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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)

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

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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 of 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...
neurons to features such as orientation, direction, and contract [29]. Not much spontaneous activity seems to be present in such single-cell experiments (see also [30]). Very low levels of spontaneous activity were also reported in experiments using patch electrodes in vivo, in motor and somatosensory cortex [31,32].

These seemingly contradictory observations can be reconciled based on three observations. First, the level of spontaneous activity is highly dependent on the state of the animal. Some of the above experiments were done under anesthesia, which may considerably limit spontaneous activity [7*]. Because intense spontaneous activity is responsible for setting a ‘high-conductance state’ in cortical neurons [8,9], some anesthetized states can artificially augment neuronal responsiveness by setting the membrane of cortical neurons into lower conductance states, making the membrane more excitable.

The second factor, already mentioned above, is that the level of spontaneous activity considerably depends on the age of the animal [25**]. Newborn or very young ferrets display very modest amount of spontaneous activity, while it is much more prominent in the adult, where spontaneous activity can be more intense than visual responses [25**]. Unfortunately, the growth of spontaneous activity with age is paralleled with axon myelination in cerebral cortex. Since myelination makes patch recordings to be increasingly difficult with age, it is possible that the relatively young age of the animals explains the low levels of spontaneous activity observed in some of the patch-recording experiments.

The third important parameter is that spontaneous activity may be specific to each layer of cerebral cortex. Superficial layers display very sparse firing, while deep layers have more profuse spontaneous activity [33*]. Whole-cell recordings are usually made in superficial layers, which may also explain the low level of spontaneous activity observed using this technique.

Taken together, these results suggest that a fully active network with prominent spontaneous activity is totally relevant to cortical information processing. In such conditions, the neurons are presumably in high-conductance states [8], as indicated by conductance measurements from intracellular recordings in awake cats [34].

Figure 2

(a) Spontaneous activity (SA)

(b) Power spectra estimated for different types of inputs (DG — drifting gratings; GEM — gratings with eye movements; DN — dense noise).

(c) Frequency scaling exponent calculated for different cells during natural images, and represented against that of spontaneous activity. Figure modified from [35].
Intracellular and computational evidence for dominant internal dynamics

Another set of evidence is provided by model-based analyses of intracellular recordings in vivo. Figure 2a shows examples of intracellular recordings of cat V1 neurons during spontaneous activity (SA) and the presentation of natural images (NI) [35] (original data from [36]). To measure statistical similarity, the frequency scaling exponent was computed from the power spectrum of the signals (Figure 2b), yielding exponent values for different stimulus conditions. Remarkably, the exponents were very close between NI and SA conditions (Figure 2c), but not for other stimulus conditions (not shown). This analysis shows that the spontaneous activity of V1 has similar subthreshold statistics as during natural images, a result with is in full agreement with findings on awake animals [25**].

In an attempt to quantify the conductance variations underlying such effects, an efficient method is to compute the spike-triggered average (STA) of the synaptic conductances during different conditions. In models receiving in vivo — like background synaptic inputs at excitatory and inhibitory synapses, the conductance STAs revealed a specific pattern, with an increase of excitatory conductance and a decrease of inhibitory conductance (Figure 3a). This pattern was also replicated in dynamic-clamp experiments in vitro [37*,38] (Figure 3b).
A specific procedure was designed to estimate STAs from intracellular recordings in vivo, where the conductances are not known (unlike models and dynamic-clamp experiments where the conductances are pre-set). The estimation procedure was in two steps. First, the total conductances and their variances are estimated using a method called ‘VmD method’ [39]. Second, a maximum likelihood procedure is used to estimate the STA of conductances [37]. These procedures were tested in models and in dynamic-clamp experiments in vitro [37,39]. Application to intracellular recordings in awake and naturally sleeping cats revealed the same pattern of conductance STA with a decrease of inhibition [34] (Figure 3c).

This pattern of conductance with excitation increase and inhibition decrease is opposite to what was observed in several sensory systems. A feed-forward drive (such as sensory inputs) would predict an increase of excitation closely associated with an increase of inhibition. This is indeed what was observed in many instances of evoked responses during sensory processing [40,41,42–44]. Figure 3d shows an example of such concerted increase of excitation and inhibition in rat barrel cortex [43]. Note,
however, that one study reported a considerable cell-to-cell diversity in the conductance variations evoked by synaptic inputs; among them, some of the cells displayed a mirror image for excitatory and inhibitory conductance variations (see [41]).

Computational models can be used to further show that this pattern of conductance STA corresponds to spontaneous network activity. Sparsely connected networks of excitatory and inhibitory neurons can display ‘asynchronous irregular’ states [45], whose noisy-like properties are very close to recordings in awake animals [46]. One such state is illustrated in Figure 4a–b (model from [47]). Calculating conductances in this model revealed conductance STAs with the increase of excitation and decrease of inhibition (Figure 4c).

