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Cortical State and Attention

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Preface

The brain continuously adapts its processing machinery to behavioural demands. To achieve this it rapidly modulates the operating mode of cortical circuits, controlling the way information is transformed and routed. This article will focus on two experimental approaches by which the control of cortical information processing has been investigated: the study of state-dependent cortical processing in rodents, and attention in the primate visual system. Both processes involve a modulation of low-frequency activity fluctuations and spiking correlation, and are mediated by common receptor systems. We suggest that selective attention involves processes similar to state change, operating at a local columnar level to enhance the representation of otherwise nonsalient features while suppressing internally generated activity patterns.

Introduction

Cortical activity, even in primary sensory areas, is not strictly determined by sensory input, but reflects an interaction of external stimuli with spontaneous patterns produced endogenously¹. The form of this spontaneous activity — and the way it shapes sensory responses — is determined by cortical state. Cortical states were first studied as patterns of electroencephalogram (EEG) activity, and have more recently been shown to determine patterns of population spiking, neuronal correlation, and intracellular potentials. Because cortical spiking patterns can depend as much on state as on sensory inputs, an understanding of state is essential to study how information is processed by neuronal populations.

A classical view holds that cortical state is a function of the sleep cycle: during slow-wave sleep the cortex operates in a “synchronized” state, characterized by strong low-frequency fluctuations in cortical activity; whereas during waking and REM it operates in a “desynchronized” state in which low-frequency fluctuations are suppressed². Recent experiments in rodents have indicated a more complex picture, in which cortical state also varies within wakefulness. Although alert or actively behaving animals exhibit a highly desynchronized state, awake quiescent animals can show spontaneous fluctuations in cortical activity which are prominent although smaller than those observed during slow-wave sleep^{3–11}. Thus, the classical synchronized and desynchronized states are likely to represent two extremes of a continuum of states corresponding to varying levels of spontaneous fluctuations in neural population activity. As we argue below, the continuum is also likely to be multidimensional: there are several different behavioural and experimental conditions that all cause desynchronization, but that can have diverse effects on other variables, such as gamma frequency power and activity of different cortical cell classes.

Attention refers to an animal’s ability to selectively enhance the detection of and response to certain stimuli, at the expense of others. In this Review, we use the word attention specifically to mean “top-down” attention, in which enhanced responses are caused by a prior expectation of which stimuli will be important, rather than “bottom-up” attention, in

which the physical properties of an intrinsically salient stimulus itself directs the animal's attention. Primate studies have shown that in multiple cortical regions, attended stimuli produce larger spiking responses than unattended stimuli^{12–17}. But this is not the only effect of attention on cortical activity. Intriguingly, many of attention's other effects — such as decreased low-frequency fluctuations, trial-to-trial variability, and correlations — resemble cortical desynchronization, occurring specifically in parts of cortex that represent the attended stimulus^{18–23}.

In this Review, we first discuss the nature and mechanisms of state-dependent cortical processing in rodents, then discuss how attention modulates processing in primate visual cortex. We argue that attention involves similar processes to those causing cortical desynchronization, but operating at a local level. We suggest that this local desynchronization arises from a combination of diffuse neuromodulatory inputs, and tonic glutamatergic drive focused on the cortical populations representing the attended stimulus.

State-dependent organization of cortical activity

Modern multielectrode and optical techniques have revealed how the spiking of cortical populations is organized both within individual columns and across the cortical surface. This has provided an understanding of cortical state at the neuronal level. The organization of cortical population activity is best understood for the case of spontaneous activity. Spontaneous activity has been studied with a number of experimental techniques, including optical imaging^{3, 6, 24–28}, extracellular population recording^{8, 9, 29–34} and intracellular recording^{5, 7, 11, 35–37}, all of which paint a broadly consistent picture. Although the largest fluctuations in cortical population activity are seen in sleeping and anaesthetized animals, studies from many labs have now shown that spontaneous fluctuations in firing rates and intracellular potentials can also occur during quiet wakefulness^{3–11}. Spontaneous cortical population activity in an awake animal does not simply switch between discrete synchronized and desynchronized states, but forms a continuum of states characterized by variations in fluctuation depth that correlate at least partially with ongoing behaviours, such as whisking and locomotion^{5–7, 38}.

Figure 1 shows a cartoon illustration of neuronal population activity in synchronized and desynchronized states. The defining characteristic of cortical state, for our purposes, is the amount of common fluctuation in population spiking activity (as we argue below, other measurements such as low-frequency LFP power, spiking correlations, and variability also relate to this definition). Fig. 1a illustrates activity typical of a synchronized state, where activity fluctuates between *up phases* characterized by firing in multiple neuronal classes, and *down phases* in which the whole network is quiet (See Box 1 for a discussion of terminology). Fig. 1b illustrates activity typical of a desynchronized state, where spontaneous fluctuations are weaker. Cortical state is not bimodal; these two examples illustrate the extreme ends of a continuum of cortical state seen in awake rodents. Strong variations in cortical state are also seen during sleep (most notably between slow-wave and REM), and also under certain anaesthetics^{31, 39–41}. Urethane anaesthesia, where a continuum of cortical states is seen, ranging from states more synchronized than slow-wave sleep, to transient desynchronized epochs similar to REM or waking^{31, 32, 41}, is a frequently used experimental model to investigate how state affects cortical processing.

Box 1

What's in a name?

The study of cortical state suffers from confusing terminology, with multiple terms being used to refer to a single phenomenon, as well single terms being used with different

meanings by different authors. We here provide definitions of the terminology as used in this Review.

Cortical state

Our definition of cortical state refers to the dynamics of network activity on a time scale of seconds or more. For our purposes, the defining characteristic of cortical state is the amount of slow fluctuation in the summed activity of a set of local neurons. Cortical state is not bimodal; however for linguistic convenience we will refer to synchronized and desynchronized states to describe relative positions along a continuum.

Desynchronized state

We use the term *desynchronized state* to mean a situation in which the population rate in a cortical column fluctuates only weakly. In such a state, low-frequency LFP power is also comparatively small. Note however that neuronal coherence at high (gamma) frequencies often actually increases in the desynchronized state⁵², leading some authors to question the use of this term. The terms *asynchronous state* and *activated state* are largely synonymous with desynchronized state, although one should remember that the term activated does not refer to an increase in firing rates, as firing rates of some neurons may go down in desynchronized states.

