VOLTAGE FLUCTUATIONS IN NEURONS: SIGNAL OR NOISE?

Yosef Yarom and Jorn Hounsgaard

Department of Neurobiology, Life Science Institute, The Edmond & Lily Safra Centre for Brain Sciences, Hebrew University, Jerusalem, Israel; and Institute of Neuroscience and Pharmacology, The PANUM Institute, University of Copenhagen, Copenhagen, Denmark

Yarom Y, Hounsgaard J. Voltage Fluctuations in Neurons: Signal or Noise? Physiol Rev 91: 917–929, 2011; doi:10.1152/physrev.00019.2010.—Noise and variability are fundamental companions to ion channels and synapses and thus inescapable elements of brain function. The overriding unresolved issue is to what extent noise distorts and limits signaling on one hand and at the same time constitutes a crucial and fundamental enrichment that allows and facilitates complex adaptive behavior in an unpredictable world. Here we review the growing experimental evidence that functional network activity is associated with intense fluctuations in membrane potential and spike timing. We trace origins and consequences of noise and variability. Finally, we discuss noise-free neuronal signaling and detrimental and beneficial forms of noise in large-scale functional neural networks. Evidence that noise and variability in some cases go hand in hand with behavioral variability and increase behavioral choice, richness, and adaptability opens new avenues for future studies.

I. INTRODUCTION

Nausea, the Latin root of the word noise, is a candid expression of our inherent, sometimes emotional, reaction toward the concept of noise. These disturbing, unpredictable, and annoying events that interfere with the natural order of things and drive us away from perfection indeed cause a nauseous feeling. The cellular and molecular constituents of life itself are noisy. For this reason alone, it is not surprising that living organisms are imperfect machines. Yet, can we live without noise? Is noise the paradoxical, essential feature that derails us en route to perfection but also distinguishes us from lifeless machines? When we refer to the living brain, this fundamental question reaches a higher dimension. The fascinating structure of the brain, the precision of which is essential for survival, is comprised of noisy functional elements. The fact that the action potential, the essence of signaling in nerve cells, is a threshold phenomenon underlines the fundamental probabilistic nature of brain function. This threshold feature, which emerges from the mode of operation of ion channels, is just the tip of the iceberg of noise sources. Synaptic transmission, the mode of neuronal interactions, is quantal in nature. This notion immediately acknowledges the uncertainty in strength and timing inherent in synaptic transmission.

Given this high level of ambiguity, it is surprising to watch the flawless performance of repeatedly executed behavioral paradigms, knowing that the variance of the neuronal activity underlying the behaviors is higher than the variance of the behaviors themselves. Hence, it appears either that the neuronal activity does not fully control the behavior, an unlikely possibility, or that the variability in neural activity is not accidental and unavoidable noise but rather an integral element of brain function. The brain may operate with an arsenal of solutions for each problem. A specific solution is then recalled in a noisy, random-like process, to handle a particular problem. Here we examine the possibility that uncertainty and multiple solutions produced by noisy molecular and cellular signaling elements are fundamental to brain function and essential for the ability to find good solutions to novel problems.

II. SOURCES OF VOLTAGE NOISE

Noise is inherent to the elementary processes that form the foundation of brain function: the ion channels underlying the action potentials that transmit information along nerve fibers and synaptic transmission that enables communication between nerve cells. Recent reviews provide excellent accounts of the properties of the noise from these sources and the role of noise at the systems level (35, 36, 102) and need not be repeated here. Instead, we summarize the elementary properties needed to support our view that noise is essential for brain function. A schematic description of a hypothetical neuronal network is shown in FIGURE 1. The three main sites at which noise appears are marked, and the temporal and spectral features of the noise at these sites are summarized in the corresponding insets.
A. Intrinsic Noise: Stochasticity of Ion Channel States

The source of noise in the operation of ion channels resides in the probabilistic nature of their gating mechanisms and the variable duration of their open state (1A). Surprisingly, the conductance of single ion channels is, in most cases, rather constant. Given the high density, the significant conductance in their open state, and, for some of them, a substantial driving force for the permeable ion species, one would expect extensive and continuous fluctuations of membrane voltage. Fortunately, most of the expected voltage changes are filtered out by the membrane capacitance that acts as a dampening mechanism to prevent fast changes in membrane potential. Yet, in neocortical pyramidal cells, a nonlinear increase in voltage fluctuations was measured when the membrane was depolarized (53). Whereas the increase in fluctuation is to be expected, given the voltage dependence of ionic channels, the nonlinearity has been attributed to the activation of persistent Na current that operates as a “noise amplifier” (53). Thus a significant voltage change can occur when occasionally a group of channels activates together, and the resultant voltage change is amplified by a voltage-gated positive feedback.

