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Spontaneous and driven cortical activity: implications for computation

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The traditional view of spontaneous neural activity as ‘noise’ has been challenged by recent findings suggesting that: (a) spontaneous activity in cortical populations is highly structured in both space and time, (b) the spatio-temporal structure of spontaneous activity is linked to the underlying connectivity of the cortical network, (c) spontaneous cortical activity interacts with external stimulation to generate responses to the individual presentations of a stimulus, (d) network connectivity is shaped in part by the statistics of natural signals and (e) ongoing cortical activity represents a continuous top-down prediction/expectation signal that interacts with incoming input to generate an updated representation of the world. These results can be integrated to provide a new framework for the study of cortical computation.

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Introduction

Spontaneous activity is defined as the firing of neurons measured in the absence of sensory input. Yet, even under conditions where one attempts to minimize external stimulation the sensory end-organs remain active and generate a weak but continual input to central cortical structures. It has been known that such weak input can lead to perceptual outcomes (hallucinations), as it occurs in cases of sensory deprivation. An example is the Charles Bonnet syndrome, a condition where patients experience various sorts of visual hallucinations due to vision loss, from simple straight lines to detailed and complex pictures [1]. A lesser known but more amusing instance is the recount by Richard Feynman of his experiences undergoing sensory deprivation in one of John Lilly’s isolation tanks, after which he pondered: ‘[...] whether

hallucinations, like dreams, are influenced by what you already have in your mind—from other experiences during the day or before, or from things you are expecting to see’ [2]. Indeed, recent findings show that spontaneous activity can have perceptual consequences that reflect ‘what you already have in your mind’, as it appears directly linked to the intrinsic connectivity of cortical networks and top-down expectations. These studies highlight that there is much to learn about brain function even its quiescent state, and underlies the importance of understanding cortical responses as the fusion of ongoing activity and sensory input.

Spontaneous activity is structured in space and time

The relative low rates and apparent randomness in the spontaneous firing pattern of individual cells did not prompt early pioneers of cortical electrophysiology to suspect that they reflected anything else but noise [3]. This picture changed with the first measurements of population activity across large cortical areas, which initially relied on the use of voltage-sensitive dyes (VSDI) [4] and were recently augmented by the proliferation of multielectrode array recordings [5] and *in vivo*, two-photon imaging [6]. These new measurements reveal a number of important properties of spontaneous activity in cortical populations: correlated neural activity can be observed across millimeters of cortex [7,8] and across different time scales [9,10^{**}], the firing of individual cells can be related to the patterns of ongoing activity in its neighborhood [11,12^{**}], and the size of the fluctuations observed in the spontaneous population activity are of similar magnitude to those of the mean response to a high-contrast stimulus [7,13]. These data point to a potential role of spontaneous activity in normal cortical processing, which has motivated investigators to take a fresh look at its role in normal cortical processing.

The structure of spontaneous activity reflects the underlying connectivity

The first question is what mechanism might be responsible for the generation of structured patterns of ongoing activity. A promising working hypothesis is that the structure of spontaneous activity reflects the connectivity of the cortical network, and the rules by which neurons at different cortical locations and with different preferences for stimulus attributes connect to each other [14–17]. The presence of functional maps in primary visual cortex provides an ideal model to test this idea. It has been observed that when the spikes of a cell tuned to a

particular orientation are used to trigger the averaging of the VSDI signal in its neighborhood, a pattern emerges highlighting cortical columns matching the orientation preference of the cell [11]. This result is expected from a similar bias in lateral connectivity inferred from anatomical and spike crosscorrelation data [8,18]. Interestingly, such patterns also emerge in the total absence of an external visual stimulus [19], as if the cortex were to be spontaneously ‘hallucinating’ a physical stimulus with a particular orientation [16]. Theoretical studies have demonstrated that this behavior is expected from an underlying connectivity scheme where nearby cells with similar orientation preferences excite each other, while those with different orientation preferences inhibit each other [15,17,20]. Similar connectivity analyses are now being attempted across cortical areas using BOLD signals [21]. The key revelation from these studies is that the activity of cortical networks under weak input may be used to reveal their intrinsic connectivity, one that may in fact be masked under conditions of strong sensory stimulation.

