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The role of the thalamic reticular neurons in alpha- and gamma-oscillations in neocortex: a mechanism for selective perception and stimulus binding

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Review

Abstract. The long-term objective is to understand how large masses of neurons in the brain process information during various learning and memory paradigms. Both time- and space-dependent processes have been identified in animals through computer-based analytic quantifications of event-related extracellular potentials. New nonlinear analyses have been introduced that presume that the fine-grain variation in the signal is determined and patterned in phase-space. Some neurons in the primary visual cortex manifest gamma-band oscillations. These cells show both a nonspecific phase-alignment (response synchrony) and a specific tuning (orientation tuning) when stimuli are presented to their receptive fields. This dual regulation of the sensory cells is proposed to underlie stimulus binding, a theoretical mechanism for "object" perception. Nonlinear analytic results from gamma-activities in a simple model neuropil (olfactory bulb) suggest that neuroplasticity may arise through self-organization, a process in which a nonlinear change in the dynamics of the oscillatory field potentials is the hallmark. This self-organization may follow simple dynamical laws in which global cooperativity among the neurons is transiently brought about that, over trials, results in enduring changes in the nonlinear dynamics of some neurons. In conclusion, the sculpturing of the synaptic throughput in the sensory cortex (stimulus binding) may be associated with the irregular phases of the gamma-activities and may result from both specific and nonspecific systems operating together in a nonlinear self-organizing manner.

Key words: nonlinear dynamics, low-dimensional chaos, theoretical model of perception

NONLINEAR DYNAMICS OF BRAIN ELECTRICAL ACTIVITY

The electrical activity of the brain looks noisy, irregular and random, but it is not (Adey 1972, Bullock 1976). New methods in nonlinear dynamics show that the fine-grain variations are low-dimensional, and therefore cannot be equivalent to stochastic noise. Furthermore the electrical activity manifests a type of nonperiodic behavior that is, mathematically speaking (Elbert et al. 1994), chaos.

Low-dimensional chaos is a nonlinear deterministic process, meaning that it is caused by relatively few antecedent events, not an infinitude of them. These antecedents are characterized by the minimum number of orthogonal variables or degrees of freedom of the continuous variable space they define. The application of this new mathematics to biological data suggests that some activities have a small number of dimensions (degrees of freedom). This small number leads to the expectation that the underlying process may actually be less complex than thought.

The brain, however, has enormous complexity. The reductionist strategy of studying individual neurons cannot be expected to lead to an understanding of the higher brain functions, such as perception, attention and learning, because these higher functions all have emergent properties, manifested in behavior, that cannot be understood from explanations at a lower level (Freeman 1995). Each cognitive mechanism is dependent on the simultaneous cooperative interactions of millions of neurons, the coupling of which is both dynamically variable and mathematically nonlinear. Even in strongly-nonstationary spontaneous-EEG data the signal exhibits unique nonlinear properties (Kowalik and Witte 2000). Introducing an external stimulus makes more order in the EEG dynamics and "improves" the nonlinear deterministic character (Elbert et al. 1994, Lutzenberger et al. 1994). Consequently, if the intricacies of higher brain processes are ever to be understood, new techniques for the analysis of these neural activities will be needed to decipher the seemingly irregular biological activities. These new methods take into account not only experimental limitations associated with biological systems but also these coupled to poorly fulfilled conditions required for the mathematical analysis (Skinner et al. 1992, Kowalik and Elbert 1994, Kowalik and Leiber 1998).

Although scalp-recorded EEGs have poor spatial resolution, this is not necessarily so for the potentials recorded at the brain surface. For example, in a simple-system model of neocortex, the olfactory bulb, it

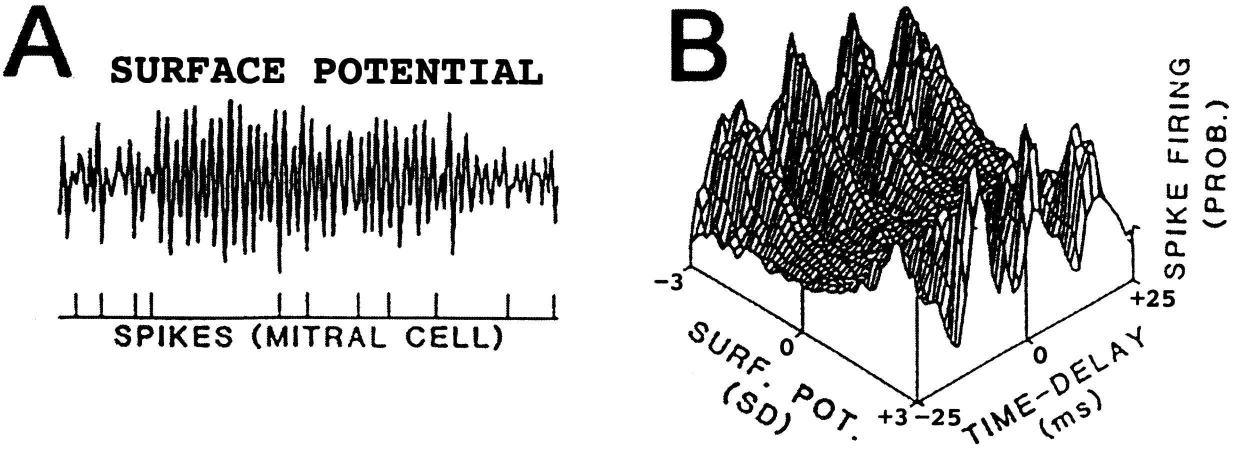

Fig. 1. Data recorded from the olfactory bulb of a conscious rabbit illustrating the relationship of the time of firing of a mitral cell and the phase of the overlying surface potential. A, a surface potential simultaneously recorded with the extracellular spike activity of an immediately underlying mitral cell. B, a three-dimensional plot of the probability of firing of the extracellular spike with the surface potential amplitude for all time-delays just before (-) and after (+) each spike. Note that at 0 time-delay there is a quarter cycle delay to the nearest probability peak (just to the right of 0); this is because the open-field dipole of the granule cell produces the surface potential, not the closed-field dipole of the mitral cell. To produce the data in this figure, the mitral cell must fire at the same phase of the surface potential each time it fires. When the mitral cell membrane potential oscillates it drives the granule cell through a graded-release synapse and the resultant membrane potential then results in the recorded surface potential.

has been found that the probability of firing of an action potential in a mitral cell, i.e., the output neuron of a functional unit, is time-locked to the oscillatory field potential recorded from the surface immediately above it (Freeman 1995). This covariation found within a functional unit is illustrated in Fig. 1.

The olfactory bulb has a laminated structure and small functional units (i.e., collections of cells that operate together) that are equivalent to neocortical columns. The local field potential around a functional unit results primarily from membrane voltage oscillations originating in the granule cell, not in the mitral cell itself. The granule cell is a neuron that provides recurrent inhibition to the mitral cell after it fires. Its membrane oscillations therefore phase lag those of the mitral cell by about a quarter cycle.

Most of the bulbar neurons have dendrites that symmetrically radiate away from the cell body, but this is not the case in the granule cells. They have what is called an open anatomical field because the dendrites manifest considerable asymmetry. This open-field structure creates a long electric dipole that projects currents, ones powered by the postsynaptic potentials, out beyond the cell's anatomical limits.

The interstitial currents can be projected far away, reaching even the spaces between the cells of the scalp. These long-distance projections happen because the resistivity of the extracellular space is only 1/100th that of the typical neuron membrane through which the return currents must pass. In the equivalent electric circuit the membrane resistor is 100 times larger than the extracellular one. This makes the long electric dipole a constant-current generator (i.e., as opposed to a constant-voltage type) and thus drives currents over relatively long and distant pathways.

The open-field anatomy generally occurs in at least one type of neuron in any type of functional unit. In neocortex the pyramidal cells, which are also output neurons of the functional units, have this open field structure. Because of the long-dipoles of the pyramidal and granule cells, spatial recordings can be made non-invasively in both the neocortex and the bulbar model. With this surface-potential technology one can hope to know where, when, and to what degree individual neurons and/or their functional units are active within the neuropil.

The surface potentials manifest low-dimensional chaotic activities (Skinner et al. 1991). If each surface potential were the wide-band sum of many independent signals, then they would be very "jittery" in appearance and not manifest low-dimensional variation. Therefore the electrogenic argument (that a surface potential represents the unique activity of a single open-field neuron, or a few operating together) and the dynamical argument (that the surface potential signal is low dimensional) are supportive of one another.

CHARACTERISTICS OF GAMMA-BAND POTENTIALS: LOW-VOLTAGE, HIGH-FREQUENCY, IRREGULAR-PHASE, GLOBAL-DISTRIBUTION

In both the neocortex and the bulb, it is the subject's interest in the stimulus environment, brought about by the novelty, rarity, or CS+ character of the evoking stimulus, that is associated with complex dynamic changes in what are called the gamma-band potentials (Mitra and Skinner 1992, Freeman 1994). The gamma-band activities range between 30 to 110-Hz in humans (Pantev 1995) and 20 to 90-Hz in cats (Gray and McCormick 1996). They are the noise in many signal-averaged event-related potential (ERP) studies which utilize the scalp-recorded EEG. That is, the gamma-activity cannot be seen in these EEG potentials using conventional averaging methods, because the frequency and phase of the individual gamma-waves are so variable and "jittery" that they are rejected along with the amplifier noise. These small high-frequency potentials however, may reflect the most important cognitive processes (Skinner et al. 1991, Mitra and Skinner 1992, Freeman 1994, 1995). The question now becomes: How does one quantitate these "jittery" activities?

