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Early steps toward understanding neuronal communication

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Abstract

Purpose of review: The computational power of the brain arises from the complex interactions between neurons. One straightforward method to quantify the strength of neuronal interactions is by measuring correlation and coherence. Efforts to measure correlation have been advancing rapidly of late, spurred by the development of advanced recording technologies enabling recording from many neurons and brain areas simultaneously. This review highlights recent results that provide clues into the principles of neural coordination, connections to cognitive and neurological phenomena, and key directions for future research.

Recent findings: The correlation structure of neural activity in the brain has important consequences for the encoding properties of neural populations. Recent studies have shown that this correlation structure is not fixed, but adapts in a variety of contexts in ways that appear beneficial to task performance. By studying these changes in biological neural networks and computational models, researchers have improved our understanding of the principles guiding neural communication.

Summary: Correlation and coherence are highly informative metrics for studying coding and communication in the brain. Recent findings have emphasized how the brain modifies correlation structure dynamically in order to improve information processing in a goal-directed fashion. One key direction for future research concerns how to leverage these dynamic changes for therapeutic purposes.

Keywords

Correlation; Coherence; Variability; Attention; Disconnection Syndromes

Since Paul Broca's landmark descriptions of focal lesions underlying disfluent aphasia in the mid-nineteenth century (1–3), neuroscience has appreciated that certain cognitive and computational functions seem localized to different parts of cerebral cortex, and that focal damage to those areas impairs the corresponding function. A century later, Norman

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Geschwind introduced the idea that some neurological disorders may not be best explained by focal damage to specialized cortical areas, but rather due to damage to or aberrant development of the fibers connecting such areas, and that therefore atypical communication between those areas was the cause of dysfunction (4, 5). Geschwind termed these cases “disconnection syndromes,” some salient examples of which include schizophrenia (6), attention deficit disorders (7, 8), and autism spectrum disorders (9, 10). Since a fundamental problem for these syndromes concerns inter-area communication, uncovering the principles by which parts of the brain interact is essential to understanding the etiology of these disorders, as well as to identify potential therapeutic targets. Moreover, since nearly every important brain function involves coordination between functionally specified sub-units, basic research into the interactions between parts of the brain forms the foundation of systems and cognitive neuroscience. This is true not only for the study of coordination between brain areas distributed across the cortex at the centimeter scale, but also includes the study of computations performed by interactions between individual neurons at the microscopic level.

Correlation as an index of neuronal coordination

How might one study neural coordination? One very natural approach is by measuring the strength of correlation between two neural sources. When the nature of interaction is periodic, then *coherence*, the frequency-domain analog of correlation, may be measured. While correlation and coherence cannot tell us whether two signal sources are *directly* interacting in the strictest sense (the two signals may be only indirectly related via a third signal, for example), these metrics index a straightforward functional relationship that is easy to measure and can be highly informative. Two key contributions of studies of correlation structure to neuroscience are guiding the development of biologically plausible artificial models of neural networks, and constraining mathematical theories of neural computation.

Computational models have the advantage over biological circuits that the parameters governing their behavior are completely known to the researcher, and it is possible to modify one of these parameters at a time and observe the resultant effects. To ensure that such models are biologically plausible, it is important that the statistics of the behavior of the simulated neural populations match what is seen *in vivo*, and the correlation of activity between pairs of neurons has been a common metric for such comparisons. In one recent example, Rosenbaum and colleagues (11) investigated how the spatial distribution of synaptic connection probabilities in an artificial neural network affected the structure of correlated spiking activity. By systematically varying the spatial parameters of the network, they were able to compare the correlation structure of the artificial neurons to that of real neural networks recorded from monkeys. Another study compared the correlation structure of simulated networks to that of *in vivo* observations in order to test relative contributions of inhibitory and excitatory influences during selective attention, and found that the *in vivo* correlation results could be explained by an attention signal that selectively targeted inhibitory neurons (12); and the results of subsequent modelling study suggested that this emphasis on inhibitory neurons by attention was not only sufficient to see the changes in correlation we observed, but was most likely necessary also (13). In this way, researchers

can test which aspects of neural network organization are key contributors to the statistical structure of biological neural activity, and make predictions about how that statistical structure might be affected by different perturbations of network parameters.