Spontaneous activity interacts with external stimulation

Spontaneous activity can then offer a handle into brain connectivity, but does it play a functional role in cortical computation? It could be, for example, that external stimulation is so strong that effectively erases any traces of ongoing activity, a situation that would weaken the notion of spontaneous activity as having a significant role. All indications are that this is not the case. First, it has been shown that the variability of responses to repeated presentations of the same stimulus can be largely accounted by the ongoing activity present just before the onset of the stimulus [22]. The simple addition of the spontaneous state of the cortex at the time of stimulus presentation to the mean response provided a reasonable model to explain the responses of the cortex to individual presentations. This result implies that external stimulation does not overwhelm the ongoing cortical activity but interacts with it. Second, external stimulation can lead to response patterns across the cortical population that are similar to those observed in the spontaneous regime, as if thalamic input were to trigger a set of stereotyped response patterns [23–25]. Consistent with this notion of attractors, the cortical responses evoked by natural stimulation appear to be very similar to those observed spontaneously [26,27,28]. Such states may be temporarily protected from being disrupted by external when the network is a so-called UP state [29], providing a type of short-term memory mechanism.

The interaction between the input and the ongoing cortical state depends on the strength of the feed-forward thalamic signals [9,12,30,31]. Strong sensory stimulation drives the cells in the network to de-correlate and respond largely to their local thalamic input. When

the stimulus is weak, lateral interactions in the cortex have a substantial influence on the cortical responses [12]. Cortical computation operates in a feed-forward regime for strong stimuli, relies on feedback and top-down signals for weak stimuli, and adopts an intermediate regime for moderate inputs [12,32]. Such adaptations occur locally at each retinotopic location, so that areas of the image with high contrast are processed in a feed-forward fashion, while areas of low-contrast rely more on contextual influences (driven by lateral interactions) and top-down predictions. The fact that large areas of natural images contain low-contrast signals [33] suggests that vast areas of primary visual cortex may rely on contextual information to generate an accurate representation of the sensory input.