Synchronized state

We use the term *synchronized state* to mean a situation in which the average population firing rate in a cortical column fluctuates strongly at a timescale of ~100 ms or slower. In such a state, low-frequency LFP power is high, although power at gamma frequencies may decrease. Other terms used for this state include *deactivated* and *inactivated*; once again one should remember this does not necessarily imply lower firing rates, or ion channel inactivation.

Up phase and down phase

The terms “Up State” and “Down State” were originally used to refer to the two modes of the bimodal distribution of membrane potentials seen in intracellular recordings of striatal and cortical neurons *in vivo*¹⁹⁸. Subsequently, however, the usage of these terms has widened to include any periods of spontaneous depolarization and hyperpolarization, even when the histogram of membrane potentials is not bimodal. Furthermore, as intracellular Up and Down states occur during phases of strong local network spiking and silence, respectively, the terms are now also used to refer to spiking and silent phases of population activity, even in the absence of intracellular recordings. Spontaneous depolarizations and spiking periods also go by other names such as *population bursts*¹⁹⁹ or bumps⁴.

To add further confusion, the Up State and Down State are not, in our usage, actually cortical states. A cortical state (as the term is used in this Review) refers to a global pattern of cortical dynamics — such as the desynchronized or synchronized state — that changes over a time course of seconds or more and is defined by fluctuation magnitudes or power spectra that can only be computed from several seconds of data. Up and down states occur at timescales of ~100 ms, and are thus not states, but phases of an ongoing fluctuation. For the sake of clarity, we therefore use the terms *up phase* and *down phase* in this Review.

Spontaneous cortical activity during sleep can display slow, regular, rhythmic patterns⁴². By contrast, the spontaneous fluctuations seen in cortex of awake rodents typically have an irregular structure, and the length and depth of the up and down phases varies from one period to the next. These waking patterns are therefore not well described as ‘oscillations’.

Recordings of different cell types have shown that the firing and membrane potential of most, if not all, cortical neuronal classes increase in the up phase, although differences in the precise timing of neuronal firing relative to the onset of the up phase exist both between and within cortical neuronal classes and layers^{10, 37, 43–45}.

Relation of cortical state to pairwise correlations

When the firing rate of a neuronal population is modulated by global fluctuations in activity, the activity of neuronal pairs is generally positively correlated. This idea can be mathematically expressed by describing the relationship between the (weighted) mean of pairwise correlation coefficients and the variance of the population rate (see Box 2). If more pairs are positively than negatively correlated, the mean pairwise correlation is positive, and so the population rate has large variance, indicative of coordinated global fluctuations that are typical of a synchronized state. If no neuronal pairs are correlated, the variance of population activity is small, and the neuronal population is in a desynchronized state. However, a mean correlation of zero does not require every single pair to be uncorrelated; it is also possible to have a desynchronized state in which positive correlations between neurons exist, but are counterbalanced by an equal number of negative correlations³² (See Box 2).

Box 2

Mathematical relationship between fluctuation and correlation

Intuitively, one would expect that if a set of neurons show a common fluctuation in firing rate, their activity will in general be positively correlated. To make this idea precise, consider a population of N neurons, and let x_i refer to the instantaneous firing rate of the

i^{th} neuron, as could be measured by counting spikes in some timebin. Then $\frac{1}{N} \sum_i x_i$ is the population rate in the corresponding timebin. For any set of random variables x_i it holds that

$$Var(\sum_i x_i) = \sum_i Var(x_i) + \sum_{i \neq j} Cov(x_i, x_j) = \sum_i Var(x_i) + \sum_{i \neq j} a_{ij} Corr(x_i, x_j)$$

where $a_{ij} = \sqrt{Var(x_i)Var(x_j)}$.

This equation therefore implies that the variance of the population is dominated by a (weighted) mean of the correlation coefficient of all cell pairs. If the population rate does not fluctuate and has small variance, one must therefore have a mean correlation close to zero. This could happen either when all neurons fire independently, or when positively correlated cell pairs are counterbalanced by an equal number of negative correlations. Conversely, when mean correlations are non-zero, this implies large fluctuations in population rate even if the correlations are themselves of moderate order (e.g. <0.1).

The figure shows four illustrations of this relationship, for simulated spike trains of 128 neurons of equal firing rate. In each row, the left panel shows 2 s of simulated data, with the blue raster representing the spikes of all cells, and the red trace representing the instantaneous population rate; the middle panel shows a histogram of population rates over 50 s of simulated data; and the right panel shows the histogram of correlation coefficients over all cell pairs. Black curves in the right two histograms correspond to outlines of the histograms for independent Poisson neurons.

- A. The neurons fire as independent Poisson processes. The population rate has low variance and the mean correlation is zero. The width of the correlation histogram reflects the expected size of statistically insignificant correlation coefficients arising from random fluctuations.
- B. The neurons fire as inhomogeneous Poisson processes, modulated by a single fluctuating rate function. The population rate has high variance, and the mean correlation is positive though of modest magnitude. This data resembles cortical activity in a synchronized state.
- C. The neurons are modulated by a common sinusoidal oscillation, but with phases distributed evenly across the population. As for the independent cells of (A), the population rate has low variance and the mean correlation is close to zero. In this case, however, the correlation histogram is wider than in (A), indicating an equal number of significantly positively and negatively correlated pairs. This pattern illustrates how it is possible for a population to be modulated by a common oscillation (such as hippocampal theta), while remaining in a desynchronized state.
- D. The neurons display a more complex pattern of cell assembly activity. However, population activity has low variance, as positive correlations between neurons frequently joining in one assembly are counterbalanced by negative correlations amongst neurons that only rarely do so (c.f. Ref. ²⁰⁰). As in (C), the population rate has low variance, and the mean correlation is close to zero, but the distribution of correlations is wide, indicating an equal number of significantly positively and negatively correlated pairs.

Relation of cortical state to local field and intracellular potentials

Fluctuations in cortical population activity are strongly correlated with local field potential (LFP) patterns. The LFP can show large differences between sleeping, quiescent awake, and actively exploring animals. Although the physics underlying local field potentials is complex, periods of strong firing in a column are generally accompanied by depth-negative waves generated by local excitatory synapses^{46–48}. The down phases of the synchronized state are accompanied by depth-positive LFP waves of smooth appearance, reflecting a lack

of spiking and synaptic activity. In synchronized states, alternations between up and down phases in fluctuating population activity therefore give rise to local field potential patterns of strong low-frequency power (Fig. 1a). In desynchronized states, smaller fluctuations in global firing rates are mirrored by less LFP power at low frequencies (Fig. 1b).

