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Correlations and brain states: from electrophysiology to neuroimaging

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Summary of recent advances

Neural activity in cortex is correlated, an observation that has traditionally been attributed to neurons receiving input from a shared and limited presynaptic pool. Recent studies have shown that correlations are also strongly influenced by network fluctuations that operate over a range of spatial and temporal scales, extending in some cases across cortical areas. These fluctuations are sensitive to internal states and external drive, so that correlations themselves depend strongly on cognitive state and stimulus properties. Given their potential impact on population coding, this modulation of correlations may play an important role in sensory processing.

The activity of cortical neurons is correlated. Correlations are seen as shared fluctuations in responsiveness in the absence of changes in sensory drive or motor output. They occur over a range of time scales, from the precise temporal alignment of spiking (synchrony) to co-modulation of firing rate over many seconds [1,2]. They are typically measured by computing cross-correlation functions, which reveal the relationship between a cell's spiking and the firing of another, or by comparing trial-to-trial fluctuations in spike counts evoked by repeated presentations of the same stimulus.

Correlations are of interest for three interrelated reasons. First, they can strongly affect population coding, with their impact depending on their relationship to neuronal tuning and on how information is extracted from the population. Second, they may provide a signature of perceptual and cognitive processes that involve modulation of ensemble behavior rather than neuronal firing rates. Third, they can provide insights into the functional architecture and dynamics of cortical networks.

The effect of correlations on population coding has been reviewed thoroughly by Averbeck et al. [3, see also 4]. Here we focus on recent studies that have investigated how correlations in cortex are affected by internal states and external drive and on the network dynamics and mechanisms that underlie them. This work, using techniques ranging from intracellular recording to functional MRI, has revealed that correlations are affected by cognitive state, strongly altered by stimulus drive, and arise in part from network fluctuations that occur over a range of spatial and temporal scales.

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Modulation of correlations by internal state and stimulus drive

A hallmark property of the electroencephalogram (EEG) is that it desynchronizes when subjects become engaged in a task, suggesting that arousal disrupts correlated ongoing activity. This decorrelating effect of arousal has been recently observed at the neuronal level using paired whole-cell recordings in awake mice. In an elegant study, Poulet and Petersen [5] showed that the membrane potentials of cells in barrel cortex fluctuate at low frequencies (1–5 Hz) and in a highly correlated manner when mice are quiescent [see also 6]. During active whisking correlations are weakened, due primarily to the suppression of these coherent fluctuations. This effect is not due to sensory input recruited by whisking, as it occurs even when the afferent pathway has been severed. Instead, correlations appear to be weakened by an internal signal when the mouse switches to active exploration.

Whereas arousal decorrelates activity, several groups have proposed that attention enhances correlation—specifically, synchrony—within a local population [see 7 for review]. In these studies, strengthened synchrony is suggested by an increase in coherence between spikes and the gamma frequencies (30–80 Hz) of the local field potential (LFP), indicating that spiking is more tightly locked to rhythmic local activity at this frequency. More recently, Fries et al. [8] reported that attention also enhances spike-spike coherence at similar frequencies. The purported benefits of this attentional modulation are that higher coherence provides better temporal alignment of inputs to postsynaptic sites, thus enhancing their efficacy, and that it opens a “temporal window of communication” between cortical areas.

There are three factors that may explain the difference between the suggestion that attention enhances correlations whereas arousal suppresses them. The first is simply that arousal and attention are different phenomena and so modulate correlations differently as well. Second, attentional studies reporting enhanced correlation have relied on frequency domain analysis, such as coherence, which may capture effects not easily detected in cross-correlation functions [8]. Indeed, studies that have measured the magnitude of synchrony under different attentional conditions have found either weak [9] or no modulation [10]. Finally, and perhaps most interestingly, the difference may reflect the time scale considered—arousal reduces low frequency co-fluctuations whereas attention studies focus on an enhancement of coherence at higher frequencies. Although not emphasized as strongly, attention has also been shown to reduce spike-LFP and spike-spike coherence at low frequencies (<20 Hz). Consistent with this finding, spiking correlations in primate area V4, when measured over hundreds of milliseconds, are weakened by attention [11]. Together these findings suggest that the most functionally relevant effect of attention, like arousal, may be to suppress co-fluctuations occurring on slow time scales.

