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Perspective

Signals and signs in the nervous system: The dynamic anatomy of electrical activity is probably information-rich

(electroencephalogram/evoked potential/event-related potential/local field potential/nerve impulses)

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ABSTRACT **The dichotomy between two groups of workers on neuroelectrical activity is retarding progress. To study the interrelations between neuronal unit spike activity and compound field potentials of cell populations is both unfashionable and technically challenging. Neither of the mutual disparagements is justified: that spikes are to higher functions as the alphabet is to Shakespeare and that slow field potentials are irrelevant epiphenomena. Spikes are not the basis of *the* neural code but of multiple codes that coexist with nonspike codes. Field potentials are mainly information-rich *signs* of underlying processes, but sometimes they are also *signals* for neighboring cells, that is, they exert influence. This paper concerns opportunities for new research with many channels of wide-band (spike and slow wave) recording. A wealth of structure in time and three-dimensional space is different at each scale—micro-, meso-, and macroactivity. The depth of our ignorance is emphasized to underline the opportunities for uncovering new principles. We cannot currently estimate the relative importance of spikes and synaptic communication vs. extrasynaptic graded signals. In spite of a preponderance of literature on the former, we must consider the latter as probably important. We are in a primitive stage of looking at the time series of wide-band voltages in the compound, local field, potentials and of choosing descriptors that discriminate appropriately among brain loci, states (functions), stages (ontogeny, senescence), and taxa (evolution). This is not surprising, since the brains in higher species are surely the most complex systems known. They must be the greatest reservoir of new discoveries in nature. The complexity should not deter us, but a dose of humility can stimulate the flow of imaginative juices.**

A profound revolution lurks in our basic concept of how the information-bearing elements of the nervous system communicate. Two views coexist, mutually derogatory but not mutually exclusive, with little effort to discover the wider whole.* The dichotomy concerns such central questions about how brains work that I feel driven to put it under a spotlight.

One common view, which we may dub the *unit window*, is that, with rare exceptions, neural communication consists of successions of nerve impulses in neurons, encoding messages in their intervals, decoding at axonal terminals into an analog dose of transmitter that restarts the cycle in the next cell. A principal problem in explaining higher functions is seen as the adequacy of sampling of units.

The contrasting view, which we may call the *population window*, does not deny any of this except the implication that it embraces all the significant aspects of neural activity in organized cell assemblies. Major features of the dynamics of non-randomly assembled arrays, on this view, include their nonspike, more slowly fluctuating potentials, their changing degrees of population synchrony, and their rhythms and large-scale patterns. These and other features are worth attention whether they are only *signs* (telltale measures, like the electrocardiogram) or also *signals* for neighboring cells (causal, parts of the codes). Signs can be quite significant for understanding, even if they are believed not to be also signals—a judgment that would be premature for many slow potentials. A principal problem for investigation is how to interpret the compound field potentials in terms of unit activity.

The nervous system probably uses many codes, with an unknown but substantial variety of signals. It offers an overlapping set of signs of the activities in the massively parallel array of low- and high-speed sending and receiving elements. Many features of this diverse set are, I believe, still unrevealed; they are latent signs. Evidence has accumulated for many forms of signals in addition to spikes†: graded local circuit variables of marked variety are known, electrical and chemical, spatial and temporal. In spite of a large literature on spike communication between neurons, our knowledge is too scanty to say that it is all or 95% or any particular fraction of the neural communication. Nonspike and extrasynaptic communication are known but their relative importance is not. Far from the whole truth is any model or mental picture confined to action potentials shuttling around neural networks. Such a view may be temporarily heuristic and partly correct but is incomplete and simplified in major respects.

Electrical activity in brain tissue, compared with other signs of activity (chemical, metabolic, vascular), has unique values. It can be recorded with high temporal resolution and high spatial resolution (down to single channels) in three dimensions. This advantage over other signs of activity is particularly clear when multiple, closely spaced electrodes are used. Other methods for visualizing activity have also been productive of insights: voltage-sensitive dyes, oxygen consumption, local temperature (8), blood flow, positron emission tomography, magnetic resonance imaging, and other indicators.

Purpose of This Essay. My aims in this paper are, first, to remind readers of the wide disparity of views about the electrical signs in the brain and, second, to assert the following propositions about local field potentials (LFPs), especially their slow components.