Fluctuations in population activity correlate strongly with fluctuations in intracellular voltages of multiple neuronal classes^{7, 45, 49, 50}. The strength of membrane potential fluctuations thus also varies with cortical state, with periods of strong low-frequency LFP showing large intracellular fluctuations, and periods of LFP desynchronization showing more steady intracellular potentials^{5, 7, 11}. Intracellular recordings in awake rodents again reveal a continuum of states, rather than a switch between discrete synchronized and desynchronized states¹¹.

Relation of cortical state to gamma oscillations

Cortical desynchronization has often been linked with increased power of gamma frequency oscillations (25–100 Hz), which have in turn been proposed to assemble neurons into synchronous groups that are capable of strongly driving their targets⁵¹. Gamma power increases when cortical desynchronization occurs during active behaviour in rodents³⁸, or after electrical stimulation of basal forebrain, brainstem cholinergic, and nonspecific thalamic nuclei^{52–55}. However, the correlation between desynchronization and gamma power is not absolute. For example, in rats, stimulation of dorsal Raphe nuclei causes a decrease in low-frequency LFP power and a simultaneous decrease in gamma power⁵⁶. Moreover, selective attention in primates uniformly decreases low-frequency power, but can either raise or lower gamma power, depending on cortical area and task^{18, 21, 22}. Finally, although local gamma power in visual cortex is typically increased by visual stimuli, the correlation between gamma power and firing rate is also complex, with certain stimuli being able to increase gamma power without changing, or even decreasing neuronal firing rates^{57, 58}.

Coordination of spontaneous population activity across areas

Electrical recordings have shown that neuronal correlations and LFP coherence decay as the lateral distance between recording sites increases^{33, 34, 59, 60}. Recent results have revealed a spatiotemporal picture of cortical activity that can explain these findings. In synchronized states, cortical activity often takes the form of spatially extended travelling waves^{6, 9, 27, 61–65}. Despite variations in trajectory from one wave to the next, these waves share a number of characteristic features, such as timescales of the order 10–100ms and remarkable bilateral symmetry⁶⁶. The passage of a wave through a cortical column initiates a local spiking pattern that is independent of the wave direction⁹. The correlated fluctuations seen in any one column during synchronized states are thus part of much larger patterns that spread out across the cortical surface.

Fluctuating spontaneous activity is not restricted to cortex, but is also found, among other areas, in thalamus^{67, 68}, basal ganglia^{69, 70}, cerebellum⁷¹, and hippocampus. Hippocampal spontaneous activity has been particularly well studied, and is similar to that in neocortex, with a few key differences. The hippocampal equivalent of the synchronized state — the “large irregular activity” (LIA) seen during immobility and sleep — consists of periods of near silence punctuated by “sharp waves” of strong population activity whose occurrence is correlated with the timing of cortical up phases^{72, 73}. Unlike in cortex, however, hippocampal sharp waves are accompanied by a 150–200Hz “ripple” oscillation⁷⁴. In the hippocampal equivalent of desynchronization, known as the “theta state,” sharp-wave fluctuations are suppressed, leading to a steadier spiking pattern; but unlike in the neocortex, this relatively steady activity is superimposed with a rhythmic 6–10 Hz theta oscillation. The

character of the hippocampal theta oscillation is also fundamentally different to the fluctuations of cortex in the synchronized state. In the latter, all neurons show increases in firing in the up phase and decreases in the down phase, resulting in a strongly fluctuating population rate during the synchronized state. By contrast, individual hippocampal pyramidal cells show phase relationships to the theta rhythm that vary between neurons, and even within individual cells from moment to moment^{75–77}. This results in a pyramidal cell population whose summed firing rate is only weakly modulated by theta phase⁷⁸ (see Box 2).

How does state correlate with ongoing behaviour?

The behaviour dependence of brain state has been best studied in the hippocampus. In the rat hippocampus, the theta state occurs during behaviours such as walking, running, rearing and exploratory sniffing, whereas LIA occurs during behaviours such as waking immobility, eating, grooming, and defecation⁷⁹. Although various terms have been used to characterize the circumstances under which these states are seen in rats (e.g. “voluntary” or “exploratory” for theta, “automatic” or “consummatory” for LIA), the precise list of behaviours for each state is species-dependent^{80, 81}. The mechanisms and significance of these species differences are still poorly understood.

In neocortex, variations in state during waking are more subtle than in the hippocampus, and were not detected in early studies based on visual inspection of pen-chart EEG recordings⁸² (Figure 2a). However, spectral analysis later revealed a suppression of low-frequency LFP power in actively behaving awake rats compared to awake but immobile rats⁸³. In head-fixed mice, cortical activity becomes desynchronized during behaviours such as whisking or ball-running^{5, 7, 38} (Figure 2b). The effect of behaviour on cortical state can be greatly amplified by pharmacological treatments: for example, after delivery of the muscarinic antagonist atropine, large, slow, sleep-like cortical activity occurs during quiet rest but this activity is suppressed during locomotion⁸⁴ (Figure 2a, 2c).

Mechanisms controlling cortical state

What are the mechanisms responsible for control and maintenance of cortical states? We will divide this question into three: how can a cortical area maintain a desynchronized state; what produces the fluctuations of the synchronized state; and what causes a cortical area to switch between states.

How can cortex maintain a desynchronized state?

As discussed earlier, the level of fluctuation exhibited by a neuronal population is related to the mean pairwise correlation of the constituent neurons. It has long been recognized that two neurons can be correlated without having a direct synaptic connection, and that a correlation can also arise from excitatory or inhibitory inputs shared between the two cells⁸⁵. Conversely, one might expect that any two neurons that share a large number of inputs – such as neighbouring pyramidal cells of cortex – will necessarily display correlated activity. This is indeed seen in feed-forward network models, where even uncorrelated inputs can lead to synchronous spiking output^{86–88}. Furthermore, neuronal pairs in primates frequently have noise correlations of the order 0.1^{33, 89–93}, numerically close to that predicted on the basis of anatomically shared connections⁸⁶. It was thus suggested that such correlations are an inevitable property of cortical shared connections, and result in a reduction in coding capacity as shared noise cannot be averaged out efficiently^{86, 92}.