Nerve impulses are generated by voltage-gated ion channels (10, 60). An explosion-like mechanism that uses a positive-feedback loop generates, upon reaching threshold, an all-or-none response. Although the all-or-none nature of the nerve impulse implies a noise-free unchangeable entity, the threshold characteristics entail the fundamental probabilistic nature of impulse generation. Indeed, a transient depolarization just above threshold may increase the probability of spike generation so that a spike is generated on every trial. However, the latency of spike generation may well vary (jitter) as much as tens of milliseconds. An example is shown in FIGURE 1C. A simulated synaptic current is injected into a neuron, and the three superimposed responses clearly demonstrate a jitter of up to 20 ms in spike latency. Needless to say, in a neuronal network, a jittery response with an order of magnitude in temporal variability will generate a substantial amount of noise.

We categorize these two manifestations of noise as intrinsic noise, that is to say, sources of noise within the neuron. This noise is expressed as random changes in the membrane potential, voltage noise, or jitter in spike timing, temporal noise. The same two types of noise also exist in a category of noise sources known as extrinsic or synaptic noise.

B. Extrinsic Noise: The Probabilistic Nature of Transmitter Release

The quantal nature of synaptic transmission is well documented (FIGURE 1B; REF. 58). Although evidence suggests that the size of a single quantum is rather constant, the release of quanta is overly probabilistic in nature (58). Hence, at low release probability, synaptic transmission is an all-or-none process, whereas at high release probability, the amplitude of the postsynaptic response varies in a random fashion with the number of quanta released. Either way, the probabilistic nature of synaptic transmission induces postsynaptic voltage noise. Furthermore, the probability of synaptic release has a tem-
toral aspect; it varies in time (FIGURE 1A). Indeed, from the arrival time of an action potential to the releasing site at synaptic terminals (arrow in FIGURE 1B), the probability of release rises within a millisecond to a maximum and then gradually declines to the lower probability at rest (82). Hence, there is a certain degree of uncertainty regarding the precise time of release. This is a significant source of temporal noise when the release probability is rather low.

In short, we distinguish two aspects of noise: a voltage component and temporal component. Although this is a somewhat artificial distinction, since the voltage noise by definition has a temporal aspect to it, we feel that variable amplitude in essence differs from timing uncertainty. These two types of noise can originate from intrinsic channel noise or extrinsically from noisy transmitter release.

III. SYNAPTIC NOISE IN NEURONS EMBEDDED IN NEURAL NETWORKS

A. Background Synaptic Activity

Neurons embedded in synaptically interconnected networks invariably display rapid ongoing fluctuations in the otherwise “resting” membrane potential of a magnitude that exceeds channel-induced noise in isolated cells by one or two orders of magnitude (53) (see FIGURE 1D). This is due to the backflow exocytosis of transmitter from the thousands of afferent synaptic terminals that contract most neurons. The random vesicular release unrelated to signaling (see above; Ref. 37) adds an additional dimension to the noise problem. This massive bombardment of synaptic input occasionally causes the membrane potential to reach threshold, generating spontaneous spike activity (see FIGURE 1D). Via recurrent connectivity, even more noise is generated (67). In addition, spike activity never ceases completely in the normal brain. Intrinsic pacemaker properties maintain spontaneous generation of action potentials in certain types of neurons even in the absence of synaptic input (2, 43, 46). In the normal brain, background synaptic noise therefore degrades the fidelity of synaptic integration, i.e., the translation of membrane potentials in the cell body to impulse patterns in the axon. In their seminal work on cat spinal motoneurons, Calvin and Stevens (21, 22) studied the variability of the intervals between action potentials (ISI) during steady depolarization. They established quantitatively that background synaptic activity was the predominant source of variability in the ISI (21, 22). These findings also illustrate the general principle in neural transduction that firing patterns in axons are produced by ever-changing blends of synaptic input and intrinsic response properties.