These results show that the same pattern of opposite conductance variations is seen in different cases, when the neuron is driven by stochastic synaptic activity in models (Figure 3a) or dynamic-clamp experiments (Figure 3b), or in the awake animal (Figure 3c). This pattern is also seen in models of self-generated network activity (Figure 4c). However, a different pattern of concerted conductance variations is seen in many sensory systems (Figure 3d).

**Proposed scheme to account for the different experiments**

To account for the disparity of the above results, a simple model of a neuron receiving two input sources was simulated. First an ‘intrinsic activity’ consisting of stochastic release at excitatory and inhibitory synapses, and second, an ‘external input’ consisting of a controlled stimulation of an independent set of excitatory and inhibitory synapses (see scheme in Figure 5). For weak external inputs, the activity is dominated by intrinsic activity and one recovers the pattern of opposite conductance variations (Figure 5a). For medium input strength, an additional component appears in the conductance
STAs (Figure 5b). For strong inputs, the latter component dominates, and the STAs consist of concerted variations of excitation and inhibition (Figure 5c).

These simulations suggest a coherent picture to explain all the above results. If the neuron’s spiking is mostly dominated by intrinsic network activity, then the conductance STAs display opposite variations of excitatory and inhibitory conductances. This is the case for neurons receiving random inputs (either in models or in vitro; see Figure 3a,b) or in a self-generated spontaneous activity state in a network (Figure 4c), as well as in awake animals [34] (Figure 3c). Conversely, when the external input is strong compared to spontaneous activity, the conductance STA consists of a concerted increase of excitatory and inhibitory conductances (Figure 5c), similar to many observations during sensory responses [40,41*,42,43] (see Figure 3d).

Interestingly, the fact that the same opposite pattern is found in awake animals, suggests that the spiking in the awake cat is also determined mainly by spontaneous activity, while the direct effect of afferent activity is not visible. This is in full agreement with the results reviewed in the first part of the paper, where the statistical similarity between spontaneous and evoked activity also suggests that the direct effect of afferent activity is either negligible or dominated by the ‘intrinsic’ activity of the network.

Conclusions
In summary, the intracellular and computational results reviewed here collectively suggest that the spike-triggered conductance patterns is a very powerful way to determine whether a system is dominated by its internal activity, or is driven by afferent activity, as summarized in Figure 5. This approach makes a number of predictions, which are briefly discussed here.

First, it suggests that in many sensory systems, the measurements reporting a concerted conductance increase can be explained either because the level of spontaneous activity was very low (which may be in part because of anesthesia), or because the input was unusually strong. The fact that a large diversity of conductance combinations was observed in some cases [41*], including concerted and opposite conductance variations, suggests that part of these observations is due to different network states with different levels of spontaneous activity in the system. Such conductance measurements should be corroborated with an analysis of the level of spontaneous activity to verify what component of the conductance variations is really due to the input.

Second, the finding that most spikes in awake cat association cortex are due to spontaneous activity and not to afferent volleys indeed suggests that most of the computing of this brain area is done internally, while the processing of afferent inputs is limited. Whether this is specific to that particular area, or constitutes a general principle of brain computation, should be addressed by future work.

Finally, the results reviewed here are in total agreement with the original proposal of Llinas and Paré [23**] that most of the brain activity is internal, intrinsic and ongoing, while the effect of sensory input is a modulation of this internal activity. It is also in agreement with the similarity between activity patterns during natural viewing and spontaneous patterns [25**,35] (see Figures 1 and 2). The fact that most of the spikes in the awake cat are due to spontaneous activity also supports these findings.

Note that the fact that the sensory drive triggers internal dynamics is not necessarily inconsistent with the low levels of spontaneous activity reported in some experiments (such as [30]). Because of the dense recurrent connectivity in cortex, such low-level spontaneous activity can still be associated with highly active subthreshold membrane potential dynamics, as indeed found intracellularly in awake animals [5].

Previous computational approaches have modeled the interaction between spontaneous activity and sensory inputs based on the data available at the time [48*,49,50]. It was also proposed that the spontaneous activity of cerebral cortex exhibits several distinct states, similar to a finite-state machine [51]. No electrophysiological evidence for such multiple states has been provided; it rather seems that spontaneous activity consists of a continuously changing state, modulated by the sensory input. Spontaneous activity may also represent a form of prediction of the sensory input (reviewed in [15]). Modeling such interactions represents a considerable challenge for computational studies.

Thus, the proposal that ‘wakefulness is a dream modulated by the senses’ [23**] still holds, and seems to be in agreement with electrophysiological and conductance measurements. This view offers original ways to interpret some pathologies which may be due to disorders of intrinsic activity, which could give rise to various symptoms of altered processing, such as daydreaming, inattentional blindness, mind wandering, or schizophrenia. Further work should carefully integrate and measure spontaneous activity, and view it not as ‘noise’, but as an integral component of brain computations.

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