Although for any two neurons a correlation of 0.1 is small, this level in fact indicates prominent global fluctuations in population firing (Box 2). If it really were the case that such correlations were inevitable, a truly desynchronized state would be impossible. However,

recent studies have shown that mean correlations very close to zero can occur in V1 of behaving primates⁹⁴ and in somatosensory and auditory cortices of rats in the desynchronized state under urethane anaesthesia³². The cortex must therefore have some mechanism to enforce decorrelation even in the face of multiple shared inputs.

The answer to this conundrum may lie with inhibition (Figure 3a). Although shared inhibitory inputs lead to positive correlations⁹⁵, this effect can be cancelled if the excitatory and inhibitory inputs to a pair of neurons are themselves correlated. Theoretical analysis suggests that if inhibition is fast and strong enough, recurrent networks self-organize into a state in which the fluctuations produced by shared connections are rapidly ‘tracked’ by inhibitory interneurons, leading to extremely small mean correlations in large networks³². This analysis also predicts that despite a mean correlation close to zero, a substantial number of neuronal pairs should remain correlated, but with approximately equal numbers of positively and negatively correlated cell pairs. This prediction is borne out in rat cortex, both in the desynchronized state and within up phases of the synchronized state³².

What causes fluctuations during synchronized states?

If positive correlations do not inevitably arise from shared inputs, why are they so frequently observed? The relationship between mean pairwise correlation and the variance of population rate allows us to ask the same question in a different way: why do neural populations activity exhibit spontaneous fluctuations in population rate? And why do sensory stimuli induce responses whose population rate varies from one presentation to the next? We address spontaneous fluctuations now, and will discuss sensory-evoked correlations in the next section.

The fact that fluctuating spontaneous activity occurs even in isolated cortical slices and slabs^{96, 97} suggests that intracortical mechanisms may have a primary role in generating them. Many cellular and synaptic processes have been implicated in the generation of these fluctuations, but all these processes can be understood within a single conceptual framework, known as the theory of *excitable systems* (Fig. 3b). In this framework, spiking in the up phase is sustained by recurrent synaptic activity^{96, 98}. But after a period of prolonged firing, a number of adaptive processes occur that steadily reduce the excitability of the network, such as synaptic depression^{99, 100}, a build-up of afterhyperpolarizing K⁺ conductances⁹⁶, and decreased ATP levels¹⁰¹. After enough adaptation, the network’s ability to sustain firing fades, leading to a period of network silence. Subsequently, after enough “rest,” the synapses and cells recover, and the network can again sustain recurrent activity. Computational models based on these principles are able to produce data very similar to those obtained *in vivo* and *in vitro*^{31, 102–105}. A key feature of this mechanism is that the down phase is caused not by synaptic inhibition but by disfacilitation, i.e. the temporary absence of synaptic drive^{49, 106}. Both *in vitro* and *in vivo* studies suggest that within a cortical column, the up phase is generated in layer V, from where it can, but does not always spread to superficial layers^{10, 96}.

This scenario also explains why spontaneous cortical fluctuations spread as travelling waves. Once a certain region of cortex has entered an up phase, lateral excitation from this region can spark an activity in neighbouring cortex, but a second wave cannot pass until sufficient time for recovery of synaptic and cellular adaptation. Models of spatially coupled excitable systems are known as an *excitable media*, and have been used to describe diverse phenomena including forest fires, wave propagation in cardiac tissue, and stadium waves at sporting events¹⁰⁷.

What causes changes in cortical state?

Several mechanisms have been implicated in cortical state shifts, including increased activity of subcortical cholinergic and monoaminergic nuclei, as well as sustained glutamatergic inputs from thalamus and potentially other cortical regions^{82, 108}. Much of the work we review here is classical but, despite its relevance, it is rarely discussed in the modern literature.

The cholinergic system plays an important, but not exclusive role in controlling cortical state. Lesions of the basal forebrain – the primary source of cholinergic input to cortex – increases low-frequency LFP power⁸³, whereas electrical or pharmacological stimulation of basal forebrain or cholinergic brainstem nuclei causes cortical desynchronization that is blocked by systemic or cortically applied muscarinic antagonists such as atropine^{52, 53, 83, 109}. Cholinergic basal forebrain and brainstem neurons show increased firing during cortical desynchronization^{109–112}. Nevertheless, cholinergic input is not necessary for cortical desynchronization: although atropine causes a strongly synchronized state in awake immobile rats, actively behaving rats show atropine-resistant desynchronization^{82, 84} (Figure 2a). Moreover, selective lesions of cholinergic neurons in BF are not sufficient to abolish cortical desynchronization¹¹³.

What might be responsible for ACh-independent desynchronization? Stimulation of other neuromodulatory systems can cause desynchronization, although in some cases this occurs via their effects on the basal forebrain^{114–117}. Serotonin may play an important part in ACh-independent desynchronization, as suggested by the atropine resistance of desynchronization induced by dorsal Raphe stimulation, and by the ability of serotonin depletors combined with atropine to block desynchronization even during active behaviour^{115, 118, 119}. Cortical norepinephrine release plays an important role in reducing spontaneous fluctuations as rats wake from anaesthesia, at least in layer 4 of primary somatosensory cortex¹²⁰. Neurons in cholinergic and other neuromodulatory nuclei exhibit diverse and rapid modulation of firing rate by salient sensory stimuli, behavioural events, and cognitive factors such as attention and expected reward, which is consistent with control of cortical state on a moment-to-moment basis^{121–129}.

An additional mechanism implicated in cortical desynchronization involves increased tonic firing of glutamatergic afferents from the thalamus and perhaps elsewhere. Tonic thalamic firing increases under several conditions that are associated with cortical desynchronization^{130–134}. This may in turn reflect thalamic neuromodulation; the thalamus receives strong cholinergic input from the brainstem, which depolarizes thalamic relay cells and can shift them to a mode of steady tonic firing, both by direct excitation of relay cells and by disinhibition resulting from cholinergic inhibition of thalamic reticular neurons^{135–137}. Increasing tonic relay cell firing (by microdialysis of the unspecific cholinergic agonist carbachol into somatosensory thalamus) causes desynchronization of barrel cortex¹³⁸, suggesting that tonic glutamatergic input from thalamus is sufficient to desynchronize barrel cortex.

