

Is There a Neural Code?

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EGGERMONT, J. J. *Is there a neural code?* NEUROSCI BIOBEHAV REV 22(2), 355–370, 1998.—Rate coding and temporal coding are two extremes of the neural coding process. The concept of a stationary state corresponds to the information processing approach that views the brain as a decision maker, adopts rate coding as its main strategy and endorses the single- or few neuron approach. If information derived from sensory stimulation is used to continuously update the brain's internal representation of the world, then neural codes may change with time through learning. As a consequence, the same spike sequence may be interpreted differently (or evoke a different behavior) later in the day. This non-stationary viewpoint is embodied in the representational model of brain function that stresses learning and plasticity and employs temporal coding in neural assemblies. We argue that the switching between quasi-stable brain states as a result of learning is more relevant than the neuronal patterns, and the correlations between them, that are found during stationary states. The neural code likely resides in the activity patterns that cause this state-switching. © 1998 Elsevier Science Ltd. All rights reserved.

Rate coding Temporal coding Population coding Cardinal cells Neural assembly Plasticity Brain as a dynamical system Synchronized EEG Brain states State-switching

INTRODUCTION

Setting the stage

A BY now classical example of a correlation between gross hippocampal electrical activity and different types of behavior (113) about a quarter century ago started a small industry to relate single-unit firing patterns in the limbic system to the oscillatory and irregular EEG states of the hippocampus (11). Undoubtedly this was inspired by the hope that a more precise correlation between single-unit activity and behavior could be found than that between the few distinguishable types of gross brain activity and a larger variety of behavioral states. Such a precise correlation could elucidate the nature of a neural code. The question that I wish to address in this paper is: does such a neural code exist in reality, or only in the minds of neuroscientists?

Perkel and Bullock (85) asked around the same time: “Is the code of the brain about to be broken?” They subsequently listed a large number of potential neural codes that “made sense” to the neuroscientist of that time. As we will see, “making sense” or “having meaning” is crucial to the notion of a code; it indicates that coding occurs in context. The meaning aspect should, however, be considered strictly in the context of the subject's behavior. This behavior will select those aspects of neural firing that make sense for the animal's behavior and thus to the brain which determines, and is affected by, the behavior. The information encoded in a train of neural action potentials is interpreted by higher order neurons and it is also interpreted by the neuroscientist who designed and performed the experiments. There need not be any correspondence

between these two interpretations. The biological interpretation (by other neurons) is the result of evolutionary adaptations; whatever resulted in enhanced survival was conserved. The interpretation by the neuroscientist, however, may be influenced by the ruling paradigm in the particular field of research.

Information processor or representational system?

Thinking in terms of neural coding and decoding, one implicitly considers the brain as an information processing system. The brain is also often supposed to be endowed with a “world” representation; as a consequence *recognition* (a match with that internal representation) and *novelty* (no match) are relevant issues. This adds a semantic aspect to information processing. So it is conceivable that a stimulus contains a lot of information in some theoretical sense because of its improbability (98) and is nevertheless easily recognized. In that case both the information content and behavioral meaning of the stimulus, its recognition, is high. It is also conceivable that a rare stimulus is not recognized, is completely new. In that case the information content will remain high, but the behavioral meaning may be low. Which of these two conditions produces the most relevant information for the brain or the subject, is often left out of discussions about neural coding. Is information derived from sensory stimulation used to continuously update the brain's internal representation of the “world” (e.g., hippocampal place cells (43); head direction cells in limbic system (120))? If that is the case then neural codes may change with time through learning, i.e., the same spike

sequence may be interpreted differently (or evoke a different behavior) later in the day.

Coding and meaning

Preselecting stimuli from an ethologically relevant set which may have an "innate" neural representation (106,107) will optimize the probability of recognition by the subject. However, at the level of the individual neuron, stimuli outside the ethologically relevant set (such as clicks or tone pips in the auditory domain, and spatial gratings or Walsh patterns in the visual domain) are often equally likely to produce strong responses. Can these so called simple stimuli be used at all to infer potential neural codes? If individual neurons can be considered as simple filters, they may extract identical information (i.e., produce the same response) from an ethologically meaningless sound and from a biologically relevant sound. Extracting ethologically relevant features may thus require very specialized cells or populations of neurons that combine the individual features.

Bursting as a code?

Information about some stimulus attribute may be contained in mean firing rates, stimulus-modulated firing rates, synchronized firing rates and/or very precise timing differences between the firings of two (or more) neurons. But also the duration of a burst of impulses, the number of spikes within a burst, the rhythm of firing or the existence of temporal patterns in a small time window may be used. As early as 1964, Burns and Pritchard suggested that bursting without a change in long-term firing rate could be a code used for edge detection in certain cells in visual cortex (15). Around the same time (96), it was found that ganglion cells in *Aplysia* were sensitive to the patterning of spikes within a burst; in other words, burst patterns may function as "passwords". Cattaneo et al. (21) found that burst spikes played a very important role in carrying visual information. Indeed, only these spikes were tuned for spatial frequency, orientation and velocity of the grating, while both the rate of isolated and burst spikes varied as a function of stimulus contrast. The selectivity of complex cortical cells for spatial frequency, orientation and velocity was much greater when the burst component of the discharge was considered in isolation from the overall discharge. The existence of two carriers for the transmission of visual information may be advantageous: cells receiving the messages from the complex cells can potentially distinguish whether the sender of information is active only spontaneously (only isolated spikes) or when it is visually stimulated (and fires spikes in bursts). Burst-spikes of single units in primary auditory cortex are, on average, far better tuned to tone frequency than the isolated spikes of the same units (41). Does this mean that "bursts" are a code or that, specifically asynchronous, burst-firing represents a more sharply tuned "brain state" than does the isolated spike firing?

How many codes?

Is only one type of coding used by the nervous system? In other words, is there a unique neural code? Or is the statement "anything goes" a better characteristic for a neural code: whatever works for the nervous system would be a

potential code. It could also be that different stimulus attributes are represented by different codes. Stimulus attributes can be distinguished into qualitative and quantitative ones. The qualitative ones relate to topographically mapped ones, such as place in the visual field or frequency of a sound; the quantitative ones relate to, e.g., the intensity of the stimulus. In addition there are the stimulus attributes arrived at by computational processes; among those are spatial position of a sound and depth of a visual scene (65). The output of those processes at the level of the brainstem or midbrain may again be coded entirely differently than those for the ones that result from topographical mappings.

Rate or synchrony coding?

Very often, combining timing and firing rate information may be relevant for the optimal representation of a stimulus (118). Synchronization codes (population timing codes) potentially make sense when high spontaneous firing is present, since they circumvent the problem of saturation of firing rates at higher stimulus intensities. Rate coding may be sufficient in the absence of spontaneous firing or low spontaneous firing rates. For instance, the threshold of activation of auditory nerve fibers may be defined in terms of a percentage increase in firing rate or in terms of a given change in the synchronization of the firings with the stimulus waveform (58). The latter definition may result in thresholds that are up to 20 dB lower than for firing rate; however, behavioral thresholds compare much better with a firing rate criterion. This exemplifies that subjects and experimenters may use different criteria. However, of two potential candidate codes, the one that carries the biologically relevant information more efficiently is, at least from an information-theoretic point of view, likely the one used by the nervous system. It is, of course, equally likely that potential codes are used in combination.

Single unit or ensemble coding?

Is coding done by individual neurons (or small local groups) or is it a distributed process involving large parts of the nervous system (7)? What reads the code, i.e., decodes the message? Is the reader a distributed system or is it a "cardinal cell"? Is there a local decoder in an information theoretical sense or is there an integral sensori-motor system that is genetically set up to react appropriately, that is plastic and endowed with the benefits from learning to respond adequately in any situation? The plasticity may affect either the sensory part or the more central parts of the system or both. These sensori-motor coordination systems are feedback systems so there is no unidirectional flow of information as in classical information transmission systems, and this makes a formal treatment difficult.