B. Synaptic Noise During Functional Network Activity

Until recently, the interplay between noisiness and regularity in spike generation during functional network activity has been out of reach. New experimental techniques and analytical tools are now fueling progress in characterizing how the complex dynamics of these parameters may contribute to network function in behaving animals (15). Patch recordings from neurons in vivo in anesthetized and awake animals reveal a complex relation between the intrinsic response properties of neurons, synaptic input, and spike patterns. Even early processing of sensory synaptic input is superimposed on a fluctuating postsynaptic membrane potential in olfaction (23), in vision (4), in hearing (32), and in the whisker system (19, 87). It is not yet clear to what extent this background synaptic activity represents unavoidable noise or the early processing of sensory information. It is evident, however, that the character of the background synaptic activity in lamina II-III neurons in the barrel cortex changes with the functional state of the animal. During quiet wakefulness, the subthreshold membrane potential undergoes slow synchronous oscillations in large populations of neurons as reflected in the local field potential and the electroencephalogram (87). At the onset of active whisking, the slow oscillations are replaced by rapid, low-amplitude fluctuations in membrane potential, desynchronized among neighboring neurons (87). The background synaptic activity therefore seems to be a state-dependent variable that integrates with the specific sensory synaptic input even in early stages of sensory processing. The desynchronized state during a sensory stimulus, associated with decreased variability in membrane potential fluctuations and firing rate, is general across sensory modalities and cortices (27). It has been proposed that irregular Poisson-like firing in the desynchronized state may be a fundamental way to represent and process uncertainty in the brain (68). However, the issue of variability and correlated and uncorrelated noise in population coding and how it affects information processing is well documented (5, 32) but not well understood (6). A crucial limitation is that studies based on patch recordings in unanesthetized animals are still few and far apart.

One of the most convincing examples of a constructive role of noise in information processing is demonstrated in the work of Ferster and colleagues (4). They propose that noise solves the problem of contrast invariance of the orientation curve of neurons in the visual cortex. The problem of contrast invariance was first described by Sclar and Freeman (95). They noted that the width of the orientation curve is independent of stimulus contrast, which is correlated to the intensity of the input. Considering the iceberg effect, one would expect that the stronger the input, the wider is the orientation curve. Even the feed-forward model of Hubel and Wiesel (52) predicts that the membrane potential will show orientation insensitivity, whereas measuring spiking
activity will result in widening of the curve at higher contrast. Ferster and colleagues (3, 4) found that most of the discrepancy between the anticipated result and the experimental observations can be resolved if membrane potential noise is taken into account. Their experiments suggest that the noise, largely independent of the strength of the input, operates as a linearizing device, smoothing the threshold characteristic of spike generation. Hence, the average membrane voltage, which is orientation invariant, is linearly translated into spike rate by the noisy fluctuations in membrane potential.

The possibility that voltage noise serves as a linearization device that overcomes the problem of nonlinear translation of voltage into spike trains will be discussed below.

C. Balanced Inhibition and Excitation: The High-Conductance State

Neurons in isolation respond to steady depolarization with a stream of action potentials occurring in a predictable temporal sequence, i.e., with highly correlated interspike intervals. The specific pattern is determined by the intrinsic response properties of neurons that are cell specific. The specificity is determined by the density profile of voltage- and \( \text{Ca}^{2+} \)-gated ion channels in the membrane along the somato-dendritic axis (66) and by the structure of the neuron (69). However, highly irregular firing has consistently been reported from cortical and subcortical neurons during functional network activity. This includes spontaneous firing, firing evoked by sensory stimuli, as well as firing during motor activity in anesthetized, decerebrate, or awake animals (20, 28–30, 50, 70, 78, 86, 106). Irregular firing at a constant average firing rate is a surprisingly unlikely outcome of temporal integration of random excitatory synaptic input (97, 101). The simplest and most straightforward scenario that leads to irregular firing is high intensity of ongoing inhibitory and excitatory synaptic activity (31, 42, 96, 97, 101). This explanation for irregular firing became even more attractive when the implications were explored mathematically (107, 108). The theoretical analysis showed not only that a state of approximate balance between inhibitory and excitatory synaptic input to individual neurons emerged naturally in simulated networks of inhibitory and excitatory neurons, but also that such networks led neurons to fire irregularly as predicted (107). The balanced state was also shown to be characterized by chaotic dynamics even with constant input and to provide networks with faster response time than the integration time of individual neurons (107, 108). Although these high-level predictions have not yet been tested experimentally, considerable independent evidence now suggests that the balanced state is a widespread phenomenon in a diversity of neural networks in both vertebrates and invertebrates (3, 9, 11, 31, 81, 94, 97, 98, 112).