How could neuromodulatory and tonic glutamatergic inputs suppress fluctuations in cortical activity? Neuromodulatory systems and metabotropic glutamate receptors have diverse effects on different classes of cortical neurons and synapses, in a manner that may further vary as a function of cortical area and age^{139–150}. These multiple receptor systems probably allow fine-tuning in a high-dimensional space of cortical operating modes. Nevertheless, their effects also have several similarities, which paint a basic picture of how these systems can reduce cortical fluctuations. First, multiple neuromodulatory systems and metabotropic glutamate receptors affect the firing mode of pyramidal cells, reducing bursting, afterhyperpolarization and adaptation, and promoting tonic firing^{141, 143, 148, 150–158}.

Second, multiple neuromodulatory systems cause a reduction in the strength of recurrent excitatory synapses within cortex, with a concomitant reduction in synaptic depression^{146, 159–161}. Third, metabotropic glutamate and multiple neuromodulatory systems cause tonic depolarization of cortical layer V pyramidal cells, where cortical fluctuations are thought to be generated^{150, 162, 163}. These three processes should switch the cortex from a mode in which bursting and recurrent excitation lead to rapid increases in population rate that are then dampened by adaptation, to a mode in which tonic depolarization causes neurons to maintain relatively steady activity. Simulations based on both detailed biophysical models and simple dynamical systems support this picture^{31, 102, 104, 105}.

Recent results suggest that cortical state is in fact a multidimensional continuum, with different forms of desynchronization reflecting non-identical changes in cortical operating mode. As mentioned above, gamma power may either increase or decrease during desynchronization. Furthermore, the firing rates of individual neuronal classes can differ between desynchronizing conditions: putative fast-spiking interneurons fire faster during locomotion³⁸, in more difficult discrimination tasks¹⁶⁴, and after artificial elevation of thalamic firing¹³⁸; but during rodent whisking, fast-spiking interneurons fire slower whereas non-fast-spiking interneurons fire faster⁴⁵. Many non-fast-spiking interneurons are excited ionotropically by acetylcholine and serotonin receptors¹⁶⁵ and inhibit fast-spiking interneurons¹⁶⁶, whereas fast-spiking interneurons receive strong glutamatergic drive from thalamus¹⁶⁷. One might therefore speculate that the difference between these types of desynchronization reflects a different balance in neuromodulatory versus tonic glutamatergic drive. Modern techniques such as optogenetics and enzyme-linked electrochemistry¹⁶⁸ may help to resolve the full space of cortical states and the roles of different afferent systems on state and information processing.

Cortical state and sensory responses

Cortical sensory responses correlate strongly with state. However, the way state shapes sensory processing is complex: one cannot simply ask whether responses are larger or smaller in one state or another; instead the effect of cortical state on neuronal responses appears to depend on the specific type of stimulus the system is confronted with. Nevertheless, some commonalities are beginning to emerge from studies of multiple sensory areas. In particular, it appears that isolated punctuate stimuli (which could also be labelled as salient, unexpected, brief stimuli) are able to generate substantial responses regardless of cortical state, whereas temporally extended or rapidly repeated stimuli are “filtered out” in synchronized states, but efficiently processed in the desynchronized state (Fig. 4).

Responses to simple punctuate stimuli (for example, whisker deflections and auditory clicks) have been well studied in barrel and auditory cortices in rodents. When discussing how a sensory response is modulated by state, we must consider both how the response differs between synchronized or desynchronized states, and between the up and down phases within the synchronized state. In rat auditory and somatosensory cortices, the initial response (up to ~50ms) to a punctuate stimulus is larger in synchronized states and quiescent animals, than in desynchronized states and actively engaged animals^{130, 169, 170}; larger auditory onset responses are also seen in passive compared to behaviourally engaged ferrets, with smaller onset responses for more difficult detection tasks¹⁷¹. Within the synchronized state, the initial response does not depend strongly on phase, with stimuli arriving in the up and down phase evoking initial responses of approximately equal magnitude^{31, 172}, a phenomenon that may be related to suppression of firing variability by stimulus onsets¹⁷³. The later stimulus response period (after ~50ms) shows more complex dependence on state and phase^{31, 172}. In synchronized states, punctuate stimuli can trigger long-lasting up phases that can spread over the cortical surface^{6, 61} — a phenomenon that may be related to

observations that receptive fields of sensory cortex neurons are often wider in synchronized states than in desynchronized states^{40, 174}. In the desynchronized state, the response to a single punctuate stimulus is typically simpler, consisting of a brief response followed by a transient ~100ms suppression below baseline and a depth-positive LFP wave in all but the most desynchronized conditions^{31, 175}. Despite the apparent complexity of these results, such state-dependent sensory responses can be quantitatively predicted on a trial-by-trial basis by a simple excitable system model, using parameters derived from spontaneous activity preceding the stimulus³¹.

Presentation of repeated or temporally extended stimuli reveals another aspect of state-dependence. Although the response to the first in a train of rapidly repeated punctuate stimuli is larger in synchronized than in desynchronized states, response adaptation is stronger in the synchronized state, so by the end of the train responses that are equal between states or smaller in the synchronized state^{130, 170} (Fig. 4a). In rat visual cortex, temporally extended movies of natural scenes are more faithfully represented after basal forebrain stimulation¹³² (Fig 4b), and responses to continuously drifting gratings are larger in visual cortex of running compared to stationary mice³⁸. These data might appear to conflict with the smaller responses to isolated punctuate stimuli in desynchronized somatosensory and auditory cortex. However, it seems unlikely that this is due to a difference between sensory modalities, as the representation of temporally extended amplitude-modulated noise stimuli is also more faithful in desynchronized auditory cortex¹⁷⁶ (Fig 4c). We therefore suggest that the effects of desynchronization on neuronal responses to sensory stimuli are similar across modalities: onset responses are smaller, but adaptation is reduced, leading to enhanced representation of repeated or temporally extended stimuli.