One way is to use spatial averaging, a method which employs closely spaced electrodes (i.e., as opposed to temporal-averaging using one electrode). Freeman and associates (Freeman 1994, 1995) used an 8 x 8 electrode array to record surface potentials from adjacent functional units in the bulb. After an odor presentation a brief inspiratory burst occurred at each of 64 electrodes. Each of these spindle-shaped oscillating amplitudes was reduced by finding the root-mean-square value. Each RMS-value was then used as a coordinate on each axis of a 64-dimensional vector. The resultant vector, like the rabbit, could distinguish among odors.

Another spatial averaging method was also employed by these same investigators. The pattern observed in a phase contour map (referenced to the mean phase of all 64 electrodes) was found to distinguish among odors. That is, the electrodes in which gamma activities of the same phase were observed were interconnected on an 8 x 8 map by a single contour line. Different phases were represented by different contour lines. A relatively stable and graded contour pattern (i.e., one made of all contour lines) was then found to be evoked by each odor. That is, the patterns were specific to the odors..

Neither of these spatial measures, however, had good reliability in representing the specific sensory features of the odor. For example, if the animal was distracted neither measure would show the spatial pattern response; or if the evoking stimulus no longer held any meaning for the rabbit (e.g., it became habituated or extinguished), then it would not evoke any changes in the spatial vectors or contours. Because of this rather capricious odor-sensitivity, the bulbar gamma-band activity was interpreted (Freeman 1994) to be more related to the nonspecific perception of the odor (e.g., "a meaningful odor is present!") than to its specific sensation (e.g., "it is wintergreen"). The capricious short-term response of the bulbar activity stands in contrast to the sensory specificity of its own sensory receptors, and of sensory receptors in general. Sensory receptors always respond to an adequate stimulus within its sense modality, even if the animal is distracted or anesthetized.

It was proposed that the reliability problem might be due to the use of the RMS amplitude, a stochastic measure. Instead of applying linear stochastic methods to the bulbar gamma-activity, Skinner and associates (Mitra and Skinner 1992) employed nonlinear deterministic ones. These latter measures do not presume anything about the amplitude, frequency or phase of the signal, such as, for example, that its "jittery" variation is normally distributed around a mean. The Correlation Dimension (D2) was one of the first measures used, as it is insensitive to the conventional changes in a signal. What the D2 quantitates in the signal is its "jitter." That is, D2 measures the degrees of freedom of the variable space of the generator that produced the time-series.

Figure 2 shows these D2 results, as well as those obtained using a different dimensional algorithm. The upper portion shows that the Point Correlation Dimension (PD2) works better on nonstationary data than does the D2 algorithm. The PD2 algorithm is time-dependent, as a dimensional estimate is made at every point in time (note that it is also abbreviated PD2i to emphasize this feature). It is the restricted scaling region in the PD2i algorithm that makes it insensitive to nonstationarities. This feature enables it to track dimensional changes in the data-stream as it shifts from being made by one generator to being made by another.

In Figure 2A the nonstationary data (upper) are concatenated subepochs made by sine-, Lorenz- and Henon-generators. The running subepoch means of the separate PD2i values are within 4% of the known values made by the D2 algorithm on a single stationary data-type. The

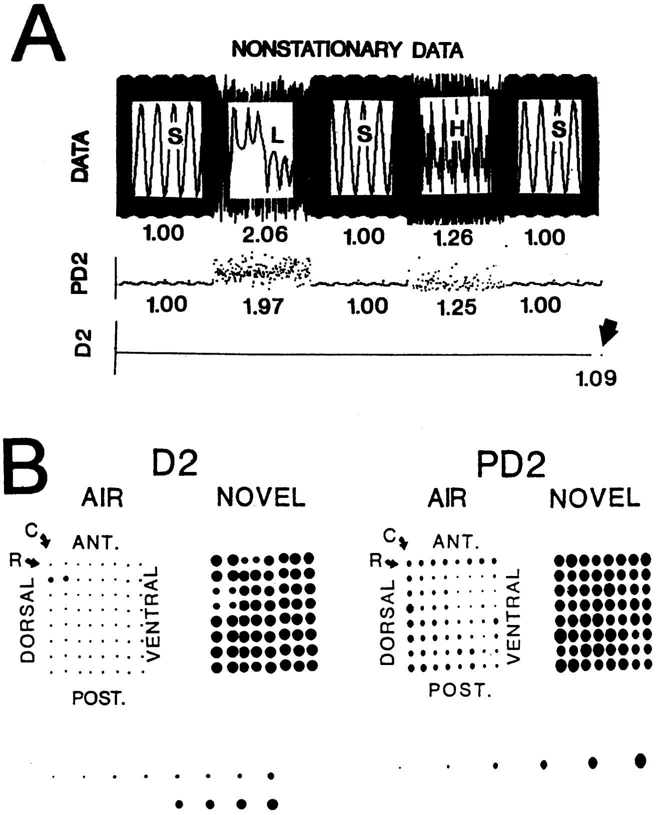

Fig. 2. Correlation Dimension (D2) and Point Correlation Dimension (PD2) of nonstationary data (A) and of spatial arrays of nonstationary surface potentials (B). In (A) the nonstationary data were made by sine- (S), Lorenz- (L), and Henon-generators (H). In (B) the data were recorded when either air (AIR) or a novel odor (NOVEL) was injected into the nose-cone of a conscious rabbit. Note in (A) that the D2 algorithm produces only one output value to characterize the recorded nonstationary epoch (arrow), whereas the PD2 tracks dimension in time. Only the PD2 shows in (B) a gradient of dimension surrounding a minimum during the control (AIR), whereas both algorithms show the global dimensional increase to a single value following the presentation of a novel odor (1.3 sec epochs were analyzed). Calibrations: 4.6 to 6.4 dimensions.

D2 algorithm lumps all of the variation together and its single value for the whole epoch (arrow) is at the mercy of any nonstationarities that might be in the data.

The lower part of Figure 2 shows bulbar surface potentials of the same type seen in the previous figure that are recorded using an 8 x 8 electrode- array. The D2 and PD2i algorithms were applied to brief 1.3-s epochs recorded just before and after odor presentation. The reason brief epochs were analyzed is because of the requirement for data stationarity in the D2 algorithm. That is, the generator of the activity was required not to change while the data were being sampled; the reasoning was, the briefer the sample the less likely a nonstationarity. The findings (Mitra and Skinner 1992) with both D2 and PD2i were somewhat like those found by Freeman and colleagues (Freeman 1994, 1995), using the RMS amplitudes. The bulb responded globally, by rising to a single higher dimension, and nonspecifically, as any interesting stimulus (e.g., novel odor) was sufficient to produce the effect.

There was something else about the bulb that could be seen only by the PD2i measure - the activity was definitely not global during the resting state. That is, following a novel odor presentation the bulb appeared to organize some of the previously disparate and unrelated gamma-activities into little subgroups that now had their own unique dimension during the resting state. More about this enduring change in the resting state will follow. The point here is that even though the amplitudes, frequencies and phases varied between all electrodes, some surface potentials became spatially uniform in their "jittery" response to the novel stimulus. The global PD2i-response (dimensional increase) was transient, as the bulb quickly disorganized back into spatially separate functional subsystems (i.e., small adjacent subgroups had different PD2i values). It is concluded that the spatial uniformity of the PD2i-response is evidence that previously independent neurons can be temporarily recruited to function harmoniously within a single global system.

The gamma-activity in the primary sensory neocortex may also have such global recruiting and nonspecific sensory characteristics. Recently Gray and associates (Gray and Singer 1987, Gray and Singer 1989, Gray et al. 1989) and Eckhorn and associates (Eckhorn et al. 1988, 1993) showed in the visual cortex of mature cats that an alignment of phase occurs among the gamma-activities of all cortical columns that have the same line-orientation sensitivity. This occurs when a moving object is introduced into only one small receptive field. That is, nonstimulated sensory columns of a specific line-orientation sensitivity responded to a second stimulus to their own receptive field by aligning their evoked gamma-activity phases to the gamma activity evoked by the first stimulus. The timing of the sensory evoked gamma-phase is not related to the sensory process of the evoking stimulus, but to the common gamma-phase for that particular type of orientation column. This nonsensory-related phase control, called "response synchrony", is apparently physiological, as no anatomical substrates have been found that could span the 7-mm distances between separate columns of the same specific line-orientation sensitivity.

It is known from developmental studies that the visual environment in which a kitten is raised generally determines in the adult what columns will have what feature-sensitivity (e.g., what line-orientation sensitivity, what ocular-dominance sensitivity, etc.). How this experience-induced control of a functional unit's firing behavior is related to the nonspecific phase-alignment that occurs at the gamma- frequencies is not yet understood (Gray and McCormick 1996). The response-synchrony, however, or something like it, has been hypothesized (Gray and Singer 1989) to underlie what is called, stimulus binding (Milner 1974).

Stimulus binding is a theoretical construct in which raw stimulus attributes are thought to be bound together physiologically to create a perceptual object or image (von der Malsburg and Schneider 1986, Singer 1993). Although there are not yet any systematic physiological studies to support this idea, it has appeal because it could be a way to integrate specific sensory features, like line-orientation, into a perceptual object, like my food dish (Gray and Singer 1989). If this is so, then response synchrony should be modifiable by short-term associations (classical conditioning) as well as those long-term ones related to feature detection (line-orientation).