1. Anatomical substrate

In several primary sensory cortical regions, the intensity of inhibitory synaptic activity scales with excitatory synaptic activity evoked by specific sensory stimuli (3, 47, 110). In a recent study by Okun and Lampl (79), in which the spontaneous activity of cortical neurons was studied, the close correlation between inhibition and excitation was unequivocally demonstrated. By simultaneously recording from two cortical neurons, each held at different membrane potentials, they noted that the magnitude of excitatory and inhibitory potentials was positively correlated. Detailed experiments in slices from the somatosensory barrel cortex provide the substrate for such correlation (57, 99). It was found that a spike train in a layer 5 pyramidal cell, the cells that constitute the major output of the cerebral cortex, not only evokes monosynaptic excitation in a small number of neighboring pyramidal cells but also activates a large number of Martinotti cells, a distinct subclass of inhibitory interneurons. These in turn form divergent and convergent recurrent inhibitory synaptic contacts with local layer 5 pyramidal cells and Martinotti cells. In fact, this simple organization provides a powerful feed-forward and recurrent inhibition that closely correlates with the magnitude of excitation. The identification of a specific microcircuit structure that automatically provides correlated changes in the average inhibitory and excitatory activity is particularly important in the present context. Most significantly, a circuit mechanism has been identified that readily and by design leads to a rapidly fluctuating balance of excitation and inhibition.

2. Gain control

The noise generated in the balanced state affects the effective gain of neurons as manifested in their current frequency curve. The slope of this curve, the “neuron gain,” is insensitive to membrane voltage and conductance (33, 40, 49, 74, 75, 88) but effectively modulated by the level of voltage noise. This effect has been studied by Chance et al. (25) in layer 5 pyramidal cells in slices from the somatosensory cortex in rats. Simulated excitatory and inhibitory unit conductances generated by independent Poisson processes were fed into the neuron via a patch recording electrode. In this way, the effects of synaptic noise on neuronal gain could be explored over a wide range of parameters. This experimental paradigm demonstrated that concurrent inhibition and excitation reduced the effective neuronal gain. This happened because depolarizing synaptic transients elicited action potentials from average membrane potentials well below the spike threshold (25, 38, 48, 49).

3. Sensitivity and stability control

One of the fundamental consequences of the supralinear recruitment of inhibition with increasing excitatory syn-
aptic activity is a parallel increase in average input conductance. In this way, concurrent excitation and inhibition leads to an efficient way of scaling input conductance with synaptic activity. At low levels of synaptic activity, neuronal sensitivity to individual synaptic input is high but decreases with increased synaptic activity due to increased conductance and reduced gain. However, the ability of the neuron to emit spikes is maintained. Over a wide range in this regime, the magnitude of the fluctuations in subthreshold membrane potential covaries with synaptic intensity and average conductance (11, 62). In addition, the average membrane potential is only moderately sensitive to synaptic intensity in the balanced state and may remain close to threshold. The question of stability in balanced networks already addressed theoretically (107, 108) has also been submitted to elegant experimental analysis (67). If many neurons are near threshold, a single action potential in an excitatory neuron might cause “run-away” excitation in avalanche fashion (85). A careful analysis of this scenario by London et al. (67) was performed in the rat barrel cortex. Their combined computational and experimental work shows that a single action potential in a layer V pyramidal neuron leads to action potentials in ~28 postsynaptic neurons. They also show that this leads to detectable changes in unit activity in the network for up to 100 ms. But this does not lead to run-away excitation because the postsynaptic cells are both excitatory and inhibitory and thus eventually anneals the perturbation. These findings are in agreement with spikes produced by random fluctuations in membrane potential due to uncorrelated inhibitory and excitatory events. If so, the brain must code by means of firing rate rather than precise spike timing or use very large depolarizations for accurate timing. The experiments favored rate coding because large depolarizations were rare and spikes were readily generated in their absence (67). However, this is not always the case. In the primary auditory cortex in awake rats, the membrane potential in sparsely spiking neurons fluctuated in a distinctly nonrandom fashion at rest and during auditory stimuli of short and long duration (32). Furthermore, the occasional action potential in these neurons was triggered by isolated non-Gaussian depolarizing events, bumps, presumably due to sudden increases in synchronized synaptic input.

4. Effect on firing pattern

In vivo experiments demonstrated that concurrent inhibition and excitation during network activity was associated with a severalfold increase in conductance (13, 81, 89). With such an increase in conductance, the interspike interval is no longer determined by slow currents underlying spike afterhyperpolarizations and pacemaker potentials (1, 11, 12). Instead, action potentials in the high-conductance state are predominantly elicited by depolarizing transients during the noisy fluctuations in membrane potential produced by the intense concomitant inhibitory and excitatory synaptic activity (8). In this state fluctuations in conductance and membrane potential are crucial elements in gain modulation in contrast to invariance of orientation selectivity (3, 4, 24, 39).