(*i*) Slow potentials are not redundant with or predictable from data on spikes.

(*ii*) A wide variety of sources of fluctuating currents, not simply classical spikes and postsynaptic potentials, contribute to the LFPs, which are vector sums of the intercellular currents of many cells.

Abbreviations: EEG, electroencephalogram; EP, evoked potential; ERP, event-related potential; LFP, local field potential.

*Notable exceptions go back to Adrian, Jasper, and others, cited in ref. 1; a modern one is ref. 2.

†The scattered literature on extrasynaptic influences, including the effects of slow field potentials, is partially represented in ref. 3 and on the following pages of ref. 4: 14–19, 20–24, 46–53, 97–111, 116–123, and 545–568.

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(*iii*) The intimate, dynamic structure of the activity is information-rich about the underlying cellular and intercellular processing, brain states, localization, forms of cooperativity, and stages of development and of evolution. A number of suggestions are made for significant insights available to new research.

(*iv*) Quite probably, sometimes and in some places, LFPs act as causes as well as effects. Some are strong enough to exert influence on cells, changing the probability of firing or dragging them into synchrony, hence are part of the coding of information. Other LFPs are no doubt too weak to be causes and are only effects but are still valuable as telltale signs.

Only touched upon or quite neglected in this paper are many active issues that occupy workers in this field. My concern is to underline our ignorance relative to the wealth of descriptive detail waiting to be examined, and thus to emphasize the opportunities for new research.‡

Wide Spectrum of Activity. Electrical activity comprises a wide spectrum from "resting" or standing ("DC") up to several kHz. The spectrum is commonly subdivided into two categories, *spikes* and *"slow" potentials*. A major theme of this piece is the unfortunate dichotomy of the literature on these two categories and the paucity of knowledge concerning relations between them. This situation, combined with the limited use, so far, of multielectrode, wide-band recording and analysis, results in an inadequate understanding of the spatiotemporal organization of activity, especially in higher cerebral cell assemblies. I use "cell assemblies" to include the possibly underestimated role of glial and other nonneuronal contributions. Detailed studies of aspects of cortical activity (9–13) illustrate how rich in phenomenology our domain is.

The full spectrum of electrical activity includes both the most direct signs we know of the effective signals and codes and also compound vector sums of them. Together, they add up to the richest available information about any living system, even more than the number of synapses and of impulses arriving at them. This is because the four-dimensional pattern includes this information plus the distribution in time and space of LFPs, synaptic as well as nonsynaptic activity, linear and nonlinear cooperativity properties, and their fluctuations with time and locus.

Classification of Electrical Signs. A crude classification of electrical signs in the brain distinguishes seven kinds.

(i) *Intracellular potentials.* These are single unit signs usually representing one compartment of the cell: synapse, soma, dendrite, axon, or terminal. They are often used only for observing fast components, called action potentials or spikes and synaptic potentials. Slow intracellular shifts are diverse in nature, form, causation, and properties. Neither the interior nor the immediate exterior of the cell is likely to be isopotential much of the time. A classical theory, still untested and pregnant (14), proposed that a standing gradient exists between dendritic and axonal poles of the neuron, hence a continuous current, with assorted consequences.

(ii) *Extracellular single unit spikes.* These can be seen only within ≈50-100 μm of the active unit, and even for such a distance may have to be a large cell or fiber. They are usually recorded through high-pass filters that prevent slow potentials from being seen. Slow potentials are, however, generally present, down to <1 Hz. They can be partly time-locked to nearby spiking cells and partly independent of the spikes. Spike-triggered averaging can give a blurred impression of some of the slow waves, selecting components time-locked to the chosen spike form.

(iii) *Multiunit activity* is also localized, usually to within 100–200 μm. This term refers to fast, spiky activity of several units, perhaps three to five or a few more, rising sufficiently above the noise level that most of them are potentially discriminable with windowing circuits or template-matching software.

(iv) *Hash*. This term is jargon for fast, spiky activity of such small amplitude that one cannot discriminate or estimate well the number of units it represents. It is often best detected with audio monitors and is the most useful method for small cells. Such activity can be highly local.