Signal and noise

Coding of signals in communication systems is often done to reduce the effects of noise on signal transmission. The all-or-none action potential in itself is one way in which the effects of noise are reduced, but the effects of synaptic noise on the generation of a single spike can still be profound. Does a neural code exist that has such noise

immunity? Could neural synchrony serve as part of such a code? Could bursts or coincident firings act to enhance the signal-to-noise ratio or figure-ground distinction in the nervous system (5,44,86)? Are bursts facilitating transmission to other cells (41,110) and, because of the strong divergence of cortical neural connections, induce synchronized firing in the receiving group of cells? Bursts, by virtue of their all-or-none character may convert the average, stationary, sigmoidal neural response function into a short-term, non-stationary, binary response function like that of a McCulloch–Pitts neuron.

In the following I will discuss some of these questions. Because coding is generally defined with respect to the neural correlates of stationary behavioral or brain states, and because I will argue that it is the transitions between brain and behavioral states that are relevant, there need not be a neural code in the classical sense. As yet, neural correlates of the non-stationary transitions between these brain states are not well defined.

CODING AND INFORMATION

The genetic code

In the life sciences the concept of code has received the strongest endorsement by its success in genetics. All genetic information that can be inherited is coded in a hierarchical fashion by means of nucleic acid (DNA and RNA) bases which are translated into amino acids which, in turn, build proteins. The four nucleic acid bases combine in strings of three (codons) to code for the 20 different amino acids found in nature. Most amino acids are therefore coded by more than one codon (redundancy); in addition, three codons are used to indicate a “stop” or “end-of-chain” sign. So there are four letters and 64 three-letter words, of which only 21 are functionally different (including the “stop” sign). The 20 different amino-acid “words” build sentences (sequences) of say 100 words long, as in the formation of proteins. This can be done in any of 20^{100} combinations, which allows a very large number of things to be represented (24). Because the survival of genes was determined by the environment, natural selection has ruled the vast majority of these combinations as not viable. This emphasizes that context determines what codes are meaningful at present.

Information

Three aspects of information can be distinguished: its syntactic, semantic and pragmatic ones (70). Again, it is stressed that information as such has no absolute meaning; it exists only in a certain context, i.e., between two semantic levels. The syntactic dimension of information covers the relation of “characters” to each other. It is the centerpiece of “classical” information theory, as put forward by Shannon (98,99). The semantic aspect of information, expressed in the “meaning” of a message (context wherein it happens), is largely absent in Shannon’s information theory: the set of possible symbols is a priori defined and the “state” of the recipient is not supposed to change.

Shannon’s information theory shows that one can measure the quantity of information in a message by the smallest number of symbols required to formulate the

message. The information content of a message x_k with prior probability $p_k = p(x_k)$ is

$$I(p_k) = -\log_2(p_k), \quad (1)$$

where \log_2 stands for the logarithm with base 2.

This quantification of information assumes some prior knowledge on the part of the recipient. This knowledge is characterized by the probability distribution P of all p_k . That means that the receiver knows in the statistical sense the composition of the character set to be used. As a consequence, Shannon’s information theory provides no information in an absolute sense, but it is fixed once that composition is defined.

The expectation H of a single message out of a set of N with summed probability equal to one is:

$$H = \sum p_k I(p_k) = -\sum p_k \log_2(p_k). \quad (2)$$

H becomes zero when one of the probabilities $p_k = 1$, and consequently its logarithm is zero. H obtains its maximum value when all probabilities p_k are equal, i.e., when there is no prior knowledge of the likelihood of a particular message.

Given a prior probability distribution of messages P and a posterior probability distribution, after encoding, Q , the gain in information is defined as

$$H(Q|P) = \sum q_k [I(p_k) - I(q_k)] = \sum q_k \log_2(p_k/q_k). \quad (3)$$

One characteristic of Shannon information theory is that it always refers to an ensemble of possible events and analyzes the uncertainty with which the occurrence of these events is associated.

One and the same sequence of symbols contains an amount of information that may vary according to the semantic level with respect to which this information is defined. The quantity p_k therefore expresses the prior semantic knowledge of the recipient: the more improbable its arrival, the greater the information content of an event. In the context of our analysis we may ask: how far does neural information exist independently of the observing neuroscientist? Or at what semantic level does neural information begin to operate?

The pragmatic aspect of information reveals itself whenever a message or an event, in the widest sense, alters the state of the recipient. Two essential and complementary components of the pragmatic aspect of information are *novelty* and *recognition* or *confirmation*. The element of surprise, or novelty, of the particular event is quantified in a meaningful way by the Shannon information measure I_k . Meaningful messages confirm the understanding by the recipient, or else they may confirm or establish semantic structures in the recipient. The concept of confirmation is related to the communications-theoretical idea of redundancy and to experience and recognition.

In Shannon’s information theory, novelty implies a great deal of information. However, the pragmatic content of completely novel information is practically zero, since no recipient can make sense of it. When only confirmation occurs, there is no information transmitted at all in the sense of Shannon. But without confirmatory information there can be no comprehension or recognition. This points to a major problem in the straightforward application of Shannon’s information theory to the behavior of living

systems and, consequently, to the action of their neural systems.

CODING IN THE BRAIN

The neural code

The neural code can be loosely defined as the way information (in the syntactic, semantic and pragmatic sense) is represented in the activity of neurons. The fundamental unit of information and signaling in the nervous system that we will consider is the action potential. Because action potential amplitude is reasonably constant, all information is supposedly carried by action potential number and timing. It is possible to consider coding at the level of the molecular structures, such as synaptic receptors (10), or at the level of the resulting analog signals, such as membrane potentials (85). However, I will entertain the more restrictive interpretation of coding by the resulting action potential trains, because membrane potentials are part of a generalized electrochemical coding strategy that comprises electrical impulse activity of different rates and patterns that release specific transmitter combinations from particular neurons (10). The result of these electrochemical and chemo-electrical transformations has to be passed on by spike trains. What information cannot be carried by those spike trains is lost.

The existence of a code assumes neural elements that do the *encoding* and other neural elements that do the *decoding*. The encoding is performed by the sensory receptor/sensory afferent combination and is specified completely by the probability of a particular single-unit spike train or set of multi-unit spike trains (z_i) in as many sensory afferents, conditional on the ensemble of stimuli ($x_k \subset X$) presented. Both x_k and z_i are functions of time. The summed conditional probability across all spike trains in the simultaneous recording and all stimuli in the ensemble is given by:

$$P_e = \sum p_{ik}(z_i|x_k), \quad (4)$$

with $\sum p(x_k) = 1$. If the state of the system is invariant and synchrony between the activities of the spike trains is not an issue, the set of spike trains may also be obtained in sequential recordings. This in a sense constitutes a test for the presence of invariance and the absence of a role for neural synchrony: simultaneous and sequential recordings will, in that case, give the same summed probability.

The decoding problem is completely specified by the probability of a particular stimulus waveform ($x \subset X$) conditional on the spike train of a single neuron or group of neurons:

$$P_d = \sum p_i(x|z_i). \quad (5)$$

The signal time function, $x(t)$, that maximizes this conditional probability function is a likely stimulus. This procedure implies a maximum likelihood estimation of the sensory stimulus that could have induced the observed neural activity pattern. In other words, spike train decoding is a method for generating an optimal (characteristic) stimulus for the neuron that produces, on average, that particular spike train. This is the best possible estimate of the stimulus

as it presents itself to the sensory neuron after preprocessing (filtering) by, e.g., cochlear hair cells or retinal elements. This “kernel” estimation can be done by reverse correlation, a generalized spike-triggered averaging procedure, both linear and for higher orders (9,38,108). “The internal neural map of the external sensory environment can (thus) be most clearly understood through an inverse mapping of the physiological signal flow in the nervous system”. For example, “the sensory interpretation of the activity pattern of a population of independent low-frequency auditory neurons in a Gaussian auditory environment is equal to the sum of characteristic stimuli of active neurons convoluted with the autocorrelation matrix of the stimulus ensemble” (60). The combination of non-linearities in spike generation and the filter characteristics of the synapse results for many neural networks in an essentially linear transmission of analog signals from presynaptic cell bodies to postsynaptic dendrites. Therefore, the dramatic all-or-none non-linearities of spike generation may not be as important as the graded analog dynamic properties of nonspiking regions of the cell (9).

The problem of reading a neural code in this view is, thus, essentially the problem of building an inverse filter that operates on the spike train(s) to produce a real-time estimate of the unknown stimulus waveform (50). Stimulus reconstruction is not necessarily what the animal is trying to do; however, it is of the same nature as the problems that the animal must solve, such as stimulus recognition and classification in relation to their survival value (1).