Other intriguing consequences of the high-conductance state, when present, include quenching of intrinsic response properties (1, 31), shortening of the membrane time constant and the synaptic integration time (12), as well as the yet unexplored recalibration of synaptic weights with change in electrotonic cable structure.

The high variance in interspike intervals often observed in vivo cannot entirely be accounted for by random bombardment with uncorrelated inhibitory and excitatory synaptic activity. However, in vitro experiments by Stevens and Zador (103) demonstrated that the high variance may readily be obtained by assuming transient temporal correlations in synaptic input. The fundamental parameters that determine the synthetically induced fluctuations in postsynaptic membrane potential are therefore, in addition to synaptic weights, the intensity and correlations of concurrent excitatory and inhibitory presynaptic activity.

5. Role in functional network activity

Direct evidence for noise-driven irregular firing due to concurrent inhibition and excitation during functional network activity has been obtained in the spinal cord (1, 11). In the isolated carapace spinal cord preparation from the turtle, scratch network activity can be induced by a mechanical stimulus in the receptive field on the carapace as illustrated in FIGURE 4 (59). Dramatic increases in synaptic input activity in motoneurons have been reported during scratch episodes in vivo and in vitro (1, 90). During each episode, the intensity of excitatory and inhibitory synaptic activity is maintained in near balance. The depolarizing waves that drive spike activity are produced by a correlated increase in inhibitory and excitatory synaptic activity as evidenced by the concomitant increase in average conductance and amplitude of the fluctuations in membrane potential (1, 11, 12). For this reason, motoneurons fire irregularly during scratching. It remains to be seen to what extent neurons in mature spinal motor networks are driven by flexible stochastic synaptic interactions (11) rather than being locked-in in clocklike networks of weakly coupled cellular oscillators (45).

IV. SPIKE TRAIN VARIABILITY

A. Variability Measurements

There is a general consensus that the neural code is embedded in trains of action potentials. It is also agreed that these trains are translated via the muscular system into specific
behavior. It is thus rather puzzling that the spike trains exhibit a large degree of variability. The well-documented inherent variability in the biophysical mechanisms that generate spikes (see above) encompasses almost all levels of neuronal processing. An example of trial-to-trial variability is shown in Figure 2. It depicts the activity recorded from a cortical neuron in the monkey motor cortex performing a simple and reproducible hand movement. It is obvious that each behavioral trial is associated with a different spike train. However, it is not equally obvious how to quantify these differences. This is a widespread problem, since similar trial-to-trial variability appears at all stages from early sensory processing as seen in Figure 3 to the final common path in motoneurons as in Figure 4. The firing patterns are not repeated in successive seemingly identical trials, sensory or motor.

The most commonly used parameter is the average rate of firing. However, even with this insensitive parameter the results are contradictory. Chestek et al. (26) reported long-term stability (lasting for days) of firing rates over repeated trials, whereas Lee et al. (64) report significant variations. Regularity of spike trains can also be used to quantify the variable spike trains. The Fano factor (FF) is a common measure in this respect (27, 70, 97, 104) (see also Figure 4). A more refined analysis of variability is obtained by combining the FF with CV^2 (76). An alternative approach was used by Grana et al. (44) in which stability and variability in spike trains in response to natural sound stimuli was highlighted in a multi-dimensional analysis of spike-trains and discrimination matrices. The differences in spike trains can be expressed in spike timing, in average spike rate and the instantaneous interspike interval, as well as in the degree of regularity in individual cells and in neuron populations (6, 7, 18, 93, 105, 109). In our opinion, however, it is not possible a priori to decide which measure is functionally relevant, and none of the measures gives away which part of the variability is due to noise. Unfortunately, this question can only be answered once the neural code is known. Only then can the “irrelevant” information be identified.

B. Expression and Interpretation of Variability

Regardless of the definition of noise in the nervous system, the high variability of spike trains on one hand and the accuracy and reproducibility of movement on the other puzzled neuroscientists (26, 92). Three conceptually different approaches to this problem have been proposed. The claim by the first approach is that “accurately” reproducible behavior is in fact not free of variation (see Figure 2). Careful analysis will reveal minute trial by trial differences.