Recently Skinner and Molnar (1999a,b) showed that during the 500 ms that follows a stimulus presentation, the gamma activity is not phase-locked to the the stimulus and manifests a dimensional reduction, that is, if the stimulus is reinforced. But the gamma activity is phase-locked and does not change in dimension if the stimulus is unreinforced. It thus appears that event-related uncoupling of the gamma-activity to the evoking stimulus is combined with a dimensional reduction in the "jitter", and both effects are produced by the classical conditioning. What is very interesting about the comparison of the two processes is that 500-ms is also the usual duration of the gamma response synchrony (Gray and Singer 1989) that occurs among functional units with similar feature properties.

PSYCHOPHYSIOLOGY OF GAMMA-BAND ACTIVITY

The psychophysiology of the gamma-band activity recorded in humans underscores its importance in perception. Although spatially smeared by the scalp, the cortical gamma-activity evoked by a meaningful word is found to be greater in power than that of a nonsense word (Lutzenberger et al. 1994). This result suggests that the less resolved gamma-activity may still reflect the ongoing process by which meaning is established. In the frontal lobes gamma-power is increased by as much as 50% during a task in which the subject is trying to make sense of a paradoxical input (Basar-Eroglu et al. 1996). During a speed reaction task gamma-power is increased in the fast responders relative to the slower ones (Desmedt and Tomberg 1994). Interestingly all of these gamma-potential phenomena have been found to be consistent with the logical requirements for detecting and studying stimulus binding (Desmedt and Tomberg 1994, Joliot et al. 1994). Thus the understanding of the neurophysiological mechanism(s) underlying the cortical gamma-band potentials is fundamental to the study of the higher cognitive processes in the brain.

NEURAL REGULATION OF CORTICAL GAMMA-BAND ACTIVITY

In the olfactory bulb model the integrity of circuits outside the bulb is required for the generation of its 20 to 70-Hz activities (Gray and Skinner 1988). Similarly the isolated cortical slab does not spontaneously show any gamma activity. Although some neurons in the upper layers of the cortex have membrane properties that may tune them for gamma-oscillations (Gray and McCormick 1996), they do not seem to show this activity unless coaxed by outside input. So where are the cortical inputs coming from to drive the cortical gamma-band activities?

Pedroarena and Llinas (1997) have shown in brain slices that the thalamocortical neurons are capable of gamma-band oscillations (Ca-channels in dendrites), but only when their membrane potentials are rather non-physiologically depolarized beyond -45 mV. Blockade of a thalamic relay nucleus does not prevent its stimulus-evoked gamma-response from occurring in its primary sensory cortex (Brett et al. 1996). So, the pathways that drive the cortical gamma-activity must pass through pathways other than the classical thalamocortical radiations.

Regulation of sensory systems during attentive behavior was studied in cats by Skinner and Lindsley (1967). The results suggested that the nonspecific systems, that is, the midline and intralaminar thalamus in combination with the mesencephalic reticular formation, were involved in the regulation of evoked-potential amplitude in the sensory cortices during selective perception. As shown in Fig. 3A both the frontal cortex and mesencephalic reticular formation (MRF) were found to converge anatomically at the rostral pole of the thalamus and exert their effects upon the thalamic reticular nucleus (ThR), a thin perithalamic shell which contains neurons found to exert inhibitory control over the ascent of sensory information through the thalamic relays (Yingling and Skinner 1975, Skinner and Yingling 1977).

The same convergent input that controls the thalamic gating of sensory input was also noted to control the cortical alpha desynchronization generally associated with arousal and attentional behaviors (Skinner and Lindsley 1967, Yingling and Skinner 1975, Skinner and Yingling 1977). That is, a single system seems to control both the specific sensory evoked potentials and the nonspecific synchronous activities. An important observation was that the ThR cells fire irregularly in the range of the gamma frequencies during EEG desynchronization, but show bursting behavior at the same mean level of firing during the alpha rhythms (Steriade and Wyzinski 1972, Yingling and Skinner 1975).

Survival behaviors occur during intense alpha desynchronization (alerting, attention, orientation). The focus of Natural Selection that led to the rapid encephalization of the forebrain (frontal lobes) was examined during the 1930's, and it was concluded that the focus was an "orchestrator" that simultaneously regulated both the sensory input channels and the autonomic output channels during a moment of crisis. More recent work on the joint sensory and autonomic regulations during attentive behaviors (and alpha-desynchronization) supports this early hypothesis. Figure 3B summarizes these studies and shows that indeed there is simultaneous regulation of the ascent of sensory input and the descent of autonomic support by the frontal cortex following presentation of a meaningful stimulus event.

More recently a concrete connection has been made by Steriade and associates (Steriade et al. 1996a,b) between the cortical gamma-band activities and the nonspecific thalamo-cortical and mesencephalic-reticular systems. This clarity came through the use of intracellular recordings that showed both action potential firings and membrane oscillations in association with the EEG. Activation of the mesencephalic reticular cholinergic system potentiates the occurrence of finding a cortical cell firing and oscillating at the gamma-band frequency, and it enhances the gamma-activity in marginally rhythmic neurons. The cortical desynchronization, including that low-voltage high-frequency activity seen between alpha-spindles of various sorts, was found by these intracellular studies not to be a cessation of the alpha waves, but a replacement by the irregular gamma-band activities. Thus the term, EEG desynchronization, which is traditionally associated with attentive perceptual behaviors, should be replaced by gamma oscillation.

Three alpha-activities (spontaneous spindles, recruiting responses, barbiturate spindles) were originally used by Magoun, Lindsley, and Jasper in the 1950's to delimit physiologically what they thought were the boundaries of the nonspecific thalamo-cortical system (Magoun 1963). The term unspecific was carefully used in such a way as not to be confused with the term nonspecific. Nonspecific meant that a neural response could not be related to any specific sensory features of the evoking stimulus. For example, a novel stimulus of any sensory source would nonspecifically arouse a sleeping cat and desynchronize the alpha activity. In contrast, unspecific meant a response in a primary sensory neuron that could not be tied to its specific sensory or labeled-line attributes. Such a cell was thought to function according

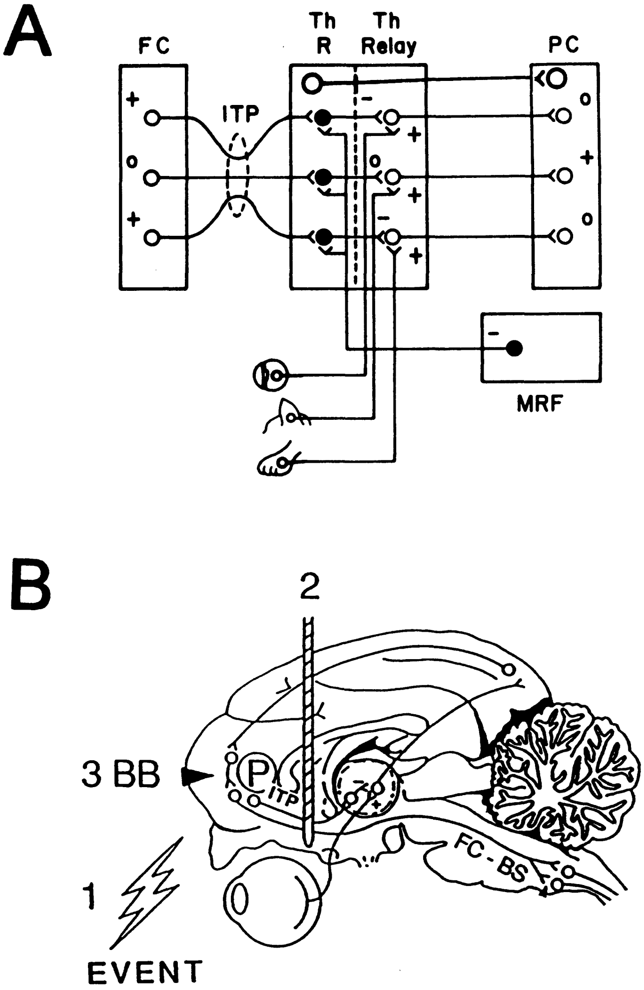

Fig. 3. A focus for Natural Selection: thalamic gating of the ascent of sensory information and autonomic regulation by the frontal cortex (FC) and mesencephalic reticular formation (MRF). A, thalamic Gating System. Descending projections from FC travel through the inferior thalamic peduncle (ITP) project upon the thalamic reticular neurons (ThR) in the rostral pole of the thalamus; these same ThR neurons receive highly-bifurcated terminals from cells in the MRF that are inhibitory. The ThR cells are themselves inhibitory and project specifically to the thalamic relay nuclei (Th Relay) to control the ascent of specific sensory information to primary cortex (PC). Compiled from Skinner and associates (Skinner and Lindsley 1967, Yingling and Skinner 1975, Skinner and Yingling 1977). B, event-related cortical responses and autonomic regulation. When a meaningful stimulus event (1) is presented to a conscious animal, it evokes outputs from the frontal granular cortex over two important pathways (2). One pathway (ITP) projects to the rostral thalamus to control the thalamic reticular cells during attention to the evoking stimulus and the other (FC- BS) projects to the brainstem to regulate autonomic responses in anticipation of behaviors the stimulus might release. Analysis of the cortical process (P) shows it to be beta-adrenergic (3), as meaningful stimuli activate the beta receptors and their second messengers (norepinephrine-release, cyclic AMP accumulation), which in turn reduces a slow outward potassium current (extracellular K activity reduction) thus causing a slow membrane depolarization and an extracellular event-related slow potential. Such a beta-adrenergic mechanism is known from in vitro slice preparations to regulate synaptic efficacy (LTP, LTD). All of these electrochemical events occur in association with the event-related increase in dimension of the cortical gamma-activity. Adapted from Skinner (Skinner 1984).

to the doctrine of "specific nerve energies," yet was involved in more than just simple sensation. This old distinction may have important implications for current thoughts about feature detectors and stimulus binding, as the same cell may be involved in both the specific and the unspecific functions of, say, line-orientation.

