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Toward a quantitative description of large-scale neocortical dynamic function and EEG*

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Abstract: A general conceptual framework for large-scale neocortical dynamics based on data from many laboratories is applied to a variety of experimental designs, spatial scales, and brain states. Partly distinct, but interacting local processes (e.g., neural networks) arise from functional segregation. Global processes arise from functional integration and can facilitate (top down) synchronous activity in remote cell groups that function simultaneously at several different spatial scales. Simultaneous local processes may help drive (bottom up) macroscopic global dynamics observed with electroencephalography (EEG) or magnetoencephalography (MEG).

A local/global dynamic theory that is consistent with EEG data and the proposed conceptual framework is outlined. This theory is neutral about properties of neural networks embedded in macroscopic fields, but its global component makes several qualitative and semiquantitative predictions about EEG measures of traveling and standing wave phenomena. A more general "metatheory" suggests what large-scale quantitative theories of neocortical dynamics may be like when more accurate treatment of local and nonlinear effects is achieved.

The theory describes the dynamics of excitatory and inhibitory synaptic action fields. EEG and MEG provide large-scale estimates of modulation of these synaptic fields around background levels. Brain states are determined by neuromodulatory control parameters. Purely local states are dominated by local feedback gains and rise and decay times of postsynaptic potentials. Dominant local frequencies vary with brain region. Other states are purely global, with moderate to high coherence over large distances. Multiple global mode frequencies arise from a combination of delays in corticocortical axons and neocortical boundary conditions. Global frequencies are identical in all cortical regions, but most states involve dynamic interactions between local networks and the global system. EEG frequencies may involve a "matching" of local resonant frequencies with one or more of the many, closely spaced global frequencies.

Keywords: binding problem; cell assemblies; coherence; EEG; limit cycles; neocortical dynamics; pacemakers; phase locking; spatial scale; standing waves; synchronization

1. Introduction and prologue

The conceptual framework proposed in this target article is based on the idea of neocortical dynamic behavior at multiple spatial scales, ranging from molecules to neurons to overlapping local and regional cell groups of different sizes to global fields of synaptic action density. Interaction across these hierarchical levels (or spatial scales) may be essential to the dynamics (and, by implication, to behavior and cognition), the way hierarchical interactions are important in human social systems. For example, a social network requires preferential interactions between individuals, but its dynamic behavior is influenced (top down) by the global social environment. Thus, remote social networks with no direct connections can exhibit correlated activity. These ideas do not entirely contradict classical neurophysiological views of focal control (bottom up) mechanisms. Rather, they suggest dynamics that are more fully integrated across spatial scales, potentially using the full range of bottom-up and top-down interactions, analogous to multiscale social interactions among persons, families, neighborhoods, cities, and

*The relationship between the synaptic action fields proposed in the target article and cell assemblies is clarified with Figure R1 (p. 416) of the Response. (This figure was not available to Commentators.)

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nations. For example, the U.S. Federal Reserve Chairman, Alan Greenspan, is analogous to a small-scale local network. His words and actions strongly influence global economic behavior (bottom up). However, Greenspan is himself influenced (top down) by many larger scales, including groups of private persons, the U.S. Congress, and the global economy.

Considering the enormous complexity of brains and our experience with successful models of relatively complex physical systems, distinct mathematical theories are required for each level (spatial scale). Such theories are directly connected only to data recorded at the same level, although good theories strive for some overlap with adjacent scales to show cross-scale connections. For example, electrophysiological data span about 5 orders of magnitude of spatial scale, ranging from microelectrode tip (0.0001 cm) to electroencephalography (EEG) scalp electrode (1 cm), which records neural source activity space averaged over regions much larger than the electrode owing to passive current spread in the volume conductor. A major accomplishment of twentieth century neurophysiology was the connection of membrane recordings to theory. New large-scale theories must exploit these data, but may use quite different mathematical methods to obtain connections to data obtained at the same large scales. Large-scale theories typically contain "control parameters," which depend on neurotransmitter action at smaller scales but may not be derived from smaller scales without the introduction of new organizing principles.

Many subfields in physics are concerned with multiscale theory. For example, theoretical connections have been derived between the distribution of molecular velocities in a gas and its pressure, temperature, viscosity, or electrical resistivity (in the case of ionized gas or plasma). With certain assumptions, these macroscopic variables may be calculated from microscopic variables; however, such calculations require verification with macroscopic experiments. Another physical example involves theoretical connections between microscopic and macroscopic electromagnetic fields. The precise laws of electromagnetics at microscopic scales (Maxwell's microscopic equations) were first developed using the approximate macroscopic data available at the time, although the validity of such an extrapolation to microscopic scales was far from obvious (Jackson 1975). An important part of this process was the development of distinct connections between macroscopic electromagnetic fields and space averages over molecular fields. A critical aspect of modern electromagnetic theory is the identification of macroscopic control parameters describing magnetic, dielectric, and resistive properties of large "assemblies" of these molecules. Thus, we are able to define the electrical resistance of a macroscopic mass of material simply, even though macroscopic resistance actually depends on very complicated actions of small-scale electromagnetic fields.

Here I focus mainly on a small part of the brain's dynamic complexity, the very large-scale fields of synaptic action density, of which scalp EEG is believed to provide a crude measure. Such "field" may consist of an excess of excitatory or inhibitory synaptic action (e.g., active inhibitory synapses per cubic millimeter at time t), providing perturbations about some background level of synaptic excitation or inhibition in large tissue masses containing tens of millions of neurons. These synaptic fields of membrane current sources are distinguished from the electric and magnetic fields (EEG and MEG [magnetoencephalography]) that they produce. The synaptic fields may be both influenced by and act back on smaller scale activity; for example, the synaptic fields can interact with neural networks embedded within the same tissue. No direct influence of weak electric or magnetic fields (EEG or MEG) on neural activity is suggested here, however. Rather, the action of macroscopic (e.g., space-averaged) fields of synaptic activity on local or regional neural networks is proposed. This idea and other contributions to a "physiology of neural mass action" or "macroscopic physics of neocortex" may ultimately provide some insight into the dynamics of smaller scales, for example, the cooperative workings of local and regional cell groups. However, distinct theories are required at such smaller scales.

Since entering the neuroscience community with an engineering physics Ph.D. in 1971, I have both struggled against and been educated by the multiple, often conflicting subcultures of neuroscience. Conflicts have often involved the proper role of mathematics in explaining data obtained at distinct spatial scales. Such conflicts may reflect profound scientific questions or merely "scale chauvinism," and they occur in many fields (e.g., economics and physics), as well as in neuroscience. This experience provides part of the motivation for this target article: to consider relations between mathematical theory and experiment generally and to apply these ideas to multiscale neocortical dynamics, EEG, and cognitive events. The intended audience is a broad (and not necessarily mathematically sophisticated) one; a primary goal is facilitating communication between disparate subfields. The reader is asked not to prejudge this effort, based perhaps on negative views of mathematics or reductionism in neuroscience. A largely neutral view of mind-brain issues is adopted here (e.g., reductive materialism or "emergent dualism," as phrased by Scott, 1995, are fully consistent with the proposed conceptual framework). Emphasis is placed on practical strategies to encourage fertile marriages of theory with experimental data. Some of these ideas are explored in more depth in my books (Nunez 1981a; 1995).

Interdisciplinary studies of brains are likely to proliferate, and genuine brain theory requires a firm footing in experimental data. But so-called theories can cover a wide range of approaches, including analyses of membranes, neurons, and artificial neural nets, and even ambitious attempts to connect quantum effects to consciousness. EEG data may be used in support of such work. If so, this semiquantitative description of neocortical dynamics, spatial scale, and EEG may provide a useful gauge of putative experimental connections.

1.1. EEG and mental states

Consider the following experiment. Place two electrodes on a subject in one room and feed his EEG signal to a computer display in an isolated location. Monitor the subject's state of consciousness over several days, and provide this information to someone following the unprocessed oscillations of scalp voltage. Even a naive observer, unfamiliar with EEG, will recognize that the voltage record during deep sleep has larger amplitudes and contains more low-frequency content. Slightly more sophisticated monitoring and training allow the observer to identify accurately distinct sleep stages, depth of anesthesia, and seizures. Still more advanced methods reveal robust connections of EEG to more detailed cognitive events.

We are now so accustomed to these EEG/brain state correlations that we may forget just how remarkable they are. The scalp EEG (or MEG) provides a very large-scale measure of neocortical dynamic function. A single electrode provides estimates of synaptic action averaged over tissue masses containing between 10 million and 1 billion neurons (Nunez 1995). Most human studies are limited to extracranial recordings, with space averaging a fortuitous data-reduction process, owing to passive current spread in the head volume conductor. Much more detailed local information may be obtained from intracranial recordings. However, the number of intracranial electrodes implanted in living brains is very small compared to anything approaching full spatial coverage, even for recordings at intermediate spatial scales. Thus, in practice, intracranial data provide information that is different from – not additional to – what is obtained from the scalp, in apparent contrast to the views of some physiologists.

Intracranial recordings provide smaller scale measures of neocortical dynamics, with scale dependent on electrode size. A mixture of coherent and incoherent sources generates the small- and intermediate-scale intracranial data. The smaller the scale of intracranial data, the more likely such data will appear to be independent of scalp data, which are mostly the result of coherent sources with special geometries that encourage superposition of fields generated by many local sources (Nunez 1981a). Intracranial EEG is often uncorrelated or only weakly correlated with cognition and behavior, which are more easily observed at large scales. We are lucky. The technical and ethical limitations of human intracranial recording force us to emphasize scalp recordings, and these methods provide estimates of synaptic fields at the large scales closely related to cognition and behavior.

Although cognitive scientists have good reason to be partly content with the low spatial resolution obtained from scalp EEG data, explorations of new MEG and EEG methods to provide somewhat higher spatial resolution continue. A reasonable goal is to record averages over "only" 10 million neurons at the 1-cm scale to extract more details of the spatial patterns correlated with cognition. This resolution is close to theoretical limits caused by the physical separation of sensor and brain-current sources.

1.2. EEG coherence and brain state

There exists a voluminous literature concerning relations between EEG and cognition, but here I focus on high-resolution coherence studies that are more closely connected to the central theoretical issue of this target article – locally versus globally dominated dynamics. Coherence is a specific quantitative measure of functional relations between paired locations. Coherence is a squared correlation coefficient; it measures phase consistency recorded at paired locations, for each frequency component in the EEG. For example, if two regions exhibit an EEG coherence of 0.36 at some frequency, a large-scale dynamic correlation coefficient of 0.6 is implied between these regions at this frequency. Such correlated neocortical activity can result from direct connections between the two regions, common input from the thalamus and other neocortical regions, or both.

Paired locations in dynamical systems may exhibit high coherence in some frequency bands and, at the same time, low coherence in other bands in the same set of data. Furthermore, coherence depends on measurement scale. Calling on our analog sociology, we expect that correlations between human activity in New Orleans and Paris will depend on whether correlations between individuals, or averages over entire city populations, or something in between is measured. Thus, the qualitative idea of "synchrony," often used in the EEG literature, requires a more substantive definition to be fully useful as a descriptor of dynamic behavior.

Although coherence may appear to be an ideal measure of brain function, interpretations of experimental EEG coherence are often confounded by technical limitations. Raw scalp coherence between electrode sites closer than about 8–10 cm is typically large or moderate only as a result of passive current spread and reference electrode effects, even when the underlying cortical sources are uncorrelated (Nunez 1995; Nunez et al. 1994; 1997). Thus, measured EEG coherence changes as a function of brain state may be small. This can magnify interpretation problems resulting, for example, from artifact and low statistical significance of coherence/brain state correlations. However, erroneous high coherence can be largely eliminated using high-resolution EEG to estimate dura potential from dense scalp arrays before calculating coherence. As a result, fractional changes in coherence with brain state changes are larger, more robust, and more dependent on specific electrode pair than with the usual EEG methods of low spatial resolution (Nunez et al. 1999).

Coherence measured at small scales with intracranial electrodes (e.g., 2 mm diameter) is often zero at all frequencies for separation distances greater than a few centimeters (Bullock et al. 1995). Given the problems with scalp coherence measures, it is not surprising that the validity of moderate to high scalp coherence has been questioned. However, earlier studies by the author estimated coherence from selected periods of high-amplitude alpha rhythm using pairs of bipolar electrodes (Nunez 1974b; 1995). The use of close (1–3 cm) bipolar electrodes eliminated reference electrode and mostly eliminated volume conduction contributions to coherence at distances greater than about 4 or 5 cm. Anterior/posterior coherence over one hemisphere between locations separated by about 20 cm was often greater than 0.7 or 0.8 at the peak alpha frequency in these high-amplitude alpha data. However, coherence outside narrow bands (typical widths of 1–2 Hz) centered at the alpha peak typically fell off sharply. Coherence estimates for the full 8–13 Hz alpha band were much lower (Nunez & Pilgreen 1991). This suggests that studies of broad band coherence, historically the most common approach in EEG (see, e.g., de Munck et al. 1992), can result in erroneous low estimates of underlying source correlations.

In a recent experiment, the author alternated 1-minute periods of resting (slowly counting breaths to facilitate relaxation) with summation of series like $(1 + 2 + 3 \ldots)$, up to sums of several hundred. In 60-channel data there are $60 \cdot 59/2 = 1{,}770$ coherences to be followed. Coherences at 9 Hz (near the peak frequency), calculated from neck-referenced EEG, are plotted versus electrode separation distance in Figure 1. The upper plot shows coherences obtained during three alternating minutes of the eyes-closed, resting state. The lower plot shows coherences for three alternating minutes of eyes-closed, mental calculation (the "cognitive state"). High spatial resolution coherences ob-

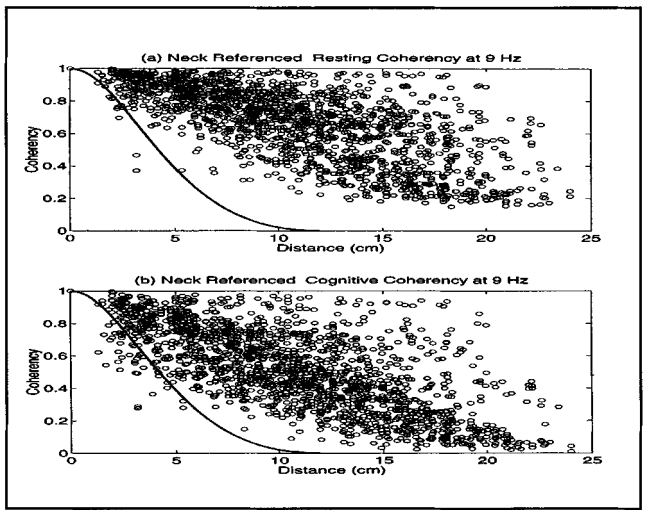

Figure 1. Raw (neck reference) coherence (also called "coherency") as a function of interelectrode separation. Coherence is a squared correlation coefficient; e.g., a coherence of 0.49 is equivalent to a correlation coefficient of 0.7. Sixty-four–channel EEG data were recorded in Melbourne and studied in New Orleans. Four channels were excluded because of possible artifact. A coherence estimate is shown for each of the remaining $60 \times 59/2 = 1{,}770$ electrode pairs. The upper plot refers to data recorded during three 1-min periods when the author had eyes closed and was slowly counting his breaths to facilitate relaxation. These periods were alternated with three 1-min periods when the author summed series such as $(1 + 2 + 3 \ldots)$ to sums of several hundred, also with closed eyes. Corresponding coherences are plotted in the lower row. The solid line is the analytic estimate of raw potential coherence expected from uncorrelated radial dipole sources at the depth of cortical gyri, uniformly distributed over the upper one-half of a spherical volume conductor model (Srinivasan et al. 1997).

tained from the same data sets are shown in Figure 2. The high-resolution coherences are mostly lower than neck reference coherences and exhibit larger percentage changes between states because all reference electrode and most volume conduction contributions have been eliminated. The solid lines are estimates of scalp (Fig. 1) and dura (Fig. 2) potential coherence owing to uncorrelated, widely distributed radial dipole sources at the approximate depth of cortical gyri (Nunez 1995; Srinivasan 1995; Srinivasan et al. 1996; 1998).

We made reasoned attempts to control for confounding effects such as arousal and task familiarity (Nunez 1995; Nunez et al. 1999). However, for purposes of this target article, the main point is that robust relationships between distinct brain states and large EEG coherence changes were demonstrated, independent of precise interpretations of these states. Such coherence data provide important quantitative measures of local versus more global dynamic behavior at large scales. As such they are closely related to the conceptual framework and specific theory presented here. The data indicated the following:

1.2.1. Brain states with high EEG coherence are common. In the study described here, coherence outside the 9–10 Hz band centered at the alpha peak was substantially lower than peak coherence. This suggested that volume conduction and reference electrode contributions to erroneously high coherence were, in fact, largely eliminated by high-resolution methods because volume conduction is independent of frequency in this frequency range (refer to Nunez 1995; Nunez et al. 1997; 1999). It should be noted that each high-resolution electrode estimates source activity averaged over dura surfaces in the 10-cm^2 range, whereas conventional methods involve surfaces of perhaps 50–100 cm^2 (Nunez 1995). Thus, conventional and high-resolution methods estimate coherence at somewhat different spatial scales. These data show that coherent brain states are not unusual, with the strongest evidence for moderate to high resting coherence obtained at the 10-cm^2 scale because volume conduction is small and reference electrode effects are absent.

Comparisons of unprocessed (reference) EEG data to various simulations suggest that large-scale coherence is also much larger in the resting state (Nunez et al. 1999), but this low-resolution evidence is somewhat weaker than the high-resolution evidence. In Figure 1 (top panel), resting reference coherence at large distances (e.g., 15–25 cm, where volume conduction effects are small) ranges from about 0.2 to 1.0, depending on paired locations. In Figure 2 (top panel), resting spline-Laplacian coherence at the same large distances varies from about 0.0 to 0.8 in the same data. However, such high-resolution methods may underestimate dura coherence because they remove the long-wavelength part of the spatial spectrum of dynamic activity, which cannot be easily distinguished from volume conduc-

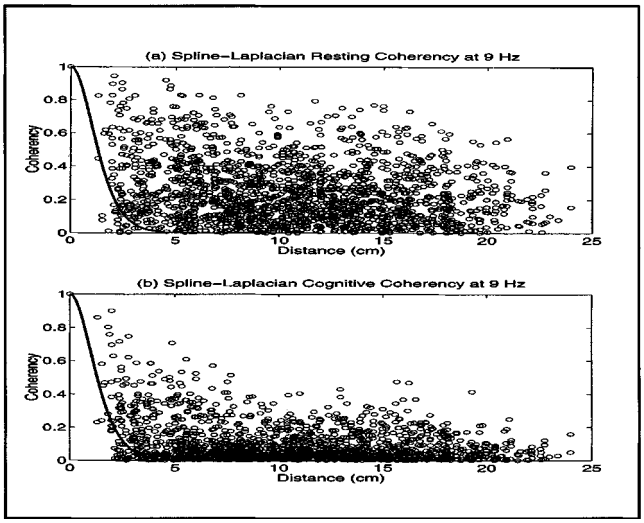

Figure 2. High-resolution coherence as a function of interelectrode separation. The same 60-channel raw data used in Figure 1 were first passed through the New Orleans spline – Laplacian algorithm to estimate potential distribution on the dura surface, thereby minimizing volume conduction distortion and eliminating reference electrode contributions to coherence estimates (Nunez 1995; Nunez et al. 1997; 1999). Large resting Laplacian coherences were obtained at 9 and 10 Hz, but not at other frequencies. The largest coherence decreases between resting are cognitive states involved frontal-to-frontal sites. Melbourne dura image methods yielded similar coherence plots. The solid line is the analytic estimate of scalp Laplacian coherence expected from the same uncorrelated, radial dipole sources used to plot the solid line in Figure 1. Because high resolution methods filter out the longest waves from the spatial spectrum of source activity (which we are not able to distinguish from volume conduction), high-resolution coherence may underestimate actual source coherence (Nunez et al. 1997; 1999).

tion (Nunez et al. 1997). Thus, coherence values that are intermediate between the estimates shown in Figures 1 and 2 may provide a more accurate resting coherence picture for the broad spatial scale of roughly 10–100 cm^2. Resting coherence values greater than 0.5 (dynamic correlation coefficients greater than 0.7) are therefore quite common at large distances near the alpha peak frequency.

1.2.2. Alpha coherence decreased and theta coherence increased during mental calculations. There were large, robust decreases in coherence for many paired sites between states of resting and mental calculation in the 9–10 Hz alpha band. This was observed for both raw and high-resolution coherences, but percentage changes were largest with high-resolution coherences because there were no reference effects and volume conduction was minimal with high-resolution methods. Coherence in the 4–5 Hz theta band between electrode pairs at many widespread locations were consistently higher during mental calculations than resting coherence ($p < 0.005$), although the magnitudes of these changes were much smaller than alpha coherence changes. Anterior/posterior theta coherence increases were especially robust. Similar theta (4–7 Hz) coherence increases between prefrontal and posterior cortical association areas were recently reported during working memory retention using a digitally linked-ears reference (Sarnthein et al. 1998).

Such coincident coherence changes in opposite directions for different frequency bands may challenge simplistic interpretations of "EEG synchrony," but the local/global mathematical theory outlined in section 5 suggests that such dynamic behavior can occur naturally in the context of known physiological mechanisms. For example, one may conjecture that there are specific neural networks operating at theta frequencies during mental calculations. If such phenomena occur at sufficiently large spatial scales, they may produce larger EEG coherence between regions that include parts of the same network. The fact that such theta coherence changes are small relative to alpha coherence changes may be mainly the result of poor spatial resolution. For example, if two parts of a neural network each underlie 1 cm^2 of dura surface, but each electrode records EEG from sources under 10 cm^2, only small EEG coherence changes can be expected, even when coherence changes in the network are large. Different neuromodulatory influences (and corresponding control parameters) may be more efficient for different frequency bands, perhaps because of their actions in different cortical layers (Silberstein 1995b). If this is so, the general large-scale reduction in alpha coherence may coincide with more specific (and perhaps smaller scale) increases in theta coherence.

1.2.3. Alpha coherence changes were largest for frontal-to-frontal electrode pairs. The effect shown here is much more detailed than traditional "alpha blocking" reported in many early studies involving mental calculations. Alpha amplitude was lower during mental calculations as expected, with the largest state changes with amplitude occurring over posterior regions. However, the alpha rhythm persisted in both states, and the largest coherence state changes involved frontal-to-frontal sites, consistent with generally accepted ideas about the important role of frontal cortex for higher mental processing. Of course, these large-scale coherence reductions can easily coexist with very specific coherence changes in either direction at scales too small to observe from the scalp, for example, in synchronous cell groups (Bressler 1995; Silberstein 1995b). In our analog social system, coherence of croissant consumption for the whole cities of Paris and New Orleans may decrease when the state of the world changes, but these data do not necessarily tell us about croissant coherence between specific pairs of smaller scale human assemblies – neighborhoods, persons, and so on – in these same cities.