**Figure 2** Variable activity of neuron in the motor cortex during hand movement. A: experimental set-up. The monkey controls movement of cursor on a video screen by a manipulandum. B: trajectories of the cursor movements on repeated trials. C: raster-plots of spike-timing in a neuron in the motor cortex during 30 repeated trials. Raster-plots aligned to movement onset. (Figure kindly provided by E. Vaadia.)
that reflect the spike train variability (26). The solution offered by the second approach is that the average spike train at the network level is rather invariable. Due to redundancy and extensive convergence, spike train variability of individual neurons is eventually filtered out en route to the output stage. The third approach assumes that spike train variability plays a major role in information processing and complex computation and thus has a meaning of its own and cannot, and should not, be regarded as noise (92). We suggest that spike train variability, which is an unavoidable consequence of noisy processes, is an essential feature of network activity, enabling fast and efficient adaptations to new and unexpected environmental circumstances.

C. Noisy Sensory Motor Transduction

Variability is an integral element in spike generation and synaptic transmission. In principle, transmission of spike patterns from cell to cell and from layer to layer through a network should therefore unavoidably be degraded by the accumulation of noise at each step (6). This prediction is confirmed by a detailed analysis of the sequential sensory motor transduction for pressure-induced local bending in the leech. In this system, mechanical sensory stimuli as well as the resulting motor behavior can be recorded with great accuracy (84, 111) and related to the spike activity in nerve cells in the intercalated central nervous system (113). Local bending is primarily elicited by skin indentations that activate the mechanosensory P cells (61, 65, 113). P-cell firing is highly reproducible in response to direct depolarization (84) and to tactile mechanical stimulation of the skin (112). Not surprisingly, P-cell firing displays much lower variance than the bending behavior elicited. On the other hand, the dozen or so cells in the leech ganglion that respond to activation of a P cell show higher spatial and temporal variability than the local bending they produce. A key observation may explain how variability in behavior is contained. Action potentials in the coactivated interneurons in the ganglion turn out to be poorly pairwise correlated and exhibit a high degree of statistical independence. It is this property, combined with ensemble averaging and long integration time in muscles, that secures a smooth and reproducible motor behavior despite the irregular and variable activity of the motoneurons. The stochastic properties of synaptic transmission, the low release probability in many synapses, and the massive convergent and divergent connectivity is probably the main source of uncorrelated noise in neurons (35). For this reason, the finding that highly reliable spike trains in early sensory processing degrades in neurons at later stages in the CNS en route to behavioral output may apply to nervous systems in general. Unfortunately, systematic investigations in large-scale nervous systems, such as in mammals, are not yet feasible. From the trial-to-trial variance of spike counts and spike timing in a few, randomly chosen units during behavior, it is not really possible to extract the underlying neuronal algorithms.
D. Noise, Variability, Choice, and Decision Making

Organisms continuously respond and adjust to their environment. In animals this capacity to adapt is greatly enhanced by brain function. Brains provide a wide selection of often very different behavioral responses to seemingly identical stimuli. Recent experiments provide evidence that neuronal noise and variability play a fundamental role in how behavioral choice is made (16). In a reduced preparation of the leech, activation of mechanosensory neurons can lead to swimming or crawling network activity in the ganglionic motor network. In this preparation, more than 80% of the neurons in one of the ganglia involved in the behavior can be monitored simultaneously (17). Under experimental conditions, in which the chance of either behavioral response to the stimulus is equal, the activity of the neurons monitored was followed from the application of the stimulus until the onset of clearly identifiable swim or crawl network activity. The first striking observation is that a very large fraction of the neurons were activated immediately after the stimulus in the build-up period before the onset of the behavior. Next, only ~5% of the active neurons fired in a manner that predicted the behavioral outcome, and a particular ensemble from this subgroup predicted the outcome much earlier than any of the neurons individually. Taken together, this suggested that the decision mechanism is preceded by a general arousal of the network, followed by the expression of activity patterns that gradually diverge into either a swim or a crawl. It could not be decided from the experiments whether the statistical nature of the behavioral choice to the same stimulus was due to the stochastic nature of the decision-making network activity or depended on trial-to-trial differences in well-defined but unknown state variables in the preparation. It was also unclear if the predicting neurons were causally involved in the decision-making mechanisms or merely reflected it (15). Manipulating the activity of any one of the predicting neurons during the arousal and decision-making period by hyperpolarization or depolarization did not bias the behavioral choice. However, such a biasing effect was obtained in another neuron not belonging to the early predictor neurons. The statistical nature of choice was illuminated by the fact that although the bias was statistically significant, the activity of the neuron was overruled in some trials. It is interesting to note that network activity in the leech is associated with widespread feed-forward inhibition which clearly mediates gain modulation (9). It remains to be seen if this concurrent excitation and inhibition also underlie statistical decision making (15) and the high spatial and temporal firing variability (83, 113) in network neurons during local bending.
Irregular firing and trial-by-trial variability has been observed in neurons during functional network activity in organisms ranging from leech and Aplysia (94, 112) to behaving monkeys (97). Is this an unavoidable disturbing by-product of neuronal signaling that the nervous system must deal with or could it be a fundamental part of brain function that enables decision making and adaptive behavior? A recent radical proposal suggests that the Poisson-like variability in neuronal firing implements a simple way of performing Bayesian inference in population coding neural circuits (68). It is implied that variable firing in neurons in sensory systems expresses the inevitable ambiguity about the external physical reality represented by sensory stimuli. Fluctuating spike rate and trial-to-trial variability in the population of neurons affected by the stimulus is taken to represent genuine uncertainty about the external world. In such population coding networks, new theoretical insight shows that noisy correlated and uncorrelated firing can have consequences ranging from increase to decrease in the information content in the network (6). Therefore, the question we started out with is still with us. The role of variable and noisy firing of neurons in brain function may turn out to be a tractable and meaningful question only in the context of known neural codes.