In addition to making predictions about the structure of neural networks, neural correlations can provide important constraints for computational theories of brain function. This is because correlation and coherence are closely related to the concept of *information* in a formal mathematical sense. Information theory formalizes a communication system as comprised of a *transmitter*, which sends a message to a *receiver* (14). If the activity of the receiver is perfectly correlated with the activity of the transmitter, then the maximum amount of information was conveyed. In practice, noise is always added to the message, which reduces the correlation between the transmitter and receiver, and reduces the information conveyed. The corrupting influence of noise can be mitigated by transmitting multiple copies of the message through separate channels. If each channel is affected by noise randomly and independently, then the original message can be reconstructed with greater fidelity by looking at the features that are shared across multiple message copies. This strategy only works, however, if the noise is uncorrelated across channels. As noise becomes increasingly correlated across transmission channels, it becomes increasingly difficult to overcome. Thus, within a transmitter, the magnitude of *noise* correlation is inversely related to the amount of information that can be conveyed (14). One of the key conceptual issues of contemporary neuroscience concerns how to relate parts of the nervous system to parts of such a theoretical communication system. One straightforward interpretation is that a presynaptic neuron functions as a transmitter and a postsynaptic neuron serves as a receiver, in which case greater correlation suggests improved communication. However, multiple neurons in a population that process similar types of information could also be considered as multiple, redundant channels of a common transmitter, despite that they might synapse on each other. In this case, greater correlation (specifically, noise correlation) suggests diminished communication. These two example possibilities provide a window into a general principle: changes in correlations can have opposing effects on neural communication depending on the roles of the neurons being measured; roles which may be dynamic and context-dependent. By measuring the correlation structure in the brain, and observing how changes in correlation structure relate to improvements or detriments to behavior, we can form inferences about how parts of the brain should be conceived as parts of a communication system.

As we mentioned, noise correlation is particularly problematic between channels encoding redundant information. For visual neurons, one definition of noise is the trial-to-trial variations in response strength to repeated presentations of a stimulus, and so-called noise correlation can be estimated by measuring the correlation in this trial-to-trial variability between neurons. One recurring observation about the correlation structure of the brain is that within visual cortical areas, the strength of such noise correlation between a pair of neurons is directly related to the similarity of stimulus tuning preferences between those cells (15–20). At first blush this arrangement presents a conundrum, because from an information-theoretical standpoint if the source of shared trial-to-trial variability for a pair of neurons was truly noise then such a correspondence of signal and noise correlations would be highly detrimental to coding (21, 22), and it seems unlikely that the brain would evolve

such a maladaptive correlation structure. One factor important for resolving this conundrum is that neural populations can encode multiple types of information simultaneously. That is, some trial-to-trial variability is not merely “noise”, but is in fact information about things uncontrolled by the experimenter, such as internal states, that the brain has mechanisms to decode (23–25). One finding that lends support to this idea is that correlation structure within a neural population changes depending on which types of information are most relevant in a given context.