We emphasize that state-dependent changes in cortical representations do not necessarily arise from changes in cortical processing, but could also reflect changes in lower structures. Indeed, in synchronized states thalamic relay neurons show an enhanced propensity to fire in “burst mode,” which may emphasize the response to the onset of a stimulus train but may interfere with linear representation of temporally extended stimuli¹⁷⁷. During desynchronized states, increased baseline firing of thalamic relay cells may cause depression of thalamocortical synapses, which would reduce the response to the first stimulus in a train, but reduce the potential for further adaptation, as these synapses are already close to fully depressed¹⁷⁰.

Why would it be beneficial for an animal to enhance responses to sudden punctuate stimuli, but suppress responses to temporally extended stimuli in the synchronized state? One suggestion relates to the different behavioural needs of active versus quiescent animals. The fine details of ongoing continuous sensory stimuli may be of little relevance to a resting animal, so nothing is lost by filtering them out and allowing cortex to exhibit the endogenously generated patterns typical of a synchronized state. However, a punctuate stimulus such as a sudden unexpected sound or touch, may signal the need for an immediate behavioural response. Larger responses to punctuate stimuli in the synchronized state might thus serve as a “wake up call,” enabling appropriate motor responses to unexpected events in passive animals^{6, 178}.

Cortical state and attention in primates

The classical view of cortical states is that they are global, synchronizing or desynchronizing all cortical areas simultaneously. With regard to the sleep cycle this is generally the case (with certain exceptions such as cetaceans¹⁷⁹). However, a growing body of evidence suggests that in awake primates, selective attention also affects the level of cortical

desynchronization at a local level, at a reduced scale compared to differences between sleep and waking. In this interpretation, the maximum desynchronization is restricted to a small patch of cortical tissue that represents the attended stimulus while cortical tissue representing non-attended parts of the sensory world would be in a more synchronized state. We argue that such local changes of state can explain results from multiple labs on attention-related changes in changes in and LFP power, response variability, and correlation (Table 1).

One of the hallmarks of cortical desynchronization is a decrease in low-frequency LFP power. Studies in multiple visual areas have shown that attention directed to the receptive field of the recorded neurons near the recording electrode results in decreased low-frequency LFP power, compared to attention directed outside the receptive field^{18, 21, 22} (Figure 2c). This result implies that attention modulates the size of low-frequency fluctuations at a local level: if attention simply caused desynchronization uniformly across the cortical surface, this would not change LFP power depending on receptive field location. Surprisingly, attention-associated low-frequency desynchronization can be accompanied by either increased or decreased gamma LFP power, a finding that is reminiscent of the differential effects on gamma power after stimulating different subcortical structures in rats (discussed above). The circuit mechanisms underlying these dissociations between low-frequency desynchronization and gamma power are as yet unknown.

Also consistent with local desynchronization, attention reduces trial-to-trial variability and firing rate correlations between neurons. Responses to repeated presentations of an identical stimulus vary from trial to trial, and variations in the responses of neighbouring neurons are typically correlated in cortex of an awake primate⁹⁰. These “noise correlations” typically reduce the information that can be encoded in populations^{92, 180, 181}. Recent studies have shown that in area V4, both variability and noise correlations are reduced when attention is directed to the receptive field of the recorded neurons^{19, 20, 23}. Coherence analysis suggests these correlations arise from low-frequency (<5 Hz) fluctuations in rate correlated across the neuronal population¹⁹, resembling a more synchronized state, which attention desynchronizes. Reduced noise correlations are also found in rodent auditory cortex after spontaneous desynchronization³¹ and in visual cortex after basal forebrain stimulation¹³², where reduced correlations were mediated by cortical muscarinic mechanisms.

The effects of attention in primates vary throughout the response time course, similarly to the effects of cortical state in rats. Immediately after a stimulus appears in the receptive field, spike count variability and correlation in V4 are suppressed regardless of whether the stimulus was attended to. During the sustained response period, however, variability and correlation increase in unattended conditions^{19, 20}. This effect is similar to the effects of state on responses to punctuate stimuli in rat auditory and barrel cortex^{31, 172}, where the initial response is largely independent of cortical state and phase and thus not highly variable from trial to trial, but the later response shows strong variability in the synchronized state. Also similarly to desynchronization in rodents, attention reduces the adaptation of V4 responses to repeatedly presented visual stimuli¹⁸².

Circuit mechanisms of attention in primates

Although the circuit mechanisms of top-down attention are still largely mysterious, recent primate experiments have begun to cast light on the question, in particular the contribution of different receptor systems. Once again, strong parallels to cortical state are indicated, in particular an important role for the cholinergic and glutamatergic systems. In behaving primates, iontophoresis of ACh or muscarinic antagonists respectively increases or decreases the effects of attention on spiking patterns in V1¹⁸³ and V4¹⁸⁴. It appears unlikely, however,

that cholinergic input could be solely responsible for attentional modulation within cortex: despite topographic organization of basal forebrain projections at the level of cortical lobes and regions¹⁸⁵, it seems unlikely that cholinergic afferents have the spatial specificity to target a small patch of cortex representing an attended stimulus. Thus, although cholinergic mechanisms are involved in attentional modulation in visual cortex, they probably work in interaction with other systems. It may be that cholinergic drive is critical for setting the network to be maximally responsive to localized glutamatergic feedback from higher cortical areas (Figure 5; Ref. ¹⁸⁶).

A role for glutamatergic feedback projections in producing the local effects of attention has been demonstrated by studies of the frontal eye fields (FEF). FEF projects to extrastriate visual cortices, these feedback projections are glutamatergic, and spiking activity in FEF correlates with attention¹⁸⁷. Elegant studies have shown that microstimulation of appropriate parts of FEF shift the focus of attention as measured at the behavioural level¹⁸⁸, and produce a modulation of neuronal coding in V4 similar to that seen with attention¹⁸⁹. As described above, a combination of cholinergic and tonic glutamatergic input is likely to place cortex in a strongly desynchronized state.

The mechanisms by which glutamatergic feedback could increase the gain of visual cortical responses are unknown. However, one intriguing suggestion involves the NMDA receptor. Because of the voltage-dependent nature of NMDAR-mediated glutamate responses, postsynaptic depolarization might multiplicatively increase the excitatory currents induced by other inputs¹⁹⁰, a proposal supported by recent results on the effects of NMDA antagonists on responses in macaque V1 during a visual task¹⁹¹. Additionally, it is possible that focused glutamatergic input could cause localized ACh release, either through presynaptic glutamate receptors on cholinergic fibres^{192, 193} or by activating cholinergic cortical interneurons¹⁹⁴.