(v) *Nonspike, graded, fast fluctuations*. These are in the range of ≈5-25 ms wide (≈40-200 Hz, if rhythmic) and may be either rhythmic or transient. They make up a minor but significant part of the electroencephalogram (EEG) spectrum in vertebrates and the major part in most invertebrates, except cephalopods. The generators are usually assumed to be postsynaptic potentials but probably include as well several other kinds of graded dendritic, somatic, and axonal terminal events. Quasisinusoidal oscillations in this frequency band are much studied in particular places and conditions (fly optic lobe 80- to 100-Hz oscillations; mammalian cerebellar cortex 200-Hz rhythm; mammalian visual cortex 40- to 80-Hz wave bursts). The limited evidence on the spatial extent of examples of this class points to a diverse set from localization within ≈1 mm to strong correlation between cortical columns 7 mm apart, even when intervening columns are poorly correlated. Single units like squid axons can ring with subthreshold amplitude at several hundred herz, but the examples of this class in mammalian brains belong within the category of compound LFPs and are believed to depend on population synchrony. It is premature to generalize that this class of LFPs always spreads farther than the foregoing classes, but the best-known cases appear to act that way and the unproven assumption attributes this to some form of synchronization–for example, a common driver or a reverberating circuit.

(vi) *Slow potentials*. These are in the range of ≈25-10,000 ms wide (≈0.1-40 Hz, if rhythmic) and also may be either rhythmic or transient, and they make up most of the EEG spectrum in vertebrates and a significant but usually minor part in invertebrates. The generators are usually assumed to be synaptic potentials, more or less synchronized. I would argue that a number of additional sources are likely to contribute in various degrees in various places or conditions. Speaking of subdural or intracerebral recordings, the spatial extent varies much more widely than the foregoing categories. The shapes of field potentials evoked by sensory stimuli are commonly different when the electrode is moved <1 mm. Volume conduction can be detectable occasionally out to many centimeters ("far-field" potentials such as the auditory brainstem response visible after averaging many hundreds of trials). Possibly this variation is due to the size of the generator or length of a dipole. A general reference on recording techniques, besides older and still useful books, is ref. 15.

A major reason for the diverse spatial extent of slow LFPs is active synchronization, which must involve a variety of mechanisms, generally unknown. Synchrony is usually judged by eye, a quite unreliable method. It can be quantified, however, by plotting coherence§ as a function of distance

‡I must admit another motivation. This is a plea that spike workers take a bit of extra trouble to control power-line interference and insert impedance changers close to the preparation so that the filters can be opened to record a wide-band channel. Their valuable data can then be correlated with slow potentials—by others if they are not themselves so moved. This would be a significant contribution toward bridging the gulf between knowledge of spikes and slow potentials—far beyond simply sharing animals.

§Coherence is a pairwise estimate that measures the fraction of the energy in each frequency that maintains a fixed phase (of whatever value) between the two time series, throughout the sample epoch. It is normalized for power and gives a value between 0 and 1.0 for each frequency. The method of choice for measuring the synchrony in a population, this has been studied in a few species of mammals, including humans, a few reptiles, fish, and invertebrates, based on

between loci. Variation of subdural or intracortical coherence values from pair to pair and sample EEG segment to segment is great, indicating spatial and temporal microstructure. One often sees two loci only a fraction of a millimeter apart with little or no coherence above the chance level. This means that the volume conduction of each LFP to the other electrode is trivial compared with the local activity, that the common reference is, in such recordings, quite inactive, and that coherence can have microstructure. Other meaningful and surprising findings include the lack of independence, indeed a strong agreement, between widely different frequency bands, belying the common assumptions of many independent oscillatory generators. The scalp EEG shows quite a different picture of coherence, which I cannot summarize here.¶

(vii) *Infraslow potentials*. Fluctuations of standing potentials that extend to periods longer than 10 s, even to minutes, are quite general, but are seldom studied. They can be larger in amplitude than any of the usual faster waves and quite possibly tend to be larger in extent, although evidence is meager on these points. Such fluctuations probably bias, selectively, the likelihood of neurons firing, according to their orientation, tuning, and "resting" excitability level—as do similar fields artificially imposed [Rusinov, Morrell, Porter, Rowland, *et al.*; see references in Adey (3)].

Classification should recognize that any of the seven classes can be a component of the ongoing EEG, without intentional stimuli, or of the response to a sensory or cognitive stimulus or the absence of an expected one. The domain of evoked potentials (EPs) or event-related potentials (ERPs) is extremely heterogeneous—in form, composition and latency, locus, and dynamic properties.