Correlation structure in neuronal populations is context-dependent

Because neural correlations have important consequences for the information-processing capacity of the brain, one question of particular interest is the degree to which correlation structure can be modified. In addition to improving our understanding of how healthy brains manage the information-processing problem posed to the brain, knowledge of the ecological and artificial mechanisms by which neuronal interactions might be steered has enormous potential for guiding the development of therapeutic interventions for disorders of neuronal coordination. In fact, correlation structure in the brain has been seen to vary substantially within individuals in a number of contexts, such as during learning (26, 27), memory (28–30), sensory stimulation (12, 15, 16, 31–33) and motor intention (34–36). Correlation structure even appears to change spontaneously in the visual cortex of anesthetized animals, with encoded information shuttled between different subpopulations of neurons within primary visual cortex (37). One domain in which modulations of correlation strength have received particular interest is selective attention (12, 38–45), which is the cognitive ability to focus processing resources on certain pieces of information out of the limitless total amount of information available in the environment. Because selective attention directly concerns information-processing limitations, it is a particularly appealing target of inquiry for understanding the relationship between correlations and information in the brain. Moreover, shifting the focus of selective attention occurs rapidly on sub-second time-scales (46), suggesting that the mechanisms by which attention modifies correlation structure are easily reversible and do not rely on wholesale re-wiring of neural circuitry; two properties which would be desirable for potential future therapies.

Within a brain area processing visual information, attention tends to cause a decrease in correlated trial-to-trial variability (12, 38–42, 44, 45). To the extent that neurons within a cortical area encode redundant information, information theory predicts that decreasing the correlation of noisy fluctuations between such neurons should improve the information carrying capacity of the population in general (14), and indeed decreases of within-area correlations can account for substantial behavioral benefits of selective attention (12, 41). However, the information redundancy within a brain area is not complete, as neurons are tuned for different parts of space and visual features. Further confirming information-theoretical predictions, the attention-related changes in correlated variability for pairs of neurons within a brain area vary in relation to the extent of the redundancy between them (39). In the extreme case, this can be manifested as some attention-related *increase* in correlation for neurons with opposite feature tuning preferences (39). The key result is that attentional selection seems to lead to changes in correlation that would increase the information-processing capacity of a neuronal population. Recently, it was demonstrated that

for mice, activation of basal forebrain cholinergic neurons is sufficient to cause these changes in correlation structure in visual cortex (47). Within visual cortex, attention-related decorrelation seems dependent on NMDA-type glutamate receptors (40). Observations such as these provide an important clues about the mechanisms by which information-processing is shaped in the brain, which not only advances our knowledge of healthy brain function, but may someday lead to therapeutic interventions in those same processes.

Correlation structure between brain areas is context-dependent

A relatively small number of studies have examined spiking activity of neuronal populations in two distinct brain regions simultaneously. A common thread that has emerged in attention-related changes in noise correlation, in a variety of experimental contexts, is an increase in correlation *between* cortical areas critical for processing the to-be-attended information. This has been found between multiple pairs of brain areas, such as primary visual cortex and the visual motion-sensitive middle temporal area (MT) (43), between visual area V4 and the frontal eye fields (48), and also between medial and lateral frontal cortex (49). This pattern of results is in contrast to the correlation decreases that are typically observed *within* a single cortical area with attention, but it is consistent with an improvement in communication between a transmitter and a receiver (14). The complex effects of attention on correlation are a prime of example of how neurons can fill varied roles as parts of a communications system; often filling multiple roles at the same time depending on the scale of measurement being considered.

One weakness of correlation as a metric of neural coordination is that it is insensitive to the direction of information flow. In other words, correlation does not disambiguate which neural population functions as a transmitter and which functions as a receiver. A related approach to measuring correlation is to fit coupling terms in a regression model to ask how well knowing the spike trains of one neural population enables prediction of another neural population at a later time. Recently, Yates and colleagues (50) applied this approach to test for evidence of a direct transmitter-receiver relationship between MT and the lateral intraparietal area (LIP), each of which had previously been separately shown to be involved in a visual motion perceptual decision-making task. They found that direct coupling accounted for almost none of the relationship between MT and LIP, suggesting that the functional interaction between those areas was likely indirect. This result reinforces the importance of exercising caution in interpreting correlated activity between brain areas, and to consider the potentially mediating role of unobserved neural populations.