Summary and outlook

Large changes in cortical state are seen between waking and sleep. These changes are controlled by alterations in neuromodulatory and tonic glutamatergic input, which change the dynamics of cortical networks and alter their propensity to generate fluctuations. Recent research suggests that similar mechanisms control the more subtle variations in state seen in awake animals. Furthermore, it appears that cortical state can be controlled at a local level, with the strongest desynchronization seen in patches of cortex that represent attended stimuli. Computational, *in vitro*, and *in vivo* research in anaesthetized animals suggests that these fluctuations are generated by excitable system dynamics, reflecting the interaction of fast recurrent excitation and slower adaptive processes; further research is required to verify that excitable system dynamics also underpin the more subtle spontaneous fluctuations seen in quiescent or inattentive awake animals.

Cortical state appears to be a multidimensional continuum, with variables such as gamma power and interneuron firing rate showing diverse changes depending on how desynchronization was induced. Future work with modern techniques such as optogenetics and enzyme-linked electrochemistry may soon reveal how multiple neuromodulatory systems shift cortical operating mode in a multidimensional space of states.

The effects of cortical state on sensory responses are complex. However, a theme emerging from work in multiple modalities is that sudden, punctate stimuli are able to generate large cortical responses in both states, whereas temporally extended stimuli are only faithfully represented in cortex during desynchronized states. This could be a manifestation of a more general phenomenon in which stimuli of strong bottom-up salience can produce large

responses regardless of state, whereas desynchronization enhances responses to stimuli that are of themselves more subtle while decreasing the response to unattended and bottom-up salient stimuli. Future work is required to test this hypothesis.

Cortical state does not simply affect sensory responses, but also changes the character of cortical spontaneous activity. More synchronized states are defined by larger low-frequency fluctuations in population firing and local field potentials, as well as higher spontaneous and noise correlations. Similar effects are found locally within cortical columns that represent unattended stimuli. What function might these spontaneous fluctuations have, and why would they be preferentially expressed in cortical areas that are not involved in representing attended stimuli? We suggest two, non-exclusive, possibilities. The first is that synchronized states represent a “power save” mode. Synaptic activity uses a great deal of energy, and if fluctuating activity means a column is electrically active less of the time, this presumably releases more energy for other functions. The second possibility is that the fluctuations of the synchronized state are themselves a signature of non-sensory information processing. In the absence of sensory input, the brain is still active, engaged in processes such as mental imagery and memory recall, which presumably arise from structured cortical activity independent of external stimuli. Human fMRI studies have revealed complex large-scale fluctuations in BOLD activity, which are at least partially related to the underlying anatomical connectivity matrix^{195, 196}. Understanding the relationship between BOLD and cortical state is an important topic for future research (Box 3).

Box 3

Cortical state and resting state networks

A complementary view on spontaneous cortical activity comes from studies in humans using functional magnetic resonance imaging (fMRI)^{195, 196}. As with electrical recordings, these studies suggest that spontaneous activity is not simply noise, but a structured signal related to behavioural and cognitive factors. Spontaneous BOLD activity shows slow (<0.1 Hz) spatiotemporally patterned fluctuations, with positive correlations within a number of “resting state networks” but weaker or negative correlations between networks^{201, 202}. The resting state networks consist of groups of functionally and anatomically related cortical areas, for example sets of regions involved in visual or auditory processing, as well as a “default mode network” whose activity is greatest in resting subjects. Fluctuations in the spontaneous activity of these networks correlate with natural fluctuations in task performance²⁰³.

How might these observations relate to the phenomena described in this Review? It seems unlikely that spontaneous fluctuations in BOLD correspond to up and down phases, as their timecourse is at least an order of magnitude slower. Instead, a number of observations suggest that the BOLD signal may be related to local cortical state. BOLD correlates with LFP power both spontaneously and in response to sensory stimuli, with the strongest correlations seen in the gamma band^{204, 205}; visual cortical BOLD increases with visual attention in a topographic manner, with larger increases for more difficult detection tasks²⁰⁶; and cortical blood flow can be controlled by neuromodulatory activity²⁰⁷. These findings would seem to suggest that BOLD should increase during cortical desynchronization. Nevertheless the exact relationship of BOLD to cortical state is not yet fully clear. Although BOLD reliably correlates with gamma power, the correlation between spontaneous BOLD and lower-frequency LFP power varies between animals and can be positive²⁰⁴. This result might appear puzzling, as gamma and low-frequency power are themselves typically anticorrelated. One explanation may be that the space of cortical states is high dimensional. Under some conditions, gamma and low frequency power exhibit a positive correlation²¹, indicating that different LFP power

bands may relate differently to a high dimensional space of states; understanding the relationship of the BOLD signal to this space is an important topic of future work.

Although there are many similarities in the structure of spontaneous and sensory-evoked cortical activity patterns, they differ in their laminar profile, with spontaneous up phases initiated not in the thalamorecipient cortical layers but in the deep cortical layers, which receive feedback projections from higher order cortices^{10, 197}. In addition, unlike sensory-evoked activity, spontaneous up phases typically cover large areas of cortex and could for example reflect coordinated recapitulation of recalled memories, including modality-specific reactivation of appropriate sensory areas.

From this perspective, suppression of spontaneous fluctuations could be interpreted as a form of attention — not between competing sensory stimuli, but between the internal and external worlds. Subjective experience suggests that when we need to detect a subtle stimulus such as a quiet sound, internally generated distractors (such as a tune running through one's head) can be as much of a hindrance as competing external stimuli. Accurate detection of subtle stimuli might thus require suppression of structured spontaneous activity as well as nonattended sensory inputs. Systems to control the state of cortical processing in a column-specific manner may provide animals with a “toolkit” with which to adaptively route sensory and nonsensory information through the brain, to help them survive in a complex and changing world.