1.2.4. Complicated patterns of coherence and coherence state changes occur in narrow frequency bands. Coherence patterns were often very specific to bandwidths of 1–2 Hz and specific electrode pair, especially with high-resolution coherence. Such specificity of coherence patterns was obtained over the 1–20 Hz range. For example, 3-, 5-, and 7-Hz coherence behaved differently, as did 13-, 15-, and 17-Hz coherence. Of course, one has less confidence in beta coherence measures because of possible muscle artifact contributions, although these were not evident in the raw data. However, these data generally support the idea that studies of broad-band coherence can miss important properties of the dynamics.

These data appear inconsistent with the very simple pictures often proposed, such as when EEG sources consist of a few isolated "alpha generators" or "dipoles." Apparently, there are robust and very detailed changes in the strength of "binding" at macroscopic scales between brain states. By analogy, if Parisians and New Orleanians follow similar eating habits, croissant consumption coherence will be high in a band of frequencies near 1/24 hr, but coherence may be high or low in other frequency ranges, depending, for example, on differences of supply or holiday habits. One may guess that neocortical dynamics is not simpler than croissant dynamics. Thus, the complexity of coherence patterns is not surprising.

Another recent coherence project used a 148-channel MEG system to record steady-state visually evoked magnetic fields in order to study binocular rivalry (Srinivasan 1999; Tononi & Edelman 1998). The subject viewed incongruent images with each eye, but was conscious of only one image (perceptual dominance periods) or a mixed image (nondominance periods). The image that was perceptually dominant alternated every few seconds. For purposes of this target article, two general results stand out. First, for sensors separated by more than 20 cm, coherences at the driving frequency (7.41 Hz) were mostly moderate to high (roughly 0.4–0.9). Second, interhemispheric and, to a lesser extent, intrahemispheric coherences were generally larger during periods of perceptual dominance. Again, very complicated, robust patterns of coherence were correlated with brain state.

1.2.5. Stable structure with nodal lines occurs in both states. High-resolution plots of magnitude and phase over the scalp reveal regions separated by several centimeters, with voltage oscillations 180° out of phase. Because there are multiple regions, "zero-phase-lag" conditions easily occur over large distances (e.g., 20 cm or more). These regions appear to be delineated by nodal lines (lines of zero amplitude), in a manner expected of standing waves and predicted by the global theory presented here and in earlier articles (Katznelson 1981; 1982; Nunez 1972; 1974a;

1974b; 1981a; 1981b; 1981c; 1989a; 1995; Nunez et al. 1977). The magnitude and phase patterns do not typically exhibit large changes over time, except for magnitude reductions in the 9–10 Hz band during the periods of mental calculation.

By contrast, magnitude and phase patterns may be sensitive functions of frequency. This was demonstrated in several subjects with 64-channel steady-state-evoked potential studies, in which magnitude and phase patterns (projected to the dura surface with high-resolution methods) at the stimulus frequency exhibited large changes with only 1 Hz change in stimulus frequency (Nunez 1995; Silberstein 1995a). I suggest that such changes are the result of to the dynamic response of neocortex to input at different temporal frequencies rather than to changes in the spatial distributions of extracortical input. Again, these data support the concept of standing neocortical waves.

Currently, work is under way at the Brain Sciences Institute in Melbourne to study spatial-temporal properties of steady-state, visual-evoked potentials recorded with a 131-channel system. The goal of this work is to obtain robust data on dynamic responses of neocortex and to connect these data to theoretical models. For example, Silberstein (1995b) has suggested that resonant behavior near 10 Hz may be more pronounced in "hypercoupled" brain states (corresponding to more global behavior). By contrast, 40-Hz resonant behavior may occur more easily in "hypocoupled" states (corresponding to more local behavior). It should be possible to manipulate the effective strengths of different cortical coupling mechanisms with various drugs and test this postulate. In the context of the dynamic theory presented here, such manipulation of brain chemistry alters local and global neocortical control parameters.

1.2.6. Skeptical of EEG data? Neuroscientists may be skeptical of EEG reports, given that, as a whole, the scientific reputation of EEG lags behind that of many scientific fields. One problem that has plagued many cognitive EEG studies has been a failure to separate brain rhythms from artifact convincingly. Whereas the typical peaked alpha spectrum is quite distinct from any known artifact, low-amplitude scalp EEG frequency components above about 15 Hz are typically indistinguishable from muscle activity (see review by Gevins & Cutillo 1986). However, EEG data are far too important to neuroscience to throw out the proverbial "baby." In fact, many sophisticated experiments in cognitive science have shown that EEG and evoked potentials are strongly correlated with specific cognitive tasks (Gevins & Cutillo 1986; 1995; Silberstein 1995a).

In the work of Silberstein, artifact problems were substantially reduced by using a steady-state evoked potential visual "probe" (a 13-Hz flicker) and obtaining brain responses in a narrow frequency band covering the 13-Hz driving frequency. Because artifact power is typically distributed over a wide frequency band, total artifact power in narrow bands (e.g., less than 0.1 Hz) can be expected to be much lower than signal power in the same band if the brain produces a moderate- to high-amplitude response at the driving frequency (Regan 1989). This has been demonstrated recently in studies involving purposeful addition of known artifact (Silberstein et al. 1992) and in studies of narrow coherence peaks in the 40-Hz steady-state – evoked potential (Silberstein et al. 1998). When such critical technical issues were properly addressed, EEG proved to be a robust measure of large-scale neocortical dynamic function. EEG is moderately to strongly correlated with brain state. This basic property should encourage vigorous consideration of experimental EEG data and related theoretical tools by neuroscientists from multiple subfields.

2. A conceptual framework to support neocortical dynamic theory

The following outline of a semiquantitative conceptual framework for neocortical dynamic behavior is sufficiently general to embrace brain theories applied to different experimental designs, spatial scales, and brain states. The framework draws on work by many scientists and is directly applicable to large-scale neocortical dynamics evidenced by EEGs recorded from human scalp. It also has broader implications for brain information processing. The proposed framework includes the following ideas, generally progressing from the most easily defended to the most speculative.

2.1. Mathematical motivations

There can be several motivations for developing mathematical theories of macroscopic, neocortical dynamic behavior, such as the spatial-temporal patterns exhibited by brain state-dependent field variables. For example, so-called brain theories may originate from a general interest in complex systems and nonlinear mathematics. However, such work is often divorced from genuine neuroscience. For example, mathematical "theory" or neural network models often contain "free" (nonphysiological) parameters and lack experimental predictions. Although this kind of work can provide useful metaphorical connections between real and model systems, it should be distinguished from genuine theory.

2.2. Communication

Genuine, physiologically based neocortical dynamic theory is essential to rapid development in cognitive science and neurology, even though such theory may provide only very crude descriptions of real brains. Without some quantitative framework, it is difficult for neuroscientists from different backgrounds to communicate subtle ideas or even to form well-posed questions about brain information processing. For example, the theory proposed here helps to pin down concepts such as "binding," "functional integration," "synchronous activity," "zero phase lag," and "hierarchical level," thereby suggesting refinements for qualitative ideas and, it is to be hoped, leading to specific quantitative explanations for data recorded at the appropriate scale. This being the case, the theory should be useful, even if it is later proved wrong.

2.3. Experimental design

Quantitative dynamic theory is essential for making more informed experimental choices, that is, picking the small subset of experiments that, with limited resources, can ever be carried out. In addition, experimental design involves many microdecisions biased by the experimenter's often semiprivate view of brain operation. Reference to theory provides a means by which such biases can be known and evaluated in the context of new experimental designs.

2.4. Dynamic and cognitive connections

Many robust correlations between large-scale EEG dynamic, cognitive, and behavioral measures have been established during the past 70 years. There are strong motivations to establish physiologically based quantitative theories of EEG by treating brain tissue in terms of dynamical systems, consisting of neural mass elements interacting by means of interconnecting fibers. Such developments are likely to mimic methods used in several physical science fields and may largely ignore cognitive data during early stages. However, once plausible connections between EEG dynamics and the underlying physiology are established, these data should naturally combine with other known correlations between EEG and cognitive/behavioral data. In this indirect manner, quantitative physiological bases for cognitive/behavioral data can be pursued.

2.5. Cell assemblies and macroscopic fields

Several theoretical models based on genuine physiology and anatomy suggest that neural networks at multiple microscopic and mesoscopic scales (e.g., local and regional networks) exist naturally in a background of macroscopic field activity (e.g., synaptic action density) and that important hierarchical interactions take place across these distinct scales (Freeman 1995; Haken 1999; Harth 1993; Ingber 1982; 1983; 1995a; 1995b; Ingber & Nunez 1990; Jirsa & Haken 1996; 1997; Kelso et al. 1999; Nunez 1974a; 1981a; 1981b; 1981c; 1989a; 1995; 1996; Robinson et al. 1997; 1998a; 1998b; Silberstein 1995b; Uhl & Friedrich 1998; Uhl et al. 1998; Wilson & Cowan 1973; Wright & Liley 1996). The macroscopic fields, for which EEG provides a crude measure, can act to synchronize or otherwise bind distinct neural networks (Jirsa & Haken 1997; Nunez 1995; 1996; 1997), thereby providing connections to cell assembly theory (Hebb 1949; Phillips & Singer 1997; Singer 1993).

2.6. Local/global field theory

A specific quantitative theory of neocortical dynamics is outlined here (Nunez 1972; 1974a; 1974b; 1989a; 1995). Although many ideas may be modified by future work, the theory embraces several general concepts that are likely to endure: Brain state is described in the context of theory by physiologically based control parameters that change as a result of neuromodulatory action. These control parameters also partly determine dominant EEG frequencies. Neural network activity is believed to operate in a background environment of standing waves of "synaptic action" (modulation of the number of active synapses per unit volume). Excitatory and inhibitory synaptic action and action potential density are treated as macroscopic field variables, influenced by the global boundary conditions, as determined by the size and geometry of neocortex and corticocortical connections.

The word "field" may be confusing to nonphysical scientists, although its use here is fully consistent with standard use in the physical sciences. I am not describing putative interactions between the small electric and magnetic fields (measured with EEG and MEG) and neural firing patterns. The "fields" described here are simply the numbers of active excitatory or inhibitory synapses in large tissue masses. For example, suppose multiple neural networks with natural frequencies f_j are embedded in the global neocortical system. Such networks may be formed by Hebbian mechanisms and may physically overlap other networks having different natural frequencies. Each network may be viewed as embedded in inhibitory and excitatory macroscopic fields of synaptic action resulting from the combined activity of all other networks plus tissue that is not part of any network. Most networks may be inactive in any particular brain state as the result of inhibitory dominance. Activation of each network may require a threshold level of modulation of the excitatory synaptic action field (relative to the inhibitory field) at one of the natural frequencies of the neural network. Furthermore, activation of a network may "drive" global field modulations at matching natural frequencies (in the manner of "internal pacemakers"). Thus, these fields of synaptic action may facilitate synchronous activity in remote cell assemblies having no direct connections. In this view, EEG dynamic behavior involves a state-dependent mixture of "local" (more dominant functional segregation) and "global" (more dominant functional integration) processes (Friston et al. 1995; Ingber 1995a; Ingber & Nunez 1990; Nunez 1981a; 1981b; 1981c; 1989a; 1995; Tononi & Edelman 1998). Faulty control parameters may lead to "hypocoupled" or "hypercoupled" brain states, for example, neurological and neuropsychiatric diseases (Bressler 1995; Silberstein 1995b).

2.7. Experimental support

The theory provides explanations (mostly qualitative, some quantitative) for a dozen or so disparate experiments, described in Nunez (1995). Taken in isolation, any one of these observations could have multiple origins. Taken as a whole, however, the experimental data provide strong support for the general, semiquantitative framework proposed here, and moderate support for the specific quantitative local/global theory. The theory was developed in the same spirit as earlier ideas on "neural mass action" (Freeman 1975; Lashley 1931) and the idea that "dynamic interplay of neural activity within and between its subsystems is the very essence of brain function" (Mountcastle 1979). The corticocortical fiber systems, which provide massive positive feedback between close and distant regions (Braitenberg 1972; 1977), are an essential part of the global aspects of the theory.

The current version of this dynamic theory is incomplete even in the limited context of macroscopic fields. For example, the theory is silent on most cognitive questions because it was developed specifically to describe EEG, not behavioral or cognitive correlates. Another problem is that "cognitive theories" often contain ill-defined concepts that are hard to pin down experimentally. However, the limited dynamic theory outlined here makes predictions about EEG data in several experiments specifically designed to test global predictions of the theory. If proved only partly valid, it should influence future cognitive theories.

3. Experimental/theoretical connections in dynamical systems

Many physical and biological processes can be represented by some field variable, f(x,t), where x represents a vector location (in one, two, or three coordinates) in some medium and t is time. The word "field" can be used to describe

nearly any mathematical function of space and time; however, it is most useful to science when related to measurable variables. For example, macroscopic EEG electric fields (which are easily measured) are believed to be generated by modulations of large-scale synaptic action fields (which are not generally measured). The spatial-temporal patterns of fields developed in a medium constitute its dynamic behavior. A dynamic theory may involve many such fields and associated coupled equations, but only some are directly accessible to experimental measure. Here I focus on "genuine physiological theory," which I define as a set of equations for fields containing physiological parameters, in which at least one of the fields can be measured. Example fields from analog physical systems include seismic, ocean, sound, electromagnetic, and probability waves (either classical or quantum), in which properties of the medium are described by the appropriate equations. In some cases, the dependent variables (fields) of these equations are directly measurable (e.g., pressure, ocean surface displacement). In other systems, measurable quantities must be derived from the dependent variables using separate equations. For example, the dynamics of plasma in a fusion reactor (either human-made or star) are often described in terms of probability density functions P(x,v,t), where v is electron or ion velocity. However, measurable quantities such as pressure and temperature involve integrals of such distribution functions over the velocity variable.

In brain science, neocortical theory may predict certain spatial-temporal distributions of current source activity (e.g., synaptic action fields), but such brain sources must be related to measurable electric fields through properties of the head volume conductor. Although the appropriate relationship (Poisson's equation) is well known and exact solutions are available, these solutions depend on tissue boundaries and electrical resistivities that are known only approximately. Thus, even a perfect theory of neocortical dynamics (e.g., describing synaptic fields) can produce ambiguous experimental connections to EEG, especially when such experiments are not specifically designed to test theory. To minimize this problem, use should be made of our general understanding that the head volume conductor acts as a low-pass spatial filter of brain source activity. That is, only the long wavelength part of the spatial spectrum of source activity is recorded on the scalp. Thus, scalp EEG data are generated by a selective collection of "synchronous" neural sources and can be quite different from intracranial data. Scalp electric fields (or potentials) reflect only a small part of the full spatial spectrum of synaptic fields.

3.1. Input/output relations in physical and biological systems

In system science (e.g., in electrical engineering), the system (or medium) input g(x,t) is related to its output f(x,t) by rules that generally vary with the state of the system. For this formulation to be useful in experimental science, measurable variables must be identified. That is, the medium operates on input in some way to create output that is partly predictable. Such predictions may involve specific mathematical output functions only of time f(t), as in the case of input/output in the simple electrical or mechanical systems studied by engineering students, or predictions may involve the statistical properties of an ensemble of spatial-temporal functions $f_j(x,t)$ in more complex systems. We may represent such a system by a "grey box," with the boldface symbol $\boldsymbol{D}$ depicting a mathematical operator, representing the dynamic properties of the system that determine input/output relations. Such medium properties are often modeled by differential, integral, or integrodifferential equations, in which case the relation between input g(x,t) and output f(x,t) in the model system is governed by an equation of the form (Morse & Feshbach 1953):

$$\hat{\boldsymbol{D}}[f(x,t)] = g(x,t) \tag{1}$$

Here $\hat{\boldsymbol{D}}$ is the appropriate mathematical operator, and the "hat" symbol distinguishes the model system from the genuine system, which is governed by the (typically unknown) operator $\boldsymbol{D}$. To the common charge that "physicists oversimplify biology," a guilty plea must be entered. However, engineers and physicists also oversimplify complex physical systems, and such simplifications have played a critical role in the advance of science and technology during the past several centuries. One reason for this success is that Equation (1) may strongly influence experimental designs. Another reason is that it forces discussion to a controlled quantitative context. For example, scientists must advocate better-defined positions on controversial issues and are barred from many opportunities to deny past positions, later proved inconsistent with experiment. An important aspect of this process, which typically separates genuine theoreticians from mathematicians, is the choice of the approximations needed to obtain $\hat{\boldsymbol{D}}$, appropriate for the practical problem at hand. Thus, a large artistic element is required for theoretical science, just as for experimental science.

3.2. Control of system state

The system operators $\hat{\boldsymbol{D}}$ include "control parameters" that describe the state of the system (Haken 1983; Nunez 1995). For example, an electrical resistance may be a control parameter in a circuit designed to act as a tuner. Some tuners are used to pick out narrow frequency bands of antenna current owing to a broad spectrum of electromagnetic fields transmitted from many locations. One "controls" the TV picture (e.g., output information f(x,t)) by changing the resistance of a variable resistor in the tuner. In an analogous manner, a simple view of neocortex is that of a system with input action potentials and EEG output, with neocortical state controlled by different kinds of input from the midbrain. Of course, neocortex has many other "outputs," including behavior, but here we focus on EEG, which is a cognitive and behavior correlate and has many spatial-temporal properties that are just beginning to be explored in detail.

The control parameters determining cortical state involve neuromodulatory (chemical and electrical) input from the midbrain. Such control may itself be influenced by neocortical dynamic behavior (just as a TV viewer may be influenced to change channels); however, one may reasonably seek approximate theory in which such chemical and electrical feedback mechanisms take place much more slowly than EEG oscillations. In this case it appears reasonable to neglect such complications for fixed-state theory.

I emphasize that the formalism of Equation (1) is based on the assumption that input and output are related in some systematic way. There is no assumption here that the system

is linear or otherwise "simple." In the neocortical example, we need only note that, by holding brain state approximately fixed, observed EEG is partly predictable rather than random. That is, we are often able to make relatively accurate predictions about the general statistical behavior of EEG spatial-temporal patterns associated with distinct behavioral or physiological states. This principle is well established within the EEG community, although outsiders might rightly question the quality and repeatability of published EEG studies, especially those claiming to quantify fine distinctions between similar brain substates or with data likely to contain substantial artifact. For example, we can easily distinguish deep sleep from REM sleep, but would be skeptical of claims that current EEG methods could reliably determine dream content. To take another example, we are more likely to believe results based on frequency bands with high signal-to-noise ratio (e.g., alpha) than studies involving an unknown signal-to-noise (e.g., scalp beta).

3.3. Limitations on experimental verification

We can identify several limitations on attempts to check a proposed theoretical operator $\hat{\boldsymbol{D}}$; that is, to verify a neocortical dynamic theory with experimental data.

3.3.1. The measured output $\hat{f}(x,t)$ is only an approximation of the actual output f(x,t). In the case of scalp EEG, potentials are typically sampled at between 20 and 131 scalp locations over upper brain regions. The electrodes are located about 1 cm from the nearest neural sources. Scalp potentials are spatially low-pass-filtered versions of dura potentials as a result of this electrode separation and the poorly conducting skull, both of which act to spread currents and smear potential patterns. MEG avoids tissue distortion, but not distortion caused by sensor separation (Malmivuo & Plonsey 1995; Nunez 1995; Srinivasan et al. 1999; Wikswo & Roth 1988).

The information content of intracranial recordings is also severely limited by the small numbers and fixed sizes of electrodes, which allow sampling of potentials (space averaged over the volume of the electrode tip) at only a few locations. Thus, each experimental measure applies to a particular spatial scale, and experimental connections are appropriate only to theory $\hat{\boldsymbol{D}}$, derived at the same scale. Many publications of "brain mathematics" have avoided this central issue of matching experimental with theoretical scale; they should be categorized as metaphorical descriptions rather than genuine brain theory.

This failure is perhaps not surprising given that connecting the dependent variables of equations to experimental measures is often far more difficult than solving the equations. I believe both neuroscientists and mathematicians often fail to fully appreciate this point. The former tend to place all studies involving mathematics in a single category. The latter often fail to distinguish between mathematical methods (or computer simulations) and genuine theory. Neuroscientists have also been guilty of "scale chauvinism." For example, dynamic behavior in isolated neurons or small networks has been extrapolated to large networks without justification. In extreme cases, EEG has been dismissed as an "epiphenomenon."

3.3.2. The input g(x,t) may be unknown or known only approximately. For example, the input function to the ocean surface from wind forces is, at best, known only approximately (Kinsman 1965). Can we check theories of ocean waves $\hat{\boldsymbol{D}}$ when measured output depends on both $\hat{\boldsymbol{D}}$ and the input g(x,t), which is only partly known? In the case of evoked (or event-related) potentials, we have substantial, but still imperfect, knowledge of the cortical input function g(x,t). Spontaneous EEG involves input that is largely unknown. The measured output f(x,t) depends on both the input g(x,t) and system properties $\hat{\boldsymbol{D}}$, so how can one verify a neocortical dynamic theory? In extreme cases of bad theory, the assumed input $\hat{g}(x,t)$ might be adjusted to make output f(x,t) appear to confirm $\hat{\boldsymbol{D}}$, the classic case where conclusions of a "theory" are simply the summation of its assumptions.

3.3.3. With our current stage of knowledge, any brain or neocortical theory $\hat{D}$can, at best, be only a crude approximation to the real system *D*. We might well consider such approximate theory a resounding success if it were able to describe a few brain states with only moderate (but quantitative) accuracy. An important feature that appears to distinguish brain states is the relative importance of local versus global contributions to the large-scale dynamic behavior measured with EEG. This is determined by competition between functional segregation and functional integration in neocortical tissue. Dynamic and behavioral brain states are believed to be controlled by electrical and neurotransmitter input from the midbrain, which occurs on much longer time scales than EEG oscillation periods.

3.3.4. Are our theories good enough to be wrong? Given these limitations, can we develop falsifiable theories of neocortical dynamics? In the famous parlance of physicist Wolfgang Pauli, can we create theories "good enough to be wrong"? For many complex physical systems, which also have severe limitations on verification, the answer is clearly "yes." In comparing such systems to neocortex, there is both good and bad news. On the negative side, brain tissue is much more complex than "complex" physical systems. However, in contrast to the case with many physical systems, experimental EEG data obtained for multiple brain states at macroscopic scales through several smaller scales are abundant. This provides reason for optimism. Given the practical success of theories developed in engineering and physics (even when such theories later proved to be very limited or even completely wrong), I suggest in the following section that neuroscience should tentatively mimic some of the established methods of physical science and evaluate the results, without deciding in advance how far to carry this paradigm.

Brain science has experienced a long debate concerning localized versus distributed function, but neuroscientists now generally agree that, although specific cell groups perform elementary functions, complex functions require integrated interaction of many areas throughout both hemispheres (Bressler 1995; John et al. 1997; Luria 1966). The issue of local versus global dynamics, as measured with scalp and intracranial electrodes of different sizes, parallels the brain function issue. There have been many suggestions of brains operating between the extremes of locally versus globally dominated dynamics (Andrew & Pfurtscheller 1996; Friston et al. 1995; Haken 1999; Ingber 1995; Ingber & Nunez 1990; Jirsa & Haken 1997; Nunez 1981a; 1981b; 1989a; 1995; 1996; Silberstein 1995b; Tononi & Edelman

1998; Tononi et al. 1994). If this is so, any comprehensive dynamical brain theory must include local networks and global fields simultaneously. However, no such comprehensive theory, including realistic, multiple neocortical networks, is likely to be developed soon. Even if it is developed, such a theory would necessarily contain many unknown control parameters, so anything approaching full verification appears impossible in the near future.