Different Qualia of the Two Windows. The *unit window* is fascinating and satisfying because neurons are not all alike. They are not merely elements in a network whose achievements depend on connectivity. Beyond their diverse transmitters and modulators are the personality differences that combine to determine output as a function of input. Neurons that fire selectively in response to complex stimuli, like colors, faces, or familiar arms of a maze, often live side by side with others of contrasting preferences. Each such discovery, simple or complex, feels like a piece of a puzzle that will lead toward cellular understanding. Many laboratories are recording extracellular spikes from 5 to 10 units simultaneously in laboratory mammals, and a few have recorded from 100 or more. The unit window has a virtually infinite horizon, especially as more units are followed for longer periods under reproducible behavioral states. But it will always remain fragmentary if unrelated to LFPs.

The *population window* via ongoing LFPs, EPs, and ERPs may not appeal to the same researcher appetite but certainly can reveal features of the organized ensemble that could hardly, if ever, yield to unit analysis. This window shows that objective neural responses are available to correlate with subtle higher nervous functions such as kinds of attention, or expectations met or replaced by unexpected stimuli. This window has revealed subtle changes in brain state, the discriminability of slightly different stimuli, the near-threshhold stimulus, and a hitherto unknown sense modality. It can dissect subtypes of surprise and say something about the relative roles of cortical subdivisions. It contributes to the how questions as well as the what.

Particularly rich are the variety of measures provided by EPs and ERPs, such as the succession of faster and slower, positive and negative deflections, their shapes and latencies, amplitudes and phase relations, and modulations by all kinds of influences. Many forms of descriptive analysis ("system identification") have only begun to be applied, including both linear and nonlinear higher moments. They strongly suggest the participation of cellular populations that are not sampled by microelectrodes hunting for unit spikes—perhaps small cells or cellular processes, perhaps with nonspike, graded signaling without or between spikes. They are particularly good for working out pathways, for distinguishing subsystems, and localizing events in situations where units cannot do so. They have uncovered anatomically unexpected influences, such as the strong telencephalic input to the cerebellum in fish and the modulation of sensory response in the tectum and cerebrum by timely cerebellar stimulation. The response to an omitted flash, that we can observe even in the retina, and the alternation between two forms of response at critical ranges of flash repetition rate, are examples of findings that should lead to single unit analysis (4).

Unstimulated, ongoing EEGs distinguish sleep stages, diagnose neurological conditions and localize some of them, and disclose rhythms, coherences, quadratic phase coupling, and other features of dynamics. Even when sampling is limited to the scalp, far from the brain, and to ≈20 electrodes, the number of useful measures, analyses, and algorithms that have been applied to 20 parallel time series is formidable, permuting cognitive state, simultaneous stimulation, directed attention, drug status, and other variables. In human subjects, with strict control of procedures, clinically justified recording has extended to 60 or more subdural, pial-surface electrodes, plus 20 contacts on deep temporal lobe probes traversing the amygdala and hippocampus, on both sides, plus 20 or more scalp electrodes. Routinely the recordings are wide-band (commonly 0.5–100 Hz), and continuous for 24 hr per day for 2 weeks, in digitized form. This data set has only begun to be analyzed.

Variety of Generators. The sources of the observed electrical activity are probably more diverse than is usually assumed. In addition to summated spikes and synaptic potentials, a number of other sources are known or likely, and their relative contributions doubtless vary with the situation (place, electrodes, brain state, etc). After-potentials of action potentials (of either or both polarities in succession) often exceed the spikes in total power. Axonal terminals may commonly or perhaps generally produce graded and labile signals following the all-or-none impulses in the axon. Increasing evidence indicates that many junctions release transmitter tonically or after slow, graded presynaptic activity and not only in response to presynaptic impulses (20). In suitable places we see pacemaker potentials (spontaneous activity which depends on steady-state conditions but fires or oscillates at intrinsically determined times (21–23). These can be undulatory oscillations or "relaxation oscillations" (gradual depolarization interrupted by reaching firing threshhold) or stochastic miniature transients.