The brain as a representational system

Is it the role of the nervous system to evaluate the signals from the senses (coding) by transforming that information into a command signal (decoding) for the effector system (muscles or glands)? Alternatively, is it the role of the nervous system to periodically check the validity of its internal representation (world model) with the outside world and to affect its muscles to adjust the world view to the internal model or to update its neural connections to adjust this internal representation to the external world? It is likely that both roles are important because of requirements posed by behavioral adaptation.

The first role can be equated with the information processing model of the brain and will be discussed further in the next section. The second role corresponds with a representational model of the brain. Representational models rely almost exclusively on the pragmatic aspects of information, whereas the information processing models tend to be more heavily weighted toward the syntactic aspects. Both models require the incorporation of the semantic aspects of information and they may thus represent the endpoints of a continuous “model” scale. Representational models are inherently plastic, because of the continuous updating of the internal “world” model; the information processing models, on the other hand, require rather fixed or only slowly changing decoders to function properly. One could state that representational models change their parameters on a time scale slower than the time it takes for information processing. It is then probably not too much of a leap to suggest that information processing models can be embedded within representational models. This can be formalized in models similar to those for associative memory

(68) and can be summarized in two equations:

$$y_h(t) = x_h(t) + \sum w_{hk}y_k(t), \quad (6)$$

$$\dot{w}_{hk} = \alpha y_h(t)[y_k(t) - y_{kb}], \quad (7)$$

where $x_h(t)$ is the input firing rate provided by neurons outside the modifiable network to cell h , $y_h(t)$ is the output firing rate of cell h . The w_{hk} are the coupling strengths between cells h and k from within the neural network, y_{kb} is the spontaneous firing rate of cell k and α determines the degree of learning (determines the rate of change of the synaptic strength, $\dot{w}_{hk}(t)$). This learning rate is slow compared to the interaction between the neurons. Eqn (6) is known as the neural interaction equation (61), i.e., the information transmission part of the brain model. Eqn (7) describes the way the synaptic couplings between cells change with time. An early version of these equations (17) was published by Caianiello, who called them respectively the neuron and mnemonic equations. There is one view that takes exception to this ‘‘adiabatic learning’’ hypothesis which requires the synaptic connections to change slowly. This was expressed (74) by von der Malsburg in a ‘‘correlation theory of brain function’’ that required fast modifiability of synapses on a time scale of a fraction of a second, in addition to the slow changes in synaptic strength as expressed in Caianiello and Kohonen’s models. The learning part of the model was again in the slow, structural, changes in connection strengths, but the required fast modifiability of the synapses eliminates the existence of decoders with even semi-constant properties.

A subject has some expectancy about the probability of various environmental occurrences stored in its internal representation (70), and incoming sensory information is continuously checked as to whether it corresponds, within certain error, to this internal representation; the set w_{hk} of neural connectivities. This requires re-entrant, creative, systems (28,61) with a definite role for thalamo-cortical (78) and cortico-cortical loops (79). In fact, Mumford proposed (78) that the thalamus acts like ‘‘an elaborate 7th layer of the cortex’’ and functions as a ‘‘blackboard’’ on which the cortex writes and from which it reads. This could be the place where the internal representation of the world is stored and continuously updated.

Are sensory stimuli just igniting pre-existing assemblies that contain world representations (2)? Are synchronized nerve cell membrane oscillations the mechanisms that bind various stimulus features into a coherent whole (52) or are they merely the ticks of a clock that determine the time points for enhanced synchrony or correlation to be used in information processing (12,56)? Oscillations occurring synchronously in vast areas of the brain, such as theta oscillations in the limbic system, likely are not used in information processing per se, but in resetting the activity in particular neural populations. For instance, rhythmic theta bursting in the hippocampus generally co-occurs with a desynchronized, or actually a fast synchronized (105) EEG in neocortex and vice versa. What, if any, is the role of the reticular thalamic and the parabrachialis nuclei in controlling (switching between) the various response modes of the thalamocortical cells (101)? Is locality of oscillations related to their coding capacity: slow wave oscillations (< 1 Hz) are synchronous over the entire cortex (and typically occur when the cortex shuts down, sleep), the alpha

range shows more restricted synchrony (representative of area shutdown), whereas gamma band activity appears to be spatially very restricted but may be synchronous in patches that are far apart (104).

The brain as an information processor

‘‘If we choose to view the brain in informational terms, i.e., as an adaptive signaling system embedded within the external environment, then the issue of which aspects of neural activity constitute the ‘‘signals’’ in the system is absolutely critical to understanding its functioning’’ (19). Information theory provides a framework for adding up the many different discrimination abilities relevant to real-world signals. The theory also allows comparison of different stimulus dimensions with respect to their discriminability. Of course, behavioral experiments would be more definitive in assessing this discriminability.

What aspect of neural firing carries the information? Is it mean rate (26,95) which requires integrators with relatively long integration times, short-term modulated rate (31,97,121), precise temporal codes that require coincidence detection (2,103), patterns (25,96) or bursts (5,13,15,21,38,41,101), spatial distribution of active (mostly defined in terms of firing rate) neurons (48,87) or the mass action of all membrane potentials (45)?

Does an individual spike or a pattern of spikes point to something in the external world (9,60)? Such labeled-line codes signal which features are present in the stimulus. These codes are also called spatial or topographic codes; the neurons that are active signal what stimulus modality or stimulus quality is present. The amount of activity (usually firing rate) of the neurons presents a weighting of the relative importance of the stimulus features to which they respond.

Do individual action potentials carry information or do they do so only in combination? Combinations of action potentials form serial patterns in individual units (e.g., patterns or bursts) or parallel patterns across units. In evaluating this, one has to realize that the nervous system is spontaneously active. How does the nervous system or any particular decoder distinguish between spontaneous spikes and stimulus-induced spikes? In practice, in a neurophysiological experiment, this distinction is performed by the experimenter through signal time-averaging, thereby enhancing the activity that is stimulus-locked over that which occurs spontaneously.

A major task of the central nervous system (CNS) is to determine whether a particular spike pattern in afferent neurons is caused by an external stimulus or must be attributed to spontaneous activity. For instance, the activity caused by an external stimulus will produce a percept; spontaneous activity by definition does not. In addition, stimulus intensity discrimination requires that the difference in afferent neural activity for two intensities can be distinguished from spontaneous fluctuations. Several strategies could be employed. The first requires the evaluation of the number of spikes that a neuron produces over a certain time period and estimation of a mean firing rate. This estimate is then compared with a stored ‘‘norm’’ of spontaneous rate for that particular neuron. The decision ‘‘stimulus present’’ is based on the probability that the spike rate is above the norm. Because of the stochastic nature of the neural firings, this

decision making must be a statistical process and may require lengthy evaluation periods to increase accuracy and sensitivity. This evaluation can be performed faster by an ensemble of neurons: because the spontaneous rate of the ensemble will be less variable than the rate for individual neurons, the comparison can be made in shorter time with greater precision. The problem of how and where the “norm” is stored remains, however. This comparison mechanism is implicitly assumed in optimal processor theories of brain functioning (53).

An alternative strategy is to compare the detailed firing patterns of at least two neurons with, e.g., the same characteristic frequency (CF) or the same orientation tuning: when the neurons fire at about the same time an external stimulus is very likely. The decision will be more reliable as more neurons are simultaneously compared. Comparisons within a small ensemble of otherwise independently firing afferent neurons may thus result in a fast and reliable indication for the presence of an external stimulus. For instance, a typical inner hair cell in the basal turn of the cat’s inner ear is innervated by about 20 independently firing auditory nerve fibers (62) with three different spontaneous rate and threshold value ranges. Activation of a cochlear inner hair cell will automatically result in synchronous release of transmitter at some of its synapses and, therefore, in the synchronization of the firings of some of these neurons. The amount of synchronization in the auditory nerve fibers increases with intensity and will be determined largely by the amount hair cell depolarization. One may assume, for moderate stimulus levels, that six to seven nerve fibers innervating a particular hair cell will be active simultaneously.