It is far easier to test brain states that are close to extreme ends of this local-global gamut of brain dynamics with limited versions of theory that appear to match such states approximately. In this target article I focus on comparisons between global theory and EEG data obtained in states of relatively high coherence, which are more likely to have strong global contributions. In addition, I show how local neural networks can fit naturally with global theory, while acknowledging that local network properties are mostly unknown. However, if local effects can be minimized by selective experiment, perhaps verification of global aspects of the theory can be obtained. In a similar manner, local theories can be checked with experiments in brain states or for other conditions in which global effects may be neglected. Such experiments are more likely to involve intracranial electrodes, which are sensitive to locally dominated dynamics.

4. Representation of dynamic properties with Fourier transforms

Complicated spatial-temporal patterns and their relations to experimental data are often greatly simplified using Fourier transform methods. That is, the dynamics of many systems are most naturally expressed in the spatial-temporal frequency domain. In particular, a system's input g(x,t) and output f(x,t) may be represented by their multidimensional Fourier transforms $G(k,\Omega)$ and $F(k,\Omega)$, respectively. Here k is vector wave number (or spatial frequency) and Ω is temporal frequency. In the case of potentials measured on the dura or cortical surface, k is a vector with two components (k_x, k_y), representing spatial frequencies in two surface coordinates. For purposes of these general remarks, we consider neocortex and its potential fields to be isotropic so that we need not worry about directional-dependent properties. In this case, we interpret the vector wave number k as simply its magnitude $(k_x^2 + k_y^2)^{1/2}$.

To visualize the general spatial-temporal dynamics described here, imagine the dynamics of a rough ocean surface. The surface is composed of a wide range of waves, each with wavelength equal to 2π divided by wave number (k), ranging from ripples to intermediate-length, wind-driven waves to tides. Note that this description of EEG (say at the dura surface) in terms of such mathematical "waves" of many wavelengths is fully general. That is, it does not depend on the nature of the dynamics, such as whether genuine "wave phenomena," as this term is used in the physical sciences, actually occur or whether the dynamical system is linear. It is simply a mathematical transformation that has proved useful in a variety of physical and biological systems.

Dynamics on a closed surface may be represented more naturally by special functions of the spatial coordinates such as the spherical harmonic functions (essentially functions of latitude and longitude on a sphere) than by the spatial sine and cosine functions associated with the wave numbers k_x and k_y. However, such special mathematical functions are qualitatively similar to sine and cosine functions. Thus, this general, semiquantitative discussion is not sensitive to characterization of spatial properties in terms of "spatial frequencies" or "wave numbers." Brain waves in a spherical shell are discussed by Katznelson (1981), by Nunez (1995), and in the Appendix to this target article.

4.1. Input/output in linear systems

Several motivations for working with the Fourier transforms of input g(x,t) and output f(x,t) are evident. In the case of linear systems with slowly varying control parameters, transformed input G(x,t) and output F(x,t) are related by the simple multiplication

$$F(k,\Omega) = H(k,\Omega)\, G(k,\Omega) \qquad (2)$$

Here the transfer function $H(k,\Omega)$ depends on the mathematical operator $\hat{\boldsymbol{D}}$ of Equation (1). Thus, a complicated differential or integral equation (1) relating input to output may be replaced by the algebraic equation (2), providing an enormous conceptual simplification. This relation tells us quite a bit about the likely output f(x,t) or its Fourier transform $F(k,\Omega)$, even when we possess minimal knowledge of the input g(x,t) or $G(k,\Omega)$. For example, Equation (2) shows that $F(k,\Omega)$ tends to be large over ranges of spatial or temporal frequency where $H(k,\Omega)$ is large, except for inputs $G(k,\Omega)$ that happen to be very small in these same frequency ranges. Also, when the input approximates spatial-temporal white noise, that is, when $G(k,\Omega)$ fluctuates about a constant level over broad bands of spatial and temporal frequencies, the predicted output $F(k,\Omega)$ is approximately proportional to the theoretical transfer function, thereby allowing quantitative verification of the theory (H or $\hat{\boldsymbol{D}}$). Freeman (1975) has pioneered applications of these methods of linear systems theory to time-dependent data recorded in neural tissue at relatively small scales. If input- and output-dependent variables are time- but not space-dependent, as in the case of most common electric circuits, the transfer function depends only on temporal frequency; $\hat{H}(k,\Omega)$ may be replaced by $\hat{H}(\Omega)$.

4.2. Measured output versus actual output

A second motivation for using Fourier transformed variables, which clearly applies to studies involving scalp EEG, is that a relatively simple relationship (Poisson's equation) is known to relate the measured output [scalp potential, $\hat{F}(k,\Omega)$] to actual dynamical system output [e.g., dura potential, cortical current density, or synaptic action, $F(k,\Omega)$]. In an idealized brain medium (Katznelson 1982; Nunez 1981a; 1995) this relationship may be expressed as

$$\hat{F}(k,\Omega) = \hat{V}(k,\Omega)\, F(k,\Omega) \qquad (3)$$

Here $\hat{V}(k,\Omega)$ is the transfer function of the head volume conductor, which depends on Poisson's equation, tissue resistivities, and tissue boundaries. Obtaining progressively more accurate head models used to determine $\hat{V}(k,\Omega)$ provides an important ongoing engineering challenge, but the qualitative behavior of $V(k,\Omega)$ is fairly well understood. In the low-frequency range of EEG scalp potentials, $V(k,\Omega)$ can be accurately approximated by V(k); that is, tissue volume conduction is approximately independent of temporal

frequency (Cooper et al. 1965; Malmivuo & Plonsey 1995; Nunez 1981a; Plonsey 1969). Furthermore, passive tissue properties (especially skull) and large electrode-source separations combine to low-pass filter the cortical output $F(k,\Omega)$ spatially. Thus, $V(k)$ decreases sharply even at moderately high spatial frequencies (Nunez 1995; Srinivasan 1995; Srinivasan et al. 1996; 1998). In some brain states, higher temporal frequencies above the alpha peak are observed to have more power at higher spatial frequencies. In such cases, three-dimensional plots of $\hat{F}(k,\Omega)$, and perhaps by implication $H(k,\Omega)$, contain "mountain ranges" depicting such relations. (Imagine k and Ω as axes plotted on a surface, with $\hat{F}(k,\Omega)$ plotted out of the plane and being large along a particular pathway across mountain peaks, as shown in Fig. 3).

Observed differences in EEG temporal frequency spectra between cortex and scalp are believed to be caused by the combined behavior of the dynamic $H(k,\Omega)$ and static $V(k)$ transfer functions (Katznelson 1982; Nunez 1981a; 1995a). For example, volume conduction attenuates the high spatial frequencies that form part of the dynamic signal $F(k,\Omega)$. In addition, consider a putative brain state in which $F(k,\Omega)$ tends to be largest along a "mountain range," as in Figure 3. In the physical sciences this peaked region is called a branch of the dispersion relation, $\Omega = \Omega(k)$, for the particular wave phenomenon. In relatively simple wave media, the dispersion relation has a single branch. In such cases, for example, the usual sound or light waves, there is

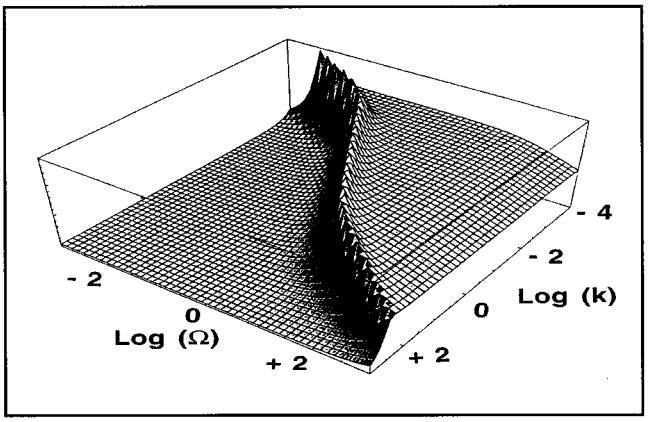

Figure 3. An idealized estimate of the transfer function (vertical axis) for ocean surface waves $\hat{O}(\Omega,k)$ is plotted versus the logarithms of angular frequency ($\Omega = 2\pi$/period) and wave number ($k = 2\pi$/spatial wavelength). The waves of largest wave number (short wavelengths) are ripples. Ripple dynamics are dominated by surface tension and have very short oscillation periods. By contrast, dynamics at long wavelengths (e.g., swells through tides) are dominated by gravitational forces. These forces together with the physical properties of water tend to constrain dynamic behavior so that waves satisfy a dispersion relation relating temporal frequency (Ω) to wave number (k), as indicated by the "mountain range" shown here and in Equation (4). Ocean surface dynamics are driven by input functions of space and time, but the transfer function is independent of such input. The inputs include wind, which drives waves of different wave numbers preferentially depending, for example, on the size of the driving weather system. A larger weather system will tend to produce more wave energy at longer wavelengths, corresponding to lower frequencies. The moon and sun's gravitational forces mostly drive the longest waves (tides). Only the longest waves are strongly influenced by global boundary conditions.

a unique relation between temporal frequency and spatial wavelength (or wave number). By contrast, complex physical media may have multiple branches of the dispersion relation or no dispersion relation at all, as discussed in section 4.3.

One important engineering challenge in EEG is to obtain more accurate volume conductor models $\hat{V}(k)$ and computer algorithms so that dura potential [$F(k,\Omega)$ or $f(x,t)$] can be reliably estimated from discrete scalp measurements [$\hat{F}(k,\Omega)$ or $\hat{f}(x,t)$]. Such approaches have been labeled "spatial deconvolution," "software lens," "deblurring," and "cortical or dura imagining" (Cadusch et al. 1992; Gevins & Cutillo 1995; Gevins et al. 1994; Le & Gevins 1993; Nunez et al. 1997; 1999). The surface spline-Laplacian of the scalp potential field provides an alternate, relatively robust, and model-independent method that gives estimates of dura potential that are typically similar to model-dependent dura imaging (Babiloni et al. 1996; Nunez 1995; Nunez et al. 1997; 1999; Perrin et al. 1987; 1989; Srinivasan et al. 1996; 1998); the spline-Laplacian should not be confused with the far less accurate nearest-neighbor (e.g., Hjorth) Laplacian.

4.3. Dynamics constrained by dispersion relations

A third compelling reason for following Fourier-transformed variables is that the transfer functions $H(k,\Omega)$ of many dynamic phenomena tend to be "contained" in relatively small regions of the (k,Ω) space, even though a very wide variety of complicated output behavior $f(x,t)$ may occur. For example, dynamic outputs of musical instruments (string, membrane, or air column displacement) and other wave phenomena typically obey dispersion relations $\Omega = \Omega(k)$, even though a wide range of musical sounds or other oscillatory phenomena may be produced by the same system. Thus, Fourier-transformed variables typically behave more simply than nontransformed variables, although there are important exceptions such as spatial-temporal chaos in turbulent fluids. For example, when discussing electromagnetic radiation in a vacuum, engineers typically take such dispersion relations for granted by referring to wavelength ($2\pi/k$) and temporal frequency (Ω) interchangeably, because the simple dispersion relation is $\Omega = ck$, where c is light velocity. Thus, one may speak unambiguously of "microwaves" in relation to longer waves (at lower frequencies) called "radio waves." A one-to-one correspondence between frequency and wavelength is taken for granted with electromagnetic waves in a vacuum. However, when electromagnetic waves travel through material media, field dynamics can be far more complicated. In extreme, but not unusual, cases dispersion relations may not exist. This is more likely to occur in nonlinear media but can also occur in linear media, such as linear plasma. Another example is illustrated in Figure 3, which shows an idealized transfer function $\hat{O}(k,\Omega)$ for ocean waves over a wide range of wavelengths ($2\pi/k$), from ripples to long, wind-driven waves to tides. The water wave dispersion relation relating temporal frequency (Ω) to wave number (k),

$$\Omega = k(g/k + bk)^{1/2} \tanh(kh), \qquad (4)$$

depends on three control parameters, g (the acceleration of gravity), b (related to surface tension), and h (ocean depth). The term on the far right is the hyperbolic tangent function. A wide variety of ocean wave dynamics is possible, de-

pending on the input function G(k,Ω) and control parameters. However, Newton's laws and the properties of water subjected to surface or gravitational forces effect a substantial restriction on the dynamics, as given by Equation (4). Thus, even if the input wind forces are unknown, we may expect ocean wave dynamic behavior F(k,Ω) to be somewhat similar to that shown in Figure 3, at least at large distances from sources of surface disturbance. That is, any sailor knows that water surface dynamics can be very complicated when nontransformed data are followed in the spatial-temporal domain. However, the water medium obeys Newton's laws, which place relatively severe limitations on dynamic behavior likely to be observed. Such restrictions are not so apparent to sailors observing the nontransformed sea surface but reveal themselves to oceanographers in the Fourier-transformed variables. If the input wind forces approximate spatial-temporal white noise, that is, G(k,Ω) relatively constant but with random fluctuations, the high mountain range in Figure 3 is expected to rise above the lower mountains associated with input forces that may be random.

To imagine dynamic behavior with no dispersion relation, consider a plot similar to Figure 3, but with multiple peaks and valleys similar to a portion of the Rocky Mountains. In this example, a particular choice of wave number k can be associated with a wide range of temporal frequencies. A storm in the ocean may drive ocean wave dynamics. The surface within the storm system (called the "near field") will generally satisfy no dispersion relation; both the surface and its Fourier transform will look like rocky mountains. By contrast, at some distance from the storm (called the "far field" or "wave field"), the nonwave parts of the surface disturbance are removed as a result of water dynamics. We are unlikely to use the term "wave" to describe spatial-temporal dynamics lacking well-defined dispersion relations. Rather, words such as "turbulence" or "spatial-temporal chaos" may be more appropriate. "Waves" are very special spatial-temporal fields for which the dynamics are severely restricted when viewed in Fourier-transformed space, although little hint of such restriction may be evident from nontransformed space-time observations.

Another common characteristic of waves is that Ω is a monotonically increasing function of k for most frequencies, wave numbers, and wave media. (Exceptions are labeled "anomalous dispersion"). If this holds true in brain dynamics, high temporal frequencies will be attenuated in the observed scalp potentials $\hat{F}(k,\Omega)$, as an indirect result of spatial filtering by the volume conductor rather than any dependence of V(k) on temporal frequency, an experimental finding that has been reported for alpha and beta rhythms (Pfurtscheller & Cooper 1975). An example simulation plotted in Figure 6 (p. 388) illustrates this idea.

4.4. Extension to nonlinear systems

A possible objection to the approach outlined above is that "the brain is nonlinear." That is, if the dynamic operator $\hat{\boldsymbol{D}}$ of Equation (1) is nonlinear, there is no simple definition of a transfer function, and Equation (2) is generally not valid. However, in engineering practice, Equation (2) is often applied to complex nonlinear systems, not because of "linear psychosis" but rather because it provides a useful bridge to deeper theoretical and experimental study. For example, in physical media, a relation between input g(x,t) and output f(x,t) can often be approximated by one or more linear relations, each applicable to a narrow range of the input function, or the relation (or operator) may be approximated by a linear relation in certain states of the system, perhaps when a control parameter multiplying a nonlinear term in $\hat{\boldsymbol{D}}$ is small. Linearization also may make a theory more robust over more applications, even though it may be less accurate in specific applications.

Given our current limited knowledge, any dynamic theory of neocortical function (linear or nonlinear) can, at best, be expected to provide a very crude approximation $\hat{\boldsymbol{D}}$ of the actual system $\boldsymbol{D}$. Thus, it may make sense to develop preliminary linear theory, partly to guide new experimental work, with the goal of later development of more accurate, nonlinear theory. My own bias has led me to seek crude success with experimental connections to linear theory before substantial effort is directed to nonlinear theory. One obvious reason is that a nonlinear theory must depend on the specific kind of nonlinearity employed. It is not enough to say that a system is "nonlinear"; a theoretical model must choose the type of nonlinearity from a number of potential candidates. This choice (often a relatively arbitrary assumption) must involve additional control parameters that are probably unknown for brain tissue. However, several extensions of this global theory using various nonlinear approaches are described in section 5.3.8 and the Appendix in the context of EEG experiments.

One ambitious, fully nonlinear theory of neocortical dynamics aims to derive rules of interaction in tissue at intermediate (mesoscopic) scales from rules at smaller scales (Ingber 1982; 1983). This mesoscopic approach of nonlinear, nonequilibrium statistical mechanics bears a complementary relation to the macroscopic local/global theory proposed here, similar to the relationship between the kinetic theory of gases and fluid mechanics. In contrast to many artificial neural networks, Ingber's statistical theory is based on genuine neocortical physiology. One interesting prediction is that the number of neural firing patterns that can simultaneously persist for several seconds is in the range of 5 to 10. Such patterns may store short-term memories that are known to be limited to 7 ± 2 items, for example, for auditory patterns (Ingber 1985). Another prediction involves the 4 ± 2 rule for visual pattern storage. Stability, duration, and statistical interactions of firing patterns appear to be consistent with short-term memory data. These apparent connections to memory may be fortuitous; however, they suggest fertile ground for future work. For example, preliminary attempts to reconcile the microscopic/mesoscopic statistical theory with the macroscopic global theory are noted (Ingber 1995a; Ingber & Nunez 1990).

5. A local/global theory of large-scale neocortical dynamics

In this section I outline a preliminary theory of the large-scale neocortical dynamics appropriate for verification, modification, or falsification based on scalp EEG. The theory emphasizes a combination of local and global physiological mechanisms. I use the term "local theory" to include dynamic descriptions based on intracortical (and possibly thalamocortical) feedback "circuits," with signal delays perhaps resulting mostly from postsynaptic potential rise and

decay times. Negative and positive feedback mechanisms at millimeter scales are critical to such theories. I also include dynamics at the single-neuron level in the category of "local theory," for example, intrinsic membrane oscillations (Jahnsen & Llinas 1984a; 1984b). This unequal division of dynamic behavior into a single "local" category, encompassing multiple spatial scales, and a single-scale "global" category is constructed to facilitate contact with large-scale EEG data. The dynamics of blood flow provides an analogy. We may categorize blood as a mixture of fluid and cells. The cells encompass dynamic behavior at many small scales not subject to macroscopic measurements. However, a biomedical engineer's practical description of the fluid-blood system is likely to contain only large-scale cell characteristics (representing aggregate small-scale properties) subject to macroscopic measurements.

Local theories are most compatible with functional segregation, and global boundary conditions are typically neglected to simplify analyses. These "infinite brain" approximations that neglect boundary conditions essentially assume that the spatial spectrum of neural activity at long wavelengths (comparable to a circumference of neocortex) contains negligible power. Thus, boundary conditions have no influence on predicted dynamic behavior, for example, on the interference of propagating neocortical synaptic fields. Local field potential theories having apparent connection to EEG include work by Wilson and Cowan (1972; 1973), Lopes da Silva et al. (1974), Freeman (1975), van Rotterdam et al. (1981), Zhadin (1984), and Liley et al. (1999). Any such theory (linear or nonlinear) can be represented by the "Local Network" box in Figure 4. Linear versions can be described by the local transfer function $L(\Omega;Q)$.

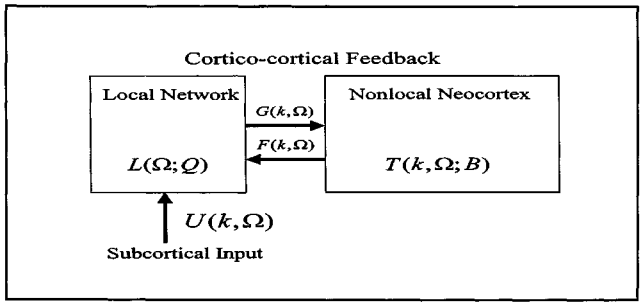

Figure 4. The box on the left represents "local" processes in neocortex at scales between roughly a millimeter and a few centimeters, including both positive and negative feedback. The local network may or may not include thalamocortical feedback. "Nonlocal" neocortical tissue is defined here as sufficiently distant that propagation delays along corticocortical fibers, which are neglected in local network models, are substantial. Although such distinct separation between local and nonlocal processes is artificial, it simplifies this presentation. Such simplification does not change the essential features of predicted dynamic behavior, as shown by the more comprehensive analysis given by Nunez (1995). This general picture applies to both linear and nonlinear processes. If linear approximations are valid, local $\hat{L}(k,\Omega;Q)$ and global $\hat{T}(k,\Omega;B)$ transfer functions can be defined so that differential equations are replaced by algebraic equations. A plausible approximation for long-wavelength scalp waves is $\hat{L}(k,\Omega;Q) = \hat{L}(\Omega;Q)$, as discussed in the text. From the definition of transfer functions, the local output is $G = \hat{L}(U + F)$ and the nonlocal output is $F = \hat{T}G$. When these equations are combined, $G = \hat{H}U$ is obtained, where the local/global transfer function $\hat{H}$ is given by Equation (5).

By "global theory" I mean that signal delays are mainly the result of finite propagation of action potentials along corticocortical fibers that provide positive feedback between multiple cortical regions. Furthermore, periodic boundary conditions owing to the closed neocortical surface typically exert important influences on the dynamics because of the required interference of synaptic fields. This approach emphasizes functional integration in neural tissue. Global theory of EEG has been published by Nunez (1972; 1974a; 1974b; 1981a; 1981b; 1981c; 1995), Katznelson (1981; 1982), Srinivasan (1995), Jirsa and Haken (1997), and Haken (1999); it is represented by the "Nonlocal Neocortex" box in Figure 4.

The term "regional circuits" has been used to describe dynamic processes intermediate between local and global (Silberstein 1995b). An important example might be a neural network in which both synaptic and propagation delays contribute to its dynamic behavior. Such "regional circuits" (e.g., large neural networks) fit naturally within the general conceptual framework of this target article but are not included in the specific theory outlined here. Inclusion of such regional networks within global fields may be an important part of twenty-first century neuroscience (Haken 1999; Ingber 1995a; Jirsa & Haken 1997; Tononi & Edelman 1998).

5.1. Competition between functional segregation and integration

Both local and global mechanisms are well established in neuroscience. However, their relative importance to neocortical dynamic behavior and EEG is controversial. Attempts to combine local and global effects and to evaluate their relative importance have been published by Nunez (1981a; 1981b; 1981c; 1989a; 1995; 1996; 1997), Nunez and Srinivasan (1993), Srinivasan and Nunez (1993), Tononi (1994), Silberstein (1995b), Friston et al. (1995), Wright and Liley (1996), Jirsa and Haken (1996; 1997), Robinson et al. (1997), Tononi and Edelman (1998), Haken (1999), and Liley et al. (1999). Local/global theory includes interactions between the two boxes in Figure 4.