The term unspecific was first used by Lorente de No to describe early anatomical data from the primary sensory cortex. Lorente de No had observed in Golgi-stained material, as illustrated in Fig. 4A, that the specific sensory relay neurons projected topographically to short-axon stellate cells in the middle layers of their respective sensory cortices. The terminal endings (e.g., from ventralis posterior thalami, VP) were bushy and suggestive of redundant synaptic contacts to assure the safe transfer of sensory information. The small stellate neurons (e.g., to the left of the bushy arbor) projected to nearby pyramidal cells (e.g., to the left of the stellate cell). The pyramidal cell was a different type of neuron with long apical dendrites (i.e., ones that form an open--field). The apical dendrites all extended to the surface layers. The pyramidal cell axons he noted projected either to other parts of the cortex or to the thalamus.

The upper portion of the apical dendrites, piercing the first three cortical layers, received inputs only from non-bushy and rather sparse axon terminals, as shown in

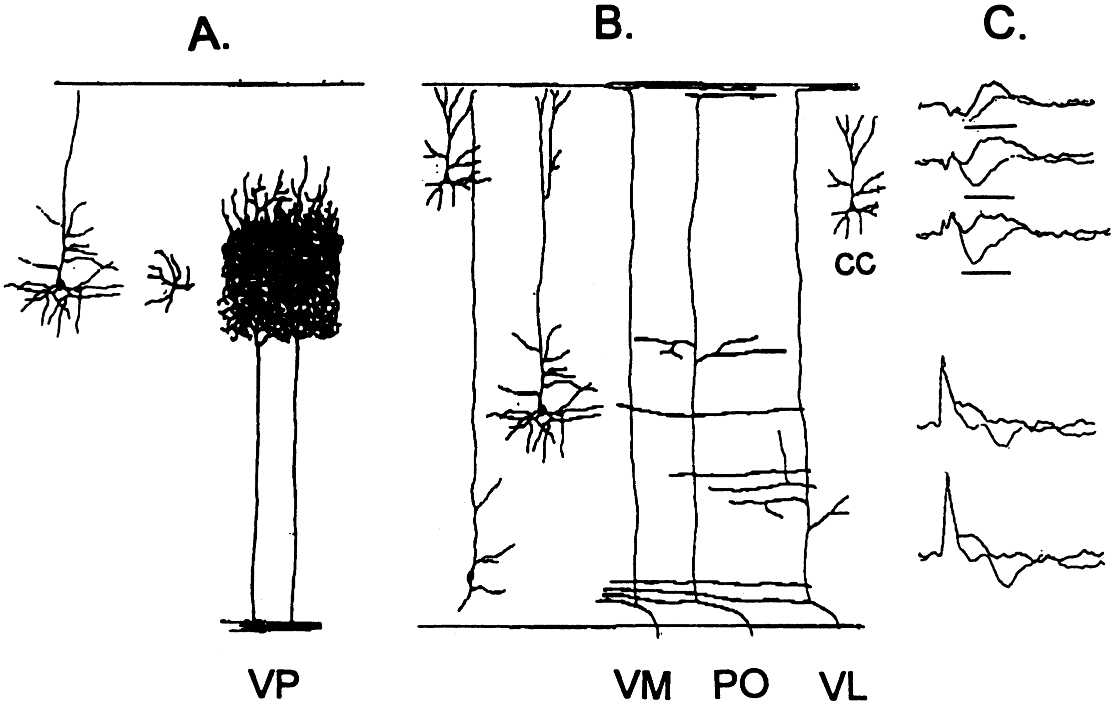

Fig. 4. The "unspecific" neocortical sensory system receives projections from the "nonspecific" thalamocortical association system. A, Specific Sensory Component. This shows the drawings of Lorente de No in which a highly arborized axon terminal from a thalamic relay cell projects onto a short-axon stellate cell, which in turn projects onto a long-axon pyramidal cell. B. Unspecific Sensory Component. This shows drawings of pyramidal cells by Lorente de No, each of which has an apical dendrite that extends to the upper cortical layers. The axon terminals from identified rostral and midline thalamic nuclei (VM, PO, VL) are shown from Herkenham's studies to innervate the upper three layers of the cortex, presumably making synaptic contacts with the apical dendrites that enter this region; the specific sensory neurons to not project into this upper region. Adapted from (Herkenham 1979, Steriade and Llinas 1988). C, event-related potentials recorded from the different cortical lamina of the primary auditory cortex in response to a tone reinforced by electric shock. The aversively conditioned responses (large ones) are compared to those observed during habituation (8 trial averages, each). Only the traces from the upper three layers showed statistically significant differences (lines at bottom indicate $P<0.01$). The upper three layers constitute the domain of the "chattering cells" (CC), pyramidal cells which show gamma-frequency responses. The upper layers are also the domain of the distal portion of the apical dendrites of all the other pyramidal cells in the area. Adapted from (Molnar et al. 1988).

Fig. 4B. These sparse terminals did not come from the specific sensory nuclei in the thalamus. He did not know what their origin was, but he speculated that they served an unspecific sensory function.

The source of the unspecific terminals remained somewhat elusive. Finally, in definitive studies using horseradish peroxidase and labeled amino-acid uptake, Herkenham (Herkenham 1979, 1986) showed that it was projections from neurons exiting the rostral pole of the thalamus that innervated the upper three layers of the unspecific system. The origin of these fibers was the midline and intralaminar nuclei, as well as some nuclei in the rostral and ventral thalamus. Thus the nonspecific system of Magoun, Lindsley and Jasper turned out to be the source of the unspecific projections of Lorente de No.

Figure 4B shows the sparse terminals coming from the rostral and midline thalamic nuclei (VM, PO, VL). As illustrated by the three terminals at the right, they provide inputs to the upper dendrites (surface layer) in their unspecific pyramidal connections, but they also have some connections to other dendritic layers where the cell bodies of various types of pyramidal cells are located (left 3 neurons in Fig. 4B). These recipient pyramidal neurons are the same ones activated by the sensory thalamus *via* the stellate cells that give rise to sensations, according to the doctrine of "specific nerve energies," yet they have unspecific inputs on their more distal apical dendrites that come from structures with neural responses that are known to be completely nonspecific. The implication of this finding for the understanding of a sensory mechanism, say, line-orientation, is that the same neuron that gives rise to the sensory feature is also involved in a nonspecific mechanism of some kind that projects to unspecific upper-dendritic terminals. Could this nonspecific/unspecific system be the one related to stimulus binding?

Basar-Eroglu et al. (Basar-Eroglu et al. 1996) and Varela (Varela 1995) have recently argued that the gamma-system, like the one underlying the alpha activities, is holistic and widely distributed. Based on the above mentioned works of both the Skinner and Steriade laboratories, showing gamma-firing and alpha-bursting in the same cells, the two systems may turn out to be the same one. Similarly mechanisms underlying feature-detection and stimulus-binding may share neurons and have functions that are qualitatively not quite so separate as different names and histories might imply.

The ThR cells adjacent to the thalamic relay nuclei play a pivotal role providing the inhibitory gates on the ascent of sensory information to sensory cortex. But what drives them at the high gamma frequencies? A small extrathalamic cryoblockade (< 3-mm in diameter) when made bilaterally in the anterior thalamic radiations between the rostral thalamus and frontal lobes (i.e., in the inferior thalamic peduncle, ITP) causes the ThR neurons to become completely quiescent. The same effect results from complete ablation of the frontal cortex. During either type of blockade the ThR neurons cannot be driven by thalamic stimuli to the midline and intralaminar nuclei, stimuli that would normally evoke the bursting pattern associated with recruiting responses (Skinner and Lindsley 1967, 1971). Similarly the ThR cells cannot be driven when the mesencephalic reticular formation is stimulated (Yingling and Skinner 1975, Skinner and Yingling 1977), nor can recruiting responses be produced in either the cortex or the thalamus (Magoun 1963).

These extrathalamic influences on ThR activities are important, for they present a completely different picture of how the neurons function than that understood from *in vitro* work in the thalamic slice preparation. In the slice, the ThR cells can be activated by stimulating the thalamus (Steriade and Llinas 1988). This return of ThR driving that results from the surgical slicing, however, is likely to be due to removal of some important mechanism that normally prevents the driving. For example, if all cortex is surgically removed, after removal of the frontal cortex (which blocks recruiting responses), then thalamic recruiting responses can once again be evoked (Valesco et al. 1968). But in the absence of the surgical isolation, the thalamus does not directly activate the ThR neurons. They are under some more powerful controller. That is, the thalamo-ThR route is simply not powerfully functional if the brainstem and neocortex maintain their attachments to the thalamus. So what is this extrathalamic controller of ThR cells?