Spontaneous activity in the auditory system is normally inaudible, because the auditory nerve fibers fire independently and may fail to produce sufficient synchronous firings to activate certain cochlear nucleus cells. Stimulus-induced changes may be audible, because neighboring nerve fibers start firing more synchronously with the stimulus (58) so that their firings become correlated. This correlation either increases the level of activity in higher centers or allows synchronous activity to proceed up to the cortex and causing correlated activity between distinct auditory cortical areas (39).

Our senses appraise the outside world in a parallel fashion that results in neural activity patterns organized in topographic maps (such as the various tonotopical maps in auditory cortex) of the brain. Neurons that have overlapping receptive fields, i.e., auditory neurons innervating the same hair cell, will show a covariance in instantaneous firing rate as well as a coincidence in the occurrence of spikes as a result of stimulation. The topographic mappings combined with lateral suppression will ensure that coincidences in firing times will occur predominantly between neighboring units. Coincident firings generally form a subset of the firings of a group of neurons and may allow us to extract the relevant information from the neural “noise”. For example, in the case of rather broadly tuned auditory neurons in the midbrain of the frog, the subset of coincident firings was found to represent particular stimuli (37). Hence at least in the sensory periphery synchrony of neural activity across units seems required to decide between spontaneous and stimulated activity.

In subjects suffering from tinnitus, ear noise, the sponta-

neous activity of the auditory system becomes audible. A straightforward extrapolation of the correlation theory of brain function, elucidated above, suggests that the spontaneous activity of nerve cells became correlated as a result of pathology. Salicylates and quinine in high doses produce tinnitus in humans and presumably also in animals, as shown by conditioning experiments (57). In these experiments rats or guinea pigs were conditioned to noise from a loudspeaker, and subsequently showed the conditioned behavior upon administration of these drugs. In acute experiments we showed (80) that the peak width of the cross-correlogram between the activity of auditory cortical neurons was significantly decreased and peak strength was 81) after administration of both drugs. This suggests that synchronous neural activity may be an important aspect in the perception of real or “phantom” sound.

Combinations of spikes likely signal stimulus quantities such as stimulus level; typically a cell’s firing rate increases with increasing stimulus intensity, at least in the sensory periphery. Cells are found in auditory midbrain and cortex that have a best intermediate intensity for which the firing rate is maximal; firing rate decreases both for lower and higher intensities. Often *average firing rate* (in a preselected time window) is the only candidate for a neural code that is seriously considered by non-neuroscientists (e.g., neural net modelers) and by most neuroscientists outside the field of audition. Auditory stimuli have an inherent temporal structure, something that is largely lacking in visual stimuli, that invites temporal codes. The timing of individual action potentials with respect to others in the same cell (*neural pattern*) or to spikes in other cells (*neural synchrony*) is a powerful alternative to firing rate and represents far more information about the stimulus than firing rate, even in the visual system as work by Richmond’s group (46,64,82) has shown.

Decoding of spiking neural activity (1) can thus be done through optimum linear estimators implemented in single neurons, in small local groups or distributed over large populations (networks) of neurons. One can thus argue that rate coding and temporal coding are just two extremes to be considered in the decoding process. A simple, long duration, rectangular kernel will extract a firing rate; an oscillatory kernel will only extract spikes that have the same periodicity as the kernel.

Single cell versus neural assembly coding

One of the oldest contrasts in the relation between neural activity and behavior is that between the single neuron (or few neurons) and the neural ensemble as the unit of coding. This dichotomy has been around forcefully since Barlow’s manifesto proclaiming the single unit as the physiological substrate of psychological entities (6). If one thinks that only a few neurons are sufficient for decoding, one likely believes in cardinal cells, grandmother cells, bug detectors, etc. Such cells only respond to the presence of a particular bug or grandmother and not at all to other stimuli. Strange as it may seem, even the neural assembly idea allows such cells. They are ultimately the result of the high interconnection and continuous reverberation of neural activity within the assembly. All cells in the assembly become “cardinal cells” in this view and the assembly is then just a reliable but very plastic superneuron (100). Others believe that

the distributed spatial pattern of synaptic strengths does the decoding, and so it is the assembly's output and not the individual neuron's activity that matters. Individual neurons may still be the dominant coding units for near threshold stimuli and other just noticeable differences in psychological (behavioral) tasks. This has been formalized in the *lower-envelope principle* (7), which states that sensory thresholds are set by those sensory units that have the lowest threshold for the particular stimulus used. Thus thresholds may be represented by a limited set of sensitive neurons (see also subsection below: "The few-neuron rate code") and are little influenced by the presence or absence of responses in the enormous number of other neurons that are less sensitive to that stimulus.

Results (46,64) at suprathreshold levels of stimulation show "that striate cortical neurons are not specialized for encoding information for just one or a few simply defined features (as cardinal cells). Instead, each neuron simultaneously encodes information about many features at multiple scales of size. Thus, single neurons contribute to the encoding of several or even many different kinds of features, and any single feature is coded jointly by many different neurons. No neuron can be regarded as encoding information about any single feature, i.e., there is no optimal stimulus." Hence, cardinal cell actions disappear at levels sufficiently above threshold and the assembly takes over.

RATE CODES VERSUS TEMPORAL CODES

Rate coding

Coding by average discharge rate alone necessitates a "labeled line" or "place" coding, because there is no other means internal to the spike train itself for conveying what kind of signal it is representing. The idea of rate coding therefore is synonymous with the use of spatial receptive fields (visual and somatosensory) and frequency tuning curves (auditory), although these can theoretically also be constructed for temporal coding (58).

Rate codes can be interpreted only by neurons or populations of neurons that have long integration times. Neurons can be considered as *leaky integrators* with time constants that vary throughout the nervous system. In the periphery neurons have short, few millisecond, time constants and so do most interneurons in the cortex. In contrast pyramidal cells in sensory neocortex have time constants of 10 ms (75,109) and even 30 ms for some pyramids in hippocampus (110). Is rate coding therefore limited to the thalamus and cortex? An alternative approach is to consider integration time constants with respect to the average inter-spike intervals (ISI) that have to be processed (69). If the time constant is short relative to the average ISI then rate coding is unlikely (the unit may act as a coincidence detector or more appropriately a co-firing detector), but if the time constant is long with respect to the ISI then rate coding is feasible. If, as in cortex, firing is characterized largely by bursts with long inter-burst intervals, this simple classification either breaks down or the neuron alternately must act as a rate detector (for the spikes in the bursts) and as a coincidence detector of the bursts.

Are *spatial codes* relevant? Various response properties are independently mapped on the two-dimensional cortical surface and thus result in a continuously varying overlap for

certain response properties (51). Neighboring cells are assumed to have very similar properties and they certainly do in auditory cortex (36). This homogeneity is a requirement for the existence of cortical modules or columns. For neurons with slowly changing properties as a function of distance, optimum linear detectors may read out population codes.

Patchy codes are found when a stimulus activates many non-contiguous parts of the cortex. They may be the result of neurons with short correlation distance through axon collaterals with patchy connections (111) or alternatively result from anisotropic neuron properties for, e.g., intensity representation along an otherwise homogeneous dimension such as for frequency sensitivity (87). Are such spatio-temporal patterns selected for, are they the result of the emergence of spontaneous order, or are they just a consequence of economic wiring of the sensory periphery to the cortex? Topographic maps have a correlation structure that is mainly the result of the anatomical ordering and overlap of receptor and motor fields (102); usually their correlation structure is context independent but can be changed by deprivation or learning (76). Functional or computational maps, such as that of auditory space, mainly have an organization or ordering through their correlation structure. Distance between neurons in a functional map has thus to be seen in terms of synchrony or correlation strength rather than as a physical separation. Neural units with strong correlations can be considered close in the neural organization; units with weak correlations have a larger functional distance (66,67). It is therefore possible that particular neurons in, e.g., the thalamus and cortex are "closer" than two neurons in the cortex itself (78). Furthermore, because neural correlations are stimulus dependent (4,30,34,44), functional maps may differ for different stimulus conditions and are plastic.