Dendrites and somata appear to have various kinds of graded, slow fluctuations. More or less sudden changes of state also occur. One of these is an abrupt switch from a spike firing pattern whose histogram matches the LFP to a different pattern. "Plateau potentials" appear in some situations when a threshhold input leads to a maintained depolarization, lasting until another special input causes repolarization. In recent years some neuroglia have been shown to be capable of active potentials (changes in membrane conductance, presumably due to specific ion gates) in addition to their passive potential shifts. Some glial cells change potential within a few millisec-

multichannel recording from regularly spaced electrodes on the pial surface or within the brain (16–18). Average coherence is found to fall to 0.5 in 7–10 mm on the pia mater in humans, 4–6 mm in rat and rabbit, 2–3 mm in gecko and turtle, ≈2 mm in elasmobranchs, and <0.5 mm in the neuropil of the gastropod *Aplysia*. The variation around these means is greater for recordings within the neuropil than on the surface.

¶In terms of literature, the major part of this category concerns the scalp-recorded EEG and evoked or event-related potentials, commonly read from ≈20 electrodes at ≈4-cm spacing, but in some laboratories with closer spacing and upwards of 120 electrodes. The effect of observing through the skin and skull is mainly spatial smoothing by looking at a large cone of brain; this tends to reduce the recorded amplitude and the relative strength of higher frequencies, although the skin and skull are not considered to be serious frequency filters (19).

onds and appear to participate in some forms of neural processing [the whole issue 8 (pp. 305–369) of volume 19 of *Trends in Neuroscience* is devoted to "Glial Signalling"; see in particular ref. 24]. Pial and ependymal membranes are likely to be sources of slowly changing as well as standing potentials, and local fields must exist at blood vessel walls from the fluid flow.

Neurons are highly heterogeneous, not only in size, chemical messengers, and connectivity but also in many properties, such as the tendency to produce small or partial spikes, brief or lasting graded slow depolarizations or hyperpolarizations, rebound or persistence, and posttetanic potentiation or depression. Intracellular studies have shown signs of more than one spike-triggering zone, with different thresholds. A given cell may abruptly switch its dynamics, for example from the type that shows large depolarizing slow waves to a given input, with a large decrement in spike height during a burst, to the opposite. The variety of known generators besides spikes and synaptic potentials has increased over the years and seems sure to increase further.

Variety in Cooperativity. Two approaches have been used to look into the *relations between components* of the electrical activity of the brain, whether between slow waves and spikes or between components of the slow waves. I do not here discuss synaptic circuitry and the consequent relations between spikes in different neurons.

(*i*) About 60 years ago investigators began to examine the occurrence of nerve impulse *spikes and slow waves* simultaneously, in the ongoing EEG and in EPs. A wide variety of techniques have been used, and a wide variety of results have been reported. Instead of a bibliography I cite only a few compendia: refs. 3, 10, 11, and 25–28).

Already in 1969 MacKay (25) reviewed "numerous attempts" to establish clear statistical spike/slow wave relationships and found the reports "surprisingly disparate." Some single units fire at moments obviously related to the concurrent LFPs of EP or EEG waves, whereas other units do not. The latter may have a consistent relation only to waves of a certain kind or form. Some spikes show no discernible relation to the slow field-potential fluctuations, or they do so only by averaging the EEG around a trigger of a certain shape. This permits extremely feeble time-locked components to become visible, as the uncorrelated waves gradually average out. Sometimes a statistical relation with an EP wave increases or even reverses in sign with stimulation. It may be clear for late but not early waves; it may vary with brain state, motivation, or training (29, 30).

These findings are to be expected, given the great variety of response types among units in the brain, with quite different types, often near each other. Even in cortical columns, units that are similar by one criterion, such as best orientation of a visual stripe, are generally different by other criteria, such as the functions of intensity, background, stripe width, movement response, and priming stimuli. Cross-correlated firing of impulses by two or more neurons, with or without a characteristic lag, is believed to be important as a code for some forms of information in the input. Correlation of firing and a slow LFP may be a result or a cause of cross-correlated firing among cells. If correlated firing or synchronized LFPs have some kind of cognitive or general significance, it is probably one that distinguishes mammals from reptiles, amphibians, and fish. The evidence, though meager (16), suggests less synchrony or more rapid coherence decline with distance in the latter groups and little correlated firing except when there is a common driver or chain driving.