Here, I favor neither side of this controversy, although my own work has been mostly on the global side, where more contact with large-scale (scalp) EEG data has been achieved. Rather, I suggest that, given our current meager understanding of physiological control parameter ranges, we should focus on the likelihood that both local and global mechanisms generally contribute to dynamic behavior. One or the other may be more dominant in different brain states, or perhaps over different wave number ranges of the dynamics. By analogy, surface tension, gravity forces, or bottom effects may dominate ocean waves, depending on control parameters and wavelength, as shown by Equation (4). With this approach, local versus global arguments of brain function and EEG reduce to issues of relative magnitudes of local and global control parameters occurring in each brain state. By analogy to our social system, the dynamics of croissant consumption may reflect both local (e.g., family) and global (e.g., television) influences.

5.2. A local/global neocortical transfer function

A local/global neocortical transfer function, derived from known physiological processes but with seemingly appro-

priate linear approximations to input/output in neural tissue at centimeter scales, follows directly from Figure 4 (Nunez 1989a; 1995). That is, action potential output from the local network (G) is the product of the estimated local/global transfer function ($\hat{H}$) and subcortical input (U), where

$$\hat{H}(k,\Omega;B,Q) = [\hat{L}(k,\Omega;Q)]/[1 - \hat{L}(k,\Omega;Q)\,\hat{T}(k,\Omega;B)] \quad (5)$$

The dynamic transfer function $\hat{H}$ takes on this relatively simple form, in which it depends on only two control parameters (B,Q), provided that the ratio of characteristic global (corticocortical, τ_g) to local (e.g., PSP rise, τ_l) times is fixed. Also, the wave number (k) and frequency (Ω) are nondimensional variables here, normalized in terms of characteristic intracortical and corticocortical interaction lengths and propagation speed, also assumed to be fixed parameters in this introductory discussion. Here $\hat{L}(k,\Omega;Q)$ is a local transfer function dependent on a local control parameter Q. A semicolon separates the independent variables k and Ω from control parameters. In several local theories, Q is proportional to the product of intracortical inhibitory and excitatory feedback gains in local circuits. The global transfer function $\hat{T}(k,\Omega;B)$ depends on a global control parameter B, which is proportional to positive feedback gains established by corticocortical fibers. Both B and Q are independent of delay times in this model. It is assumed that they change with brain state as a result of neuromodulatory influences on the strengths of local (positive and negative) and global (positive) feedback. Equation (5) is based only on linear processes. However, a set of nonlinear differential equations, which include cubic nonlinear negative feedback mechanisms, is proposed by Equations (23) and (24) in the Appendix. These equations describe much more complicated input/output relations, but many of the general ideas are adequately illustrated by the linear description.

A derivation of Equation (5), definitions of nondimensional variables, estimates of the physiological parameters, a semiquantitative solution, and studies of the effects of various assumptions are presented in Nunez (1995). This work is too lengthy to repeat fully here. However, the basic idea is illustrated by Figure 4. Synaptic action from the midbrain $U(k,\Omega)$ provides synaptic input to a local mass of neocortical cells (box at left). "Local" positive and negative feedback by intracortical fibers (and possible thalamocortical loops, depending on specific local theory) process this input to produce output action potentials $G(k,\Omega)$. We expect this process to be nonlinear; however, if linearity is assumed in this elementary version, the local system acts according to the local transfer function $L(k,\Omega;Q)$. The local output action potentials $G(k,\Omega)$ then provide excitatory input to the entire nonlocal neocortex through corticocortical fibers. The global neocortical system integrates this input according to the global transfer function $T(k,\Omega;B)$ to produce excitatory synaptic output $F(k,\Omega)$, indicated by the box at the right. Complications such as the distribution of corticocortical fibers must be considered to derive $T(k,\Omega;B)$. However, this second stage is believed to be fundamentally linear because it essentially assumes that the number of active synapses (output) is proportional to the number of action potentials (input) at earlier times. The global synaptic output $F(k,\Omega)$ provides additional input to each local mass. Although there are many physiological details to be studied in the future, the main point for this target article is that Equation (5) was derived from plausible physiology and contains separate, but complementary, local and global contributions to dynamic behavior.

In the case of dynamics on a closed (e.g., spherical) surface, we might choose to express $\hat{G}(k,\Omega)$ as $\hat{G}(n,m,\Omega)$, where the (n,m) indices label spatial frequencies in two surface coordinates (e.g., latitude and longitude in spherical coordinates). However, the simpler wave number idea is sufficient for this general outline. This theory differs from metaphorical approaches to "model" brain dynamics in that it is based on physiology and anatomy that is known, at least in outline. It is also based on a number of approximations that could turn out to be wrong or perhaps valid only for a very limited number of brain states. Readers interested in the mathematical details should consult the Appendices of this article and the Nunez (1995) book. However, for purposes of this target article, the central issue is not so much whether the theory is right or wrong but whether it provides a useful, semiquantitative environment in which to discuss the general conceptual framework outlined here. If the theory can accomplish this goal, it should provide guidance to future theoretical and experimental work.

5.3. Special (limiting) forms of the transfer function

Equation (5) illustrates several predicted aspects of EEG dynamics that may hold true, even when more accurate theories are later developed, because these features appear to have general validity, that is, they appear to be largely independent of detailed physiological assumptions of this specific theory.

5.3.1. Local/global resonances occur in several ways. As formulated here, the magnitude of the local transfer function $\hat{L}$ is less than one at all spatial and temporal frequencies because it converts synaptic input into action potential output. By contrast, the global transfer function $\hat{T}$ is larger than one because it converts action potential input to synaptic output. The product $\hat{L}\hat{T}$ is less than or on the order of one. The full (local/global) dynamic transfer function $\hat{H}$ tends to be large if the local function L is large. $\hat{H}$ will also be large if $(\hat{L}\hat{T})$ is close to one. This latter condition defines, with physiologically based mathematics, a "matching" of local and global resonances, which is a possible mechanism to facilitate interaction between remote cell assemblies, as discussed in section 5.3.6. Regions of (k,Ω) space where $\hat{H}$ is large ("mountain ranges") correspond to multiple branches of dispersion relations for the putative "brain waves." Such dynamics may exhibit large changes resulting from changes in the parameters (B,Q) that control the state of this model cortex.

5.3.2. Local properties at long (e.g., scalp) wavelengths may be independent of wavelength. Equation (5) may be used with several different local theories in which the relation between synaptic input and action potential output has been approximated as linear. Most intracortical fibers are shorter than a few millimeters. Thus, characteristic interaction lengths for such theories are much shorter than wavelengths of scalp-recorded EEG. For this reason, we might expect local transfer functions to be approximately independent of wave number in regions of (k,Ω) space where wavelengths $(2\pi/k)$ are large. This approximation has been derived mathematically in at least one such local

theory (van Rotterdam et al. 1982). In this case, $\hat{L}(k,\Omega;Q)$ may be replaced by $\hat{L}(\Omega;Q)$, where the approximation applies to all scalp recordings and all intracortical recordings using electrodes with diameters larger than several millimeters.

5.3.3. Purely local phenomena may occur. If long-range positive feedback is negligible (e.g., there are no corticocortical fibers, or the global control parameter B is small owing to specific neuromodulatory influences), the global transfer function in Equation (5) is small. In this limiting case, the full transfer function is essentially the local transfer function, that is

$$\hat{H}(k,\Omega;Q) = \hat{L}(k,\Omega;Q) \qquad (6)$$

This may be a valid approximation for some brain states. In this basic version of the theory, the cortical/white matter system is assumed to be homogeneous, but, in more detailed versions, the parameters Q and B may be functions of cortical location. Thus, we generally expect many local cell groups with different properties, together with regional networks at various scales that can perhaps be studied with intracranial recordings. Such mathematical and physiological complications will provide many future challenges, but are unnecessary to illustrate the central ideas of this target article.

I will describe one published local transfer function (van Rotterdam et al. 1982), although other local theories (e.g., Freeman 1975; Liley et al. 1999) could also illustrate the general conceptual framework. The dominant frequency band depends on rise and decay times of postsynaptic potentials (PSPs) and the local feedback gain Q. The magnitude of this gain is not known for genuine tissue. However, if the oscillations are to be weakly damped, Q must lie in a confined range. In this case, the predicted local nondimensional frequency Ω is approximately one, ($\Omega = 2\pi f\tau_1 = 1$), or $f = 1/2\pi\tau_1$ (Hz), where τ_1 is a characteristic local delay time given by the square root of the product of excitatory PSP (EPSP) and inhibitory PSP (IPSP) rise times. If EPSP and IPSP rise times (with matching decay obtained from cable theory) are about 10 and 20 msec, respectively, the dominant frequency range is near $f = 11$ Hz. However, published EPSP and IPSP rise times are typically shorter (Rall 1967), perhaps 3 and 5 msec, respectively. With these shorter delays, the $\Omega = 1$ case represents higher frequencies, in the range $f \cong 41$ Hz. One may guess, however, that local oscillations over relatively broad frequency ranges are possible in different tissue masses owing to variations in local membrane properties, feedback gains, PSP rise times, and other fixed anatomical and variable neuromodulatory influences that occur in different brain states (Liley et al. 1999; Lopes da Silva 1991; 1995; Wright & Liley 1994). A version of local input/output relations is given by the partial differential equation (14) in the Appendix.

5.3.4. Purely global phenomena may occur. In regions of (k,Ω) space where periods ($2\pi/\Omega$) are much longer than local delay times (rise and decay of PSPs), the local transfer function varies slowly with frequency, and no local resonance occurs. In this frequency range, input to the local network passes through without further processing and the full transfer function in Equation (5) is approximately

$$\hat{H}(k,\Omega;B) = \text{Constant}/[1 - \text{Constant}\,\hat{T}(k,\Omega;B)] \qquad (7)$$

Neocortical resonance is by exclusively global mechanisms in this frequency range. By setting the denominator of Equation (7) to zero, we obtain the global dispersion relation $\Omega = \Omega(k)$. Again, we may conjecture that this is a valid approximation for some brain states. The most likely corresponding EEG states may occur under anesthesia, the 3-Hz spike and wave of epilepsy, and to a lesser extent some sleep stages and the awake alpha rhythm. These states of minimal cognitive processing often exhibit widespread, spatially coherent EEG data that are most likely associated with globally dominated dynamics, as partly illustrated in the upper panels of Figures 1 and 2. For relatively small values of the control parameter B, mode frequencies are not sensitive to moderate changes in B. Rather, dominant frequencies depend mainly on corticocortical propagation velocity and wave number. Allowed wave numbers depend on global boundary conditions in the cortical shell as discussed below. The equivalent linear partial differential equation (11) and a related set of nonlinear ordinary differential equations (22) based on cubic nonlinear feedback are given in the Appendix.

5.3.5. Global oscillations are partly determined by neocortical boundary conditions. Global boundary conditions (periodic) allow oscillatory dynamics to persist only for specific wave numbers (or the n,m indices on closed surfaces). For example, excitatory and inhibitory synaptic action fields must be single-valued functions of surface coordinates if they are genuinely measurable fields. Because of the interference of propagating synaptic activity on the cortical surface, only certain discrete wavelengths of standing waves can persist, as in analog physical systems such as musical instruments, atoms, chemical compounds, resonant cavities, and so on. For example, destructive interference is expected when regions of enhanced excitatory synaptic activity interact with regions of enhanced inhibitory activity. Over time, such destructive interference tends to remove synaptic action fields that fail to match global boundary conditions.

Such fundamental connections between interference, boundary conditions, standing waves, and resonances occur throughout physical science and engineering. For example, in simple one-dimensional systems such as string or wind musical instruments, only wavelengths equal to twice the length of the system divided by an integer (n = 1, 2, 3, . . .) can persist. In more complex geometry, inhomogeneous or anisotropic systems, or systems closed on themselves, the allowed "wavelengths" (or quantum numbers n,m) are typically limited by more complex rules; however, the basic principle of wavelength restriction by boundary conditions still applies. Examples include quantum wave functions in atoms, electromagnetic radiation generated by random lightning strikes in the resonant cavity formed by the earth's surface and the bottom of the ionosphere ("Schumann resonances"; Jackson 1975), and, as suggested here, oscillations of synaptic action (and by implication EEG) in the closed neocortical/white matter "shell." The specific geometry of neocortex is not critical to these general arguments. It is necessary only that synaptic action fields propagate in multiple directions as a result of action potentials in intracortical and corticocortical fibers. Such fields must either damp out quickly or interfere on the cortical surface. Such interference between excitatory and inhibitory fields may be linear or nonlinear. In either case, we expect boundary conditions to force the occurrence of standing waves.

When the wave number restriction is combined with the

dynamic restrictions implied by the transfer function (or dispersion relation), preferred temporal frequency ranges are predicted. In other words, such systems act as band-pass spatial – temporal filters. These special (or resonant) frequency ranges emerge from a combination of tissue (or other media) properties and global boundary conditions. When periodic boundary conditions for the neocortical surface are combined with the global transfer function, Equation (7), a series of global modes (i.e., global resonant frequencies) is predicted. Detailed discussion of parameter ranges and the effects of various physiological parameters is presented in Nunez (1995). However, the basic idea is simple. The purely global theory predicts lowest frequencies (e.g., fundamental and lower overtones) in the general range $f = 1/2\pi\tau_g$ (Hz), where τ_g is a characteristic global delay time; τ_g is roughly 10–30 msec, as a result of action potential propagation (6–9 m/sec) along the longest corticocortical fibers (10–20 cm), which have the strongest influence on dynamics predicted by the global theory. Thus, the predicted frequency range for the lowest (fundamental) mode is roughly $f = 5$–16 Hz.

Of course, much more detailed analyses are required to include the effects of distributed corticocortical fiber lengths, propagation speed distribution, feedback gain, and so on. Most of these details do not appear to alter the general semiquantitative results outlined here (Nunez 1995). However, when the global feedback gain parameter B is increased above certain mode-dependent critical values, mode frequencies (fundamental and overtones) can decrease sharply, in a manner suggestive of transitions from the awake to sleeping states or varying depths of halothane anesthesia (Nunez 1995).

When the parameter B is small to moderate, the lowest (fundamental) global mode is roughly in the 10-Hz range, within a factor of perhaps two or three. By contrast to the local oscillations discussed in section 5.3.3, a large number of global mode overtones can occur, but these are equal at all cortical locations. Such overtones can be very closely spaced; they are not generally harmonics of the fundamental.

5.3.6. Most brain phenomena involve combined local and global effects. I have conjectured extreme cases when local, Equation (6), or global, Equation (7), processes dominate neocortical dynamics. However, most brain states probably involve both large-scale functional integration (facilitating global contributions to the dynamics) and functional segregation (enabling local effects). Figure 5 illustrates two examples of local/global dynamic behavior in the model system, described by the transfer function, Equation (5). The nondimensional frequency Ω is normalized with respect to the global delay time τ_g. In Figure 5 (top panel), the local delay parameter τ_l is chosen so that both local and global processes contribute to preferred frequencies in roughly the 0–10 Hz range. By contrast, Figure 5 (bottom panel) shows an example where only global mechanisms contribute substantially to the lower frequency range. In addition, however, local and global mechanisms combine to provide activity at a higher frequency range, perhaps $f = \Omega/2\pi\tau_g = 33$–46 Hz. Although the physiological parameters, which determine the specific shapes of the transfer function and mode frequencies, are not known with sufficient accuracy for close quantitative comparison with EEG data, all parameters in these examples are in plausible physiological ranges. That is, in contrast to metaphorical approaches to modeling, the theory contains no "free" parameters. These parameters have a physiological basis. Thus, future adjustments based on new, independent experiments can be anticipated.

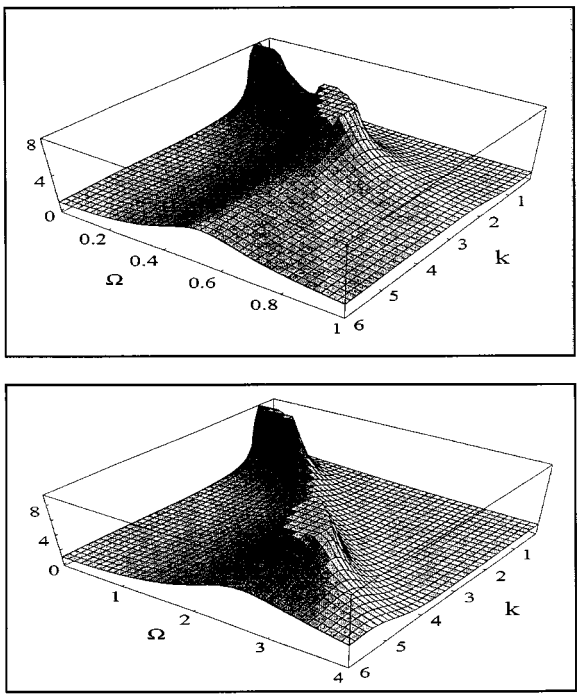

Figure 5. The theoretical transfer function derived for a model neocortex and given by Equation (5) is plotted versus nondimensional frequency (Ω) and wave number (k). Ω is normalized with respect to a characteristic global delay time τ_g, which equals $\lambda(v)^{-1}$, where λ^{-1} is a characteristic length for falloff of corticocortical fiber density and v is action potential speed in these fibers. Frequency (Hz) is given by $f = \Omega/2\pi\tau_g$. Wave number is normalized with respect to λ^{-1}. In these examples, both local (Q) and global (B) control (e.g., feedback) parameters are sufficiently large to exert important influences on the dynamics. In the top panel, PSP rise and decay times are chosen to be sufficiently long so that both local and global processes contribute to the approximate range 0–10 Hz. For example, if $\lambda v = (1/6\ \text{cm}^{-1})(700\ \text{cm/sec}) = 117\ \text{sec}^{-1}$, the broad peak near nondimensional frequency $\Omega = 0.4$ corresponds to about 7–8 Hz. In the bottom panel, dynamics in the range $\Omega = 0$–1 (roughly 0–19 Hz, if the same global delay is used) is dominated by global mechanisms, whereas dynamics near $\Omega = 2$ (in roughly the 38 Hz range) are determined by both local and global mechanisms. Global contributions result from influences of higher resonant modes, determined partly by global boundary conditions. These higher modes are overtones of the fundamental frequency. Such overtones are generally not harmonics.

The matching of local and global resonances may be illustrated with a physical example involving purely global modes of simple (e.g., nondispersive sound or electromagnetic) waves in a prolate spheroid shell (roughly the shape of a rugby football; Nunez 1995). These differ substantially from the putative "brain waves," but resonances are obtained from a dispersion relation equivalent to setting the denominator of Equation (7) to zero. Assuming propagation speed and surface area that roughly match neocortical/corticocortical parameters (near 6–9 m/sec and 1,500–2,000 cm^2, respectively), global mode frequencies (Hz) are something like 10, 12, 17, 18, 21, . . . , 39, 40, 42, 45, etc. These specific numbers are not critical; they are

not rigorously derived from physiology. The main point is that many closely spaced global modes may occur, which are in the general range of EEG frequencies. These preferred (or "resonant") frequencies refer to modulations of synaptic action and action potential fields about background levels; there is no guarantee that they will be observed in EEG. However, according to Equation (5), the local/global transfer function $\hat{H}$ will be large when both local $\hat{L}$ and global $\hat{T}$ transfer functions are large so that the product $\hat{L}\hat{T}$ is close to one. For example, if local networks at two locations x_1 and x_2 have resonances in the 10 and 40 Hz ranges, respectively, both will tend to be enhanced by global modulations of synaptic action in their respective frequency ranges. On the other hand, the many global modes not matching local modes may be too weak for observation as EEG.

5.3.7. EEG pacemakers. The old idea of thalamic pacemaker origins of EEG can be extracted as a very special case of the general picture presented here. For example, if only one of the local networks depicted in Figure 4 produces resonant frequencies, its dynamic behavior might be forced on the entire global system by its output G. For purposes of these general arguments, it does not matter whether the local network is located in the thalamus, in a region of neocortex, or both. The essential idea of a pacemaker is that its dominant frequencies are determined by internal mechanisms, not by feedback from external tissue masses. Such pacemakers might occur at membrane levels (Steriade & Llinàs 1988) or at multiple network levels. However, "pacemakers" (at any spatial scale) must have very restricted input to preserve autonomy. The accuracy of such membrane autonomy (Freeman 1992a; Lopes da Silva 1995) and thalamic network autonomy (Lopes da Silva 1991; 1995) has been critically questioned.

Another problem is that the pacemaker's target system can be expected to respond most strongly when the target's input frequency matches one of its own resonant frequencies (Nunez 1995). In this case, however, the distinction between target system and pacemaker is likely to be lost; we can just as easily think of the target driving the pacemaker as the pacemaker driving the target. If one insists (as some physiologists do) on crediting all EEG to "pacemakers," the local theory presented here could be described in terms of many such "pacemakers" associated with many local networks (Fig. 4). However, in a brain with dense thalamocortical, intracortical, and corticocortical connections, the dynamics of each "pacemaker" is likely to be altered by many other "pacemakers," so this label appears to provide a generally unsatisfactory description of dynamic brain behavior. If a genuine autonomous pacemaker of a particular brain rhythm were actually to be verified for a small tissue mass, the arguments put forward here strongly discourage unsubstantiated extrapolation of this mechanism to other EEG phenomena.

5.3.8. Frequency estimates, instability, and quasilinear theory. Numerical frequency estimates applied to the nondimensional frequency plotted in Figure 5 are based partly on the assumption that the local and global control parameters B and Q are close to values for which the linear theory predicts instability. This choice of parameters is consistent with weakly damped oscillations, which may be physiologically unrealistic. However, larger control parameters do not necessarily lead to instability (e.g., epilepsy), only a breakdown of the linear theory. To account approximately for nonlinearity, action potential density in a neural mass was assumed to be a sigmoid function of synaptic input (Nunez 1995), as suggested by Wilson and Cowan (1973) and Freeman (1975). The sigmoid function describes a system where increased excitatory synaptic input at moderate levels causes a steep rise in the number of output action potentials, but only small increases in output at high excitatory input. This could occur at very high excitatory synaptic input because of saturation of the neural mass, perhaps in epilepsy, but it could also be part of normal brain operation, occurring at much lower input levels owing to recruitment of additional local cortical or thalamic inhibitory feedback not included in the linear theory. This assumption leads to prediction by the purely global theory that EEG consists of a linear combination limit cycle or perhaps chaotic (in time but not space) global modes as shown in the Appendices of this article and the Nunez (1995) book.

Limit cycle behavior is well established in many fields, such as mathematics, physical science, and ecology. Limit cycles (or "self-excited oscillations") occur when damping functions change sign at large amplitudes, typically from selective external energy input in physical systems (e.g., electric circuits). The global limit cycle modes discussed in the Appendix can coexist with local temporal chaos or local limit cycles, such as those predicted by Wilson and Cowan (1973). An important message of this very crude, semiquantitative theory is that quasilinear approaches to global theory are fully consistent with the idea of complementary local and global neocortical dynamics, as shown in the Appendix.