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Glossary

Electroencephalogram	an electrical recording made from the scalp, which reflects the global structure of cortical synaptic activity
Population rate	the mean of the firing rates of all neurons in a population. Population rate does not denote an average over multiple presentations of a stimulus, but rather the averaged activity of multiple neurons at a single moment in time
Local field potential (LFP)	An electrical potential measured from extracellular space. LFP reflects primarily synaptic activity rather than action potential waveforms
Depth-negative/Depth-positive	LFP waves where a negativity/positivity is seen in the subgranular layers. This laminar specification of polarity of LFP waves is needed because cortical local field potentials typically show a reversal at or around the middle layers
Excitable systems	a class of dynamical system models used to describe various physical, chemical, and biological phenomena including lasers, chemical oscillations, heartbeat, and action potential generation. These systems reflect a combination of fast positive feedback that amplifies small perturbations, with

slower negative feedback that brings the system back to baseline once fluctuations become large

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Figure 1.

Cartoon Illustration of how population activity patterns vary with cortical state. The two panels illustrate two extremes of a continuum of states seen in awake rodents. **A.** In synchronized states, cortical populations show spontaneous common fluctuations in firing rate. During the active phase, all neuronal classes show a propensity to fire (coloured rasters), whereas during the silent phase, spiking is reduced or absent. These phases are accompanied by corresponding depolarization and hyperpolarization in intracellular potentials (red, top). Deep-layer cortical local field potential (black, bottom) shows slow negative waves accompanied by high-frequency activity in the active phase, and smooth dome-shaped positive waves in the silent phase. This type of activity is seen in drowsy or quiescent animals (right). **B.** In the desynchronized state, coordinated slow fluctuations in population activity are not seen, and low-frequency fluctuations in the local field potential and membrane potentials are suppressed. This type of activity is seen in actively behaving, alert animals (right).

Figure 2.

Cortical LFP and behaviour. **A**, In this classical pen-chart recording, the correlation between behaviour and cortical EEG is difficult to detect visually under control conditions (top two traces, showing EEG and movement activity), but is greatly amplified by application of the muscarinic antagonist atropine (bottom two traces). **B**, A recent study showing a reduction of spontaneous fluctuations during whisking behaviour, clearly visible in intracranial LFP and membrane potential, but more difficult to detect visually in the surface EEG. **C**, In monkey V1, low-frequency (2–10Hz) power is reduced when attention is directed into the receptive field corresponding to the electrode site (att RF: red, green), and is increased by application of the muscarinic antagonist scopolamine (Scop: green, black) or when attention is directed to a different location (att away: blue, black). Part A is modified from Ref. ⁸², Part B from Ref. ⁷, Part C from recordings in the Thiele lab (Herrero, Delicato, Thiele: methods details in Ref. ¹⁸³).

Figure 3. Possible mechanisms of asynchronous and synchronous activity. **A1**, Correlations generated by shared excitatory input may be cancelled by rapid recurrent inhibition. **A2**, Raster showing spontaneous activity of simultaneously recorded population from rat somatosensory cortex in a desynchronized state. Bottom trace shows population rate as a function of time, showing a small degree of fluctuation. **A3**, Histogram of pairwise correlations in this population, with a mean close to zero but long tails indicating an approximately equal number of significant positively and negatively correlated pairs (insets). The gray curve indicates the distribution of correlations that would be expected by chance. **B1**, Excitable system model of slow fluctuations in cortical activity where up phases are generated and sustained by recurrent synaptic activity before being overcome by adaptive processes. **B2**, Raster showing spontaneous activity of same population as A2, but now in a synchronized state. **B3**, Histogram of pairwise correlations in this population, showing positive mean for the whole data set (red) but a mean close to zero when considering active phases only (yellow). Modified from Ref. ³².

Figure 4.

Desynchronization suppresses responses to punctuate stimuli, but decreases adaptation and enhances representation of temporally extended stimuli. **A**, State-dependent responses to stimulus trains in barrel cortex of anesthetized (left) or awake rats (right). In synchronized states under anaesthesia and in quiescent awake animals (open circles), responses to rare punctuate stimuli are large, but responses adapt strongly at high repetition frequencies. After electrical stimulation of reticular formation (RF) or during active behaviour (solid circles), responses to rare stimuli are smaller but adaptation is reduced. **B**, Raster representation of a visual cortical unit response to repeated presentations of a temporally extended natural scene movie. Stimulation of nucleus basalis (NB) increases reliability of responses from trial-to-trial. **C**, Response in auditory cortex to repeated presentations of a temporally extended amplitude-modulated noise stimulus. Evoked LFPs (coloured curves) from two presentations of the same stimulus in synchronized (blue and cyan) and desynchronized (red and magenta) states, as well as raster representation of spikes from one cell in response to repeated presentations in each state. Black curve (bottom) shows stimulus envelope. LFP and spiking responses are more reliable in desynchronized state. Part A is modified from Ref. ¹⁷⁰, Part B from Ref. ¹³², Part C from Ref. ¹⁷⁶.

Figure 5.

Suggested mechanisms underlying widespread and focused desynchronization during state changes and attention. Increased activity of cortical neuromodulatory afferents (red [cholinergic], blue [serotonergic] and green [noradrenergic] arrows) causes a general desynchronization and reduction in spontaneous fluctuation, but may lack the spatial selectivity to desynchronize the patch of cortex representing the attended stimulus. Focused glutamatergic inputs arising from feedback connections could provide this specificity (yellow arrows), causing enhanced desynchronization and sensory responses in the regions of cortex that represent the attended stimulus. The yellow circle in the visual display indicates the focus of attention, which affects processing in thalamic and cortical areas at specific locations (indicated by the yellow patches). The distorted replication of the visual world in the different areas illustrates (approximately) the known retinotopic organization of these different areas.

Table 1

Similarities between desynchronization in rodent and attention in primate

Measurement	Effect of desynchronization or active behaviour in rodent	Effect of attention in primate
Low frequency LFP power	Reduced ^{7, 38, 53, 83}	Reduced ^{18, 21, 22}
Gamma LFP power	Increased (running, cholinergic stimulation, thalamic stimulation) ^{38, 52-55} ; Decreased (dorsal Raphe stimulation) ⁵⁶	Increased (V4) ¹⁸ ; Decreased (V1) ²¹
Trial-to-trial variability	Reduced ^{31, 132, 176}	Reduced ^{19, 20}
Noise correlation	Reduced ^{32, 132}	Reduced ^{19, 20}
Response size	Reduced (sudden punctuate stimuli) ^{130, 170} ; Unchanged or enhanced (rapidly repeated or temporally extended stimuli) ^{132, 170, 176}	Reduced (unattended stimuli) ²⁰⁸ ; enhanced (attended stimuli) ^{12, 13, 16}