Golgi material studied by the Scheibels (Scheibel and Scheibel 1967) shows collaterals from frontocortical--mediothalamic neurons branching off and presumably making synaptic contacts in the rostral pole of the thalamus. This is the location of the most thickened portion of the ThR shell. The ventral leaf of the mesencephalic reticular formation, which projects to widespread regions of neocortex, also passes through this rostral pole and gives off branches, pari passeu. The rostral thalamic cells project to the upper apical dendrites of sensory cortex, as Herkenham showed (Herkenham 1979, Steriade and Llinas 1988), that is, along with other axons from the midline and intralaminar nuclei. The projection of this rostral region onto the rest of the ThR shell uses specialized connections called dendritic bundles (Scheibel and Scheibel 1967). These connections make a large tight synaptic junction that may even pass electrotonic currents from one cell to the next.

In the cortex the long-dipoles create the ERP's that occur within a few hundred msecs after the presentation of a meaningful stimulus. Figure 4C shows ERP's recorded from different layers of the auditory cortex of the conscious cat. The cat was first habituated to a tone and then conditioned to it using cutaneous shock as the reinforcer. Only the upper 3 layers (i.e., the unspecific layers of Lorente de No) showed responses with statistically significant changes in the ERP's due to the conditioning (underlining). The small amplitude traces show ERP's to the habituated tone; the larger ones to the conditioned tone; the underlining shows where the differences are significant ($P<0.01$). This same zone in the upper three layers is also where the chattering cells reside that manifest the gamma-activity (CC).

In conclusion it appears that there is a complex neuropil anatomically structured in the rostral thalamus that physiologically integrates inputs from the frontal lobes, the mesencephalic reticular formation, and the nonspecific thalamic nuclei. This center provides holistic regulation of both alpha and gamma oscillations in the cortex. This center also appears to project upon the sensory systems *via* the thalamic gates and the unspecific upper cortical connections. This complex sensory regulation, sculptured by the forces of evolution along with autonomic regulation, may provide an important clue about how the higher cognitive processes (e.g., selective perception and stimulus binding) may be interrelated.

SELF-ORGANIZATION IN A SIMPLE NEUROPIL

We now turn to a discussion of how the changes in a neuropil might arise during one of the higher cognitive processes. In the bulbar model system they appear to occur in relation to the transient rise in global dimension. Plasticity of synaptic throughput, as seen in the *in vitro* slice preparation, is also presumably going on at this moment. For example, the time separation between the occurrence of an EPSP and the backfiring of an action potential into the apical dendrite, as shown by Magee and Johnston (Magee and Johnston 1997) in hippocampus and Markram et al. (Markram et al. 1997) in neocortex, determines whether long-term potentiation (LTP) or long-term depression (LTD) occurs. When the timing separation is in the normal range for producing LTP, then EPSP enhancement occurs, but if the dendritic action potential occurs at too long or too short a delay or it comes before the EPSP, then LTD results. It is the unspecific projections, at least in the neocortex, that likely determines this timing and thus the information throughput. The timing for LTP and LTD of course are at the gamma frequencies.

Even if modification of synaptic efficacy is fundamental in learning and perception, it does not explain how the neuropil, as a mass of neurons with billions of synapses at work, becomes organized during the process. Who or what determines whether LTP or LTD of the synapses will occur? If this organization is imposed from outside the neuropil, then an infinite regress arises (i.e., the homunculus regress). If it comes from within, then how is this done? What is becoming increasingly noticed in many physical systems, mainly in nonlinear ones, is that organization can arise from within. That is, nonlinear systems may self-organize according to some simple laws of nature (Kaufmann 1993).

Self-organization in physics is often viewed quite differently from that of Darwinian adaptation. In a physical model presented by Haken (Haken 1983) there is envisioned to be a control variable, which, at a certain point in its trajectory, leads to the synergetics of the elements within the system and thus to an orderly dynamics. For example, in the case of a pot of boiling water, the control variable is the heat of the flame; at a critical value the water molecules instead of zipping around rather randomly suddenly are organized (self-organized) into smooth convection cells. A visible geometric pattern forms at the top of the water that is caused by the intercalated mix of small upward and downward convection cells. The system has suddenly become orderly due to the dynamical synergy of the molecules. During the organized synergetic state the degrees of freedom of each water molecule suddenly becomes quite reduced. The molecule no longer has the same freedom move in any direction because of the convections. A physical model presented by Prigogine (Prigogine 1980) envisions precipitous state-transitions within the system that cause sudden large-scale changes in behavior. For example, the adding of but one more small grain of sand to a tall conical pile may cause a transition of the system from stability to that of a small, medium or large avalanche. In this model something else besides the synergy of the smallest units causes the system to change. It is the complex vector sums of the weight of the sand-grains and their respective supports that determines, in the subcritical state, when a cascade will or will not start and how large or small it will be. The degrees of freedom of the sand grains certainly increase and decrease considerably during the state-transitions and their self-organized resolutions.

Synergetics and state-transitions are not conceptually the same, nor is either one similar to biological adaptation. Each concept though is associated with a physical phenomenon in which the system appears to self-organize. At least the authors of these models use the term self-organization to describe what they think their models do. The water molecules self-organize into the coherent convection cells; the sand grains self-organize into a stable pile; the species self-organize to fit symbiotically into the niche.

It is the reduction in the degrees of freedom of the dynamics of the self-organizing systems during the synergetic, subcritical or symbiotic conditions that seems to tie them together conceptually. Just as a new species must fit in with others to survive (i.e., it is not completely free), the water molecules must fit together to cause a convection. It is this change in freedom, observed computationally as a dimensional change, that may be a general feature of any self-organizing system.

Such a thought in the past may have been considered foolish, as a system is not supposed to change its dimensions. A nonstationarity in the data stream might arise and suggest that the system has been altered, replaced or converted to another. Stated in different words, physical systems are made of fixed component parts and are not supposed to change the dynamics of their variable space over time. If something untoward happens and the properties of the data change drastically, then this change is considered to be a data nonstationarity, not a property of the system.

To maintain the old dogma, synergetics and state transitions are said to arise from control variables. If the data become quite different, then the control variable did it. In biology, however, we do not say that a control variable causes symbiosis; we look for antecedent causes. But antecedent events do not explain the process any better than control variables do. What is happening is, something in the dynamics occurs that leads to synergetics, state-transitions, and symbiosis.

Nonlinear dynamics and low-dimensional chaos theory promise to explain such complex behaviors in simple terms (Kaufmann 1993). It may be that self-organization is an intrinsic dynamical phenomenon responsible for that simplicity. Let us see if we can demonstrate this biologically. Let us see if self-organization can be observed in association with dimensional changes in two model neuropils.

First, in the olfactory bulb, an example of self-organization is exhibited in the sudden convergence of the spatially-recorded surface-potentials to the same dimensional value (see Fig. 2B, NOVEL). The sudden appearance of the global value suggests that a single system has somehow been put together (i.e., organized). It has been physically constructed from the many spatially separate subsystems that existed previously, each of which had at rest its own dimensional identity.

Let us look at this phenomenon using a simple mathematical model, the Lorenz system. The machinations of the interdependent components of this system will produce a time series at each location where the variable is expressed. These various data streams may look different from one another, but their dimensional dynamics will be the same. This is because there is only one system with its own unique degrees of freedom. It does not matter for the Lorenz generator, which uses three interdependent partial differential equations, whether one calculates the dimension from the dx/dt, dy/dt or dz/dt time series, it will be the same value in all three cases (i.e., a fractional value of approximately 2.06).

The global rise of the spatial dimensions in the bulb suggests that a system, like the Lorenz system, has been suddenly constructed from components that were previously independent of one another and had their own separate degrees of freedom. This global effect is a physiological concept sort of like that of the recruiting response, an activity which grows in size spatially with each pulse to one of the nonspecific thalamic nuclei (Magoun 1963). In the case of recruiting responses, however, the dimension of the activity goes down while the spatial size is increasing. This results because all of the underlying neurons are being brought into a single cooperative synchronization (i.e., the recruited neurons are no longer free, but must fire in concert with the electric pulses). In the bulb, after the novel odor is presented, something causes the tissues to stop functioning independently and to start functioning cooperatively, and this transition is associated with a dimensional increase. The point here is that, unlike the recruiting response, the growth of the spatial size can occur with less order or cooperation being engendered among the elements.

Now let us turn to an even simpler biological model and examine its self-organizing properties in relation to its dimensional dynamics. The isolated rabbit heart contains an intrinsic cardiac nervous system (ICNS) composed of approximately 10,000 neurons that engage in the same afferent-efferent regulations of the heart that are characteristic of the larger autonomic nervous system with its sensors and effectors (Skinner et al. 1996).

The behavior of the heart is simple: it beats rapidly or slowly and strongly or weakly. That is, the total behavior of the heart can be quantified by two variables, one related to its strength of contraction (which is inversely correlated with the QT subinterval of the electrocardiogram) and one related to its pump rate (which is inversely correlated with the RR-QT diastolic subinterval). Thus on a beat-by-beat basis, the net behavior of the heart can be monitored by simply observing the QT and RR-QT subintervals of the electrocardiogram.