The following equation for limit cycle frequencies f_{nm} (Hz) corresponding to spatial modes (n,m) provides a semiquantitative idea of the general predictions of the global theory:

$$f_{nm} = (v/2\pi R)\,[S_{nm} - b_{nm}\lambda^2 R^2]^{1/2} \qquad (8)$$

Here, v (cm/sec) and λ^{-1}(cm) are characteristic action potential speed and fall-off distance in the density of corticocortical fibers, respectively. R(cm) is a linear scale factor for the model neocortical system, for example, circumference/2π for a closed loop, radius of a sphere, or semimajor axis of a prolate spheroid. Surface shape determines the indices (or "quantum numbers") S_{nm}. The case of extreme anisotropic corticocortical fibers (e.g., only in anterior-posterior directions in each hemisphere) may be crudely represented by a one-dimensional closed loop of cortex. For the closed loop, $S_{nm} = n^2$, where $n = 1, 2, 3, \ldots$ independent of m. For the sphere with isotropic, homogeneous cortococortical fibers, $S_{nm} = n(n + 1)$, where the index n numbers the fundamental ($n = 1$) and overtone frequencies. The prolate spheroid and other more complicated surfaces or anisotropic or inhomogeneous fiber systems are expected to have limit cycle overtones that depend on both (n,m) indices. The mode-dependent parameters b_{nm} are related to the global control parameter B in Figure 3; they are generally expected to increase as the strength of corticocortical feedback is increased. If these parameters are mode independent, then $b_{nm} = (B - 1)$, as shown in the Appendix. Limit cycles are predicted in this crude quasilinear approximation for modes with b_{nm} greater than one but sufficiently small so that the term in the square root in Equation (8) is positive.

It is emphasized that the exact form of Equation (8) cannot be taken too seriously. It is derived in the Appendix only for the one-dimensional loop with mode coupling assumed to be negligible. However, in nonlinear systems, spatial modes (n,m) generally interact with each other to complicate dynamic behavior, although there is evidence in some physical systems that boundary conditions can force more regular behavior (see, e.g., Bishop et al. 1983; Nunez & Srinivasan 1993; Srinivasan & Nunez 1993). However, in this crude estimate, each limit cycle mode oscillates independently, and synaptic fields are linear combinations of these spatial modes. Generally, this approximation is not valid, and mode coupling is expected. However, for values of b_{nm} greater than but close to one, Equation (8) can perhaps provide some general ideas on how global oscillations should behave. The reason for optimism about qualitative and perhaps semiquantitative predictions is that Equation (8) originates from genuine physiology, not metaphor. If this approximate picture appears plausible, it should motivate more accurate studies of both physiology and mathematical approximations by talented scientists in the context of the global theory. In section 6, Equation (8) is used to make some predictions of global EEG phenomena that appear to be relatively robust, that is, somewhat independent of simplifying assumptions used to derive them.

To provide more quantitative demonstration of these ideas, nonlinear versions of the global and local/global theories, which include approximations to mode coupling, are derived in the Appendix. Figure 6 shows two numerical solutions to the purely global equations. The upper plot consists of the sum of five spatial modes in a rectangular medium of length three times the width. This geometry was chosen mainly for mathematical simplicity, but does have some rough correspondence to the geometry of a single hemisphere as discussed in the Appendix and in Nunez (1995). The upper plot crudely simulates dura potential. The lower plot originates with the same solution, but includes only the sum of the two lowest spatial modes or "order parameters" [$\Phi_1(t) + \Phi_2(t)$, defined in the Appendix]. That is, the volume conductor is assumed to filter spatially the higher modes between brain and scalp as indicated in Equation (3). Thus, the lower plot crudely simulates the corresponding scalp potential. However, because the underlying dynamics associate higher temporal frequencies with higher spatial frequencies (in a manner similar to linear waves satisfying a dispersion relation), spatial filtering causes the temporal filtering evident in the lower plot. Genuine properties of the volume conductor were not used here to construct the spatial filter, but the qualitative behavior shown here is probably valid as discussed on pages 57–63, 79–81, and 383–87 of Nunez (1995). The time axis is normalized with respect to the parameter τ_g, which appears to be roughly in the 10 msec range. In this case, the period shown is about 1 sec and the dominant frequency is near 11 Hz. These oscillations are caused exclusively by global delays.

Example solutions of nonlinear local/global equations derived in the Appendix are shown in Figure 7. Local frequencies – q = q(Q), perhaps determined by local PSP rise and decay times and local feedback gain Q – progressively increase down the page. With τ_g equal to 10 msec, the period shown is 2 sec, and dominant frequencies vary from about 10–18 Hz as q increases. These four example oscillations are caused by a combination of fixed global and variable local delays.

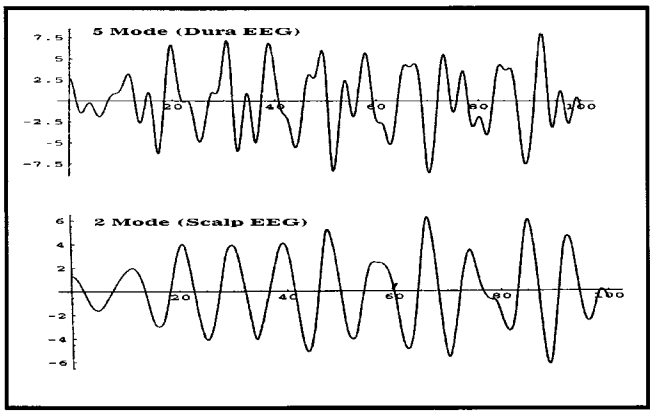

Figure 6. Solutions of the system of global mode equations (22), derived in the Appendix. The system consists of 5 coupled, second-order ordinary differential equations, each with about 40 mode-coupling terms. The vertical axis represents normalized synaptic action density at centimeter scales. The horizontal axis is normalized time [time (sec)/τ_g], where $\tau_g = 1/\lambda v$ is the characteristic global delay time, apparently in the 6–16 msec range based on long corticocortical fibers. If τ_g = 10 msec, the period shown is 1 sec and dominant frequencies are in the 11-Hz range. The upper plot is the sum of modes $\Phi_n(t)$, n = 1, 5, crudely representing dura potential. The lower plot is the same solution, but with modes n = 3, 4, and 5 removed to simulate crudely spatial filtering by the head volume conductor between dura and scalp. Other numerical solutions (not shown) indicate that increases in the linear feedback parameter B cause amplitudes to increase with minimal frequency changes for small to moderate B. Large B values produce solutions with larger amplitudes and lower frequencies. The parameters for this numerical solution are B = 2.2, A = 0.0667, k_n^2 = 1.5, 1.95, 2.70, 3.75, 5.10 (n = 1, 5, consistent with the rectangular geometry discussed in the Appendix).

6. Experimental connections to theory

The truism "any theory must ultimately stand or fall based on experiments" provides a necessary, but insufficient, paradigm for neurodynamic theory verification. First, no rational neuroscientist is likely to suggest that any current brain theory approaches the quantitative accuracy and general applicability of modern physical theories. Rather, one may hope to identify crude theory that approximately describes EEG observed in one or (we hope) several brain states. Second, it is often very difficult to interpret experimental EEG in the context of any particular theory; very few EEG experiments were designed to test theory. Thus, questions of experimental verification of the proposed local/global theory do not often have simple yes-or-no answers.

For example, local EEG theories typically contain unknown control parameters. Several neuroscientists continue the struggle to connect such theories more closely to genuine physiology. This work should be encouraged, but several barriers must be overcome, including estimating influences of multiple neurotransmitters on control parameters, such as local feedback gains. Furthermore, when purely local theories are tested (say, with intracranial electrodes), the influence of global dynamics acting (top down) on local systems is nearly always unknown. Similarly, when global theory is tested, we cannot be sure of the importance

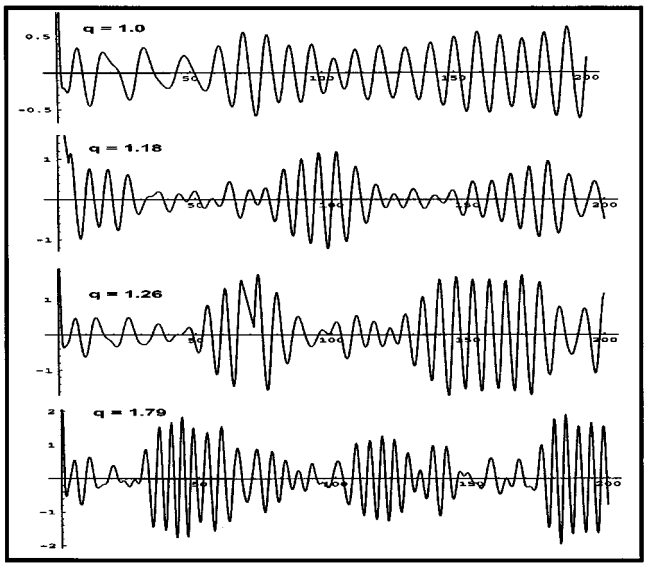

Figure 7. Solutions of the local/global mode equations (23) and (24), consisting of 10 coupled second-order ordinary differential equations, are shown (5 synaptic and 5 action potential modes). In some local theories, the local frequency q = q(Q) depends on the ratio of local to global delay times and a local feedback parameter Q. Local damping is here assumed fixed at a(Q) = 0.1. If $\tau_g = 10$ msec, the period shown is 2 sec and dominant frequencies increase from about 10–18 Hz as q increases. All four plots consist of the sum of modes $\Phi_n(t)$, n = 1, 5, crudely representing dura potential. The parameters for this numerical solution are B = 2.0, A = 1.333, k_n^2 = 1.5, 1.95, 2.70, 3.75, 5.10 (for n = 1, 5).

of local effects (say, EEG "pacemakers"). However, we appear to know much more about the physiological parameters of the purely global theory. Thus, if we are able to identify brain states in which local effects are minimal, qualitative and semiquantitative predictions of the purely global theory can be achieved.

A critic may rightly complain that this approach leaves the global theoretician with an easy way to avoid falsification of global theory. Any data found to be inconsistent with global theory can always be blamed on local effects not included in the theory. This criticism is valid; I know of no fully satisfactory way to overcome this problem in the near future. This is also a common problem with experimental verification in complex physical systems. The world's weather system comes to mind in this context. Dynamic theories of such complex fluid systems are typically successful only in limited contexts, for example, in tightly controlled experiments designed to eliminate confounding influences on simplified theories.

I suggest that success of the global theory depends on its ability to predict outcomes of an expanding class of disparate experiments involving coherent EEG phenomena, but, in the absence of such theory, it is unlikely that such experiments will ever be carried out. By "successful" I mean "useful" and partly valid for some brain states. Even such relatively modest success should provide substantial influence on neuroscience. Thus, the following summary of several dozen apparently correct semiquantitative experimental predictions of the global theory are offered, together with conjectures on the possible contributions of local and regional networks. More detailed discussions of these connections may be found in Nunez (1995).

6.1. Frequencies in the EEG range are expected

Human corticocortical propagation speeds (v) are distributed, with distribution apparently peaked in the 6–9 m/sec range (Katznelson 1981; Nunez 1995). The scale factor (R) for human neocortex can be estimated from its surface area. There are fewer interhemispheric fiber connections (mostly callosal fibers) than intrahemispheric connections, suggesting that a single hemisphere may be the more appropriate wave medium. On the other hand, a hemisphere is elongated, somewhat like a prolate spheroid for which R is the semimajor axis. These two effects tend to move R estimates in opposite directions. However, a conservative surface area range of 1000–3000 cm^2 yields R = 9–15 cm. Thus, the term $(v/2\pi R)$ in Equation (8) has a magnitude in the range 6–16 Hz.

For corticocortical fibers that span large portions of the model cortex, λR is on the order of one. Neuromodulation (state-dependent) and corticocortical fiber density (fixed) determine the parameters b_{nm}. For example, if these parameters were mode-independent, all b_{nm} would equal (B − 1) in the one-dimensional closed-loop geometry, as shown in the Appendix. This feedback gain parameter B can be crudely estimated from physiology (Nunez 1995), but has a large error range with the state of current knowledge. Each b_{nm} parameter in Equation (8) must be greater than one for the corresponding limit cycle to occur, but not so large that the quasilinear approximations are invalid. An example of waves on a prolate spheroid surface of small eccentricity illustrates the main ideas. The surface shape determines the indices $S_{nm} = n(n + 1) + \alpha m^2$, where α depends on the eccentricity of the prolate spheroid, and the indices run n = 1, 2, 3, . . . ; m = −n, + n. Suppose λR = 1, $(v/2\pi R)$ = 11 Hz, α = 0.3, and b_{nm} = 1.3 for all (n, m). The two lowest limit cycle frequencies (n = 1, m = 0,1) are approximately 9 and 11 Hz. If neuromodulatory input causes the b_{nm} to increase to 1.8, frequencies of these modes decrease to 5 and 8 Hz, respectively. For b_{nm} greater than 2.0 but less than 2.3, the mode (n = 1, m = 0) becomes nonoscillatory, and the mode (n = 1, m = 1) occurs in the delta frequency range. Still, larger b_{nm} values cause higher overtones to decrease in frequency.

The b_{nm} parameters are physiologically based, but unknown. For this reason, precise predictions of limit cycle frequencies are not now possible. However, in the model system, lower global modes in roughly the 0–20 Hz range can easily occur. This general "prediction" does not depend on model details; it is sufficiently robust to have motivated a search for dominant frequencies in this range had it been made before the first human scalp recording was made in the 1920s.

6.2. Different brain states prefer different mode frequencies

As the feedback gain parameters b_{nm} increase, perhaps as a result of subcortical neuromodulation, frequencies of lower modes decrease sharply and new, higher global modes (which are strongly damped with small b_{nm}) may occur, which decrease in frequency for still larger b_{nm} values. The global mode frequency decreases are somewhat suggestive of EEG in transitions from awake to sleeping states. Local mode frequencies are partly independent of global modes and depend on the control parameter Q. In contrast with global modes, local modes depend on cortical region.

However, local oscillations may be enhanced by matching one of the (many) global modes. In this manner, synchronous communication between remote cell assemblies having no direct connections may be facilitated (refer to the Appendices of Nunez, 1995, and this target article for mathematical support).

Mode scanning effects are expected with drugs that modulate neocortical dynamics (Katznelson 1981; 1982; Nunez 1995; Nunez et al. 1977). That is, for each model brain state, determined by the (Q,B) control parameters, there are generally different preferred frequency ranges. There are also parameter ranges where the transfer function $\hat{H}(k,\Omega)$ is relatively flat, implying that corresponding EEGs will resemble low-pass noise, with frequencies higher than about 50 Hz mostly eliminated by resistive/capacitive membrane effects (Nunez 1995). This kind of behavior is generally expected in complex, brain-like model systems and is certainly not unique to the local/global theory outlined here. However, it contrasts with the typical pacemaker idea of separate alpha, theta, and so on, "generators" operating in small, isolated tissue volumes. In the context of the local/global theory, isolated "pacemakers" defined this way dominate dynamic behavior only in the absence of corticocortical interactions and intracortical overlap between regions. Such conditions appear to be more the exception than the rule. Local or larger (regional) resonant networks may be embedded in the global system, but their dynamics depend partly on global synaptic field effects because such networks are never fully isolated from surrounding tissue.

To illustrate mode scanning, we summarize a study of human EEG recorded in a subject under varying depths of anesthesia (Nunez 1981a) that is qualitatively consistent with the purely global theory (Katznelson 1981; Nunez 1995). Very light (subanesthetic) inspired concentrations of halothane produced 12–18 Hz sinusoidal EEG (similar over the entire scalp, suggesting dominant global mechanisms). At higher concentrations, these modes decreased in frequency, and two new separate modes appeared near 1 and 8 Hz. Such specific spectral signatures (obtained by "tuning" the brain) appear to provide robust measures of anesthetic depth in each person. The data are consistent with the global theory if increased halothane concentration (in this range of relatively low anesthesia concentrations) has a net excitatory neocortical influence, thereby increasing the parameters b_{nm}. Net excitatory influences appear plausible because EEG amplitude always increased in these data as dominant frequency components decreased in frequency. Current literature on specific anesthetic actions appears somewhat mixed on halothane control (Nunez 1995), but this kind of drug (and, by implication, control parameter) connection to theory appears ripe for future study.

6.3. Complementary local and global mechanisms occur

The local/global neocortical dynamic mechanisms outlined here suggest that corticocortical coupling is controlled by neurotransmitters that alter feedback gain parameters B (or b_{nm}) and Q. Such functional coupling may profoundly influence brain state. Neuromodulatory action and cortical connection lengths (intracortical and corticocortical) both depend on cortical layer. Thus, several predictions of the most likely dynamic influences of different neuromodulators have been advanced by Silberstein (1995b). States of strongly reduced or increased corticocortical coupling may be called "hypocoupled" (excessively dominant local effects) or "hypercoupled" (excessively dominant global or regional effects), respectively. The local states are believed to be more associated with 30–50 Hz rhythms; the latter are more likely to exhibit dominant rhythms below 15 Hz. A body of self-consistent data, mostly from outside the EEG field, is reviewed that supports the idea that several neurological conditions (e.g., Parkinson's disease) are manifestations of either excessively hypercoupled or hypocoupled dynamics. These ideas appear especially subject to future experimental study of local versus global resonant behavior in steady-state evoked potentials using drugs to alter brain state. In such studies, large numbers of electrodes (e.g., 64–131) and computer estimates of dura potential can provide the spatial information required to distinguish local from global resonances. If only partly correct, these approximate ideas on the effects of drugs on resonant dynamic EEG behavior should impact clinical neurology and neuropsychiatry.

6.4. EEG may satisfy dispersion relations

The global theory suggests a tendency for dynamic behavior to exhibit temporal frequencies above the fundamental mode with progressively higher spatial frequencies. That is, "brain waves" may satisfy dispersion relations $\Omega = \Omega(k)$ or be mode-dependent as in Equation (8), in some approximate sense and in some brain states. Alpha rhythm experiments have shown this behavior for a 3-Hz band centered at the alpha peak (Nunez 1974b; 1981a). In all eight subjects studied, the spatial spectra of the high-alpha band had shorter spatial wavelengths. The general finding of an apparent EEG dispersion relation was also obtained in a study of phase and coherence structure in 189 children (Thatcher et al. 1986); however, volume conduction and reference effects made interpretation difficult.

In another study, the predicted temporal frequency/spatial wavelength relation was observed for a broad range of frequencies higher than the alpha peak (Shaw 1991; reviewed in Nunez 1995), consistent with a fundamental mode near 10 Hz. Still more support is provided by a fourth study in which higher frequency potentials (e.g., 15–30 Hz) were more strongly attenuated between cortex and scalp than were alpha frequencies (Pfurtscheller & Cooper 1975; Nunez 1981a). This latter effect cannot be explained by passive volume conduction; the attenuation of potentials generated by implanted dipole sources is independent of temporal frequency in this range (Cooper et al. 1965). However, the wave-dispersion relation hypothesis, combined with known spatial filtering of higher spatial frequencies by the volume conductor, is consistent with observed differences between cortical and scalp EEG spectra as discussed in section 4.2 and illustrated in Figure 6.

If, as in the example discussed in section 6.1, alpha rhythm consisted of the modes (n = 1, m = 0,1) near 9 and 11 Hz, respectively, the general kinds of spatial-temporal behavior described above would be anticipated. The issue is complicated by neocortical geometry (and related directional effects) and by nonstationarity of alpha, such as frequency drifts over perhaps 0.5 Hz, which make experimental interpretations more difficult. Another possible experimental connection is the well-known amplitude modulation of the alpha rhythm (Barlow 1993), the so-

called waxing and waning, which could be partly a beat phenomenon. That is, a linear sum of 9 and 11 Hz oscillations of equal amplitude will appear as a 10-Hz signal amplitude modulated at 1 Hz, in approximate agreement with many EEG data. I am not suggesting that alpha rhythm is so simple, because local networks, mode coupling, and other factors probably influence alpha dynamics, but the simple picture appears to explain several disparate dynamic behaviors.

6.5. EEG traveling waves occur; phase velocities match corticocortical propagation velocities

Several estimates of phase velocity of single hemisphere, posterior-to-anterior traveling waves have been published, but the monopolar (reference) potential velocity estimates are distorted by volume conduction. This problem was largely overcome by using a combination of MEG and bipolar EEG (Burkitt 1996; Burkitt et al. 2000; Silberstein 1995a). Traveling waves (which appear to be mixed with standing waves) make up important parts of scalp-recorded steady-state visual evoked potentials and magnetic fields (MEG), as well as spontaneous EEG (Nunez 1995). Measured phase velocities are generally in the range 3–7 m/sec along the scalp or about 6–14 m/sec along the folded cortical surface. These data agree closely with the estimated peak in the distribution of myelinated corticocortical propagation speeds of roughly 6–9 m/sec (Katznelson 1981; Nunez 1995). Also, very crude studies indicated that alpha rhythm group velocities ($d\Omega/dk$) could be estimated. Such estimates were roughly in the 4–24 m/sec range (Nunez 1974b; 1981a). Thus, important properties of EEG dynamics appear to depend on global (corticocortical) delays. There is also some evidence that effects of local delays are more prominent in intracortical EEG data, where shorter wavelengths are expected to contribute much more to the observed dynamics. For example, intracranial phase velocity estimates for dog alpha rhythm in the 0.3–1.2 m/sec range have been obtained (Lopes da Silva & Storm van Leeuwen 1978). Perhaps the parts of spatial-temporal spectra that dominate intracranial EEG data are much more strongly influenced by local effects than the spatially filtered scalp data.

The water wave analogy may help to illustrate expected differences between intracranial and scalp EEG data. Consider a floating sensor attached to the bottom by a flexible cable used to measure vertical displacements of water surface (or perhaps using satellite tracking). However, only surface displacements corresponding to water wave lengths longer than about twice the length of the sensor will be measured because positive and negative parts of shorter waves tend to cancel and not displace the sensor. Thus, in a water wave "field" on a locally windy day, with substantial power at short wavelengths, small sensors may measure very different dynamics than large sensors, which are most sensitive to long wavelengths, often generated hundreds of miles away where weather conditions may be quite different. Because shorter water wavelengths occur with higher temporal frequencies (Fig. 3), small sensors record more high temporal frequency components.

In a similar manner, an intracranial electrode of 1 mm diameter will be sensitive only to electric field wavelengths longer than about 2 mm. The scalp electrode is mainly sensitive to dura electric fields longer than about 10 cm with conventional EEG (Nunez 1981a; 1995a). With high-resolution scalp EEG, this sensitivity can perhaps be reduced to 4 cm. In contrast to the case with intracranial electrodes, such estimates for scalp electrodes are independent of electrode size for practical electrodes (of diameter less than 2–3 cm), because volume conduction rather than electrode size limits sensitivity. For complex brains, we may conjecture that scalp and intracranial electrodes measure quite different dynamics, as is often observed with EEG (Cooper et al. 1965; Delucchi et al. 1975; Nunez 1981a; Penfield & Jasper 1954; Pfurtscheller & Cooper 1975).

