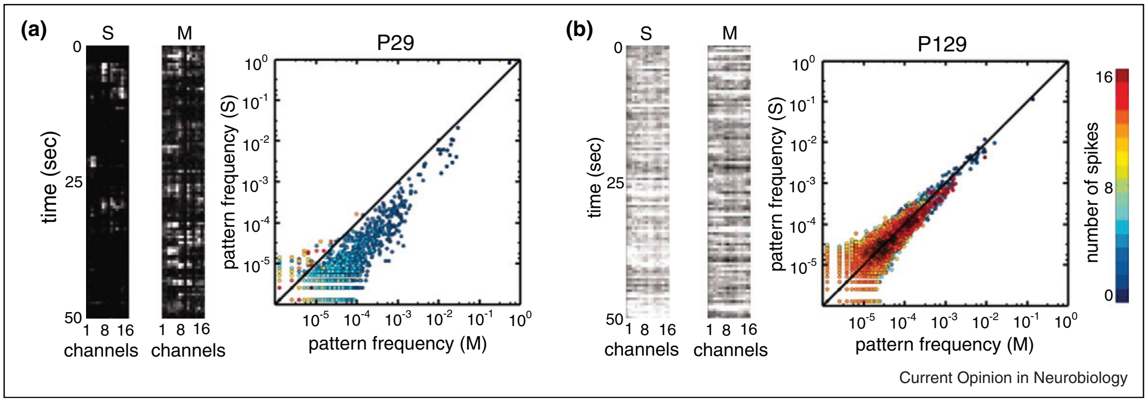
This strong spontaneous activity is classically considered as 'noise' independent of the input signal. However, experimental and modeling evidence suggest that it is significantly structured and is different from independent additive noise [15]. The present article reviews such evidence, with an emphasis on intracellular and modeling results, as well as their combination.

The intrinsic activity of the brain

The first proposal that neurons are not passive relays being driven by external inputs dates back to the early 20th century with the Belgian electrophysiologist Frederic Bremer [16••,17]. He proposed that neurons generate intrinsic and self-sustained activity under the form of intrinsic oscillatory properties. The current thinking at the time was that oscillatory activity arises from circulating waves of activity, a theory called the 'circus movement theory'. Bremer was an opponent to this theory, and he proposed instead that neurons can display intrinsically generated oscillatory activity, and that such oscillators synchronize into population oscillations, two concepts which are well known today. The presence of such intrinsic properties was later demonstrated and characterized, in invertebrate preparations of pattern generators [18,19], and in various parts of the central nervous system [20].

Looking into the morphological details, it becomes clear that the brain is not wired to be driven by sensory inputs. In cerebral cortex, the synapses arising from thalamocortical fibers constitute a small minority (a few percent), even in Layer IV, the main recipient of the thalamic

Figure 1



Similarity of network activity patterns during spontaneous activity and visual responses. **(a)** Frequency of occurrence of activity patterns under spontaneous activity (SA) versus presentation of a movie (M) in a young animal. **(b)** Same plot for an adult animal. Each dot represents one of the 65 536 possible binary activity patterns detected in the multi-electrode recording. The color code indicates the number of spikes. Black line shows equality. The left panels show examples of neural activity patterns on the 16 electrodes in representative SA and movie trials for the same animals. Figure modified from [26].

input. The vast majority of synapses arise from cortico-cortical input, either from local axon collaterals or from long-range cortico-cortical fibers [21]. In the thalamus, the synapses coming from afferent sensory fibers are also less numerous compared to the synapses arising from cortical axons [22]. So here also, the cortex is the main afferent to the thalamus, which is difficult to reconcile with the idea of the thalamus being a simple 'relay' of sensory information en route to cortex. It rather seems that the thalamocortical system is wired to favor internal processing.

At a point of view of brain dynamics, it is important to note that the brain is not silent but displays considerable spontaneous activity, independent of the sensory input. For example, during slow-wave sleep or rapid-eye movement (REM) sleep, the brain is as active as during wakefulness, despite the fact that sensory inputs are not processed [6]. Strikingly, there is little electrophysiological difference between the activity of neurons and local field potentials between REM sleep, the 'Up states' of slow-wave sleep and wakefulness [13,23••,24].

On the basis of such observations, Llinas and Paré [23••] proposed that most the activity of the adult brain is intrinsically generated, and is only influenced by the senses rather than being driven by it. With no sensory input, the intrinsic activity is left alone, which corresponds to REM sleep and the dream state. Thus, the awake brain activity is seen as a dream modulated by the senses [23••].

Following this seminal paper, several studies provided strong support to this view. First, it was shown that the spontaneous activity of the brain is not simply 'noise' but is much more structured. For instance, in the visual cortex of ferrets, it was demonstrated that the spontaneous activity — largely absent in very young animals — becomes progressively more intense and structured with age [25••]. Moreover, in the adult, the spontaneous activity was only slightly modified by the visual input. Interestingly, analyzing the spike patterns produced in response to natural images, with those produced by spontaneous activity revealed no particular resemblance in young animals (Figure 1a), but they were strikingly similar in adults [25••,26] (Figure 1b). Similar observations were made in other structures, such as the auditory and somatosensory cortices of rats [27], where spontaneous spike patterns were found to be very similar to evoked responses. In the primary visual cortex of anesthetized cats using voltage-sensitive dye imaging, not only the visual responses were of comparable amplitude as the spontaneous activity, but also the spatiotemporal activity patterns were also very similar [28].

Thus, it seems that one cannot easily distinguish between spontaneous activity and the activity evoked by natural stimuli, which shows that most of this activity is internally generated, and that the net effect of sensory input is small. In other words, these results suggest that sensory-evoked activity represents a modulation of ongoing cortical spontaneous activity [25••], very similar in spirit to the Llinas and Paré [23••] proposal.

Is there quiescence in the absence of input?

Although such findings offer a nice perspective to explain population recordings, they are not consistent with all of the available experimental data. In particular, in the primary visual cortex (V1), a large number of studies have demonstrated clear visual responses and selectivity of