The ICSN has sensory afferents that can be stimulated by brief periods of oxygen deprivation, an act which maximally activates both the chemoreceptors and the mechanoreceptors. The time-series of each of the output variables (QT and RR-QT) can be monitored and compared to see if they behave like the variables in the Lorenz system. That is, the temporal dynamics of QT and RR-QT subintervals can be monitored to see whether or not they are the same, and therefore are variables of the same system. Alternatively, like the bulb, they might be observed to have a system-integrity that is stimulus-dependent.

Before proceeding, mention should be made of another common way to examine the dynamics of a system. This method is to observe the attractor. That is, the system dynamics is characterized by the relationship of the output variables, which can be described in time by looking at their multi-dimensional plot. Such a plot would draw out a geometric figure that describes the total behavior of the system over time. For example, the three-dimensional plot of the x, y and z variables of the Lorenz system makes the famous butterfly attractor. If the attractor does not change, then the system is stable.

The attractor can also be reconstructed from its time series. A reconstructed attractor, instead of having axies that are the system variables, is made from a multi-dimensional phase-delay plot of the time series. In this case time does not flow from point to point on the attractor, but is divided up into what are called embedding dimensions and these form the axes for the plot. From the Takens' mathematical proof (Takens 1985) the system-attractor (seen in variable plots) and the reconstructed-attractor (seen in time-delay plots) are found in the limit to have the same number of degrees of freedom or the same correlation dimension (D2). The attractors may have the same dimensions, even though their geometrical shapes may be quite different. If the time-delay, Tau, is chosen just right, then the reconstructed attractor for the Lorenz equations in an embedding dimension of three will look just like the butterfly seen in a plot of the system variables.

The visualization of the attractor provides an important notion of the function of the system. For example, if the variables are plotted and found to make "a line with a negative slope" then, the system is said to have negative feedback and its function is to keep something constant. One can watch the shape of the attractor in time to see if it maintains the same function, which is another way to see if the system remains stationary.

Now how does all of this apply to the ICNS data? Figure 5 shows the results obtained when the surgically isolated heart and its intrinsic neurons are stimulated in vitro by a brief 2-min period of anoxia (arrow). The neurons on the outer surface continue to be bathed in an oxygenated medium, and extracellular recordings show them to stay within normal bounds of activity. Demonstrated in Fig. 5 are the findings that the variables (QT and RR-QT) produce a progression of different attractors (at top) during different subepochs (A-D) and these stimulus-evoked attractor-changes are associated with dimensional changes in the heart-beat dynamics.

During the control period (subepoch A) the attractor is a point. That is, there is very little or no variation in the QT or RR-QT subintervals. During the early period of anoxia (B), a distinct "negative-sloped line" becomes apparent as the attractor. First the line begins, moving to the upper-left, as QT increases from baseline, then after QT peaks, the attractor plot backtracks along the same slope line, and it continues to backtrack as QT decreases below baseline (the "spiky" activity is artifactual due to occasional Q-wave dropout). All through the B period the output variables locate points on the same "negative-sloped line attractor." The function would appear to be "maintenance of cardiac output," for when contractility decreases (i.e., QT increases), pump-rate increases (RR-QT decreases). This inverse relationship keeps the flow of blood pumping along at a constant level.

Seconds later, though, at the end of the B interval and beginning of the C interval, the attractor suddenly makes a right angle turn (attractor C). The new attractor indicates a new function. It is now a "line with a positive slope." The new function is "conservation of cardiac energy," as the subintervals both increase with time (i.e., the heart rate slows and the beat weakens). The D interval is after a 2 min time gap, and again another attractor and another function are indicated.

Because of the nonstationary changes in the subinterval attractors seen in the QT and RR-QT data, the correlation dimension algorithm (D2) cannot be used to

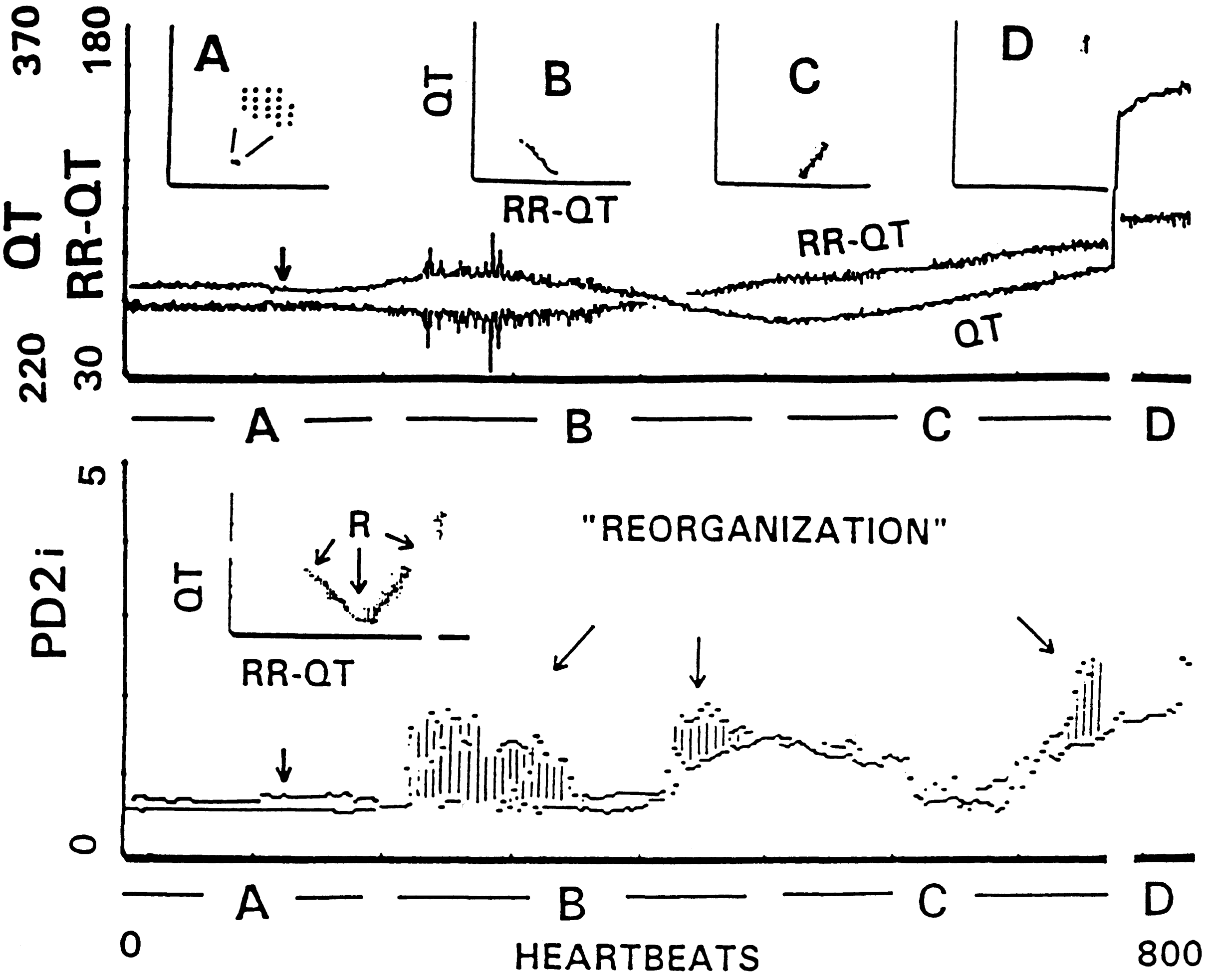

Fig. 5. An example of "self-organization in a simple model system, the Intrinsic Cardiac Nervous System. This system has two behaviors; it can cause the heart to beat more strongly (inotropy) or cause it to beat faster (chronotropy). The QT subinterval of the electrocardiogram is inversely related to inotropy and the RR-QT subinterval to chronotropy. This figure shows the temporal relationship of the PD2i's of the QT and RR-QT data series to the attractor plots of QT vs. RR-QT during the control (A) and experimental(B,C) intervals that follow a strong stimulus (oxygen deprivation, arrow) which is known to stimulate both the mechano- and chemo- receptors. Upper. QT and RR-QT intervals, with insets showing plots of QT vs RR-QT for each of the A-C and D intervals (7-fold magnification is also shown for A); QT and RR-QT scales at left apply to the insets. Lower. Temporally corresponding PD2i's for QT and RR-QT data; the RR-QT subinterval trace is offset slightly so that the baseline will not completely overlap that of QT; periods indicated by vertical-line shading are when PD2i's of QT and RR-QT are dissimilar; each shaded region precedes a change in the QT vs RR-QT relationship as indicated by the B, C and D attractors (insets) at the top and collected into a single inset in the lower panel. The shaded regions are interpreted to indicate a "reorganization" in the system, as the subinterval plots emerge with a changed attractor. The attractor of the variables changes from a point attractor (A), to a negative-sloped line attractor (B), to a positive-sloped line attractor (C). Adapted from Skinner et al. (Skinner et al. 1996).

analyze the two time-series (i.e., D2 requires data stationarity). The PD2i was therefore employed, as it was developed to deal with data nonstationarities that invariably occur, from moment to moment, in most biological data (Elbert et al. 1994). Now, how does PD2i relate to the attractor changes?