6.6. EEG can have quasi-stable spatial structure in the manner of standing waves

The essential idea of neocortical standing waves is that interference of synaptic fields traveling on a partly closed surface is expected. For example, when regions of enhanced excitatory activity (over background levels) interact with regions of enhanced inhibitory activity, we expect a cancellation effect. Interference may be nonlinear, but this does not change the qualitative idea. Standing waves exhibit multiple nodal lines (zero amplitude at each frequency) and multiple remote regions having equal phases (at each frequency). The boundary conditions then provide an apparently robust mechanism for "zero phase lag" at large (scalp) scales (Singer 1993; Thatcher & John 1977). Boundary conditions may also facilitate similar conditions in intracranial EEG although other explanations have been advanced (Robinson et al. 1997).

Driving the cortex with sine wave-modulated input can cause global resonance behavior at several frequencies. The resulting spatial patterns of scalp (or dura) potential, at locations away from primary visual cortex, will then be sensitive functions of driving frequency, for example, large changes of spatial pattern with 1-Hz frequency changes within the alpha band. Although local-circuit effects in real brains are likely to confuse the global picture of pure standing waves, several studies using steady-state visual evoked potentials have shown the predicted dynamic behavior (qualitatively). These include apparent nodal lines separating scalp regions with potentials oscillating roughly 180° out of phase (Burkitt 1996; Burkitt et al. 2000; Silberstein 1995a). The observed nodal lines appeared to be unrelated to brain fissures or sulci; their locations were sensitive to small (1-Hz) changes in driving frequency. New studies of EEG magnitude and phase patterns due to steady-state visual evoked potentials are currently underway at the Brain Sciences Institute in Melbourne using their 131-channel system. These new data, when used to image potentials on the dura surface, should provide more definitive tests of the global theory and competing ideas within the general conceptual framework proposed here.

Theoretical physicists (Friedrich et al. 1992; Fuchs et al. 1987; Haken 1999; Jirsa et al. 1995a; 1995b) recently studied experimental EEG and MEG (Kelso 1995). It was determined that for fixed brain states, spatial-temporal patterns could be accurately described in terms of two to five spatial modes. The time-dependent amplitudes of these spatial modes (which could be limit cycles or other time-dependent behavior) are called "order parameters" in the parlance of complex physical systems theory (e.g., "synergetics"). These studies suggest that EEG and MEG dynamics are governed by "field equations" for the apparent

standing and traveling waves (based on amplitude and phase structure), in a manner consistent with the purely global theory described here. Again, the filtering effects of volume conduction can be expected to have substantially reduced the number of spatial modes required to describe the data.

Nodal lines of standing waves are not easily observed in raw (reference) EEG data owing to limited spatial sampling and volume conduction distortion. However, cortical imaging and spline-Laplacian algorithms were recently applied to 60-channel, eyes-closed, resting EEG to improve spatial resolution (Nunez 1995; Nunez et al. 1994; 1997; 1999). Such data exhibit quasi-stable phase and magnitude structures in the alpha band on a second-by-second basis, consistent with standing waves.

6.7. Frequency of coherent EEG depends partly on brain size and corticocortical fiber myelination

If neocortical dynamics are partly composed of standing waves in the closed neocortical/white matter system, lower dominant frequencies (with longer wavelengths) are more likely in larger brains, provided that other influences (e.g., control parameters, propagation speeds, and local delays) are fixed. This is predicted by Equation (8) if corticocortical fibers change length in proportion to cortical size (i.e., λR = constant) and propagation speed v is constant as the scale factor R changes. The size/frequency correlation is predicted only for coherent EEG, which is more likely to have strong global contributions, not for EEG dominated by local mechanisms. The correlation coefficient between human brain and head size has been reported to be 0.85 (Blinkov & Glezer 1968). These ideas motivated a study of putative head size/frequency relations in 123 subjects, chosen for their robust alpha rhythms and extremes of small or large heads (Nunez 1981a; 1995; Nunez et al. 1977). As predicted, there was a significant negative correlation between human head size and peak alpha frequency. Correlation coefficients and significance levels were: frequency versus head size based on peak in average power spectrum ($r = -0.21$, $P = 0.02$) or based on "maximum frequency" from peak power histogram ($r = -0.23$, $P = 0.01$). Negative correlation coefficients were also obtained in subgroups of men and women and in all 6 age groups (17–78 years). The weakest correlation was in the 17–23-year age group, among whom corticocortical axon myelination was probably incomplete (Courchesne 1990; Yakovlev & Lecours 1967). Perhaps this group had more variation in corticocortical propagation speed. One may conjecture that human alpha rhythms have substantial local influences and global influences other than size (e.g., the b_{nm} parameters and propagation speed). However, the effect of brain size on the putative fundamental mode and/or other closely spaced overtones in this population was evidently sufficiently robust to measure. Future studies of size/frequency relations in EEG with more dominant global influences (e.g., anesthesia states) are suggested by these results.

One obvious confounding influence on EEG frequency/brain size relations is corticocortical myelination. For example, limit cycle frequencies in Equation (8) are proportional to corticocortical propagation speed (v) divided by linear scale factor (R). Children's linear brain scales (cube roots of volumes) are about 90% and 98% of adult scales at ages 2 and 5 years, respectively (Blinkov & Glezer 1968; Nunez 1995). Thus, size contributions to frequency changes are expected to be small during maturation. However, substantial corticocortical myelination takes place during maturation. Insofar as axon propagation speeds are increased by factors of perhaps 5 to 10 by myelination, we expect substantial EEG frequency increases during maturation. Unfortunately, there are too many confounding influences to make close quantitative predictions. For example, the proportion of myelinated corticocortical fibers as a function of age is apparently unknown. However, between the ages of about 1 and 10 years, peak EEG frequency increases from the delta range (0–4 Hz) to near 10 Hz, in semiquantitative agreement with expected increases in axon propagation speeds (Bickford 1973; Nunez 1995).

Data on cross-species comparisons of cortical EEG frequencies yield a mixed picture. One confounding parameter is the distribution of action potential speeds in corticocortical fibers in different species (because speed is proportional to axon diameter). That is, if all parts of mammal brains are scaled the same way, smaller brains would contain smaller axons. The combination of reduced propagation speed (v) and smaller size (R; or shorter corticocortical axons) would result in similar global time delays and mode frequencies. If corticocortical axon diameters were constant across species, however, the predicted fundamental modes (Hz) of standing waves, based only on a naive view of frequency/ size relations, would be something like human (10), rhesus monkey (24), dog (27), and cat (36), as discussed by Nunez (1995). Of course, we expect most EEG to have strong local and global contributions that are independent of brain size. In particular, EEG recorded from inside the cranium, which includes nearly all nonhuman data, may involve mostly local network behavior that dominates global contributions.

A related complication is that the relative importance of local versus global mechanisms and thalamocortical versus corticocortical interactions is species-dependent (Braitenberg 1977; Katznelson 1981; Nunez 1995). Candidates for globally dominated rhythms must be coherent over large regions of neocortex. Most animal studies have not reported long-range coherence data. In fact, most intracranial EEGs may be incoherent at centimeter scales, although moderate, broad-band (roughly 10–90 Hz) coherences between striate, motor, and parietal areas have been reported in monkey during performance of a pattern-discrimination task (Bressler 1995).

Data obtained from the olfactory bulb of various species are also noted. Higher EEG frequencies are typically observed in smaller olfactory bulbs (Freeman 1995; Nunez 1995), again suggesting the importance of "global" boundary conditions. In this case, boundary conditions apply to bulbs with radii of a few millimeters, which are relatively isolated from external feedback (Freeman 1975).

On balance, the available animal data are mixed. They neither strongly support nor refute the idea of standing neocortical waves of coherent EEG. However, these general ideas could impact future experiments and interpretations of cortical "synchrony," such as the distinction between high frequency (60–120 Hz) synchrony apparently imposed on cat neocortex from the midbrain (lateral geniculate nucleus) and lower frequency (30–60 Hz) synchrony apparently attributable to cortical and/or corticocortical mechanisms (Castelo-Branco et al. 1998). For example, one may conjecture global influences on local networks at frequencies

above about 36 Hz in cat. Or, perhaps global modulations contribute to the resonant peak near 28 Hz observed in dog cortex when driven with sine wave modulated light (Lopes da Silva 1970a; 1970b), or the dog's halothane rhythm, which occurs at roughly twice the frequency range of human halothane frequencies (Nunez 1995; Rampil 1980). Again, interpretation in terms of putative global mechanisms can provide motivation for new experiments to test such ideas.

6.8. EEG amplitude may decrease with increasing frequency

The basic global equations are based partly on the generally accepted idea that the number of active synapses (output) in a volume of tissue is proportional to the number of (input) action potentials. Thus, the corresponding field equation (10) in the Appendix is fundamentally linear (Nunez 1995), but is coupled to a second equation in which the roles of input and output variables are reversed. The second equation is represented by the "Local Network" box in Figure 4 and examples (at the millimeter scale) are Equations (13) and (14) in the Appendix. The basic idea is that the number density of action potentials produced in a local tissue volume (output) depends on the number of active synapses (input). This relation can be linear over only a limited range of input. For example, excitatory synaptic inputs will cause no action potentials to fire until a threshold is reached in the neural mass, and too much input can lead to saturation effects or recruitment of additional negative feedback in cortical or thalamic tissue (Freeman 1975). Thus, a sigmoid input/output relation was assumed by Wilson and Cowan in a local theory (1972; 1973). To simplify the mathematics, the sigmoid may be approximated by a cubic nonlinearity (Jirsa & Haken 1997; Nunez 1995), as indicated by Equations (13) and (14) in the Appendix. The earlier versions of the global theory proposed here essentially involve linearizing this sigmoid relation.

The predicted limit cycle modes of Equation (8) occur only for mode parameters b_{nm} greater than one. Predicted mode amplitudes are roughly proportional to the factors $(b_{nm} - 1)^{1/2}$, as shown in the Appendix. In that each mode (n,m) is also predicted to have reduced frequency as the corresponding b_{nm} increases, the theory matches (qualitatively) a well-known salient property of scalp EEG – the inverse relation between amplitude and frequency observed in a wide variety of brain states (Barlow 1993). The predicted global limit cycle modes differ from local limit cycles predicted by Wilson and Cowan (1972; 1973). In the former (global) theory delays are due to finite propagation speeds; in the latter (local) theory, delays are PSP rise and decay times. Both processes may occur simultaneously and may influence each other, but coherent activity, which is more closely associated with global theory, generally dominates EEG recorded on the scalp because of spatial filtering by the volume conductor.

6.9. A distinction between local and global alpha band activity is obtained

Changes in EEG coherence between ipsilateral and contralateral sensorimotor regions during planning of finger movements were measured. During one such planning, upper alpha band (10–12 Hz) coherence decreased whereas gamma band (38–40 Hz) coherence increased in the same data (Andrew & Pfurtscheller 1996). Other studies by the same group showed that alpha band activity consisted of a mixture of coherent activity (suggesting strong global mechanisms) with incoherent mu activity (suggesting local mechanisms), which were separately manipulated using motor tasks (Andrew & Pfurtscheller 1996; 1997; Florian et al. 1998). In some subjects, local and global alpha frequency peaks were matched within 1 Hz. In others, peaks were separated by 2–3 Hz. These data support the idea that specific local networks can generate rhythms in the alpha and gamma bands and that such rhythms can occur simultaneously with global oscillations in the same ranges, which in some states may facilitate and synchronize local rhythms.

6.10. Cognitive correlations to spatial-temporal patterns are robust

The complementary separation/interaction between local and global dynamic action fits well with the general idea that mental functions are processed within changing local and regional neural networks. Expressed another way, brain information storage and processing may involve coherent activation of large groups of cells, corresponding to independent but interacting subsystems (Bressler 1995; Edelman 1992; Grossberg & Somers 1991; Grossberg 1997; Harth 1995; John et al. 1997; Silberstein 1995b; Srinivasan et al. 1999; Tononi & Edelman 1998). Such temporary functional connectivity has been revealed in human brains by rapidly shifting spatial patterns of statistical interdependency of event-related potentials recorded with 64–128 electrodes during preparation for various cognitive tasks (Gevins & Cutillo 1986; 1995). Spatial patterns of coherence in the preparation period differ, depending on whether or not the task was performed correctly.

Steady-state visual evoked potential maps (Silberstein 1995a) also revealed robust connections between regional spatial-temporal dynamics and a visual vigilance task. Furthermore, the 60-channel alpha rhythm data shown in Figures 1 and 2 exhibited large, robust decreases in alpha coherence during transitions from resting to cognitive states. These data suggest that human alpha rhythm may be a mixture of local oscillations and global standing waves, with global behavior more dominant during resting states. The data show an interesting connection to theoretical work on the nature of brain dynamic complexity (Tononi & Edelman 1998; Tononi et al. 1994) and data obtained with functional MRI during photic stimulation (Friston et al. 1995). The measure of dynamic complexity proposed by these scientists is sensitive to the joint constraints of functional segregation and functional integration. Measured metabolic patterns of brain activity evidently occupy states intermediate between incoherence, with regionally specific dynamics, and global coherence. The intermediate states appear to have the highest complexity, perhaps because complexity requires a mixture of long and short correlation lengths.

Descriptions of brain dynamics in terms of multiple correlation lengths are similar to, but perhaps more accurate than, descriptions based on networks of various sizes (Nunez 1995). Such putative "neural networks" may be based on expected values of probability distributions of neural firing patterns (Ingber 1982; 1983; 1991). Ingber suggests that dynamic overlap of these probability distributions may be the core phenomenon underlying formation and erasure of networks on millisecond time scales. Correlation, coherence,

and complexity measures of EEG appear to provide crude, coarse-grained estimates of such dynamic overlap.

6.11. MEG phase transition explained using local/global theory

A similar approximation to sigmoid input/output in global theory was used to describe evoked magnetic field behavior (Jirsa & Haken 1996; 1997). The 37-channel MEG was driven by repeated auditory stimuli (Kelso 1995; Kelso et al. 1992; 1999). The subject was asked to push a button between each consecutive stimulus. When the stimulus rate reached a critical value (near 1.75 Hz), the subjects were no longer able to tap their fingers between each tone presentation, and switched from out-of-phase to in-phase (synchronous) finger motion. This indicated a brain state change, or "phase transition" in the parlance of complex physical systems. The spatial-temporal MEG dynamics were described in terms of a competition between two spatial modes, with time-dependent amplitudes as "order parameters" (Fuchs et al. 1992; Jirsa et al. 1995a; 1995b). The first-order parameter–time-dependent spatial mode coefficient analogous to $\Phi_1(t)$ in the Appendix–dominated the pretransition state and oscillated with the stimulus frequency; the second-order parameter, $\Phi_2(t)$, with twice the stimulus frequency, dominated the posttransition state. A differential equation was derived, partly by extending the global theory outlined here, but with auditory and sensory cortices considered as local circuits embedded within the neural tissue (Jirsa & Haken 1997). The theoretical model was able to reproduce the essential features of MEG dynamics, including the phase transition. Thus, a triple correspondence was obtained, relating behavior, MEG data, and physiologically based theory.

6.12. Macroscopic fields of synaptic action and neural networks coexist naturally

Theoretical work also suggested that the brain may act as a parallel computer at small scales through the use of local or regional neural networks, while simultaneously producing robust global field patterns at macroscopic scales (Haken 1999; Jirsa & Haken 1997; Kelso et al. 1999). Haken's work further showed that the global field equations of Nunez are of a universal type, in the sense that, in the linear limit, the field-dispersion relation for long-wavelength dynamics is relatively insensitive to corticocortical fiber distribution, adding additional support to similar studies (Nunez 1995). This suggests that several of the central ideas underlying the global field theory outlined here may survive when more accurate theories are developed. General ideas that should endure include the importance of finite action potential propagation speeds, global boundary conditions, synaptic action proportional to number of input action potentials, sigmoid relations between input synaptic action and output action potentials, and the simultaneous existence of global field modes and neural network activity at local and regional scales.

6.13. How are cell groups formed and what is their relationship to psychology?

Cognitive scientists may complain that the studies of neocortical dynamic behavior outlined here mostly ignore the main issues of brain information processing. This criticism is partly valid. However, I suggest that a much deeper understanding of brain dynamics is essential to genuine long-term progress in cognitive science. Such knowledge is required if cognitive questions are to be asked in a more quantitative scientific context. It is, in fact, probably impossible to design a cognitive EEG experiment not biased by assumptions (explicit or implicit) about brain dynamics. Experimental choices favoring global or local (e.g., dipole fits to EEG) interpretations provide common examples.

My goal here has been a relatively modest one of constructing a tentative dynamical foundation, based on both theory and EEG, on which more physiologically based cognitive and dynamic theories can be constructed. Expressed another way, any physiologically based dynamical foundation is likely to provide intermediate- and large-scale constraints on new cognitive models, in a manner analogous to constraints imposed by established physiology at the membrane or neuron level. For example, Edelman's (1992) "theory of neuronal group selection" suggests that selective coordination of complex patterns by "reentry" (repeated reciprocal interactions between cell groups) is the basis of behavior and that reentry combined with memory provides the bridge between physiology and psychology. Philips and Singer (1997) propose synchronized population codes, with dynamic activity "coordinated within and between regions through specialized contextual connections." These views appear to fit nicely with the dynamical picture painted here, as do other, overlapping ideas about "neural networks" or "distributed cell assemblies"(see, e.g., Bressler 1995; Carpenter & Grossberg 1987; Grossberg 1997; Grossberg & Somers 1991; John et al. 1997). One goal of dynamical theory development is to delineate differences between cognitive theories, for example, to pin down qualitative concepts and distinguish substantive from semantic controversies. To this physical/neuroscientist, who operates on the periphery of cognitive science, it appears that such semantic arguments and turf wars often infect scientific exchange. In this regard, the conceptual framework summarized here is an early attempt to help liberate cognitive theory from semantic straitjackets, thereby facilitating more linkage of physiology to psychology.

7. Speculative remarks on the dynamics of consciousness

I have argued that the development of neocortical dynamic theory and its experimental verification are essential to rapid progress in neuroscience, especially when fundamental issues of information processing and conscious experience are studied. This follows from the idea that intermediate- and large-scale physiology require quantitative understanding, just as we require knowledge of synapses, neurotransmitters, and action potentials at small scales. Separate theories at multiple scales, as well as efforts to cross scales, will provide formidable new challenges to theoreticians and experimentalists in the future. It is very difficult for twentieth century brains to predict whether much of the conceptual framework proposed in this article will survive in the twenty-first century. Perhaps this sobering thought should inhibit further speculation. However, I will venture some closing remarks on possible connections between this theoretical framework and mind-brain relations, while mostly avoiding what has been called the "hard problem" of conscious experience (Chalmers 1995).

We know that large-scale neocortical dynamic behavior

measured with EEG is correlated with internal experience. Today's established correlations are often only moderate, but there is reason to hope for even stronger connections in the near future using more advanced experimental methods, including improved EEG spatial resolution, advanced pattern recognition methods, closer connection to dynamic theory, and more effective integration with MEG, MRI, PET, and so on (Nunez 1995; Silberstein 1995a; Srinivasan et al. 1998; 1999). Furthermore, even with today's methods there is nearly a one-to-one correspondence between measured EEG and sentience; a crude measure of your macroscopic dynamics tells me if you have fallen asleep reading this target article.

Several theoretical studies suggest that macroscopic dynamic fields of synaptic action (estimated with EEG/MEG) are both influenced by and act back on dynamics at smaller spatial scales not easily accessible to experimental measure (Haken 1999; Ingber 1982; 1983; 1985; 1991; 1995a; 1995b; Ingber & Nunez 1990; Nunez 1995; Nunez & Srinivasan 1993; Srinivasan & Nunez 1993). Multiscale interactions, such as the "circular causality" described by Haken (1983; 1999), are an essential aspect of complex systems. It has been further suggested that such hierarchical interactions may be an essential ingredient of consciousness (Harth 1993; Ingber 1995a; 1995b), perhaps in a manner similar to hierarchical interactions in human social systems (Freeman 1995; Nunez 1995; Scott 1995). If brain information processing takes place at multiple spatial scales, one may conjecture that characteristic time scales (e.g., resonant mode frequencies) of these levels occur in the same general range. This allows information processing over several minicolumns, simultaneous with mesoscopic interactions at millimeter (e.g., macrocolumn) and global scales (Ingber 1985; 1995a; 1995b; Nunez 1989a; 1995).

Furthermore, in the context of the global theory outlined here, multiple global modes of synaptic action (identical at all cortical locations) can drive local modes of matching frequency (which vary with location), thereby facilitating a top-down mechanism for establishing coherent oscillations in widely separated cell groups. It is, in fact, possible that only synaptic modulation with matching local and global frequencies is sufficiently robust to be recorded as scalp EEG. If this conjecture is correct and multiscale information processing actually is essential to consciousness, brain evolution may have exploited synaptic plasticity at each spatial scale to effect a matching of time constants at each level. This "top-down, multiscale, neocortical dynamic plasticity" would evidently be constrained minimally at the single-neuron level but more strongly by neocortical boundary conditions (Nunez 1997). In less sober states, brains might take this conjecture even further by evoking extracranial constraints on brain development, for example, "World III" (Popper & Eccles 1977) or a recent modification, the "Platonic World" (Penrose 1995). Of course, such speculation goes well beyond supporting data. However, it does perhaps suggest that materialism and dualism are not so easily distinguished as is often proposed.

8. Appendix: Coupled mode equations for nonlinear local/global theory

8.1. Basic global equation

Decimal equation numbers used in this Appendix refer to equations derived in the book by Nunez (1995). Integer equation numbers refer to this target article. The basic global equation relating normalized centimeter scale, excitatory synaptic action density $F(x,t)$ to normalized centimeter scale action potential density input $G(x,t)$ is the integral equation

$$F(x,t) = \int_0^\infty dv_1 \int\int_{S_1} R(x,x_1,v_1) G\left(x_1, t - \frac{/x - x_1/}{v_1}\right) dS_1 \qquad (11.1)$$

This global integral equation quantifies the noncontroversial idea that the number of active excitatory synapses at any cortical location x depends on the number of excitatory action potentials produced at all other cortical locations x_1. The outer integral is over generally distributed corticocortical propagation speeds v_1. The inner integrals are over the neocortical surface S_1. Midbrain input U(x,t) does not appear in Equation (11.1); it is here assumed to enter the local box in Figure 4. If there are J excitatory corticocortical and intracortical fiber systems, the falloff in numbers of fibers with distance $/x - x_1/$ is expressed as a distribution function $R(x,x_1,v_1)$ in the form of a sum over exponential decays. That is,

$$R(x,x_1,v_1) \propto \sum_{j=1}^{J} \rho_j \eta_j(v_1) e^{-\lambda_j /x - x_1/} \qquad (9)$$

Here the sum is over J fiber systems with decay constants λ_j and associated velocity distributions $\eta_j(v_1)$. A relatively simple global equation is obtained when only one of these excitatory systems has substantial delay times (in which case $\lambda_j \to \lambda$) and the associated velocity distribution is a delta function $\eta(v_1) = \delta(v_1 - v)$. Because millimeter and smaller scale corticocortical fibers have more specificity of connections, Equation (9) may make sense only at centimeter or larger scales.