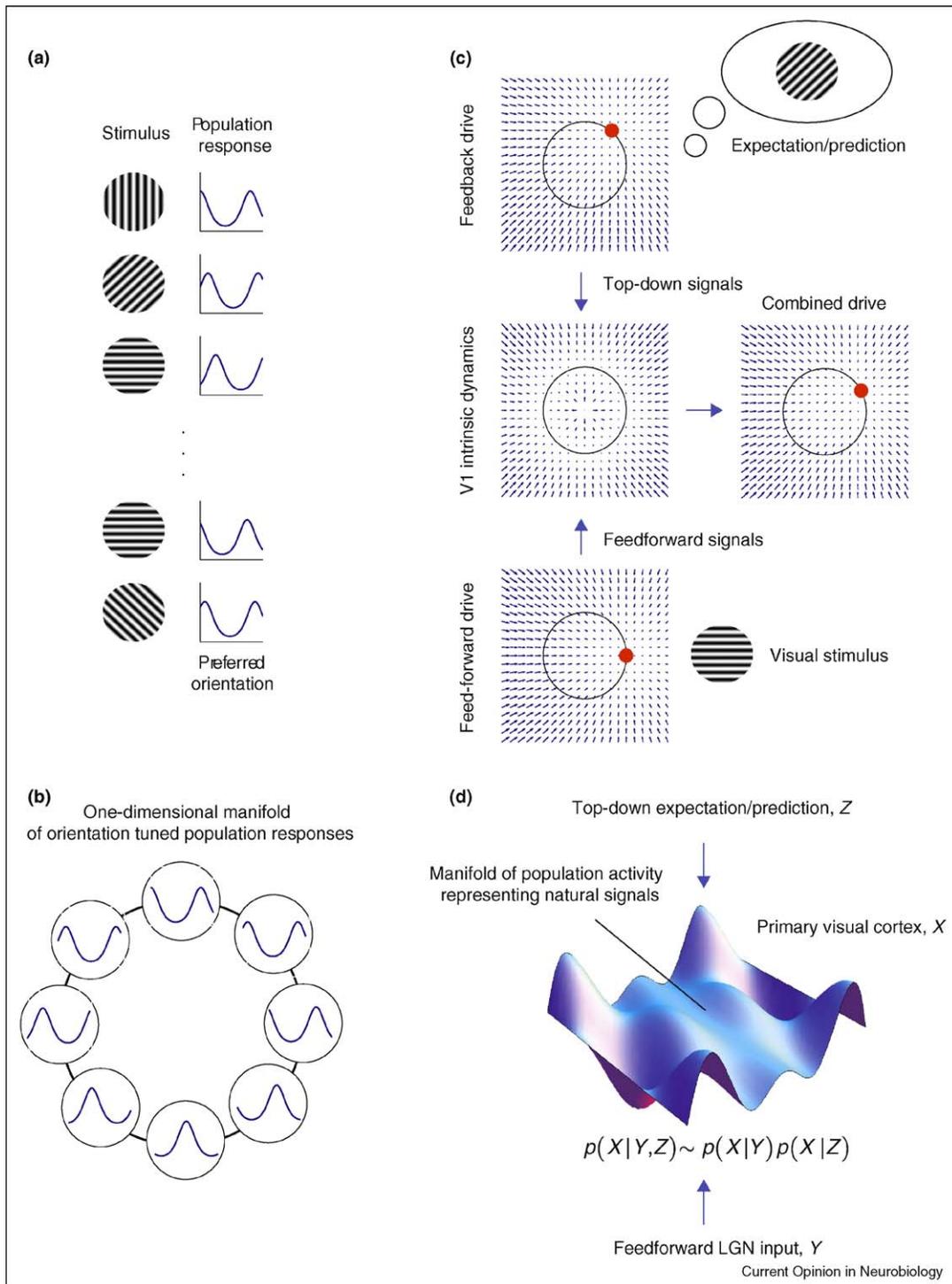
Network connectivity may be shaped by the statistics of natural stimuli

It is easy to envision how patterned spontaneous activity might be linked to the wiring of the network, but what dictates the wiring of the network itself, how do attractors emerge, and what do they mean? One idea is that evolution and developmental rules during the critical period, where cells that ‘fire-together wire-together’ [34] may shape cortical connectivity. Under some condition, one might expect such connectivity to create spatially localized ‘memories’ (or ‘attractors’) [35] representing the manifold of naturally occurring stimuli [36,37,38]. In support of such a scenario, the repetitive presentation of natural image sequences leads to activation patterns that are seen to repeat during spontaneous activity [39,40], therefore leaving a memory trace in the network. The statistics of natural images may thus contribute to shape the local network interactions which, in turn, govern the intrinsic dynamics of cortical responses. From a signal processing point projecting the input data into the manifold of natural signals may prove useful for a variety of operations, such as de-noising and perceptual filling-in [36].

Top-down expectation/prediction/attention modulates ongoing activity

Some studies have asked directly if spontaneous activity has a demonstrable perceptual consequence for the processing of external stimuli. In one such case, Super *et al.* presented monkeys with a difficult figure/ground detection task [41]. In this task the same physical stimulus may be detected in some trials, but not perceived in others. They discovered that the likelihood of the animal detecting the stimulus correlated with the spontaneous level of activity in V1 before the stimulus presentation. In other words, the ability of the animal to detect the stimulus depended critically on the state of the cortex at the time of the presentation. In another study, monkeys’ decisions in a motion detection task were correlated with the spontaneous activity of neurons in area LIP at the time of stimulus onset, and this correlation was present even in