V. CONCLUSIONS

Inherent to the basic mechanisms of the neuronal machinery, noise is an inevitable element of brain function. The stochastic nature of electric signaling in neurons implies that uncertainty is inescapable in functional network activity and behavior. However, one can argue that the stochasticity of ion channels and synaptic release may only be noticeable as threshold phenomena under special circumstances, i.e., when small voltage changes activate just a few channels or at low levels of synaptic efficacy when transmitter quanta are released in a Poisson manner. Only under these conditions will stochasticity emerge at the macroscopic level to induce random-like events that we tend to perceive as noise. However, when stimuli are of significant intensity, the brain will respond in a reliable and reproducible manner. What remains to be discussed, then, is which of these states predominate in neural circuits during brain function. Is functional network activity a purposeful mode of action where robust input overcome the uncertainty or is it by design a low-efficiency regime in which stochasticity lets unique states or solutions emerge? The fact is that most experimental observations favor the latter possibility. Low-amplitude synaptic potentials are often encountered (80), and jitter and failures are common in spiking responses to a given input. Nevertheless, specific examples to the contrary exist. Most prominently, the climbing fiber input to cerebellar Purkinje cells is a robust all-or-none synaptic input that produces a reliable and identical response for each stimulus (34). Similarly, the calyx of Held exemplifies efficient and high-fidelity synaptic transmission. These “exceptions that confirm the rule” occur at very specific sites at which uncertainty should be avoided at all costs. The climbing fiber input delivers error signals (100) in situations where fast and efficient correction is essential for survival. Efficient and reliable transmission in the calyx of Held ensures that small time differences can be accurately detected (14) without disturbing jitter and failure.

However, these exceptions apart, it seems that neurons in the brain at large predominantly operate near the firing threshold receiving synaptic input of low power and fidelity that produce modest elementary voltage changes. In this regime, uncertainties in time and voltage are bound to occur. Therefore, there is a pressing need for models and concepts that can account for the high macroscopic reliability of brain function on one hand and the high degree of microscopic uncertainty and variability on the other. There are several conceptually different approaches to this dilemma. The simplest of all is to challenge the fidelity and reliability of brain function. Indeed, careful analysis of repeated movements, the real and only output of brain function, reveals variability (see FIGURE 2 and Ref. 26). The trajectories of even the simplest movements are not identical, and kinematic parameters display considerable variation (91). To what extent these variations reflect variations in the electrical activity of single neurons are yet to be demonstrated.

The second approach to resolve the issue takes advantage of population dynamics. In this view, which is supported by experimental observations, movements reflect and are generated by the ensemble activity of an entire population of neurons. Movement direction can be accurately predicted from population vectors extracted from unit activity in relevant territories of the motor cortex (41). This suggests that each neuron in the motor cortex is directionally tuned, i.e., when a particular neuron is active the movement will be biased in a particular direction. The direction of movement is thus determined by the direction of the average vectorial summation of all the active neurons at that particular movement. It follows that variability in activity of individual neurons is averaged out with a reasonably large ensemble size. Similar concepts can be demonstrated in sensory areas of the brain where, for example, perceiving the orientation of visual input is the average orientation of all orientation-sensitive cells that were activated by the stimulus (51). Indeed, the average response can always overcome the large variability observed in single-cell activity. However, for an average response to emerge requires mechanisms to extract the population activity. But for read out, the ensemble activity needs to converge on a small number of neurons whose inherent variability will again distort the fidelity of the execution. Furthermore, recent work with brain machine interfaces demonstrates that prediction of movement direction or force can be reached by analyzing the activity of a small number of neurons. It also turns out that accurate...
movements can be achieved with a relatively small number of neurons that propel a robotic arm to a designated target (77). A logic interpretation of such observations is that even a small group of neurons can provide enough information to perform accurate motor tasks. In this light it seems wastefully inefficient to overcome the variability of single neurons by population coding.