The study of inter-area coordination is not restricted only to primates, but has also seen growing interest among researchers using mouse models of vision. One prime advantage of the mouse model is that wide-field imaging methods have enabled recording from virtually every visual cortical area simultaneously in mice, which is not currently feasible with methods available for primate subjects. In one such study, Smith and colleagues (51) inferred spiking activity from changes in intrinsic optical properties of brain tissue and measured how these activity patterns were correlated across different cortical areas in different visual contexts. This approach revealed two clusters of visual areas with a high degree of coordination, which were analogous to the well-studied ventral and dorsal visual

streams in primates known as the “what” and “where” streams, respectively. This confirms how correlation can be used to infer functional connections between areas involved in processing different types of information.

Taken together, these results suggest that inter-area spiking correlation may follow some common principles, such as generally increased correlation between functionally related areas that can be modulated depending on task demands, and also illustrate some potential interpretive considerations, such as the potential mediating influence of unobserved areas.

Compared to the literature surrounding inter-area spiking correlations, a larger body of work has examined the relationship between local field potentials in distant brain regions. A prominent hypothesis is that distinct brain areas may communicate in a quasi-rhythmic fashion, and that their coordination may therefore be well-captured by coherence measurements (52). Lending weight to this idea, attention has been shown to strengthen the coherence of local field potentials between task-relevant brain areas at specific frequencies, in particular the gamma (~60 – 80 Hz) band (53, 54). This could be taken as consistent with the spiking coordination results, indicating that attention improves information transmission between brain areas, and further defines the temporal scale of rhythmic activity that may be particularly important for this coordination. Unfortunately, coherence measurements share a drawback with correlation measurements in that they too are merely suggestive of the strength of information transmission and cannot indicate the direction of communication, such as the extent to which information might flow in a “feedforward” or “feedback” manner.

Nonetheless, evidence has been mounting that these two basic types of long-range neural communication, feedforward and feedback, may preferentially operate at different time-scales. For example, Bastos and colleagues (55) recorded electrocorticographic signals spanning nearly all of dorsolateral cortex (in one hemisphere) in monkeys, enabling them to estimate the strength of interplay between many pairs of visual cortical areas. To form inferences about the direction of information flow, the researchers used Granger causality, which is an extension of correlation/coherence that quantifies how well one signal is able to predict another. Their results suggested that information flowing in directions traditionally considered feedforward (based on prior anatomical research) is confined to the theta (~4 Hz) and gamma (~60 – 80 Hz) frequency bands, whereas feedback information is preferentially focused in the beta band (~14 – 18 Hz). A subsequent study using magnetoencephalography with human research participants replicated this general pattern of results (56), although feedback influences for humans spanned a greater bandwidth, including the alpha range, in that study (7 – 17 Hz). The inclusion of the alpha band as a channel for feedback influences squares sensibly with a substantial and growing literature implicating this frequency band in the control of endogenous selective attention (12, 57–65). Feedback activity in the alpha-beta range has been shown to enhance the feedforward propagation of visual gamma band activity (66), which further supports the hypothesis that top-down alpha activity might function as a mechanism for facilitating visual processing during selective attention. Moreover, injecting electrical stimulation into cortex at gamma frequencies has been shown to propagate in a feedforward manner, whereas electrical stimulation at alpha frequencies tends to propagate in a classically feedback fashion (67). This result suggests that the

occurrence of activity in key frequency bands is sufficient to direct information flow in the brain, and that the substrate for this directed information flow is latent in the structure of the brain's connections. This last point is important because it bolsters the promise for using electrical stimulation as a method for potentially enhancing communication between brain areas in a targeted and directed fashion for therapeutic purposes.