(*ii*) The other approach to studies of cooperativity in neural assemblies seeks measures of possible *interaction among slow wave components*, such as linear coherence spectra between loci, or nonlinear bispectrum and bicoherence between frequency components. I will briefly treat these two below, without attempting to speak of the variety of other possible measures, such as partial and multiple coherence, mutual information, maximum entropy, and chaos analysis. Variety of measures is important because our ignorance of the kinds of operations ongoing in neural assemblies is so profound that we cannot anticipate what measures should be most relevant. We are still in a stage of trying candidate descriptors that might distinguish between interesting brain states, regions, developmental stages, and evolutionary grades. Our challenge is something like asking computers that do not know languages to distinguish microphone voltage records of spoken Japanese from English or babbling. In the brain, however, we have very many channels in parallel and no assurance that the micro-, meso-, or macroscopic channel carries a coded representation of decodable information. We can train a neural net to distinguish two brain states using the EEG but would still not know what the significant dynamic features of higher moments might be. This is not to convey a message of hopeless complexity but, on the contrary, to emphasize that we need more effort on each of many fronts, and that the possibility is strong of uncovering major new principles of biological organization, as our own history already illustrates (1). *Neither spike analysis nor slow wave analysis alone is going to tell enough about how the brain works* (4).

Simple coherence has been mentioned already, with some of its dynamics in time and space. Significant in the present context is the finding that spatial and temporal variance appears to be higher for microelectrode, intracortical than for macroelectrode, pial-surface recordings. *Coherence clearly has a dynamically complex fine structure.*

Bicoherence, resulting from non-Gaussian nonlinear features such as skewness, sharp corners, and certain kinds of amplitude and frequency modulations, measures quadratic phase coupling: the proportion of energy in any two frequencies, F_1 and F_2, plus their sum, F_3, where phase of F_3 = phase of F_1 + phase of F_2. The F components can come from the same or from different channels. In a recent intracranial study (31, 32) we found that fine structure in millimeters and seconds is also present in this measure. Much of the time in sleep and wakefulness there is no bicoherence above the chance level, but it comes and goes episodically, especially during seizures.

The foregoing measures each reveal that, from 0.3 to 50 Hz, the general case is nonindependence among frequency components. Most of the spectrum, most of the time, shows no evidence of real rhythmicity. Brain activity is quite different from the Fourier model's assumptions: independent oscillators, stationarity, and linearity.

Variety of Views. The dependence of the views of different workers upon the modes of recording recalls the classical blind men and the elephant. The need I am lifting up calls for simultaneous recording of a wide frequency band from the smallest feasible electrodes as numerous and close together as possible. Present conceptions are based on incommensurate sampling, ranging from scalp recording to a variety of microelectrodes placed on or in the tissue. Such diverse electrical contacts "see" a wide range of unspecified volumes of tissue. Filters are usually used to narrow the frequency spectrum, partly by deliberate choice and partly for technical reasons. Infraslow potentials intrinsic to the living tissues are difficult to distinguish from artifacts. Spike frequencies of single units require high-impedance electrodes that are sensitive to other kinds of artifacts. Both limitations can, with some trouble, be surmounted. Similarly, the difficulties of increasing the number of electrodes and decreasing their spacing and size, to avoid excessive damage and to achieve localization are, to a degree, gradually being overcome.

The choice of "bipolar" vs. "unipolar" recording and the choice of "reference" electrode affect the view, especially if the latter is not demonstrated to be inactive. Multiple electrodes with a common, inactive reference reveal a full range of degrees of congruence of fluctuations. Slow waves on the scalp are common over distances up to centimeters; microelectrode waves in the brain can be quite different even 50 μm apart. Volume conduction does not spread all forms of activity. Perhaps the hypothetical supracellular generators are dipoles of various sizes. In any event, congruence between sites does

not necessarily mean volume conduction. It can often be shown to mean a common input.

Variety by Region. Factors beyond electrode form, placement, and amplifier filters influence the observed activity. An important but little-studied category is specificity to the kind of neural organization, including the geometric orientation of cells, for example in parallel or in radially symmetrical closed forms, or the predominance of presynaptic terminals coming from one direction. For unknown reasons, the cerebellar cortex is notably weak in the low-frequency band that dominates the cerebrum. Most of the medulla and spinal cord is usually characterized by fast, low-voltage, nonrhythmic activity—with notable local exceptions.