Several potential problems arise with the exclusive use of rate-place codes (19): (1) contrast degradation may occur because spontaneous activity and saturation of firing rates limit the dynamic range (this can be "solved" by having a range of low to high spontaneous rates distributed across the population as, for instance, found in the auditory nerve. In addition lateral suppression or lateral inhibition may alleviate the problem considerably). (2) The perception of the "pitch of the fundamental", a periodicity pitch which is not conveyed by labeled lines and present only in the temporal characteristics of firing, is difficult to explain. (3) The superposition catastrophe or multiple object problem can only be solved by selectively "attending" to the right subset of neurons. How this is done remains to be seen, but Crick's "search light", based on asynchronous bursting, may be a potential tool (23). Although Crick later refuted his own idea because of the presumed absence of bursting in non-sleep stages, recent evidence suggests that asynchronous bursting is a very common activity in all behavioral states (13,42,101) and this makes the "search light" hypothesis viable again.

I will now present two detailed examples of putative rate coding; one for single (or very few) neurons and the other for a large neural ensemble.

The few-neuron rate code

Britten et al. recorded from single visual neurons in the middle temporal area (MT, or V5) of awake behaving

monkeys (14). In this area the majority of neurons respond selectively to specific types of movement in the visual image. The stimulus used was a random-dot kinematogram in which a proportion of dots was moving in a coherent direction and the rest were moving randomly. Monkeys were trained to signal the direction of motion and simultaneously the responses of a single neuron in MT to the apparent motion was recorded. The stimulus was optimized for the receptive field properties (position and display size of the stimulus, direction and velocity of the dots) of the neuron and the psychometric function for detection of motion direction was evaluated as a function of the percentage of dots that were moving in a coherent way. On the basis of the neural response, the authors calculated how the monkey (using signal detection theory and the concept of an optimal processor) would do if it had only the neuron's responses to the null direction and that to the actual direction at its disposal. This was operationalized by assuming a second "anti-neuron" that would respond to the null-direction for the neuron under study. The results indicated that for about half the cells there was no significant difference between the psychometric functions derived from the neuronal data and those derived behaviorally. In the other half there were significant differences, but most of these were related only to differences in threshold. Psychophysical and neuronal thresholds were not strongly correlated on a cell-by-cell basis, although they were closely related on average. For about half the neurons that performed nearly exactly as the overall monkey one could say that a monkey could perform the discrimination task with the observed sensitivity, were it capable of monitoring a single pair of MT cells in a neuron-antineuron configuration. This suggests that single neurons or, at most, a few are the coding elements in a threshold of visual movement detection task, and that the decision can be made on firing rate.

Critique. By choosing the task as optimally suited for the properties of the neuron, the lower-envelope principle (7) was in fact the only thing tested. Similar detection schemes could be set up for pure tone threshold detection in primary auditory cortex whose neuronal tuning curves and thresholds are similar to those in auditory nerve. At levels close to threshold the rate intensity function and the psychometric detection function will likely be very similar. At sufficiently high levels above threshold, that particular neuron will also become sensitive to other frequencies. The iso-rate frequency response contour, known as the tuning curve, suggests that firing rate is not uniquely determining what is going on, i.e., what intensity-frequency combination is presented. In this case one needs to construct a perceptual space from minimally three types of receptors (three groups of spontaneously active populations in auditory nerve?) to code a two-dimensional (frequency, intensity) space of stimulus qualities. This is analogous to the color constancy found in visual cortex area V4, where the ratio of the firing rates in the neural channels, derived from mixing the output of the three cone types, codes for color in a luminance-independent way (119). So in the case of the MT neuron, it will likely also be sensitive to other directions of motion, other positions in the visual field, etc. This suggests that the few-neuron rate code only operates at near-threshold values or just-noticeable-difference detection.

The neural ensemble-rate code

Georgopoulos and colleagues (48,63,95) describe an extensive set of data and potential population rate codes in primate motor cortex. Neuronal activity was recorded in primate motor cortex simultaneously with the direction of arm movements in three-dimensional space. The discharge rate of 475/568 cells (84%) varied in an orderly fashion with the direction of movement: discharge rate was highest with movements in a certain direction and decreased progressively with movements in other directions, as a function of the cosine of the angle formed by the direction of movement and the cell's preferred direction. Units were generally broadly tuned for direction. Neural population coding assumes that for a particular movement direction each cell makes a vectorial contribution ("votes") for a direction in the cell's preferred direction and magnitude proportional to the change in the cell's discharge rate associated with the particular direction of movement. The vector sum of these contributions is the outcome of the population code ("the neural population vector") and points in the direction of movement in space well before the movement begins. A large class of weighting functions used to combine the individual neural data will yield perfect predictions provided that (1) the weighting functions are radially symmetric around the preferred direction, (2) the preferred directions are uniformly distributed in space and (3) that the tuning parameters are independent of preferred direction. Population codes appear to be relatively immune to cell loss.

Critique. Several similar schemes have been proposed and tested, e.g., for the role of the superior colliculus in saccadic eye movement generation (83). These schemes seem to work well on the motor side of the brain. Requirements may be that each motor neuron innervates all relevant muscles, such that the pool provides a weighted activation pattern across all relevant muscles resulting in the desired movement.

I do not know of clear examples of population-rate coding in the sensory domain. In the auditory system a rate-place code for vowel representation largely fails at higher input levels because of contrast degradation; all neurons become saturated (92). However, a shift of emphasis from high spontaneous rate (SR) fibers to low SR fibers shows a strong potential for rate as a code (72). How the shift of emphasis that is required (a search light) is made obvious to the receiving neurons in the ventral cochlear nucleus is far from clear. Intensity coding for pure tones in auditory nerve (115) or midbrain (29) seems to be based largely on firing rate and to work with small ensembles of neurons (about 10 cells), so one can imagine that intensity coding for a complex sound will require combination of small neuron pools per frequency into larger pools within a critical band.

Temporal coding

To go beyond rate coding, one can examine the statistical relations of the spikes to one another by using inter-spike interval (ISI) distributions for individual neurons or cross-correlation functions for simultaneously recorded spike trains. Temporal coding relies on coincidence-detecting neurons with short integration times, i.e., shorter than the modal ISI of a neuron. For cortical neurons the modal ISI

may be of the order of a few milliseconds, whereas the integration time is of the order of 10 ms. Is coincidence detection, and thus temporal coding, therefore limited to the sensory periphery and to interneurons in the cortex? König et al. suggest that coincidence (co-firing) detection can take place when the neuronal integration time is shorter than the mean ISI (69), which for cortical neurons is rarely less than 30–100 ms.

A system that keeps track of spike arrival times or inter-spike intervals could, in principle, convey far more information (in the sense of Shannon) than a system relying only on averaged firing rates (47,56,82), but this may simply be the result of the availability of more independent variables (to the experimenter) to solve the stimulus prediction problem. The absolute upper limit to the transmitted information is set by the number of distinguishable spike sequences given some spike-timing precision (jitter). The amount of transmitted information then measures the number of stimulus waveforms that can be distinguished from the observation of the spikes.

True coincidence detection is not optimal; an optimal multiplier neuron encodes a signal formed by smoothly weighting all of the near misses to coincidences between the spike trains. Put another way, apparent sloppiness in the detection of coincidences may actually reflect optimal multiplication (8). If cortical neurons behave as coincidence detectors, then the timing of spikes can propagate through cortex with great fidelity to convey information and to synchronize other neurons (2).

In sensory systems such as the visual that are either considered static or change only slowly in time, i.e., at the rate of occurrence of micro-saccades, smooth-pursuit eye movements and head movements, temporal characteristics in action potential sequences are usually not obvious. As a consequence, temporal codes of information processing have been largely neglected in the study of the visual system; except by Richmond's group (46,64,82), Singer and co-workers (69,102), and by Dayhoff and Gerstein (25). In sensory systems that are receptive to stimuli with a higher frequency periodic structure (the auditory, somatosensory and electric sensory system), action potentials are generally produced synchronously with this stimulus periodicity and thus with each other. Timing and synchrony in neural populations thus contain information about these periodicities. In the auditory system, for instance, neural time codes play a role both in auditory localization based on time differences between the ears (where) and in pitch, timbre and phoneme perception based on periodicities and thus on monaural time differences (what) (19).