The modulation of correlations by arousal and attention involve a change in the internal state of the animal. A recent study in visual area MT showed that trial-to-trial fluctuations in internal state can also affect correlations, in a surprisingly complex manner [12]. Monkeys were trained to perform a motion discrimination task, such as distinguishing leftward from rightward motion. The axis of motion in each session was varied so that the two recorded neurons would contribute either to the same perceptual decision (e.g. higher firing in both cells signals leftward motion) or to opposite ones (e.g. higher firing in one cell signals upward and in the other downward motion). For neurons tuned to similar directions, correlations were significantly stronger when higher firing in the two neurons indicated the same perceptual decision. The authors reproduced their findings with a simple model in which neuronal responsivity is modulated by an attentional signal whose strength fluctuates from trial-to-trial. A similar effect and mechanism had previously been reported in primary visual cortex [V1; 10]. This effect thus involves *fluctuations* in an internal variable that modulates firing, rather than a switch

from one state to another. This provides an important caveat: correlations may be enhanced—or overestimated—when internal variables are poorly controlled.

In addition to their sensitivity to internal state, correlations are strongly affected by external drive. For instance, studies in visual [2,6,13,14] cortex have found that stimulus drive reduces correlations in spontaneous activity. Strong inputs, such as high contrast visual stimuli, reduce correlations more than weak ones [2,15]. The variability of evoked responses is also lower than that of spontaneous activity [16,17]. In this vein, it is worth noting that attention increases the apparent contrast of a visual target [18]; in so far that attention reduces correlations, this may be associated with an increased potency of attended stimuli.

In summary, correlations are malleable and are modulated by some of the same factors that influence neuronal responsivity itself, including the strength of sensory drive and the internal state of the animal (arousal and attention). Even the recent history of stimulation—adaptation—has been shown to affect correlations [19]. A recurring theme in this work is that providing input, either internal or external, to a network reduces correlations in ongoing activity. Since small differences in correlations can have dramatic effects on population coding [3], this modulation may play an important role in sensory processing.

Mechanisms and network fluctuations that generate correlations

The mechanisms responsible for the modulation of correlations are not clear, but we have learned about a number of network factors that contribute. The most straightforward mechanism generating correlations is the firing of a common presynaptic neuron or pool of neurons [20]. Since each sensory event drives a unique subset of cells in the network, one would expect that the degree of common input provided to a pair of cells, and thus their correlation, will vary with stimulus properties. This is the case in V1, where correlations on time scales less than roughly 100 ms are strongest for oriented grating stimuli that fall between the preferred orientations of a pair of cells [2,6,21], and in MT, where correlations are sensitive to the speed of a visual stimulus [15]. These short time scale correlations are observed primarily between cells separated by less than 3 mm [13 and references therein]. The stimulus dependence of correlations is not a simple consequence of neurons being more depolarized and firing more strongly to some stimuli [22]. It is also distinct from the suggestion that synchrony is modulated by the gestalt properties of a stimulus, which has proved controversial both from a theoretical and experimental perspective and continues to accumulate both corroboratory [23,24] and refutative evidence [25,26].

On time scales of hundreds of milliseconds, correlations are less stimulus-dependent and seem to reflect more spatially widespread fluctuations in cortical responsivity. These fluctuations are prevalent in ongoing, spontaneous activity (see review by Ringach in this volume). For instance, voltage-sensitive dye imaging shows that spontaneous activity is strongly correlated in both time and space [27] and can involve waves of activity that sweep across cortex at speeds varying from 10–200 mm/s [28–32]. These widespread fluctuations presumably underlie the large transient depolarizations observed in intracellular recordings *in vivo*, including "bumps" [33], up/down states (described below) and low frequency (6–10 Hz) rhythmic co-fluctuations of both excitatory and inhibitory inputs [5,34]. Visual input disrupts these patterns: slow fluctuations and waves are reduced in amplitude in the presence of sensory drive [32] and during active behavior [29,35], consistent with the previously discussed reduction in correlations with stimulus drive and arousal.