Even very local differences in organization have their own signature. If one monitors the sounds of the hash with a wide-band audio system, one can learn to distinguish ongoing, spontaneous activity of several laminae in the cortex of the cerebellum and of the optic tectum, as well as the transition from white matter in the cerebrum to cortical or subcortical gray. These characteristics of regions and tissue type have not been well quantified, let alone understood. Local differences in tissue impedance might play a role; these are sketchily known but only on the centimeter scale (33–38). They are probably under control, for example, by the marked changes in volume of the intercellular space reported to occur even within seconds (39, 40).

Variety in Evolution. Multiunit spikes, even with a macroelectrode, dominate the ongoing activity for all invertebrate central nervous systems studied, except for cephalopods (4, 41, 42). Gastropods, crustaceans, insects, arachnids, xiphosurans, and annelids, even with gross electrodes on the surface, have much more obvious unit spiking than vertebrate preparations, but much less relative amplitude of slow waves (<50 Hz). The conspicuous spikes are not yet explained, but the small size of the slow potentials (with special exceptions) has been tentatively attributed to the absence or scarcity of slow wave synchronizing mechanisms (16, 17). Lower vertebrates, however (elasmobranchs, teleosts, and amphibians), show tectal, cerebral, and olfactory lobe power spectra shaped essentially like those in mammals, but the amplitudes are much smaller. Size of brain and size or packing of nerve cells do not appear to correlate with either amplitude or power spectra. The hypothesis that synchrony is responsible for the relatively large slow waves in mammals has received some support from preliminary measurements of coherence vs. distance in several vertebrate classes. The abundance and distribution of glia might play a role but they are too poorly known to hazard a hypothesis. I am expecting additional important differences to be found between lower and higher vertebrates (pallial vs. isocortical tissue) in the spatiotemporal structure of some measure of cooperativity, but so far they have eluded us.

Controversial Issues. Such issues are numerous in this field but only a few points can be made explicit here.

It is sometimes said that intercellular currents are so small they could not affect the activity of neurons. It is well established, however, that a wide range exists among neurons in their sensitivity to imposed fields. Some neurons are altered in ongoing frequency of spontaneous firing by immeasurably small changes in their membrane potentials due to external fields of a few millivolts or fractions thereof per centimeter (refs. 43 and 44 and † footnote), and I expect some are tuned to preferred frequencies.

It is often said that the major part of the EEG is the consequence of synaptic potentials from thalamocortical circuits. However, the relative importance of thalamic and of corticocortical input cannot yet be assessed, and the relative contributions of synaptic and of nonsynaptic synchronizing mechanisms are not known. The thalamic input may, of course, be crucial even though it is not the major input. But the evidence of its importance is almost confined to certain states and bands of the spectrum that are not representative of the general case.

Which rhythms are intrinsic cellular oscillations and which are due to reverberating circuits, dependent on interaction time constants of two or more cells? Examples of both classes are known, but each case has to be analyzed carefully before the origin of the periodicity can be identified (5–7, 22, 23, 45). In the olfactory bulb, only in relatively long time periods (minutes) did the probability of firing of single neurons show a statistical oscillation at the 35- to 90-Hz frequency of the EEG. A surge of excitatory input during inhalation, if it lasts for some tens of milliseconds, increases the feedback gain in the mitral-to-granule-cell circuit and its time constants are believed to account for the 35- to 90-Hz bursts (9). Cells of the inferior olive have an intrinsic 10-Hz LFP wave, usually subthreshold; they fire at ≈1 Hz, at rest, but always in phase with the population rhythm. Once again, there appear to be a variety of relations between slow waves and firing.

Does the EEG represent brain rhythms? To the extent that real rhythms occur, do they come from a number of independent oscillators—as is commonly assumed for nonharmonic frequencies? We have seen that several lines of evidence indicate frequency components of the spectrum are not independent. Each of the well known forms of rhythmic activity—such as the alpha, theta, and gamma waves,‖ and their subspecies—occurs under special conditions or brain states and may not be seen for long periods in recordings under more natural conditions than the EEG laboratory. Some, such as the classical alpha and theta waves, may be seen in certain species of mammals but not normally in many others or in some tested species of reptiles, amphibians, teleosts, and elasmobranchs. Most of the time in most animals there is little evidence of really rhythmic oscillators in the ongoing cerebral activity, let alone that rhythms account for much of the total energy. Episodically or under suitable conditions oscillations are conspicuous. Even the questions: When is fluctuating activity a rhythm? and How do we tell a real rhythm from an artifact of our analysis? are in need of discussion to distinguish the arbitrarily semantic from the methodological part.