Figure 1



Visual summary of main concepts. **(a)** Coding of orientation by a population of V1 cells. Different oriented gratings produce a profile of activity centered at a different location. Each panel shows the activity of cells with different preferred orientations. **(b)** Assuming symmetry, the resulting manifold of population activity is a circle. **(c)** Conceptual view of how intrinsic dynamics, feed-forward, and feedback drive the cortical state. In each panel, a 'force field' is shown that qualitatively describes how each of the individual mechanisms would act when the cortex is found in different states (in this case represented by the plane). The red dots indicate the equilibrium points for the feed-forward, feedback, and combined components. **(d)** A more general view of the framework. At any point in time primary visual cortex integrates feed-forward information (indicated by the variable Y) with top-down contextual information provided by extra-striate areas (denoted by the variable Z). The state of population activity in primary visual cortex is constrained to the manifold of natural signals, represented by the blue surface. One way of thinking about the integration of information is via Bayesian inference, where the V1 circuitry works to find the state within the manifold that maximizes the conditional probability, $p(X|Y, Z)$, under some assumptions [46], $p(X|Y, Z) \sim p(X|Y)p(X|Z)$. A similar arrangement can be postulated at different levels in the visual hierarchy.

cases where the stimulus had no net motion [42]. Direct contribution of spontaneous activity to intertrial variability in human behavior has also been shown by means of fMRI [43].

While it was originally proposed that neuronal noise in sensory neurons could provide a 'feed-forward' account of these phenomena, it is now becoming increasingly clear that such activity reflects a top-down expectation or prediction signal [44]. A recent experiment has taken advantage of reverse correlation methods in the binocular disparity domain to show very different temporal courses for stimulus-related and choice-related signals in V2 neurons [45]. During the trial, choice-related activity increased over time while stimulus-related signals decreased, arguing for a top-down modulatory signal of choice. Interestingly, the choice-related activity was significant at the time of stimulus presentation, consistent with prior studies and the notion of top-down expectation.

Conclusions

These results can be integrated to provide a framework for the study of cortical computation. To summarize the concepts in a simplified setting, consider the case of coding the orientation of a sinusoidal grating by V1 neurons. Each stimulus (Figure 1a, left) produces an activity profile across the population that translates along the periodic x -axis as its orientation changes (Figure 1b, right, blue curves). The manifold of this space is a circle (Figure 1b). The intrinsic connectivity of the cortex would work continuously to push the state toward the circle, meaning the circle is an attractor of its dynamics (Figure 1c, middle left). If, for whatever reason, the cortical state is found outside the manifold it is pushed back into it, as indicated by the blue arrows. Feed-forward and feedback signals can be viewed as external forces acting on the state of the cortex. Feed-forward input would push the state to the orientation signaled by the LGN (Figure 1c, bottom), while feedback input will push the state to one that would represent an expected or predicted one (Figure 1c, top). The relative strength of feed-forward drive would depend on the reliability of LGN input signaling a particular orientation, while the strength of top-down signals will depend on reliability of the predictive signal. The evolution of the cortical state will be driven by all these forces combined together (Figure 1c, right).

In this scenario, the lack of an external stimulus generates a weak feed-forward drive and the cortical state is determined largely by its own intrinsic dynamics and top-down expectations. This explains why spontaneous activity is not noise. Further, if the attractor has been shaped (via evolution or developmental rules) to represent the manifold of natural signals, it is easy to see how sensory deprivation or weak input can lead to 'hallucinations'

during deprivation [19,40**] and situations where the cortex representing signals related to expectation or choice bias [44,45]. In general, however, the manifold of natural signals is not simple a circle but could be much more complicated (Figure 1d) [36*,37,38], yet all the same ideas apply. It should be mentioned that theoretical versions of these ideas have been put forward before [46–50], and are now finding growing acceptance as general models of signal processing [36*].

The above discussion highlights the increasing need to study cortical computation in behaving animals, as it is not possible to study the effects of top-down expectations and context in anesthetized preparations. Further, measurements of population activity, such as VSDF, multielectrode arrays, or two-photon imaging will be needed to be able to detect the presence of manifold-attractors in cortical activity. Finally, analyses should concentrate on single-trial data that explain how sensory stimulation combines with ongoing activity to determine behavior.

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