Accepting the possibility that motor tasks can be specified by the activity of a small number of neurons leads to the third approach to reconcile fidelity of brain function with neuronal variability. It is conceivable that there are many ways to perform the same task. In the most simplistic way, once a need to perform is imposed on the brain it is imaginary that frantic activity goes into the search for immediate solutions. There are quite a few solutions to choose from if only a few neurons are needed for each. In fact, it is not unrealistic to predict that there are a very large number of good solutions. It follows that a part of the behavioral variability observed may represent the variety of solutions available to any given problem that confronts the brain. Hence, variation does not necessarily reflect noise or uncertainty. It may also be alternative versions of adaptive goal-directed responses in the execution of accurate performance albeit in different ways with each repetition.

What then controls the process by which the brain converges on a particular solution? It is easy to imagine that this is a kind of random process that reflects the state of the system at the time of the demand and the voltage noise inherent to constituents, the neurons, and the functional structure, the connectivity.

This seemingly imaginary scenario is actually supported by recent reports. The most notable is that of Rokni et al. (92; see also Ref. 54). In a theoretical study they try to account for a continuous shift in motor presentation of cortical neurons. They show that many different combinations of connection weights will produce the same output in redundant neural networks. They concluded that a network with a noisy learning mechanism can provide many possible solutions for any given calculation. Another study supports the idea that noise and variability may reflect increased behavioral choice and accuracy. In a face recognition task in children and young adults, the relation between behavioral performance and cortical electroencephalogram (EEG) was investigated (73). The experiments showed that increasing behavioral accuracy and decreasing response time in adults was accompanied by increased EEG variability. This surprising finding was interpreted to suggest that better performance is achieved because more solutions are available and actively searched. In the present context this supports the view that noise and variability are crucial for behavioral richness and adequate and accurate performance.

As a case in point, experiments in song birds have revealed that neuronal circuits in the basal ganglia through neuromodulation act as tunable sources of noise that let social context regulate song variability (63). Zebra finch males court females by songs gradually learned during maturation. When directed at a female, the song by an adult male is repeated stereotypically with very little variability. In the absence of females, however, males sing the same songs in much more variable and explorative ways reminiscent of how songs evolve in juveniles. For the present purpose, it is particularly interesting to note that the increased richness and variability induced by social context depends on the lateral magnocellular nucleus (LMAN), a subcompartment of the nidopallium. Although LMAN is not involved in song production, the ability to enter the variable song mode is lost after LMAN lesions. In intact males, individual LMAN neurons fire in a characteristic relation to particular elements of the song. During stereotypical female directed songs, LMAN neurons fire more regularly than in the absence of females (56). Likewise, microstimulation in LMAN during singing in the intact male induces variability in the amplitude and frequency of particular components of the song (55). For this reason, it is proposed that the neuronal circuit in LMAN serves as a switch to let the motor network that generates stereotypically goal-directed courting song enter an explorative mode that enables improvement and development through vocal plasticity and reinforcement learning.

In closing, we note that this review has focused on the expressions of noise and variability in the electrical activity of the nervous system. The empirical data have so far provided no clues that can resolve the question we posed: “voltage fluctuations in neurons: signal or noise?” Does randomness distort signaling, or is it helpful and even crucial for normal brain function? There are good theoretical reasons for believing that brains evolved to exploit “good noise” in the neural code and contain the detrimental effects that corrupt and distort signaling (72). An immediate and major goal is therefore to develop testable theoretical predictions and experimental paradigms that can distinguish and resolve the roles of noise and variability in brain function.

ACKNOWLEDGMENTS

Address for reprint requests and other correspondence: J. Hounsgaard, Institute of Neuroscience and Pharmacology, The PANUM Institute, Bldg. 12–5–9, Univ. of Copenhagen, Blegdamsvej 3, DK-2200 Copenhagen N, Denmark (e-mail: jhou@sund.ku.dk).

GRANTS

We acknowledge funding by The Gatsby Charitable Foundation and The Israel Science Foundation (to Y. Yarom) and by The Lundbeck Foundation and The Danish Council for Independent Research (to J. Hounsgaard).
DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES


