Hebb's Dream: The Resurgence of Cell Assemblies

Minireview

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Although Donald Hebb's classic book, *The Organization of Behavior* (1949), is widely known for its description of a mechanism for synaptic plasticity (the so-called Hebbian synapse), it also contains one of the most influential proposals on how interactions between large populations of neurons underlie brain processes. Central to Hebb's theory is the concept of the "cell assembly . . . a diffuse structure comprising cells in the cortex and diencephalon, capable of acting briefly as a closed system, delivering facilitation to other such systems . . ." (p. xix). In Hebb's view, individual neurons did not work in isolation, and consequently, they could not, by themselves, account for any given percept or ability. In fact, he suggested that individual neurons could participate in different cell assemblies and be involved in multiple functions and representations. Although the importance of neural populations in sensorimotor information processing had been recognized earlier (Young, 1802; Sherrington, 1906), Hebb's work was a landmark because it provided the first elaborated description of mechanisms by which neural populations could underlie a variety of brain functions.

Because single neurons can respond to a range of sensory stimuli or participate in multiple motor acts, large neural populations are required for representing the different attributes of a particular stimulus or for producing a given behavior. Population coding schemes have been proposed for several sensory modalities (reviewed by Erickson, 1968), as well as for cortical control of arm movements (Georgopolous et al., 1986) and tectal control of saccadic eye movements (Lee et al., 1988). Nevertheless, until recently, the main approach used to reconstruct both sensory and motor representations was to record, in a serial fashion, the activity of individual neurons and then try to derive a population code. Unfortunately, this approach does not allow one to investigate the potential time-dependent interactions between neurons that may be used by the brain to represent information.

The recent advent of new electrophysiological techniques, which currently allow one to record the simultaneous activity of 100–150 neurons, has sparked renewed interest in the properties of neural assemblies and their potential roles in brain function. Therefore, it is not surprising that many laboratories have begun applying neural ensemble recordings to investigate how neuronal populations encode sensory and motor information. Here, we examine some of this recent work, which suggests that Hebb's view is likely to become the rule rather than the exception.

Neural Ensemble Encoding of Sensory Information

Temporal interactions between cell assemblies in different anatomical locations were a fundamental postulate of Hebb's theory. Testing this theory would require one to record from populations of neurons distributed across multiple cortical areas and subcortical nuclei. Using a chronic multiple-electrode recording preparation, Nicolelis and coworkers (1995, 1997a) recorded from populations of neurons distributed throughout the trigeminal somatosensory pathway, from the trigeminal brain stem complex and the somatosensory thalamus to the primary somatosensory cortex, in awake, behaving rats. These authors showed that ensembles of single neurons from most of these structures exhibited widespread, synchronous oscillatory firing that began during attentive immobility and predicted the onset of rhythmic whisker movements. These oscillations were detected first in cortex and then spread to subcortical structures. The cortical and subcortical ensembles underlying such rhythmic firing have been found to contain highly distributed representations of tactile information (Ghazanfar and Nicolelis, 1997; Nicolelis et al., 1997a, 1997b). Multivariate statistical analysis (e.g., discriminant analysis and canonical correlation) revealed that in this sensory system, the precise location of a tactile stimulus could only be unambiguously predicted, on a single trial basis, when population rather than single neural responses were taken into account (Nicolelis et al., 1997b). Therefore, these results emphasized that the coordinated activity of large ensembles of neurons, distributed across cortical and subcortical structures, may provide the basis for the encoding of tactile information in mammalian somatosensory systems.

Maldonado and Gerstein (1996) were interested in determining the changes in neuronal ensemble dynamics that follow sensory reorganization induced by intracortical microstimulation in the auditory cortex of the rat. Intracortical microstimulation is known to produce a broadening of the receptive fields of cells located at the stimulation site. In addition, neurons recorded from adjacent electrodes have been shown to increase their responsiveness to the best frequency of the cells recorded from the stimulating electrode. The functional relationships between neurons distributed within the primary auditory cortex were assessed using gravity analysis, a method in which the temporal relationships between neuronal spike trains are represented as a series of clusters in a multidimensional space. In this multidimensional space, neurons attract or repel each other depending on the coincidence of their neuronal firing. The responses of up to eight neurons were recorded simultaneously following auditory stimuli and intracortical microstimulation. These experiments demonstrated that the functional clustering of a subset of the simultaneously recorded neurons, obtained during the delivery of the auditory stimuli, could be strengthened following intracortical microstimulation. The formation of a functional cluster of neurons did not necessarily relate to the anatomical distance between the cells. In other words, neurons that were anatomically close did not necessarily have a strong interaction, and neurons that were far apart did not necessarily have weak interactions. These

results showed that neural ensembles can be established transiently, that they are not necessarily composed of neurons within a circumscribed location (e.g., a cortical column), and that membership in an ensemble is mutable as a function of the induced reorganization.

Time-dependent encoding of sensory information has also been described in the locust olfactory system. In a series of elegant studies, Laurent and colleagues (Wehr and Laurent, 1996; Laurent et al., 1996) recorded from ensembles of two to five projection neurons in the antennal lobe of the locust during the presentation of various odors to the animal's antenna. Several important findings emerged from these experiments: 1) multiple neurons, distributed throughout the lobe, responded during the presentation of the same odor; 2) different odors could elicit unique responses from a given neuron; and 3) neurons that responded during a given odor presentation did so during specific epochs of the response, corresponding to cycles of field potential oscillations in the mushroom body, which receives input from the antennal lobe projection neurons. Thus, neural assemblies in the antennal lobe respond to each odor with a unique spatiotemporal pattern of firing.

Coding of Task Parameters by Hippocampal Ensembles

The hippocampus has long been implicated as a major component of a system that is involved in memory and in the representation of spatial information. In a recent study, Deadwyler et al. (1996) investigated how activity in simultaneously recorded CA1 and CA3 ensembles (10 neurons per ensemble) concurrently encodes several task-related events in a delayed-non-match-to-sample lever-press paradigm. Central to this investigation was the use by these authors of discriminant analysis and canonical correlation, which has been adapted for simultaneously recorded neuronal population data sets (Nicolelis et al., 1997b). It was shown that the spatiotemporal patterns of hippocampal ensemble firing encoded four different task-related parameters: the phase of the task (i.e., sample versus non-match phase), errors committed on the non-match phase of the task, the position of the lever being pressed, and the position of the lever presented in the sample phase of the task. It is important to note that while the firing patterns in the hippocampal cells differed from animal to animal, the same four task parameters could be extracted from the ensemble firing patterns in all animals. This indicates that the same dimensions of the behavioral task were encoded by the neuronal ensembles even though their firing patterns were not the same, and emphasizes that the activity of individual neurons is not sufficient for encoding these types of behavioral parameters. Instead, as Hebb postulated, patterns of activity must be analyzed across ensembles of neurons to determine how such information is represented.

Dynamic Encoding of Motor Behavior

In their pioneering work on the primate motor cortex, Georgopolous and coworkers (1986) elegantly demonstrated that populations of neurons could accurately predict the trajectory of arm movements. In their studies, a neural population vector was derived by pooling together the responses of serially recorded single units in different recording sessions and in different animals.

Although these vectors could be used to predict the direction of arm movement, the potential of using time as a coding dimension was lost by such an approach. This is a relevant issue, since it is conceivable that the same population of cortical motor neurons could use time-dependent coding schemes to represent different attributes of motor behavior.

The importance of the time domain in cortical motor coding has recently been demonstrated by Abeles and colleagues who obtained simultaneous recordings of six to eight neurons in the primate frontal cortex while animals performed a delayed-localization task (Abeles et al., 1995; Seidemann et al., 1996). This task required the animals to make arm movements to a remembered visual target that was flashed either left or right of a reference light. By implementing a hidden Markov model to analyze the simultaneously recorded neuronal spike trains, these authors proposed that the cortical neural ensembles go through a sequence of discrete, stable states during the delay period of the task (when the monkey must remember the target location). These stable states were characterized by a specific stationary pattern of relative firing between neurons, which changed abruptly from one state to another. In addition, these states were not time locked to the occurrence of any specific sensory or motor event, and the particular sequence of states could be used to predict, with $\sim$90% accuracy, the response of the monkey. If the correlated firing-rate modulations were eliminated from the ensemble activity, but the overall firing rate was preserved, no clear states or sharp transitions between states could be detected by the hidden Markov model. Similarly, if ensembles were formed by neurons recorded serially, the hidden Markov model failed to detect discrete and stable states of neuronal ensemble activity. This work underscores the importance of the temporal domain in ensemble coding and suggests that fundamental information processing at the level of cell assemblies may occur even in the absence of a particular sensory stimulus or motor output.

Cell assembly encoding of motor output patterns has also been studied extensively in several invertebrate systems. This work has shown that neurons within a single ganglion can participate in multiple networks that yield different behaviors at different moments in time. For example, it has been shown that some crab stomatogastric ganglion motor neurons can participate in separate feeding rhythms, the gastric and pyloric rhythms (Wieman et al., 1991). Thus, these neurons do not belong to unique stomatogastric ganglion networks, but instead, can change their activity to participate in both motor output patterns. Similarly, Wu et al. (1994) used optical recordings to simultaneously sample the activity of multiple neurons in the abdominal ganglion of Aplysia. In this preparation, large groups of neurons were activated during three gill-related motor behaviors: the gill withdrawal reflex, spontaneous gill contraction, and respiratory pumping. These motor activities were not encoded by dedicated circuits, but instead were controlled by distributed networks of neurons, whose members were selected from a larger neuronal population that participates in the genesis of multiple behaviors.

Future Directions

What we are witnessing in modern neurophysiology is increasing empirical support for Hebb's views on the neural basis of behavior. While there is much more to be learned about the nature of distributed processing in the nervous system, it is safe to say that the observations made in the last 5 years are likely to change the focus of systems neuroscience from the single neuron to neural ensembles. Fundamental to this shift will be the development of powerful analytical tools that allow the characterization of the encoding algorithms employed by distinct neural populations. Currently, this is an area of research that is rapidly evolving.

Further demonstration of a causal link between neural ensemble activity patterns and specific sensations or behaviors is necessary to demonstrate the relevance of population coding in the CNS. This issue is being approached in several ways. On one hand, information obtained at the molecular and cellular level is beginning to be applied to the investigation of circuit properties. For instance, ensemble recordings can now be combined with other neurobiological approaches, such as knockout genetics and/or the selective elimination of specific cell types (e.g., McHugh et al., 1996). These techniques will allow us to investigate what role a specific cellular population may play in information coding by large cell assemblies. At the other end of the spectrum, chronic and simultaneous multisite neural ensemble recordings can now be performed in behaving primates (Nicolelis et al., 1996, Soc. Neurosci. abstract). Since these recordings remain stable for many months, this opens the possibility of investigating how the learning of sensorimotor or cognitive tasks impacts the large-scale neuronal interactions within and between cortical and subcortical neural ensembles. These and other exciting developments promise to open a new era of investigation in systems neuroscience.

Selected Reading

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