The studies described above measured correlations within a cortical area. Recent functional MRI studies have provided a new view of interareal correlations. These measurements typically focus on very low frequency (< 0.1 Hz) components of the BOLD signal and are performed in awake human subjects in the absence of sensory drive or an explicit behavioral task (termed

the "resting state"). Under these conditions, the BOLD signal displays spontaneous fluctuations that are correlated between cortical areas. Generally these areas are also coactivated by the same behavioral or sensory events and thus seem to form well-defined functional networks [for a review see 36]. For instance, spontaneous fluctuations in a region of the somatosensory cortex are strongly correlated with a handful of other somatomotor but not visual areas. These coherent fluctuations of the BOLD signal have also been observed in isoflurane anesthetized monkeys, with correlations being stronger for lighter levels of anesthesia [37]. The use of anesthesia in this study was important: since previous studies had been performed in awake humans, it was unclear whether the observed correlations arose from uncontrolled and fluctuating internal processes.

The neurophysiological basis of low frequency BOLD fluctuations is unclear. They may be related to transitions between 'up' (depolarized) and 'down' (hyperpolarized) states which occur with a similar frequency (0.3–1 Hz) and which may also contribute to the intra-areal waves described above. These fluctuating states had previously been thought to occur only in sleeping and anesthetized animals [for review see 38] and *in vitro*. However, recordings in awake human patients have revealed slow co-fluctuations in surface potentials recorded across areas of somatomotor cortex [39] and interhemispheric correlations of spiking activity in auditory cortex [40]. Regardless of their relationship to up and down states, these data confirm directly that slow interareal co-fluctuations also occur in neuronal firing in awake subjects [see also 41 and 42 for similar data in awake animals].

The question of whether low frequency fluctuations observed under anesthesia are related to those in awake subjects raises the more general issue of how anesthesia affects correlations, particularly given recent evidence that correlations are modulated by arousal and attention. This is an important issue as much work on correlations and network fluctuations has been performed in anesthetized animals. One recent study used calcium imaging to measure activity in rat barrel cortex and reported that correlations under anesthesia are stronger and have a different spatial pattern from those observed in quiescent animals [43]. However, the anesthetic agent used in this study—ketamine, a noncompetitive blocker of the NMDA receptor—interferes with glutamatergic neurotransmission and alters basic neuronal response properties [44]. It is thus not surprising that it affects correlations as well. Other anesthetics have been shown to have different and, in some cases, minimal effects on neural sensitivity and responsivity [45], on slow cortical rhythms [46], and on correlated fluctuations in the BOLD signal [47,48]. Correlations in anesthetized animals thus depend on the anesthetic used, just as correlations in the "awake" state will depend on whether the animal is engaged in a task or quiescent or drowsy. In this sense, anesthetized and awake preparations do not form a dichotomy, but include a range of states with potential similarities and differences in correlations depending on the specific comparison at hand.

In summary, studies using techniques ranging from paired intracellular recordings to fMRI have revealed correlated fluctuations in responsivity. Since these measurements have been made with different techniques—across a spectrum of spatial and temporal scales, cortical areas and species—they almost certainly reflect a number of distinct phenomena. Nevertheless, they paint a common picture: correlations on brief time scales arise from common input recruited by a particular stimulus; under a range of awake and anesthetized conditions, correlations are enhanced by wide-spread (both intra- and inter-areal) low frequency fluctuations in network activity. Modulation of these fluctuations by internal state or external drive is one mechanism for controlling the strength of correlations.

Conclusion

Over the last several years we have learned a great deal about how cortical correlations are modified by internal state and stimulus drive and about the network behaviors that contribute to them. We now know that correlations are highly malleable. They do not arise simply from common input provided by fixed pools of presynaptic neurons. Rather, they are strongly influenced by more general fluctuations of cortical networks, which can be modulated or disrupted by either internal or external drive.

Much, of course, remains unclear. Despite some progress [e.g. 49,50], the mechanisms that govern brain states are not well understood. In addition, the impact of correlations will depend on the spatial and temporal scales over which they occur—for instance, those generated by local common input will have a different effect from interareal network fluctuations. This has not been considered extensively in evaluating the functional importance of correlations, either for encoding within a local neuronal population or, perhaps more importantly, for how they affect the propagation of information to downstream networks and the computations performed there.

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