Modern theories for periodicity pitch combine inter-spike interval distributions from many frequency regions of the auditory nerve to produce pooled inter-spike interval distributions from which the pitch is then extracted. For the vast majority of periodic complex stimuli, it was found that the pitch heard by human listeners corresponded to the most common inter-spike interval in the auditory nerve and that the salience of the pitch heard corresponded to the peak-to-background ratio in the population interval distribution (19). It has also been shown that inter-spike intervals of single auditory nerve fibers can convey spectral information suitable for recognizing speech (118). A problem that remains to be explained is the apparent absence of periodicity following by cortical pyramidal cells for rates above 50/s,

with the exception of high CF (>10 kHz) fibers in the auditory anterior field (94). These CFs are so much higher than the dominant formant frequencies that they are unlikely to be activated by speech sounds. Thus periodicity pitch detection is either done sub-cortically or the periodicity pitch has been mapped on to the spatial dimension in cortex.

One of the great advantages of temporal codes over rate codes is that correlations between spike patterns can be implemented by the convergence of axons carrying the patterns on to coincidence detectors. Pyramidal cells in cortex may perform the role of detecting coincidences between direct thalamic inputs and indirect (delayed) inputs from local interneurons, association fibers, and commissural fibers (69). Depending upon the relative directions of spike-train propagation, an array of coincidence elements can compute correlations or convolutions. Relative delays ranging from a few microseconds to tens of milliseconds could be created by the following mechanisms: (1) differences in cortical distances between pyramidal cells, (2) differences in conduction velocity of horizontal fibers, (3) multiple synaptic delays, (4) combinations of excitation and inhibition, (5) reverberating loops of different lengths, and (6) tuned intrinsic recovery kinetics of pyramidal cells. Thus a population of coincidence elements embedded in a system of relative delays can compute global auto- and cross-correlation functions which may form the basis for complex feature extraction.

I will now present two detailed examples of putative temporal coding; one for single (or very few) neuron and the other for a large neural ensemble.

The few-neuron temporal code

Of 144 low-frequency (phase-locking) neurons studied in the central nucleus of the inferior colliculus (ICC), 85% were sensitive to both interaural time differences (ITD) of noise and interaural phase differences (IPD) of pure tones (117). For most cells the discharge rate was modulated in an approximately cyclic fashion by changes in ITD. Overall intensity level had no effect on the ITD. When uncorrelated noises were delivered to the two ears, there was no sensitivity to ITDs. This emphasized the need for synchronized inputs to a hypothetical comparator mechanism in the ICC or the lower brainstem. The temporal characteristics of the responses to interaurally delayed noise were found to be characterized best by the synchronized-rate curve, which was computed by taking the product of spike count and the synchronization coefficient of the interaural phase sensitivity curve. The median frequency was highly correlated with the response frequency of the noise delay curve ($r = 0.9$, slope 1.05). Results strongly indicate support for a cross-correlation model for interaural time sensitivity of low-frequency neurons in ICC.

Similarly, interaural phase differences either in the low-frequency carrier, in the amplitude-modulation waveform of a high-frequency carrier or in a complex sound are transformed into interaural time differences by the precise phase-locking of the auditory nerve fibers and the enhancement in accuracy provided by certain populations of neurons in the cochlear nucleus. Combination of phase differences for different frequencies (components of a complex signal) allows the auditory system to reconstruct interaural delays without ambiguity (117). Neurons in the medial superior olive

(MSO) respond best when sound in one ear leads that in the other ear by an amount equal to their delay disparity but with opposite sign. The delay disparity likely results from the interposition of axonal delay lines. For a given interaural time difference a given set of neurons in MSO will be subject to the simultaneous arrival of spikes from ipsilateral and contralateral AVCN cells, and this convergence causes the MSO cell to fire. The MSO cells act as coincidence detectors. The existence of a tuned set of axonal delay lines synapsing on to the nucleus laminaris (a homologue of the MSO) of the barn owl has been demonstrated (20), and for the nucleus laminaris in the chick (84), and made plausible for the MSO in the cat (116). Thus at the level of the MSO the ingredients for a cross-correlation mechanism are present; an array of delay elements, coincidence detectors and ensemble averaging carried out by the population of activated MSO cells. In order to achieve the extreme sensitivity for temporal disparities, of the order of 2–10 μ s, the MSO units must perform an operation similar to that carried out by the octopus cells in PVCN. It is surprising that these octopus cells, which have a jitter in their firings of as low as 20 μ s, are not involved in any way with localization of sound.

So the binaural interaction for low-frequency neurons which are sensitive to ITDs resembles a cross-correlation of acoustic input after filtering and phase-locking by the peripheral auditory system (117). Ambiguities about phase may be resolved by combining inputs from fibers with different CFs and it is expected that neurons that do this have broadly tuned receptive fields. It has been shown that the auditory system, and especially the LSO, is also sensitive to the ITD of a low-frequency envelope waveform. Therefore, the cross-correlation mechanism may also involve a sensitivity to ITDs of the modulating waveform, since LSO cells phase-lock to that waveform. It was found that sensitivity to ITDs of modulation envelopes in ICC cells initially arises from the coincident arrivals of phase-locked inputs from the two ears at binaural cells, which are probably located in a nucleus lower than ICC because the mean BMF for ITD was a factor 4 higher than the mean BMF for neural synchrony in the ICC. So the observation that many parts of the peripheral and central auditory system are highly specialized to preserve the fine grained details of the acoustic waveform may be also underlying their ability to detect minute inter-aural time differences for the purpose of sound localization. To achieve this temporal resolution, the neural interaction may involve processes similar to those of cross-correlation.

Critique. This transformation of temporal coding into a map of interaural delay is only a first step in the representation of auditory space in the nervous system. Ultimately a rate–place code in the superior colliculus results that is fine tuned by calibration with the map of visual space (65).

The ensemble temporal code

The responses, characterized by both firing rate and synchronization measures, of a large set of auditory nerve fibers to perfectly periodic synthesized vowel stimuli: /I/, /ε/ and /a/ were studied by Young and Sachs (118). The profiles of discharge rate versus fiber CF showed peaks in the vowels when the stimuli were presented at low sound levels. At higher levels, the peaks in the rate profiles

disappeared, principally because of the effects of rate saturation; the contrast degradation phenomenon previously mentioned (118). A representation in terms of firing synchrony with the periodicities in the vowels was able to preserve the spectral structure of the vowel in detail and largely independent of sound intensity. The authors proposed an algorithm that required a combination of firing rate, place of activity along the cochlea and temporal information of the individual fiber's firings. The temporal information can be based on the period histogram (this requires knowledge about the stimulus, which the nervous system does not have) or on the inter-spike-interval histogram (does not require knowledge about the stimulus). The algorithm calculates the localized synchronization ratio (LSR), a combination of synchronization indices for several harmonics of the inter-spike-interval histogram for fibers with CFs within a half octave on both sides of the formant frequency, and averages this across all auditory nerve neurons recorded from. This averaged LSR (ALSR), plotted as a function of the harmonics of the inter-spike-interval histogram based on the fundamental period, represents the vowel spectrum quite accurately and is hardly affected by intensity. So in order to preserve vowel cues across stimulus level, a synchronized representation is required.

The similarity of periodicity pitch and vowel identification is evident; in both cases the problem reduces to specifying the spectrum of the complex signal. Pitch extraction, according to the cross-channel correlation model, could then occur at the level of the MSO. This mechanism would also be required to do the spectral analysis of the inter-spike-interval histograms.

Critique. There are some caveats to the suggestion that only synchrony or mechanisms relying upon synchrony can be used in speech coding. First of all, speech features such as stop-bursts and frication at the level of the auditory nerve may be better encoded in term of a rate–place profile (26). Secondly, the spectral representation of vowels may be entirely or in part based on low spontaneous rate auditory nerve fibers as a rate–place profile depending on the intensity (72). Such neurons have extended dynamic ranges and do not show saturation (115). The limiting phase-locking potential of neurons higher in the CNS is also a concern; in AI neither the fundamental nor the formants can be represented in temporal fashion. In essence, the power to represent the second and higher formants (frequencies > 1 kHz) in temporal firing patterns is already largely lost at the level of the auditory midbrain. One can likely bypass the spectral representation part and directly represent the relevant periodicities in the across neuron auto-correlograms (19).