After several mathematical steps, which cannot be duplicated here without introducing several new intermediate variables and definitions, Equation (A.10) in the Appendix of Nunez (1995) was obtained from (11.1) for the special geometry of a closed-loop model cortex. The inverse Fourier transform of Equation (A.10) yields the partial differential equation

$$\frac{\partial^2 F}{\partial t^2} + 2\frac{\partial F}{\partial t} + F - \frac{\partial^2 F}{\partial x^2} = \frac{\partial G}{\partial t} + G \qquad (10)$$

This is a simplified input/output relation for the "nonlocal" cortex in Figure 4. Jirsa and Haken (1997) also used Equation (10) in a one-dimensional, nonlinear study. Spatial variables are here normalized with respect to λ^{-1} and time t is normalized with respect to $\tau_g = (\lambda v)^{-1}$. Here $v \cong 600$–900 cm/sec is the characteristic propagation speed in corticocortical fibers, and $\lambda^{-1} \cong 5$–15 cm is a characteristic decay length in the number density of corticocortical input fibers with distance at centimeter scales. Thus, $\tau_g \cong 6$–25 msec, and one might expect oscillatory activity in the general frequency range $f \cong (2\pi\tau_g)^{-1}$ or 6–28 Hz. For reasons discussed in Nunez (1995a), the decay constant may be considered to apply to the corticocortical system with the longest fibers (perhaps $\lambda^{-1} \cong 10$–15 cm) if the corresponding fiber density ρ and excitatory synaptic gains are sufficiently large. In this case, the lower end of this frequency range $f \cong 6$–14 Hz appears more appropriate for the fundamental (lowest) mode of the putative global oscillations. Multiple fiber systems result in multiple branches of dispersion relations, as discussed in Nunez (1995).

8.2. Linear centimeter scale global equation

If the action potential density G(x,t) generated in the local tissue mass in Figure 4 is simply proportional to the sum of excitatory synaptic input from the global neocortex F(x,t) and midbrain input U(x,t), Equation (10) yields

$$\frac{\partial^2 F}{\partial t^2} + (2 - B)\frac{\partial F}{\partial t} + (1 - B)F - \frac{\partial^2 F}{\partial x^2} = B\left(\frac{\partial U}{\partial t} + U\right) \quad (11)$$

where B is the proportionality constant. The global transfer function, Equation (7), is based on this linear partial differential equation. For $B \cong 2$, the spatial modes ($n = 1, 2, 3, \ldots$) exhibit free oscillations ($U = 0$) with frequencies (Hz)

$$f_n = \frac{v}{L}\sqrt{n^2 - \frac{(B\lambda L)^2}{4(2\pi)^2}} \quad (12)$$

Here L is the longest brain "circumference" of the unfolded surface. Equation (12) is essentially Equation (11.14). Waves on spherical and prolate spheroid surfaces were also considered in Nunez (1995), but such details do not alter the general semiquantitative conclusions of this target article. If $v \cong 600$–900 cm/sec and $L \cong 50$–100 cm, the fundamental mode is $f_n \cong 6$–18 Hz, approximately independent of B for B small. As the linear feedback parameter B increases, the putative linear waves progress from strongly damped to unstable when $B > 2$. When critical values of B are reached such that the second term under the square root approaches the first term (n^2), the frequencies of the corresponding modes first decrease sharply and become nonoscillatory for still larger values of the linear feedback parameter B. However, this linear approximation should be considered only as a first approximation to more accurate nonlinear solutions.

8.3. Simple millimeter scale local equations

Consider two relatively simple, millimeter scale local equations, based on the idea that moderate to large synaptic action f(x,t) leads to the recruitment of additional "local" negative feedback mechanisms. Here the word "local" may include both intracortical and thalamocortical feedback. Lowercase symbols are used (in this Appendix only) for millimeter scale variables to distinguish them from uppercase centimeter scale variables. If no local oscillatory dynamics are included

$$g(x,t) = Bf(x,t) - Af^3(x,t) \quad (13)$$

Alternatively, if simple local oscillatory dynamics are included

$$\partial^2 g/\partial t^2 + 2a\,\partial g/\partial t + q^2 g = q^2(Bf - Af^3) \quad (14)$$

Here the parameters A and B are of order one because dependent variables *F, G,* f, and *g* are normalized. The case $A = 0$ corresponds to linear solutions described above. The parameters (a,q) depend on local properties, for example, ratios of PSP rise and decay times to the characteristic global delay τ_g and local feedback gain Q. The linear version of Equation (14) is a very simplified local theory, for example, a simple version of equations derived by Lopes da Silva et al. (1974), Freeman (1975), or van Rotterdam et al. (1982). The cubic nonlinearity in Equations (13) and (14) is an approximation to a sigmoid input/output relation, as discussed in section 12 of the Appendix to Nunez (1995) and in Jirsa and Haken (1997). Subcortical input has been omitted in Equations (13) and (14) but can be easily included, for example, for purposes of SSVEP modeling.

8.4. Relation of millimeter and centimeter scale equations

The millimeter scale equations may perhaps apply to dynamics in neocortical tissue of size corresponding roughly to something between a minicolumn and macrocolumn. By contrast, the global equation is based on decay in number density of corticocortical fibers at the centimeter scale. Thus, millimeter and centimeter scale variables are related by space averages over regions Γ

$$F(x,t) = \frac{1}{\Gamma}\int_x^{x+\Gamma} f(x',t)dx' \quad (15)$$

8.5. Nonlinear solutions in a rectangular region

The one-dimensional solution has the advantage of relative simplicity and may provide a reasonable idea of how individual modes behave. However, in one-dimensional systems, the higher modes (overtones) are often harmonics of the fundamental, but this is not true for two-dimensional planar or surface systems. Full solutions (e.g., EEG waveforms) consist of sums of such spatial modes. In order to provide two-dimensional simulations, consider coupled-mode equations in a rectangular region of dimensions $L_x = 3L_y$. Let $L_x = 30\pi$ cm crudely represent the anterior/posterior circumference of one unfolded neocortical hemisphere. Let L_y represent the lateral circumference of the same hemisphere. Boundary conditions are satisfied if solutions are expanded in spatial Fourier series in terms of the unknown functions or "order parameters" $\varphi_{nm}(t)$

$$f(x,y,t) = \sum_{n=1}^{\infty}\sum_{m=1}^{\infty} w_{nm}(t)\sin(k_n x)\sin(h_m y) \quad (16)$$

With this interpretation of the geometry, normalized wave numbers are $k_n = 2n\pi/\lambda L_x$ and $h_m = 2m\pi/\lambda L_y$, with $n = 1, 2, 3, \ldots$ and $m = 1, 2, 3, \ldots$. Half-integer wavelengths with zero amplitude at boundaries are typically allowed in rectangular systems (e.g., waves in a rectangular drum membrane), but only integer wavelengths are allowed on closed surfaces because dependent variables and their spatial derivatives must be continuous functions of surface coordinates if they represent genuine physical processes (i.e., periodic boundary conditions apply). Thus, we here force waves traveling to each edge of the rectangular region to appear at the opposite edge. That is, in contrast to the usual drum waves, no wave reflection at boundaries occurs here.

8.6. Truncated solutions for space-averaged variables

The space averaging operation relating millimeter scale to centimeter scale variables involves the integrals in x and y directions of the form

$$\frac{1}{\Gamma}\int_x^{x+\Gamma}\sin(k_n x')dx' = \frac{1}{k_n\Gamma}[\cos(k_n x) - \cos(k_n x)\cos(k_n\Gamma) + \sin(k_n x)\sin(k_n\Gamma)] \quad (17)$$

For long-wavelength modes with $k_n\Gamma \ll 1$, the right side is approximately $\sin(k_n x)$, so that lower eigenfunctions of the space-averaged fields G(x,y,t) and F(x,y,t) have the same form as the eigenfunctions of the millimeter scale fields *g*(x,y,t) and f(x,y,t). Generally, centimeter scale eigenfunctions are multiplied by the factor $1/(\Gamma^2 k_n h_m)$, which is proportional to $(nm)^{-1}$. Also, these higher order terms contain oscillatory terms such as $\cos(k_n\Gamma)$. Such higher mode contributions can perhaps be considered "noise" input in this crude approximation. These arguments provide some weak justification for using truncated-mode solutions for space-averaged variables. Such solutions are not generally accurate (Nunez & Srinivasan 1993; Srinivasan & Nunez 1993); however, they can provide some insight into general behavior of solutions with different parameters. They may also allow more accurate solutions to be obtained by including more modes.

For comparison with scalp recordings, a reasonable choice for the space-averaging scale is the spatial resolution obtained with 64-channel spline-Laplacian methods, or about 3 cm. Thus, the nondimensional averaging scale is $\Gamma = 3\lambda$, and $k_n\Gamma = 6n\pi/L_x$, $h_m\Gamma = 18m\pi/L_x$. Because each term in the eigenfunction expan-

sion for space-averaged dependent variables is proportional to $1/(k_n\Gamma)(h_m\Gamma)$, an apparently consistent truncation is obtained by keeping terms n = 1, 5 and m = 1

$$f(x,y,t) \cong \sin(h_1 y)\sum_{n=1}^{5} F_{n1}(t)\sin(k_n x) \tag{18}$$

Boundary conditions require $k_n = nk_1$. Also, the second subscript on order parameters may be dropped; only the n modes with m = 1 are retained here. The symbolic program Mathematica was used to express

$$\left[\sum_{n=1}^{5}\varphi_n(t)\sin(k_n x)\right]^3 = \sum_{n=1}^{15}\zeta_n[\varphi_1(t),\varphi_2(t),\varphi_3(t),\varphi_4(t),\varphi_5(t)]\sin(k_n x) \tag{19}$$

Also required is the term associated with $\partial g(x,t)/\partial t$,

$$\left[\sum_{n=1}^{5}\varphi_n(t)\sin(k_n x)\right]^2 \sum_{n=1}^{5}(d\varphi_n/dt)\sin(k_n x) = \sum_{n=1}^{15}\psi_n[\varphi_1,\ldots,\varphi_5,\ d\varphi_1/dt,\ldots,d\varphi_5/dt]\sin(k_n x) \tag{20}$$

Here the functions ζ_n and ψ_n generally provide strong coupling between spatial modes. Use is also is made of the identity

$$\sin^3(h_1 y) \equiv (1/4)[3\sin(h_1 y) - \sin(3h_1 y)] \tag{21}$$

8.7. Coupled-mode equations with no local oscillatory dynamics

If there is no local oscillatory dynamic behavior and no subcortical input U(x,t), the global equation (10) yields five coupled, second-order ordinary differential equations for the centimeter scale synaptic action modes $\Phi_n(t)$

$$d^2\Phi_n/dt^2 - (B - 2 - \frac{9A}{4}\Phi_n^2)d\Phi_n/dt + (1 + k_n^2 - B + \frac{3A}{4}\Phi_n^2)\Phi_n = \Im_n(\Phi_1,\Phi_2,\ldots,\Phi_5,\ d\Phi_1/dt,\ d\Phi_2/dt,\ldots,d\Phi_5/dt) \tag{22}$$

The mode coupling functions $\Im_n$ on the right sides of the 5 equations (n = 1, 5) each consist of about 40 terms. If the modes are uncoupled, the right side is zero, and each mode satisfies a combined van der Pol/Duffing equation. The centimeter scale modes $\Phi_n(t)$ are space averages of the millimeter scale modes $\varphi_n(t)$, as indicated by Equation (15).

8.8. Coupled-mode equations with local oscillatory dynamics

If local networks have weakly damped oscillatory behavior, 10 coupled second-order equations are obtained from Equations (10), (14), and (15) for the synaptic (Φ_n) and action potential (W_n) modes

$$d^2\Phi_n/dt^2 + 2d\Phi_n/dt + (1 + k_n^2)\Phi_n = dW_n/dt + W_n \tag{23}$$

$$d^2W_n/dt^2 + 2adW_n/dt + q^2W_n = q^2[B\Phi_n - A\Re_n(\Phi_1,\Phi_2,\Phi_3,\Phi_4,\Phi_5)] \tag{24}$$

where $\Re_n(\Phi_1, \Phi_2, \Phi_3, \Phi_4, \Phi_5)$ are the mode-coupling terms. Although these equations were derived for constant local parameters (a, q), one can easily imagine similar solutions with a = a(x) and q = q(x). For example, in the local theory of van Rotterdam et al. (1982), these parameters are functions of the local feedback gain Q, which is generally expected to vary with location x. In such cases, "local" oscillations of frequency q(x) can be enhanced by "global modulations" of synaptic action density. Conversely, "global" oscillations will be enhanced by matching "local" oscillations (somewhat similar to the usual "pacemaker" mechanism). The quotation marks are used to emphasize that, with these integrated dynamics, "local" and "global" mechanisms may interact strongly, in which case neither can be said to "cause" the other.

8.9. Analytic perturbation solution for uncoupled modes

It is instructive to consider a limiting case where the nonlinear parameter A is small and the expansions are truncated at the first mode (n = 1). Or, suppose the modes are somehow uncoupled, so that the functions $\Im_n$ of Equation (22) are zero. Though this is probably unrealistic, it does provide a limiting case that can be solved analytically for weak nonlinearity. With the assumption $\Im_n = 0$, a van der Pol/Duffing equation is obtained from Equation (22) for each mode. To put this equation in standard form, let $\varepsilon = B - 2$ and make the transformation

$$Z = (9A/4\varepsilon)\Phi_n \tag{25}$$

The combined van der Pol/Duffing equation then takes the form

$$d^2Z/dt^2 - \varepsilon(1 - Z^2)dZ/dt + [k_n^2 - (1 + \varepsilon) + (\varepsilon/3)Z^2]Z = 0 \tag{26}$$

Equation (26) may be studied with standard perturbation methods for ε small. That is, assume a solution of the form (Jordan & Smith 1996)

$$Z(t) = Z_0(t) + \varepsilon Z_1(t) + \varepsilon^2 Z_2(t) + \ldots \tag{27}$$

$$\Omega = \Omega_0 + \varepsilon\Omega_1 + \varepsilon^2\Omega_2 + , \ldots \tag{28}$$

The corresponding zero-order periodic solution is

$$Z_0(t) = 2\cos[(\Omega_0 + \varepsilon/2\Omega_0)t] \tag{29}$$

Or, in terms of the spatial modes $\Phi_n(t)$

$$\Phi_n(t) \approx \frac{4}{3}(\varepsilon/A)^{1/2}\cos[(\Omega_0 + \varepsilon/2\Omega_0)t] \tag{30}$$

As the linear feedback gain parameter $\varepsilon = (B - 2)$ increases, the amplitudes of the modes n increase, while the frequency remains approximately constant for small ε. The zero-order, nondimensional frequency is given by

$$\Omega_0^2 = k_n^2 - (\varepsilon + 1) = k_n^2 - (B - 1) \tag{31}$$

The corresponding frequency in Hertz is

$$f = \frac{\lambda v\Omega_0}{2\pi} \tag{32}$$

In the rectangular medium with $L_x = 3L_y$, normalized wave numbers are given by

$$k_n = \frac{2\pi\sqrt{n^2 + 9}}{\lambda L_x} \tag{33}$$

Because the rectangular medium does not provide a realistic approximation to cortical surface geometry, the choice of parameters for corresponding numerical solutions is more arbitrary than for closed-surface geometry.

In a closed loop of circumference $L = 2\pi R$, the uncoupled version of Equation (22) is altered only by the factor multiplying the A parameter. The zero-order frequency expression (31) is unaltered. However, in the closed loop, the allowed wave numbers are

$$k_n = 2n\pi/\lambda L \tag{34}$$

Substitution of loop wave numbers into the expressions for zero-order frequency (31) and (32) yields the zero-order limit cycle mode frequencies

$$f_n = \frac{v}{2\pi R}\sqrt{n^2 - (B-1)\lambda^2 R^2} \tag{35}$$

Equation (35) is identical to Equation (8) in section 5.3.8 with the interpretation $S_{nm} = n^2$, $b_{nm} = (B - 1)$, and $R = L/2\pi$. It should be emphasized, however, that Equation (8) has not been derived for general neocortical geometry and neglects mode coupling. It is used here only for very crude semiquantitative estimates.

8.10. Numerical solutions of uncoupled mode equations

The unforced van der Pol/Duffing equation (26) was integrated for ε in the range 0.1–8.0. Limit cycle oscillations were obtained with frequencies in the approximate range 20–30 cycles per $100\tau_g$ sec, where $\tau_g = (\lambda v)^{-1} = 6$–25 msec. These limit cycle frequencies are in the general range of 8–50 Hz, depending mainly on the basic time scale τ_g, relatively independent of feedback gain $\varepsilon = (B - 2)$ for ε small. For large ε (or B much larger than two), dominant frequencies decrease and amplitudes increase as discussed in this target article. Refer to Figure 10-10 of Nunez (1995) for associated numerical examples.

8.11. Numerical solutions of coupled-mode equations

Figure 6 shows two sample numerical solutions of the purely global, coupled-mode equations (22) in the rectangular region $L_x = 3L_y$. The upper plot is the sum of all five modes $\Phi_n(t)$, crudely representing dura potential. The lower plot is the sum of only the modes $\Phi_1(t)$ and $\Phi_2(t)$, crudely simulating spatially filtered scalp potential. More exact studies can allow for progressively stronger spatial filtering of higher modes as illustrated in Nunez (1995), rather than the abrupt cutoff of modes three through five shown here. However, the qualitative effect of low-pass spatial filtering indirectly causing low-pass temporal filtering is not changed by more accurate studies. Refer to Figures 1-28 and 9-9 of Nunez (1995) for related numerical studies. The period shown in Figure 6 is believed to be in the 1 sec range so the dominant frequency is about 11 Hz in both plots, but the dura potential simulation contains more high-frequency content. Oscillations shown in Figure 6 are caused exclusively by global delays.

Figure 7 shows four sample solutions of the local/global, coupled-mode equations (23) and (24). Global properties are held fixed. The local frequency q is varied as indicated. The period shown is about 2 sec with the brain parameters discussed here, so that dominant frequencies vary from about 10–18 Hz as the local frequency q increases.

8.12. Solutions on closed surfaces

The partial differential equation (10) represents the integral equation (11.1) for a one-dimensional model cortex. One is tempted to generalize Equation (10) for higher spatial dimensions simply by replacing $\partial^2 F/\partial x^2$ by $\nabla^2 F$, as in the example of a rectangular medium outlined here. However, this is not generally valid. The linear global equations were solved for a spherical surface by Katznelson (1981) and generalized in the Appendix of Nunez (1995). For a spherical surface, Equation (A.10) is replaced by Equation (A.30), which does not generally reduce to a simple partial differential equation analogous to Equation (10). Rather, by taking the inverse Fourier transform of Equation (A.30) and making use of the recursion relations Equations (A.40)–(A.42), one obtains a delay differential equation for each spherical harmonic mode $Y_{nm}(\theta,\varphi)$, analogous to the modes $\sin(k_n x)\sin(h_m y)$ for the rectangular region. For example, the following equation is obtained for the (n = 1, m = −1, 0, +1) synaptic action density modes $\phi_{1m}(t)$ in terms of the action potential density modes $W_{1m}(t)$

$$\frac{d^2\Phi_{1m}}{dt^2} + 2\lambda R\frac{d\Phi_{1m}}{dt} + (4 + \lambda^2 R^2)\Phi_{1m} = W_{1m}(t) - e^{-\pi\lambda R}W_{1m}(t-1) \tag{36}$$

Here R is sphere radius, λ^{-1} is the characteristic fall-off distance for corticocortical fibers in a homogeneous, isotropic spherical shell, v is propagation speed, and time is nondimensionalized with respect to (R/v). For the special case n = 1, Equation (36) is similar to its one-dimensional analog Equation (23), which has the same form for all modes. However, substantial differences between the spherical and one-dimensional linear solutions occur for higher modes. The most obvious difference is a large increase in possible mode frequencies in spherical geometry. This occurs as a result of the interesting property that the order of the ordinary differential equations for each spherical mode increases with n mode number, that is, n = 0,1 (second-order); n = 2,3 (fourth-order); n = 4,5 (sixth-order), and so on. Multiple branches of the dispersion relation are then obtained for linear coupling. If coupled mode equations are obtained to approximate nonlinear negative feedback, the number of first-order equations is much larger than in the one-dimensional case, for example, 12 second-order equations for truncation at n = 5, as opposed to 5 second-order equations in the one-dimensional case. The mode equations (and dominant frequencies) are independent of the m index because of spherical symmetry. However, in an apparently more realistic prolate spheroidal shell, mode frequencies do depend on the m index (Nunez 1995). Ideally, nonlinear solutions on closed surfaces will be obtained in the near future, perhaps by readers of this article. Because of the anisotropic nature of corticocortical fibers, the most realistic model geometry is not obvious.

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Sensorimotor EEG rhythms and their connection to local/global neocortical dynamic theory

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Abstract: The EEG activity recorded from the human sensorimotor cortical area exhibits rhythmic activity covering a broad range of frequencies, including alpha, mu, beta, and gamma (40-Hz) rhythms. This commentary elaborates on connections between these sensorimotor rhythms and Nunez's neocortical dynamic theory.

Two important concepts emphasised in Nunez's neocortical dynamic theory are (A) the interaction of dynamics across spatial scales whereby global processes can drive dynamics at lower spatial scales and thereby facilitate synchrony between remote local circuits and (B) complementary global and local mechanisms, that is, competition between functional integration and segregation. In the target article, Nunez refers to data from the Graz group[1] in which scalp-recorded EEG activity from the human sensorimotor area was investigated during performance of motor acts (Andrew & Pfurtscheller 1996; 1997; Florian et al. 1998). Nunez interprets these data as providing support for the concepts mentioned in the beginning of this paragraph (sect. 6.9).

Although I am mostly in agreement, a difficulty I have with the interpretation is that under conditions where the neocortex is biased toward a state of "hypocoupling" in which local networks dominate global-regional dynamics (concept B), the suggested mechanism for achieving synchrony between remote resonant local networks (concept A) is absent. In what follows, I take this point further, discussing it in the context of the Graz data, and make some speculative comments on the relationships, suggested by the Graz data, between sensorimotor rhythms and global, regional, and local mechanisms.

In the Graz data published by Andrew and Pfurtscheller (1996), alpha band activity recorded over the sensorimotor regions is followed during preparation and execution of unilateral finger movement. As mentioned in section 6.9 of the target article, the alpha band activity consisted of a mixture of coherent activity and incoherent mu activity.

The coherent activity is believed to be owing to global generation mechanisms for the following reasons: (1) The alpha peak was found to be constant at most scalp location. Partialisation of activity recorded over frontal, parietal, or occipital areas resulted in removal of the global alpha activity over the central region (Andrew & Pfurtscheller 1997). (2) Analysis of the phase velocity of the coherent alpha rhythm revealed phase velocities in the 4.8 to 5.3 m/sec range (Andrew 1997). Taking conversion factors for the folding of the neocortical surface (Nunez 1995), these estimates translate into phase velocities of 9–10 msec, consistent with propagation velocities in the corticocortical fibres.

The mu rhythm is believed to be due to dynamics at a lower spatial scale than the coherent alpha band rhythm. Thus, although occupying similar parts of the temporal spectrum, these rhythms occupy different portions of the spatial spectrum, with the coherent alpha activity having more contribution in the long wavelength part of the spatial spectrum. Support for this is seen in comparing normalised power spectra of nose-referenced and Hjorth-Laplacian data (Andrew & Pfurtscheller 1997). The relative contribution of the coherent alpha activity compared to the incoherent mu rhythm is seen to be less in the Laplacian data, this being due to the spatial filtering effect of the Laplacian operator, which removes contributions at the long wavelength part of the spatial spectrum.