As seen in the lower panel of Fig. 5, most of the time during the B and C periods the time-dependent PD2i's of the output variables show the same values. This finding suggests that the two subintervals are indeed variables of the same system. There are exceptions, however, and these dissociations (shaded areas) occur just before the abrupt changes in the attractors. The brief dissociations are described as periods of reorganization, because, (1) the dimensions of the output variables are no longer the same (i.e., the system has dissociated), and (2) when the system recovers, and the variables once again have the same dimensions, a new attractor is exhibited (Skinner et al. 1996). Furthermore the new attractor expresses a new function. Something in the neuropil has changed!

These ICNS experiments clearly indicate that an experience-dependent modification is going on in the underlying neuropil (e.g., the system that controls the QT and RR-QT physiology). After this reorganization is achieved, unitary dimensions are again observed in the output variables. That is, after the neuropil has self-organized, the variable measures again become interdependent, reduce in dimension, and are of the same system. This reduction in dimension may not be to the same value previously observed for the two variable measures (e.g., subepoch C). The convergence to the same dimension though is a sign that once again the measures are variables of the same system. They are again participating in the same system and again they have a simple relationship, but this time their relationship is different, for the attractor has changed and a new function has emerged - that is, a self-organized adaptation has occurred.

Presumably the dimensional effect seen in the ICNS dynamics employs one or more of the mechanisms underlying cellular neuromodulation (e.g., long-term potentiation of synaptic efficacy; second messenger chemistry; beta-receptor sequestering, etc.). Relevant to this proposition is the observation that repeated experiences of anoxia results in a plasticity of response (a phenomenon called, preconditioning, which protects heart cells from damage) that involves a G-protein with a subunit sensitive to pertussis toxin (Thornton et al. 1993). More recent studies (Hashimi et al. 1998) show that the mechanism is by way of adenosine A1-receptor downregulation. This alteration in the heart, like LTP or LTD in the brain, is a change in the gain of the signal pathway.

In summary, the increase in dimension of a time series recorded from a single location in biological tissue can be a sign of the spatial recruitment of additional numbers of neurons into the system (olfactory bulb model), or it can be a sign of dissociation of the system variables (ICNS model). These effects may be produced by two completely different mechanisms linked only because they are associated with an increase in complexity of the underlying system, or they may be related. Only time and observation will tell what is the case. A dimensional reduction, on the other hand, can be either a sign of the spatial breakup of the system because the evoking stimulus is no longer interesting (bulb) or it can be a sign of a renewed cooperativity among the elements of the system (ICNS). In both cases the spatial and dimensional changes appear to be related to a newly self-organized function.

COOPERATIVITY

Mayer-Kress and associates suggested that the dimensional reductions seen in biological systems may be the result of cooperativity among subsystems competing for control of the same output (Mayer-Kress et al. 1988). This is like a director's baton creating harmony among singers in an unruly choir. This interpretation has been used in several recent studies of event-related brain potentials, as mentioned above (Skinner and Molnar 1999a,b).

Although such cooperativity may account for the dimensional reduction in the dynamics of the ICNS, after the system has become reorganized, and even in the sensory evoked potentials, after they are conditioned, it does not account for the dimensional increases seen spatially in the bulb. The dimensional increase there is likely due to the increased complexity of the larger spatial system, which now has many-fold additional members (Fig. 2B). The subsequent dimensional decrease may thus be associated with the breakup of the larger choir back into smaller subgroups, each with its own director. The point here is that the bulbar type of recruiting has opposite spatio-dimensional effects to that observed for other systems, including the classical recruiting response of the nonspecific thalamic structures.

The class of dimensional measures, D2, D2i and PD2i, is based on similar nonlinear deterministic models and these measures may be inherently more sensitive to the output of a biological system than those based on a linear stochastic model, such as the standard deviation, mean, or power spectrum. This inherently greater sensitivity may arise because the underlying neuropil functions through causes and effects (i.e., it is a deterministic mechanism not a stochastic one). This proposition is supported by recent findings (Molnar et al. 1988, Skinner et al. 1991, 1993, Vybiral and Skinner 1993) which show that the PD2i has superior sensitivity compared to various stochastic measures, that is, when all algorithms were applied to the same biological data set.

The nonlinear deterministic measure, the PD2i, was shown above (Fig. 2B, PD2, AIR) to sense a gradient of cooperativity among the functional units of the bulb that could not be detected by either a stochastic measure (RMS amplitude) or by the lumped dimensional measure (D2). The reason the changes in the degrees of freedom detected by the PD2i may be a better quantifier of the event-related responses of the brain potentials is that a change in dimension is a nonstationary event and its occurrence is time-dependent. Only the PD2i addresses these features of a signal that might be detected in the data stream. The changes in the amplitude, frequency, phase, mean, variance or lumped-dimension all require data stationarity. These measures are therefore not an appropriate for the transient nonstationary biological signal. The choice of the right measure, and its attendent increase in sensitivity, enables observation of previously hidden phenomena, such as the gradient of resting dimensions seen in Fig. 2B (PD2, AIR).

The global response that occurs transiently within one gamma-system (e.g., the olfactory bulb) may occur within another (e.g., the neocortex, for which the bulb is a model). If indeed a global spatial dimension is found in the neocortical tissues in response to a meaningful sensory stimulus, then its spatial and temporal relationships with the physiological phase-alignments (i.e., gamma--activity) of the feature detectors would be of clear interest. That is, the cortical columns of a specific sensory type (e.g., a specific line-orientation sensitivity) do seem to be interconnected globally (Eckhorn et al. 1988, 1993, Gray and Singer 1989, Gray et al. 1989), and maybe these are further interconnected with other sensory detectors associated with the perception of an object (e.g., those underlying color perception, ocular dominance etc.). That is, the response synchrony seen among orientation columns might also extend to color units, ocular dominance units, and so on for the perception of a given stimulus object.

How the neurons are recruited to operate in such a global system would also be of interest. The nonspecific thalamocortical system, which has already been shown to control the sensory neurons during selective perception (via the thalamic gating system, Fig. 3A), may play a major role in this recruitment. The unspecific projections to the upper apical dendrites suggest that these nonspecific influences on the unspecific sensory terminals (Fig. 4B) have an important modulatory role on sculpturing the LTP and LTD that govern synaptic throughput in sensory cortex. This sculpturing of the activity of the primary cortical pyramidal cells may self-organize from within the specific and nonspecific sensory systems combined, because once the acquisition is complete and the attractor is formed, the spatial domains of activity diminish and the degrees of freedom reduce. Dimensional reduction is the hallmark of a self-organizing system.

PERSISTANT PHYSIOLOGICAL CHANGES DURING MEMORY (THE ENGRAM)

In both of the above biological models the dimensional changes are transient. Mishkin and associates (e.g., Mishkin and Murray 1994) have argued that for a physiological activity to be a candidate for the engram, that is, the physical representation of a memory, it must have a persistence that spans the period between information storage and recall. Neither of these transient dimensional changes is therefore a candidate for the engram-type of memory process. But the bulbar model does have such a candidate phenomenon, at least for short-term memory. It is a continuous dimensional increase and/or decrease that occurs in a small predictable region and persists over trials.

Figure 6 shows data recorded from the olfactory bulb during the acquisition of habituation, a simple form of learning (Mitra and Skinner 1992). During the control periods (column A2), a smooth spatial gradient of PD2i's with closed contours is observed within the 64--electrode array. The minima (asterisk pointer) is seen to be smoothly approached spatially such that the contours of equal dimensions resemble a graded set of rings like those forming the inside of an egg-cup. After the novel odor is presented, the "egg-cup" contours transiently