Current challenges and future directions

The computational power of the brain arises from complex interactions between neurons. With recent advances in electrophysiology and imaging enabling the simultaneous recording of activity from scores to hundreds of individual neurons at a time, both within and between brain areas, neuroscience has become increasingly focused on understanding the statistical relationships that characterize neuronal interactions. Perhaps the most straightforward quantifications of neuronal interaction are the metrics of correlation and coherence; and studies of these metrics have paid substantial dividends towards our understanding of how information is represented and transmitted in the brain. Yet, even these relatively simple quantities of correlation and coherence present substantial analytic and interpretive challenges still to address.

One salient issue is that correlation and coherence describe relationships between pairs of signals only, whereas interactions in the brain are never merely pair-wise but rather involve virtually countless signals, of which researchers endeavor to sample as many as possible. However, as the number of signals sampled increases, the number of signal pairs increases quadratically. This can quickly lead to an unwieldy amount of data to analyze, and the conclusions drawn about information represented in small populations may not generalize to larger samples (22). One approach to surmounting this challenge currently being developed is the use of so-called “dimensionality reduction” analyses to distill the immense information redundancy in neuronal populations down to the key elements (68). As with studies of correlation and coherence, the results of dimensionality reduction analyses can be compared to the properties of artificial networks to test hypotheses about the organization of neural circuits (69, 70). When the key high-dimensional features of these artificial networks can be matched satisfactorily to their biological counterparts, they could provide a powerful means to overcome the data limitations of *in vivo* experiments, since artificial networks can be grown arbitrarily large within the constraints of the ever-expanding computing power that is available, while remaining known in complete detail to researchers.

Another key issue related to studying correlations is the question of precisely which signals to measure. Here we have focused on signals recorded intracranially, in particular single-neuron spiking activity, local field potentials and electrocorticography. The exquisite temporal and spatial resolution of these methods makes them invaluable tools for investigating brain function, but their invasiveness limits their applicability to human research participants. Research with humans has also seen growing interest in inter-area correlations and coherence of late, using non-invasive neuroimaging methodologies such as EEG/MEG and fMRI. For example, atypical coherence between locations on the scalp measured with EEG has been observed in several neurological disorders suspected of involving deficient inter-area communication, including Alzheimer's disease (71), attention

deficit disorders (72), and autism spectrum disorders (73, 74). The relationship between these neuroimaging signals and the spiking activity of individual neurons remains largely unknown, however. One recent study showed that task-related shifts in the amplitude of EEG oscillations at the scalp index changes in the correlation structure in the underlying neural population (12), providing a toe-hold to link across recording scales and species, but much research into this question remains needed.

A third key issue concerns how to translate our growing understanding of correlation structure in the brain to clinical applications. For example, evidence is mounting that the brain modifies correlation structure in ways that would seemingly be beneficial for information processing during selective attention. Are such changes in correlation sufficient to cause perceptual improvements? That is, if it were possible to artificially influence correlation structure (e.g., using electrical, optical, or pharmacological stimulation) in the right brain areas at the right times, might that emulate the effects of attention? Or with respect to inter-area communication, evidence suggests that small amounts of electrical current delivered intracortically can drive activity selectively in a feedforward or feedback direction depending on the frequency of stimulation (67). Could this principle potentially be exploited in the future for cerebral neural prosthetics for the treatment of mental disorders? Would it be possible to adapt such a stimulation paradigm to non-invasive, transcranial methods? Since coordination between brain areas and neurons is fundamental to mental health, developing methods to assist or intervene in this coordination in a targeted fashion would be an immense breakthrough in the treatment of neurological disorders, and is a fitting focus for contemporary neuroscience research. These efforts will also depend on developing an improved understanding of the basic principles guiding neuronal coordination within and between brain areas that underlie the encoding and transmission of information.

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Key Points:

- Correlation among neurons is a window into neuronal computation and architecture.
- Correlation structure is not fixed, but changes in response to current behavioral goals.
- Conceptualization of neuronal populations as parts of a communication system offers a basis for understanding how brain regions interact.
- A clear framework of neuronal interactions, both nearby and distant, is necessary for the development of therapeutic interventions for many neurological disorders.