CONSTRAINTS ON POTENTIAL NEURAL CODES

One of the most important considerations in modeling the decoding of sensory information is acknowledging that the stimulus and its time of presentation are unknown to the animal. Thus one of the problems in identifying a useful code for the central nervous system is that such a code cannot in any way relate to features of the external stimulus, such as time of presentation, frequency content or position in space. For instance, one cannot use period histograms which require knowledge of the stimulus periodicities to

infer timing representation in a periodic sound, but one can use the neuron's own inter-spike interval distribution which presents the same information (58). For transient responses one cannot obtain useful information from an interval histogram and thus one needs an internal "clock". One cannot use latency as part of the stimulus-response features used in a "panoramic code" (77); but one may use spike latencies relative to an internally available global time marker such as a local field potential. Thus, internal representations or codes need to be free from external "anchors".

Global membrane potential oscillations may potentially serve as a time reference. Hopfield posits that analog information can be represented by using the timing of action potentials with respect to an ongoing collective oscillatory pattern of activity (56). The computation in this analog representation is done by combining information through pathways with different delays. The analysis requires a coherence of the oscillation across a localized set of neurons, but such coherence is common at frequencies in a broad range from 1 to 200 Hz (16). The first spike in a burst will carry information in its timing, and analog information will also be carried in the number of action potentials which occur within a cycle. If information is encoded as hypothesized, then neurons that receive little input fire with little time advance (or none at all) to the oscillatory (e.g., 40 Hz) wave, will appear synchronized with the oscillation and thereby with other neurons. These synchronized neurons and their conspicuous activity may therefore be those with the least information about a stimulus other than its presence. In Hopfield's model it is the relative timing between cortical units that conveys information about the stimulus components. If firing of pyramidal cells in certain brain regions is thus determined by, e.g., a 40-Hz internal clock, then obviously these regions do not transfer information by a rate code, nor do they transfer information by a temporal code. The only potential signaling capacity is by the list of cells that fire; a form of labeled line coding (59).

TRANSFORMATION OF CODES IN THE BRAIN

Largely because the topographical ordering of cortical maps (a simple consequence of economically wiring a topographically organized sensory periphery to more central parts), it has long been assumed that the cortex is a spatial pattern processor and consequently it has been taken for granted that all that is required for sensory coding is a rate-place code. In such a code the distribution pattern of firing rate across the cortical surface represents the stimulus. From the belief that the cortex is exclusively a spatial processor, it follows that all information which is not place coded in sensory peripheries (e.g., color, texture, periodicity pitch, acoustic space) must eventually be converted into the "common" language of the cortex, i.e., spatial excitation patterns. Because the auditory periphery is characterized to a large extent by temporal coding, there must be temporal feature detectors, e.g., in the superior olivary complex and inferior colliculus (71) which perform these time-to-place transformations. In the literature on information processing in the auditory nervous system, one finds repeatedly the suggestion that neural synchrony is important for processing in auditory nerve and in the lower brainstem, but generally

loses its importance in higher centers to be gradually replaced by a rate coding (71). It has been suggested (91) that at the level of the cochlear nucleus the recoding from a firing-synchrony to a firing-rate mechanism has already taken place. Or, as Capranica and Rose stated, "time domain processing involves a transformation from a periodicity code in the peripheral auditory system to a temporal filtering assembly in the central auditory system" (18). This may be an interpretation based on the gradual change from an event-type correlation in the auditory periphery to the rate-type correlation one finds in higher centers; for short lag times one may even detect this rate-correlation as not much more than a stimulus-induced rate increment. We have shown previously that in the auditory midbrain of the leopard frog, single-cell or population synchrony is insufficient to code stimulus intensity but that a population rate code across a modest number of cells is capable of doing so (29). In the inferior colliculus of the guinea pig (90), the mean discharge rates were greatest for those modulation frequencies which also elicited maximum synchronization. This is in contrast to more peripheral parts of the auditory system where the degree of synchronization is independent of mean firing rate, and units are not tuned to modulation frequency in terms of average rate. This suggests that the auditory midbrain acts as a decoder for temporal information and transforms the degree of synchrony into firing rate. This may ultimately result in a rate-place code as, for instance, for auditory space occurs in the superior colliculus (65).

In the auditory system (88), interaural time differences are converted in the brainstem by means of a latency-difference code into a spatial pattern of excitations. Neurons in the superior olivary complex are tuned to particular interaural time or intensity disparities. In case of ongoing signals at both ears, the time patterns are preserved in the coincidences so that outputs of such coincidence-detection arrays will also contain time patterns which are common to both ears. In case of transient signals, the result of the coincidence detection is again a transient signal. In order to allow information about stimulus periodicities to reach higher auditory centers, a large part of the output of the cochlear nucleus bypasses the lower brainstem coincidence detectors and synapses directly onto inferior colliculus cells.

The auditory thalamus and cortex form an apparent superstructure that operates with many synapses on the same cell, and uses the rate code from the inferior colliculus as its input. In cortex many inputs affect the pyramidal cell and a single presynaptic spike has potentially little bearing on the exact timing of the postsynaptic spike. Synchronous spikes in the lateral geniculate nucleus of the thalamus seem to convey an impoverished intersection of the two neuronal receptive fields (49). Remarkably, single-unit firing rate in cortex is rather independent of click stimulus periodicity, whereas the amount of spike synchronization with the stimulus clearly depends on the repetition rate (35). This suggests a re-emergence of a synchrony code at the level of the cortex potentially emphasized by the transient character of its responses. One complicating factor, at least in anesthetized animals, is that the optimal synchrony is generally found at the dominant EEG-spindle frequency in the preparation, which in itself tends to synchronize spike activity. Stimulation with periodic clicks around this spindle frequency tends to entrain this frequency (33). In the common marmoset, the dominant modulation frequency of

its “twitter” call is in the barbiturate-spindle frequency range. Auditory cortical neurons were found to be very finely tuned to the modulation frequency in the call (114). One wonders whether this is an adaptation of the call modulation frequency to a dominant brain frequency or that the temporal tuning found is a mere coincidence of the similarity of the spindle frequency and the modulation frequency of the “twitter” call.

TAKING STOCK: ONE OR HUNDRED NEURAL CODES?

1. Individual neurons can be considered as simple filters that may extract identical information (i.e., produce the same response) from an ethologically meaningless sound as well from a biologically relevant sound. Extracting ethologically relevant features may thus require very specialized cells or populations of neurons that combine the individual features. Populations of neurons may be required to provide level tolerance of coding or representation.
2. The problem of reading a neural code for an animal is essentially the problem of building an inverse filter that operates on the spike train(s) to allow real-time stimulus recognition and classification in relation to their survival value. One can thus argue that rate coding and temporal coding are just two extremes to be considered in the decoding process. A simple, long duration, rectangular kernel will extract a firing rate; an oscillatory kernel will only extract spikes that have the same periodicity as the kernel.
3. Of two potential candidate codes, the one that carries the biologically relevant information more efficiently, i.e., with fewer spikes in the shortest time or with the smallest number of neurons, is likely the one used by the nervous system. It is, of course, equally likely that the potential codes are used in combination.
4. Single cells may code for near threshold stimulus levels (the lower-envelope principle) and can then be seen as “cardinal” cells. However, cardinal cell actions disappear at levels sufficiently above threshold and assembly activity in the form of population coding is needed.
5. Rate coding is essentially a labeled-line or topographical coding. Because the auditory periphery is characterized to a large extent by temporal coding, there must be temporal feature detectors, e.g., in the superior olivary complex and inferior colliculus which perform time-to-place transformations.
6. One of the great advantages of temporal codes over rate codes is that correlations between spike patterns can be implemented by the convergence of axons carrying the patterns on to coincidence detectors. Pyramidal cells in cortex may perform the role of detecting coincidences between direct thalamic inputs and indirect (delayed) inputs from local interneurons, association fibers, and commissural fibers.
7. Most higher level decoding systems, e.g., sensori-motor coordination systems, are feedback systems, so there is no unidirectional flow of information as in classical information transmission systems, and this makes a formal treatment difficult.
8. When only confirmation occurs after receiving a message, there is no information transmitted at all in Shannon’s sense. But without confirmatory information there

TABLE 1
CORRESPONDENCE BETWEEN ASSUMPTIONS AND CODING

Stationarity	Non-stationarity
Information processing model	Representational model
Decision making	Learning
Integration	Co-firing detection
Sigmoidal response function	Binary response function
Rate coding	Temporal coding
Single neuron	Neural assembly

- can be no comprehension or recognition. How does the brain as an information processor handle this?
9. If information derived from sensory stimulation is used to continuously update the brain’s internal representation of the “world”, then neural codes may change with time through learning. As a consequence the same spike sequence may be interpreted differently (or evoke a different behavior) later in the day.
 10. One could state that representational models change their parameters on a time scale slower than the time it takes for information processing. It is then probably not too much of a leap to suggest that information processing models can be embedded in representational models.
 11. Several continua in coding that we have encountered can be fit into a scheme of corresponding entities (Table 1). The concept of stationary brain activity corresponds to the information processing approach that views the brains as a decision maker, adopts rate coding as its main strategy and endorses the single- or few neuron approach. The non-stationary viewpoint is embodied in the representational model of brain function that stresses learning and plasticity and employs temporal coding in neural assemblies.
 12. Could the thalamus act like “an elaborate 7th layer of the cortex” and function as a “blackboard” on which the cortex writes and from which it reads. Could this be the place where the internal representation of the world is stored and continuously updated?
 13. Spontaneous activity in sensory systems is normally imperceptible, because the sensory nerve fibers fire independently and may fail to produce sufficient synchronous firings to activate certain secondary neurons. Stimulus-induced changes may be perceived because neighboring nerve fibers start firing more synchronously with the stimulus, and as a consequence their firings become correlated.
 14. Are “bursts” a neural code or does bursting represent a more sharply tuned “brain state” than does the isolated spike firing? Alternatively, are bursts used to switch the brain from one state to another? This invites a look at the brain as a dynamic system.

AN ALTERNATIVE: THE BRAIN AS A NON-LINEAR DYNAMIC SYSTEM SENSITIVE TO SMALL PERTURBATIONS

Non-linear dynamics, information theory and chaos theory are all part of a general paradigm in the study of complex systems (55). A crucial property of systems described by these theories is the exponentially increasing amount of uncertainty associated with predicting the future time evolution of the system and its related information

content. This is determined by the sensitive dependence of the system upon the initial conditions, so that it takes only a very small perturbation to switch the system from one unstable state into another. Initial conditions in the case of the brain could be drawn from the set of all possible spatio-temporal distributions of action potentials; small differences in this distribution could result in vastly different states of the brain some time later. Any stimulation could act as such a disturbance.

But what does this have to do with neural coding? First of all we have to accept that brain activity can be modeled as resulting from a non-linear dynamic system. Such systems can be in stable states (isoelectric), unstable periodic and quasi-periodic states (one of the many characteristic EEG states) and possibly chaotic states. If we assume that behavior is isomorphic to a set of macroscopic states of the brain and is, furthermore, the only relevant correlate of brain activity, then the brain may be considered to operate at the edge of chaos, a state where very small changes in the controlling parameters (such as sensory stimuli) may cause large macroscopic state changes, such as from one quasi-periodic state into another (27,93). Alternatively, the brain may be stochastic and still be sensitive to small perturbational feedback just as a deterministic chaotic system (22). If one accepts this, coding by individual neurons is largely irrelevant, i.e., it does not matter whether a single-unit rate code or a temporal code is at work. The only relevance of neural firing is to be found in its capacity to induce transitions between the many unstable macrostates found in the brain and the relevant questions are related to what determines the various transition probabilities. Thus only population activity is relevant and among that the spatio-temporal patterns that determine the transitions between states are the relevant ones to investigate. It has been suggested that oscillatory states in neuronal networks may constitute a mechanism used by the nervous system to regulate changes of state in these networks (73). Any change in the firing patterns of neurons that causes a transition between macrostates, for instance a single-unit burst or an intricate multi-neuron activity pattern, now becomes important.

Recent research, applying hidden Markov models to analyze cortical multi-unit activity, suggests the existence of a finite number of distinguishable small neuronal group states (89) that correspond with behavioral states (3). These states with reasonably stable firing rates are characterized by differences in the synchronization between the firings of single neurons (3). This finite number of states may be a subset of a much larger set of states in the assembly(ies) in which the small neuronal group participates. What hidden Markov modeling does is use the firing of simultaneously recorded neurons as a multivariate Poisson process whose vector firing rates change with time. In those vectors the first component is the firing rate in a certain time window of unit one, the second component that of neuron two, etc. The hidden Markov model then segments the time-dependent activity of the local group into distinct states characterized by firing rate combinations across the units. These states can then be correlated with behavioral states of the animal. Abeles et al. found a very close correlation (3). Furthermore the cross-correlation between the firings of some unit pairs was state dependent, suggesting modifiable cross-correlations. It was furthermore suggested that "neural networks in

the cortex dwell most of the time in stable configurations of activity ("attractors" or "states"), each having distinct firing rates and neuronal interactions (3)". The switching between states seems to be initiated by sudden correlated changes in the firing rate of one or more units. Somewhat complementary, Vaadia et al. working on the same data set found that very often the averaged unit pair-correlation did not discriminate between behavioral states, whereas the temporal modulations of co-firing between two units could differ dramatically between states (112). So these two reports from the same group of researchers seem to suggest that the dynamics of neuronal firing expressed in the modulation of both short-term firing rates and co-firing between units may be important aspects of switching between brain and behavioral states.

The need for dynamic linking of neuronal groups in perception, e.g., by stimulus-induced gamma-band oscillations (52), may arise from the fact that within the few hundred milliseconds in which perceptual decisions have to be made, most single cells in cortex only fire a few, apparently stochastic, spikes. This makes them unreliable for the establishment of significant temporal correlations between individual neurons (32,34) within that short period of time. Ensemble averaging, made possible by the re-establishment of neural correlation, may significantly increase the reliability of perceptual decisions about the presence of stimulus features. Simultaneously, the stimulus-locked activity of the neuronal population, which occurs well before the induced oscillations start, is still available for estimating stimulus quality such as threshold. In this view the oscillations, gamma as well as theta and alpha, may provide an alerting, attentional channeling of metabolic resources to improve signal-to-noise ratios. Burst-firing may be part of this homeostatic process (13,23). The "places" that are firing synchronously are usually those that share a sensitivity to the same stimulus features, other than topographic place, e.g., orientation sensitivity. The neurons in those "places" have to be stimulated "in phase", that is with separate bars moving with the same speed in the same direction or with one single bar. Unless other features that the individual neurons are responsive to are correlated with, for example, this orientation selectivity, the linking provided by the oscillations is relevant only for the feature that induced them.

According to the concepts of synergetics that look for qualitative changes at macroscopic scales (54), the various brain-state modes and the switching between them are governed by order parameters. These could be the amplitudes of local field potentials which determine the macroscopic, behavioral, states and entrain the activity of individual cells. Wide-spread EEG oscillations are one particular realization of this which may lead to an enormous information compression, because this global synchronization causes a highly correlated action of individual neurons (40). Once the network reaches an attractor state, its behavior will be constant until the next transition occurs. In a stable state there is thus no or very little information processing; the only information transfer occurs when the system changes. State-switching in brain activity may thus be more relevant than the neuronal patterns and the correlations between them that are found during stable states. State-switching is likely reflected in changes in synchrony between individual neuron activities (112). Time-dependent

changes in neural synchrony (4) may signal the building up or breaking down of assemblies. When control parameters (e.g., concentration of neurotransmitters, drugs, etc.) change beyond a critical value, the system suddenly forms a new macroscopic state that is quite different from the previous one. Receptor systems in the brain are organized to detect changes in transmitter concentration as opposed to absolute concentration (10) which stresses the notion that change has higher behavioral value than steady states. Thus, the neural correlates of transitions between brain states, such as between the two theta type rhythms and the large irregular activity in hippocampus (113), that are related to behavioral states may reveal more of neural coding than an exhaustive description of single-unit properties in relation to these brain states.

Relational order, feature binding and the emergence of wholes (Gestalts) as revealed by synchronous population neural activity, may supersede the single- or few unit activity description of brain function. Relational order between individual neurons is equivalent to the existence and strength of correlation maps and sees assemblies as

more than a statistical result of the outcome of a large number of interactions among discrete neurons. Through the reciprocity of connections between the neurons in the map, which may provide a positive feedback, very small changes in just a few pair correlations may give rise to a sudden state change characterized by the formation of a new assembly. Recognizing that only very small changes are required to induce the transitions between states suggests that concentrating on the most conspicuous phenomena in the firings of neurons may not be as fruitful as focusing upon certain rare but repeating phenomena. Let the search for the neural code begin!

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