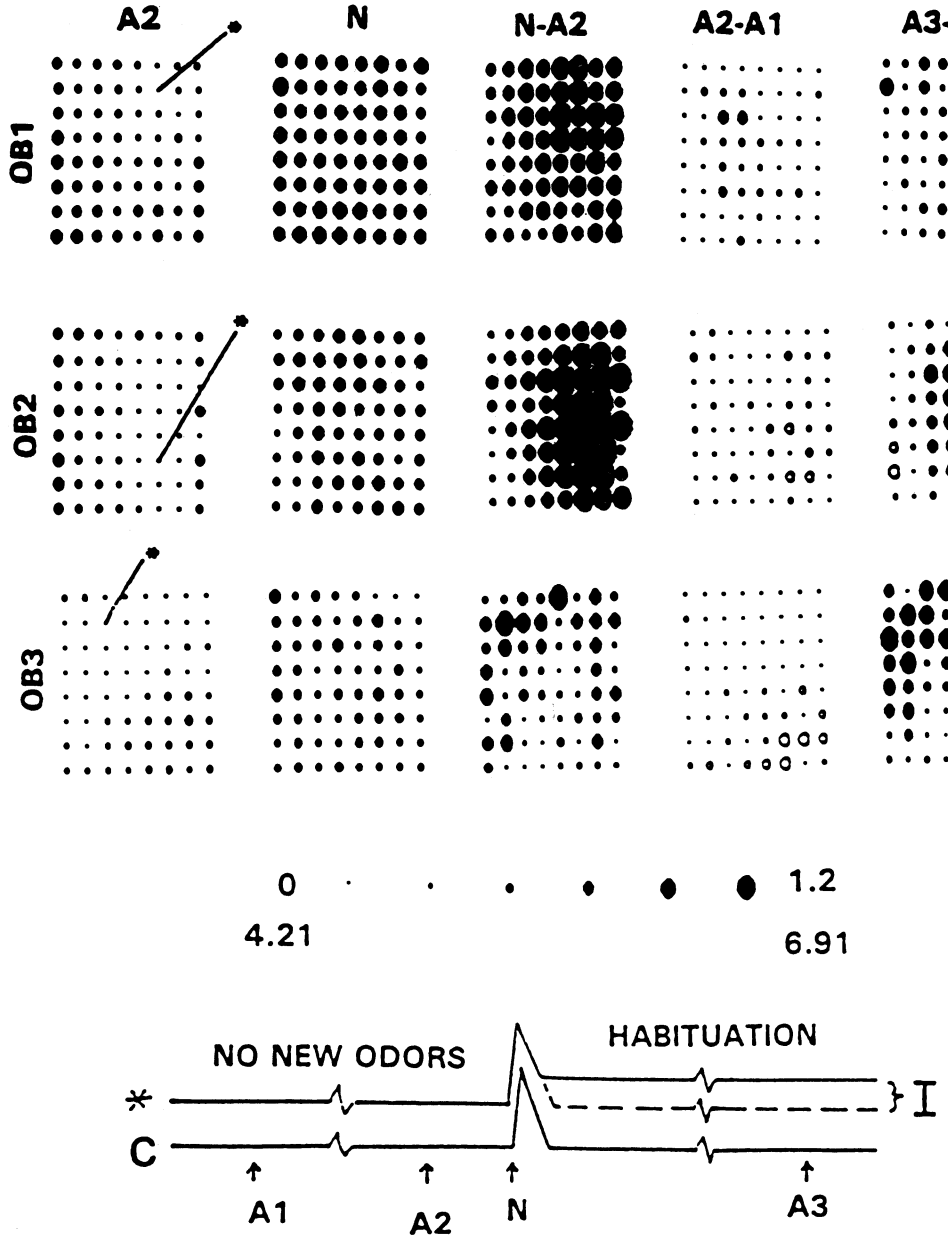

Fig. 6. Dimensional alterations of the gamma-activity (surface potentials) in the olfactory bulb model of neocortex. This figure shows the "egg-cup" dimensional gradients (* under A2 column) determined from array recordings of surface potentials in the conscious rabbit during resting control (column A2) and during control, but after modification by new acquisition of habituation (column A3-A2). Spatial-array surface-potentials (8 x 8) were recorded for 1.3 s epochs and their mean PD2i's determined (scale shown below arrays). Results are shown from 3 subjects (OB1 - OB3). At the bottom is a diagrammatic time-line that indicates when the dimensional arrays were sampled. PD2i's (horizontal lines) are shown for individual electrodes, one from the "egg-cup" minima (*) and one from a surrounding control (C). A1: first room-air control; A2: control taken later, with no new odors having been introduced into the nose-cone, only the highly-habituated discriminated odor; N: immediately after novel odor; A3: control taken after habituation is complete (after failure of novel odor to evoke sniffing behavior). The N-A2 column shows a subtraction of the gradients to demonstrate that the transient dimensional increases to the uniform "high-plain" level were largest in the region of the minima seen during the control. A2-A1 shows that no change occurs over a period with no acquisition of odor habituation. A3-A2 shows that an enduring dimensional increase (I) occurs in the region of the minima after acquisition of odor habituation. Calibrations: 4.6 to 6.4 dimensions. Adapted from Mitra and Skinner (Mitra and Skinner 1992).

converge to the global "high-plain" of a single contour (column N). It is the egg cup pattern seen during the resting state that manifests the persistent dimensional change associated with the learning and memory. The minima moves to a new location, but only if new learning occurs. The following describes the experimental paradigm that is outlined schematically at the bottom of Fig. 6.

The novel odor was presented repeatedly in a discriminant odor-habituation paradigm (i.e., the novel odor trials were intermixed with those of a highly-habituated discriminated odor). Over habituation trials to a specific odor, a change began to be apparent in the egg-cup minima observed during the resting control. The dimensions near the bottom of the egg-cup changed in such a way that the minima began to be displaced to a new location. If no new odors were presented during habituation (i.e., other than the discriminant background stimulus), then the increased PD2i's at the previous spatial minima persisted between trials and so did those at the newly developing minima.

This spatial dimensional change is best observed in comparing the A1, A2 and A3 arrays (A = air as the odor). A2 minus A1 does not show much change, because no new odors were introduced between them (see bottom); A3 minus A2, however, shows the dimensional changes that can be attributed to the new learning (i.e., habituation of a new odor). Although these dimensional increases and decreases reflect physiological activities that span the time gap between memory storage and recall, they can not represent the specific sensory aspect of a stored engram. This is because the relocation of the acquired egg-cup minima could be altered once again by additional habituation of additional odors. That is, the location of the minima is not related to any specific odor. The enduring engram is therefore nonspecific and is seen as the persistent dimensional changes illustrated in the right hand column (A3-A2). This single minima seen within the window of the electrode array may represent a composite of all specific olfactory memory in a neuropil that is constantly undergoing self-organization during the acquisition of new information.

SUMMARY AND CONCLUSIONS

The long-term objective has always been to understand how large masses of neurons in the brain process information during various learning and memory paradigms. Animal models are required to explore fully the structural, physiological and neurochemical bases. Both time- and space-dependent processes have been identified recently through computer-based analytic quantifications of event-related, extracellular, cerebral potentials (Figs. 1 and 2B). New nonlinear analyses have been introduced (Fig. 2A) that presume that the fine-grain variation in the signal is determined and patterned in phase-space. These latter algorithms appear to be more sensitive to the deterministic data variations than those that presume the variations are stochastic noise (Babloyantz 1990, Elbert et al. 1994, Pritchard and Duke 1995).

Gray and McCormick (Gray and McCormick 1996) observed that the neurons in the primary visual cortex manifest gamma-band oscillations (called chattering cells) and are located exclusively in the three superficial layers. These and possibly other pyramidal cells show both a nonspecific phase-alignment response (perceptual) as well as a specific frequency response (sensory) when adequate stimuli are presented to their receptive fields in the retina.

The upper three layers of the sensory cortex are precisely where Herkenham showed the unspecific fibers of Lorente de No terminate (Fig. 4B). These terminals arise from cells in the nonspecific thalamic nuclei (Herkenham 1979, 1986) which are controlled by descending inputs from the frontal cortex and ascending inputs from the mesencephalic reticular formation (Skinner and Lindsley 1967, Yingling and Skinner 1975, Skinner and Yingling 1977). These structures are also known to regulate the ascent of sensory information through the inhibitory action of the thalamic reticular neurons on the specific sensory relay nuclei of the thalamus. Steriade and associates have also studied these high-frequency cortical cells that manifest gamma-activities (Steriade et al. 1996). These investigators have shown that stimulation of the mesencephalic reticular formation or the ejection of a cholinergic agonist will activate gamma oscillations in their membrane potentials.

It has been suggested that during cortical gamma-activity the phase is controlled in a way that somehow creates stimulus binding. There is a lot of activity in this research area, in which different electrodes (Jagadeesh et al. 1992), species (Young et al. 1992) and intercolumn correlations (Livingstone 1996) are employed, as well as new methods for stimulating (Steriade et al. 1991b, Munk et al. 1996) and staining the cells (Steriade et al. 1984). It is unclear, however, just what is going on in the neuropil and how the neuroplasticity that leads to the binding could actually occur.

The data shown for two simple model neuropils suggests that the neuroplasticity may arise as a self-organized process (Fig. 5) in which dimensional changes are the hallmark (Figs. 2 and 5). This self-organization may follow simple nonlinear dynamical laws in which global cooperativity is transiently brought about (Fig. 2B) and eventually results in persistent activities at certain spatial locations (Fig. 6, asterisk).

Recent results in the *in vitro* slice preparation show that the temporal separation between the occurrence of an EPSP and the occurrence of the evoked dendritic action potential determines whether long-term potentiation (LTP) or long-term depression (LTD) occurs (Magee and Johnston 1997, Markram et al. 1997). Thus the precise control of the timing of the action potentials in the apical dendrites is of paramount importance in determining the modulation of synaptic throughput in cortical structures. This timing is likely to be adjusted at the gamma-frequencies and projected upon the sensory neurons by distal dendritic synapses from nonspecific thalamocortical fibers. In conclusion, it is proposed that the stimulus binding brought about by the the sculpturing of the LTP and the LTD that is determined by the phases of the gamma-activities may arise from the convergent inputs of the specific and nonspecific systems operating together in a nonlinear self-organizing manner.

We are now entering a new era in the cognitive neurosciences. The introduction of the PC into our laboratories makes it possible to study huge volumes of data collected simultaneously. It also makes it possible to study the nonlinear dynamics, that is, components of the data that previously were too computationally intensive to be examined. More appropriate measures based on deterministic models instead of the intrinsically less sensitive ones based on stochastic models are now possible because the PC has bridged across the computational limits. It is now clear that spatial as well as temporal dynamics are important, and that these dynamics are low-dimensional and nonlinear. With these new technologies and the new biological phenomena discovered with them, a linkage is being made to old but important concepts (reticular activation, thalamic gating, etc.) that have lain idle for decades. A new picture is beginning to emerge in which we can for the first time begin to see how alpha- and gamma-synchronizations in EEGs and attention and learning in behaviors are related to complex neural activities in the thalamus, mesencephalon, and frontal neocortex. In this emerging view self-organization appears to be the underlying principle in which seemingly unfathomable complexities of brain function are simplified by nonlinear processes and thus enable understanding.

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