Can a model test the explanations that have been offered and the relative roles of different factors? A digital or analog model simulating large numbers of presumptive generators in a volume-conductor and computing the vector sums of activity in a variety of subcellular generators, with somewhat realistic geometry of somata, arriving and departing axons, proximal and distal dendrites, and neuroglia would be a formidable project, beyond present facilities. I believe it could help in interpreting findings and ruling out hypotheses. Simplified models are not likely to solve the general problem: How much unpredictable novelty enters as one scales up from the unit to its local neighborhood, then to its wider neighborhood, and up to the view from the scalp? Without a realistic model, it is only a reasonable bet that a good deal of such emergent novelty and large-scale cooperativity must be commonly present in higher mammalian brains.

Concluding Remarks. I do not expand here on my views about cognate factors, such as circuitry, integrative mechanisms, codes, communication channels, and neuroethological implications (4). I would rather focus attention here on the importance of new research upon the open questions mentioned, and reiterate the need for both single-spike and slow-potential analysis, preferably in coordinated programs.

The big picture, full of holes, blank areas, and doubtless mistaken perceptions, looks like this. In every cubic millimeter of most brains, tens of thousands of microscopic generators—several in each cell, many of them subthreshold—pool their

‖These terms are often used today, not for a rhythm or wave visible above the wide-band background, or in their specific historic sense which included the brain state, but simply as shorthand to designate a frequency band, for example the alpha or 8- to 12-Hz band, even in white noise. This is a form of jargon, convenient for the writer but much less preferable for the reader than stating the numbers.

intercellular currents in a common, anisotropic, volume conductor. The resultant, with some net orientation, with both transient, episodic events and oscillatory processes, slow and fast, plus interactions between them, linear and nonlinear, plus various synchronizing mechanisms, is a temporal and spatial pattern distinct for each scale of observation—micro-, meso-, and macroactivity. It tends toward but does not average out to complete whiteness or stochasticity in any of these scales, except for brief periods. There is a great deal of micro- as well as macrostructure in the activity, hence a great deal of information. Some is trying to tell us about the ongoing processes. Some seems likely to be in a degree also influential, a causal part of the communication between cells.†

The degree of stochasticity (which is not necessarily noise), as distinct from synchrony, may be a prime variable among brain states, regions, stages, and taxa. It seems high in most invertebrate ganglia and in the spinal cord, medulla, and cerebellum of vertebrates and perhaps in the cerebrum of many fish and amphibians. Signs of LFP cooperativity are seen mainly in certain higher centers: population rhythms, coherent frequency bands, quadratic phase coupling, and generalized seizure waves. The mammalian cerebral cortex is the best known, but such signs are observed also in the cortex of the tectum and olfactory bulb, the subcortical gray of the telencephalon and diencephalon, some parts of the mesencephalic reticular formation, and some special places and states of the medulla and cord of vertebrates and the central nervous system of invertebrates (dorsal root potential, inferior olive, some drug states, insect optic lobes, snail olfactory lobes, cephalopod supraesophageal ganglion). Within cerebral cortex and other places where these signs are strong, they may not correlate well with higher functions but only with sleep, seizures, and other special states.

Rhythmic activity as seen in some synchronized EEGs may be a development of higher centers but not necessarily of higher functions. Real rhythms sometimes rise above the usual wide-band background. Four or five distinct rhythms are recognized in the band of 2 to 50 Hz, plus a few subdivisions. Usually none or one or two rhythms appear at a time, each in certain brain states and some distinct only in certain species. There may well be other rhythms buried in the wide-band background. Most of the time most of the compound electrical activity of populations of cells in the brain, in most species, appears to be mainly stochastic, at least to first-order tests. Special events, processes, and places that might qualify as more advanced on behavioral or anatomical grounds may develop signs of communal interactions beyond rhythms, with spatial and temporal microstructure, but these have yet to be defined.

My conclusion is that the three spatial dimensions of LFPs, plus their temporal structure in higher centers and species, are information-rich and ready for more imaginative deciphering than has been tried so far. When this happens, the workers responsible will use both unit and population windows as well as new ones to broaden their views.

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