Thus the data supports the idea of that global oscillations can occur simultaneously with rhythms due to processes at lower spatial scales (e.g., local resonances). The closeness in temporal frequency of the coherent alpha and mu rhythms also suggests a matching of global and local resonances for facilitation and synchronising of these local rhythms.

The effects of neuromodulatory input on the global/regional and local dynamics has been put forward by Silberstein (1995b); a brief synopsis of these ideas is given in section 6.3 of the target article. In Silberstein's article, he suggests how this global/local model can explain the Graz findings of event-related desynchronisation of the Rolandic mu rhythm and simultaneous event-related synchronisation of 40-Hz activity, which are recorded over the sensorimotor area during performance of unilateral finger movement (Pfurtscheller & Neuper 1992). The Rolandic mu rhythm is interpreted as a regional resonance. Desynchronisation of this rhythm can be considered to be a consequence of neuromodulation (due perhaps to an increased monoaminergic or cholinergic activation) of the sensorimotor cortical area. The increased neuromodulatory levels result in a decoupling of the corticocortical fibres that sustain the mu regional resonances, leading to mu rhythm desynchronisation. Decoupling of the regional corticocortical connections is associated with an increase in local loop gains within these regions, leading to resonance of local processes, which results in 40-Hz oscillations.

My problem comes in marrying concepts A and B in the context of local 40-Hz resonances. In terms of the complementary global/local model, desynchronisation of global and regional activity is a prerequisite for resonance of local 40-Hz circuits, that is, the shifting of the neocortex to a "hypocoupled" state. However, in this hypocoupled state, the suggested mechanism for achieving the synchronising or binding of remote activated 40-Hz local circuits, that of top-down driving from global/regional processes, is not present as the global/regional resonances are absent.

Let us return to the Graz data published by Andrew and Pfurtscheller (1997). We interpret the coherent alpha rhythm as having strong global mechanisms for the reasons given in the previous paragraph, and the Rolandic mu rhythm as being a regional resonance as speculated by Silberstein (1995b). For activation of local 40-Hz circuits within the sensorimotor area, we expect a neuromodulator-mediated decoupling of global-regional processes with the associated increase in loop gains of local circuits. Thus we would expect desynchronisation of both the coherent alpha activity and the incoherent mu rhythm. However, inspection of the data shows that only the mu rhythm desynchronises; the coherent alpha activity shows no movement-related changes and remains constant throughout the movement. These data thus support the idea that not only can regional resonances coexist with higher-order global resonances, but that corticocortical connections that sustain the regional processes can be decoupled due to neuromodulatory action (resulting in desynchronisation of the rhythms produced by these processes), while mechanisms sustaining the global oscillations remain intact. Decoupling of the regional corticocortical connections is associated with an increase in local loop gains leading to resonance of local processes (resulting in 40-Hz oscillations). Since global process remain intact, the top-down mechanism for achieving synchrony between remote local 40-Hz circuits is still present. The Graz movement data thus suggest a model where complementary regional and local mechanisms can occur within sustained global fields of synaptic action that serve to bind spatially separated local circuits.

As a further example of the model just described, consider activity recorded over the sensorimotor hand area and supplementary motor area (SMA) during unilateral movement. The SMA has been shown to have its own intrinsic rhythm in the alpha band. With planning of movement, both the contralateral sensorimotor's mu rhythm and the SMA's intrinsic alpha rhythm show desynchronisation (Pfurtscheller & Berghold 1989). Rhythmic activity within the alpha band recorded over both regions, showing moderate to high coherence between all scalp locations, shows no movement-related changes (the coherent alpha band rhythm discussed previously). With onset of movement, focal 40-Hz oscillations are found over the sensorimotor hand area as well as over the SMA. These 40-Hz oscillations are found to be coherent between these two regions (Andrew & Pfurtscheller 1996).

Explained in terms of the proposed model, neuromodulatory-mediated decreases in regional resonances result in desynchronisation of the mu rhythm and the SMA alpha-band rhythm, with a corresponding increase in local resonant modes that give rise to 40-Hz oscillations in both regions. The synchrony observed between these remote 40-Hz oscillations is due to top-down driving of these circuits by one of the overtones of the global process having a global mode frequency near 40 Hz. Of course, due to the spatial lowpass filtering of the head volume conductor, we only observe lower mode frequencies of the global process in scalp-recorded EEG, that is, the coherent alpha band rhythm.

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Three pertinent issues in the modeling of brain activity: Nonlinearities, time scales, and neural underpinnings

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Abstract: A critical discussion is provided of three central assumptions underlying Nunez's approach to modeling cortical activity. A plea is made for neurophysiologically realistic models involving nonlinearities, multiple time scales, and stochasticity.

The present upsurge of mathematical models of neural activity amplifies the need for reviews on recent findings and evaluations of extant approaches in the field. Nunez's target article accordingly provides a welcome platform for discussion, especially in view of his exciting premise that noninvasive measurements of cortical activity may help deepen our insights into fundamental concepts of brain functioning. The key question in this context concerns which theoretical assumptions are the most productive in generating such insights. From Nunez's article the following assumptions become apparent: (1) linear models can address all qualitative aspects of brain activity; (2) both local and global spatial properties have to be incorporated in models for brain activity; and (3) models for brain activity need to be rooted in neuroanatomy and neurophysiology. Here, we discuss the implications of each of these assumptions to identify the strengths and shortcomings of Nunez's approach.

1. Linear-nonlinear. Are linear models sufficient to account for all qualitative properties of brain activity, or are nonlinear models required? As in physics, the answer is twofold. Linear descriptions are appropriate in various instances (cf. sect. 4.4), especially within limited parameter ranges (whatever that means in neuroscience). They often allow for analytical solutions even when special topologies such as the neocortex are involved. Linear models, however, fail to describe instances of pattern formation, that is, qualitative changes. For instance, the nonlinearities in Jirsa and Haken's (1996) model are inevitable in accounting for the observed phase transitions in brain activity and behavior. The choice of these nonlinearities is not arbitrary but is constrained by the empirical properties of the bifurcation. Nonlinear extensions not only lead to better data fits but also introduce new qualities. Although technically convenient, the assumption that the structure of patterns of brain activity can be unfolded in terms of linear superpositions is too simple as such superpositions are ill-suited to describe qualitative changes between patterns.

As emphasized, for example, by Haken (1983), phase transitions provide a special entry point in the study of complex dynamics because, around critical points, an enormous reduction of information occurs due to "slaving." Although, in general, Nunez's contention is correct that "filtering effects of volume conduction can be expected to have substantially reduced the number of spatial modes." (sect. 6.6) in the encephalographic recordings, this cannot explain the reduction of dimensionality observed around phase transitions.

2. Local and nonlocal properties in space and time. We agree with Nunez that a complete description of cortical activity should include both local and nonlocal properties. Nunez correctly states that inhomogeneities of the neocortex, that is, corticocortical, subcortical, or intracortical connections, result in spatial distributions of activity. One may ask, however, whether such inhomogeneities alone are sufficient to account for all observed patterns of activity. Although distinct distances and propagation velocities along cortical connections lead to different time scales, these time scales differ only marginally and should not be confused with the time scales that are characteristic of pattern formation in complex systems. As is well known, a small number of macroscopic quantities (order parameters) can evolve very slowly, whereas many residual parts follow instantaneously or infinitely faster. The emergence of such distinct time scales coincides with the spontaneous generation of complex spatial distributions, even in cases in which the system is spatially homogeneous (e.g., the Bénard experiment).

Thus, the upshot of self-organization is that pattern formation may occur even in the absence of any preexisting spatial structure. The possibility that such a principle also plays a role in the brain motivates an alternative perspective in the study of cortical activity in which the search for low-dimensional, often abstract, quantities governing pattern formation takes central stage (Haken 1996). Apart from yielding adequate accounts of pattern formation, explicating the dynamics of these quantities may be useful in identifying generative neurophysiological structures. For example, the evolution of the probability distribution of relative phases of encephalographic signals may provide estimates for (inhomogeneous) connectivity densities. In such an approach, it becomes essential to incorporate stochastic properties of the order parameter dynamics because they play a key role in pattern formation and may provide important means for identifying relevant time scales beyond dispersion relations.

3. Physiological basis of modeling. Evidently, the neurophysiological reality of the connections between and within brain sites cannot be ignored in establishing the empirical validity of candidate models. A fundamental step in Nunez's conceptual approach is the introduction of corticocortical connections (nonlocal activity). On this basis he argues against "metaphorical approaches to modeling," asserting that his theory "contains no 'free' parameters" (sect. 5.3.6). Disappointingly, he later admits that his parameters are "*unknown*" (sect. 6.1). Consequently, the only way to obtain further information about them is to estimate their values on theoretical rather than empirical grounds. The relation between action potential input and synaptic action density, as described with Green's function, is determined by connectivity densities describing coupling strengths of neuronal populations, which are assumed to decay exponentially in space (sects. 5.3.8

and 8.1). To estimate the magnitude of this decay, two assumptions are prominent: (1) fall-off constants of the connectivity densities of all neurons are of the same order (e.g., Wilson & Cowan 1973), and (2) fall-off constants of excitatory neurons are much smaller than those of the inhibitory system (e.g., Nunez 1995). Apart from these theoretical estimates, few empirical data on the shape of connectivity densities are available (especially for corticocortical fibers). Hence, one may end up with a large variety of possible wave equations yielding various solutions. To reduce such arbitrariness, one may confine oneself to slowly evolving and large scaled waves of neuronal activity. Thus, equations can be derived that are largely independent of the particular shape of the chosen connectivity density (Haken 1999).

We have scrutinized here three central assumptions underlying Nunez's approach. We argued that nonlinearity, multiple time scales, and stochasticity are vital in the construction of dynamical models of brain activity. Placing such models on a firm neurophysiological footing may prove to be a taller order than it would be for models lacking those properties, but simply eliminating them would amount to throwing out the baby with the bath water.

Local-global interactions and the role of mesoscopic (intermediate-range) elements in brain dynamics

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Abstract: A unifing theory of spatiotemporal brain dynamics should incorporate multiple spatial and temporal scales. Between the microscopic (local) and macroscopic (global) components proposed by Nunez, mesoscopic (intermediate-range) elements should be integral parts of models. The corresponding mathematical formalism requires tools of nonlinear dynamics and the use of aperiodic (chaotic) attractors. Some relations between local-mesoscopic and mesoscopic-global components are outlined.

Linear models, amplitude-dependent nonlinearities, and phase transitions in neocortical dynamics. Nunez's work is a valuable contribution to studies on spatiotemporal dynamics of brain functions, and it opens a great adventure into the yet largely undiscovered territory of interpretation of electroencephalographic (EEG) measurements and brain imaging at the macroscopic level. Nunez introduces a local-global model of neocortical dynamics based on second-order partial differential equations (PDEs) with given boundary conditions, which usually represent periodic closure. A great advantage is that global and local effects coexist in this model. The new material is clear and thought-provoking. Qualitative considerations regarding the circular causality between local and global parts of his model and the consequences of such interactions at various temporal and spatial scales, including dispersion relationships, are the highlights of his approach.

Nunez assumes linearity of the PDEs in his search for solutions. In the Appendix he considers some of the effects of nonlinearities on his model. These considerations, however, do not develop some important aspects of nonlinearities that have crucial impact on the properties of brain dynamics at various scales. In particular, the static sigmoid input-output nonlinearity governed by the thresholds and refractory periods of neurons introduces amplitude-dependent nonlinearities, which are crucial for the rapid and repetitive phase transitions that characterize normal brain function (Freeman 1992b). These transitions lie well beyond the scope of linear analysis, for which the greatest virtue is the determination of stability by evaluation of Lyapunov exponents, after linearization of the equations at operating points far from the point attractors determined by equilibria (Freeman 1975).

PDEs suffer from the limitation that analytic kernels are usually required to get satisfactory solutions, and these are hard to come by in spatial organizations of brain activity. For this reason, we prefer to use integrodifferential equations (IDEs) or their compartmentalized equivalent, arrays of difference equations solved by numerical integration. IDEs also facilitate computations of chaotic attractors.

The role of mesoscopic elements in brain dynamics. For heuristic purposes, we define an intermediate level of brain function between single neurons or sparse networks of dendritic bundles and cortical columns operating at a microscopic level, and those large brain parts whose activities are observed with scalp EEG, fMRI, PET, and comparable optical imaging techniques in humans. We find it necessary to introduce the mesoscopic level to interpret data taken with 8×8 arrays of electrodes over cortical surfaces (Barrie et al. 1996; Freeman 1992b). These domains, having diameters of 0.5 to 2 cm, are much larger than columns, barrels, and glomeruli but they are at or below the lower limits of spatial resolution by macroscopic methods. Their properties are determined by the self-organizing chaotic dynamics of local populations of neurons, in which the delays introduced by the conduction velocities of the axons of participating neurons provide the limitations on mesoscopic sizes and durations.

Mesoscopic effects operating at spatial and temporal scales of 1 cm and 100 msec mediate between the two extremes of single neurons and the major lobes of the forebrain. They correspond in size to Brodmann's areas and in duration to psychophysical events that compose perceptions. Mesoscopic effects provide a link between extreme local fragmentation and global unity. They change continually in space and time, requiring a very close relationship between dynamic events, for example, EEG bursts, and the media through which the propagation occurs. This requires a nonlinear approach (Freeman 1992b; Skarda & Freeman 1987). In physics, the importance of intermediate-range effects is well recognized (Kozma 1998).

We illustrate the problem with Nunez's ocean wave analogy. Propagation of such waves leaves largely unchanged the properties of the water through which transmission takes place. In mathematics, the linearity of a second-order PDE formalizes this independence. Extensive interactions between the propagating signal and the neural tissue, however, reveal that nonlinear effects are essential in brains, in which the dynamics is inseparable from the medium. Neural tissues are not passive media through which effects propagate as waves do in air and water. The brain medium itself has an intimate relationship with the dynamics. There is a continuous excitation in the neural tissue, usually in subthreshold regimes. Occasionally due to external stimuli, for example, the activity crosses a threshold. At that point, the properties of the medium drastically change in a phase transition to accommodate changed external conditions. Mesoscopic elements are needed to introduce these nonlinearities, which are the essence of adaptation through perception and learning.

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Large-scale neocortical dynamics: Some EEG data analysis implications

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Abstract: The spatial time-frequency distribution matrix and associated Rényi entropy is proposed as the basis for a method that may be useful for estimating the significance of nonlocal neocortical interactions in the

analysis of scalp EEG data. Implications of nonlocal interactions for source estimation are also considered.

Nunez emphasizes the correspondence between model-based descriptions of large-scale cortical dynamics and experimental results, primarily from human EEG recordings. Although it seems likely that a definitive understanding of these dynamics will require invasive experimental manipulation on animals, enhanced analytic methods applied to scalp EEG data may be used to further study nonlocal neocortical interactions. In addition, the recognition of the possibility of such interactions has implications for the interpretation of presently used EEG source analysis methods. In the remainder of this commentary, I elaborate on these two points.

Beyond coherence – space-time-frequency distributions. Interelectrode coherence is a measure of the frequency-dependent correlation between channels, which has been used successfully to provide a quantitative view of cortical interactions, as described by Nunez. It may be possible to extend the underlying assumptions of coherence estimates to yield a more powerful and discriminating signal processing tool, the spatial-time-frequency distribution (STFD) matrix (Belouchrani & Amin 1999; Sekihara et al. 1999). Just as the covariance matrix for a multichannel data time series estimates the pairwise correlations between channels for a specified time window, the STFD matrix, defined in Eq. (1) may be seen as its generalization into the time-frequency domain.

$$C(t,f) = \sum_{l=-\infty}^{\infty} \sum_{m=-\infty}^{\infty} \Phi(m,l)\mathrm{x}(t+m+l)\mathrm{x}^T(t+m-l)e^{-4\pi jfl} \qquad (1)$$

Here $\mathrm{x}(t)$ is the (multichannel) data vector at time t, m and l are time indices, f is the frequency index, and $\Phi(m,l)$ is the convolution kernel that determines the characteristics of the time-frequency distribution (Cohen 1995).

Information content for time-frequency distributions. One benefit of the STFD approach is that it permits us to derive summary statistics, which may be used to measure such features as the time-, space-, or frequency-varying complexity of the EEG signal. For example, we may use the minimum descriptor length (MDL; see Kailath & Wax 1985) as an estimate of the complexity of the time-frequency distribution $C(t,f)$. Roughly speaking the MDL statistic estimates the optimal number of eigenvectors required to characterize the $C(t,f)$ matrix.

An alternative estimate of the information content is to use the generalized (Rényi) entropy to measure the signal complexity (Baraniuk et al. 1998; Gonzalez-Andino et al. 1999). The Rényi entropy, $S_q[C(t,f)]$ of order q for the STFD matrix $C(t,f)$ defined by Eq. (1) may be obtained as

$$S_q[C(t,f)] = \frac{1}{q-1}\log_2 \sum_{\substack{i=1,\\ i<j\le N}}^{N} c_{ij}^q(t,f) \qquad (2)$$

where c_{ij} are the upper right triangular elements of the $\mathrm{N} \times \mathrm{N}$ matrix $C(t,f)$, perhaps suitably normalized. One advantage of using the entropy as a complexity measure is that it permits us to partition the STFD matrix elements into those representing short and long spatial scale interactions. Thus it should be possible to scan an EEG time series, identifying time intervals of enhanced global correlation corresponding to low long space scale entropy compared to the short length scale entropy. This approach is currently under evaluation in our group.

There are two theoretical questions that need to be addressed more carefully regarding the application of these methods. First, the use of entropy to measure complexity is based on the identification of the distribution whose entropy is to be estimated with a probability density function. This is apparently justified when considering each of the diagonal terms individually (over either time or frequency), but it is not clear that a similar relation holds for the set of off-diagonal terms estimated for a specific time-frequency interval. This problem requires further study.

The second involves a problem arising if the c_{ij} are complex. If each of the terms in Eq. (1) is an even function of time, then $c_{ij}(f)$ will be real for each f. Since $\Phi(m,l)$ may be chosen to be an even function, this is condition is likely to be very nearly true for the EEG problem, where the physical medium combines sources from different regions linearly and with essentially no phase shift at the frequencies of interest (<1 kHz). Nevertheless, it is worth noting that even if complex-valued c_{ij} are encountered, even-order Rényi entropies will still yield real-valued estimates. The utility of these estimates will need to be evaluated in practice.

Inverse problems. The existence of large-scale dynamics may create difficulties for certain statistical source estimation procedures, unless the validity of the underlying assumptions is evaluated carefully.

We should not assume that independent components correspond to discrete (dipolar or local multipolar) sources. This may become a significant problem for greedy algorithms, such as Recursive MUSIC (Mosher & Leahy 1998), which attempt to account for as much of the variance as possible at each iteration by using localized (though not necessarily dipolar) sources. If the process to be modeled is dominated by large-scale cortical dynamics, such localized source estimation techniques are likely to be wrong, unless paired (and higher order) source configurations are taken into account explicitly.

Source estimation, when applied critically, may provide useful analytic information regarding local-global interactions. Source space coherence estimates, for example, may provide an indication of cortical regions that are jointly activated, although the prospect of $O(10^6)$ pairwise correlations when using distributed source models implies the need for powerful data reduction tools. Lastly, Pascual-Marqui et al. (1999) have proposed an extension to spatiotemporal distributed source estimation methods, which may be used to estimate wave equation coefficients, similar to those described in the Nunez target articles.

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Natural solutions to the problem of functional integration

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Abstract: Current EEG research emphasizes gamma band coherence as a signature of functional integration, that is, the solution to the binding problem. We note that spatial patterns of coherent neural activity are also observed at other EEG frequencies. If these oscillations reflect Nunez's resonant modes, they offer a solution to the binding problem that emerges naturally from the architecture of cortical connections.

A number of recent studies of perception, working memory, and motor control have measured EEG or MEG coherence to investigate functional interactions between brain areas (cf. Tallon-Baudry et al. 1997; 1998; Classen et al. 1998; Miltner et al. 1999; Rodriguez et al. 1999; Sarnthein et al. 1998; Srinivasan et al. 1999). The distinct advantage of multichannel EEG and MEG recordings is coverage of the entire brain, albeit with spatial resolution apparently limited to the centimeter scale (Malmivuo & Plonsey 1995; Nunez 1981a; Srinivasan et al. 1996). Many of these recent experiments were motivated by the observation in animal models of coherent activity in the gamma band (usually around 40 Hz) related to a number of cognitive processes requiring interactions between neural populations (recently reviewed in Singer 1999a).

One of the earliest and still the most striking of these results is the observation of coherent firing of a pair of visual neurons, one in each hemisphere, when a single contour passes through both of their receptive fields (Engel et al. 1991). When different contours pass through the receptive field of each neuron, coherence is reduced. Computational neural models also support the idea that coherence is sufficient to achieve functional integration (Tononi et al. 1992).

The postulate that gamma band coherence is the mechanism by which the brain can solve the binding problem has substantially influenced current EEG and MEG research (Singer 1999b). The interest in using EEG and MEG to investigate brain activity related to functional integration is timely and appropriate. However, the assumption that gamma band coherence in particular is necessary to achieve binding between distinct populations of neurons is not well justified. In many studies, EEG coherence at other frequencies, that is, delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), and beta (13–30 Hz), is not investigated, not reported, or dismissed as epiphenomenon, that is, unrelated to functional integration. As noted by Nunez, extracranial recordings of human EEG and MEG are measures of neuronal activity at a much larger spatial scale than either local field potentials or multiunit activity. While there can be consistencies between recordings taken at different spatial scales, there is little reason to expect them. Experimental data cited in this article provide substantive support for the idea that coherent neural activity can be observed at many temporal frequencies. Apparently, dynamic pattern forming of neural cell assemblies may be reflected in the entire EEG spectrum. Our ability to interpret these findings has been limited by the lack of connections to experimental data obtained within the brain and a theoretical framework within which results can be readily interpreted. The target article by Nunez is a major step toward developing this framework.

At the centimeter scale imposed by extracranial recording of EEG or MEG, coherence mostly reflects functional connectivity by corticocortical fiber systems (Thatcher et al. 1986; Nunez 1995). The "global" model presented in this article involves several approximations to real brains, but has been developed at an appropriate spatial scale to incorporate this critical feature, thereby facilitating comparisons with EEG or MEG coherence. The main general prediction of the model is that the brain has resonant modes, that is, relationships between the spatial distribution and temporal frequency of patterns of synaptic activity within the brain.

By contrast, computational models exhibiting gamma band oscillations are typically formulated at smaller spatial scales. For instance, gamma band oscillations emerge in intermediate-scale networks that model the early visual system of the cat with several tens of thousands of neurons (Lumer et al. 1997). The general architecture of this model comprised a primary and secondary thalamocortical system, each one equipped with a lateral geniculate and reticular thalamic nucleus and a three-layered cortical area. The anatomical connectivity of this system was crafted to incorporate details available from physiological and anatomical research on the cat visual system, and it demonstrated that vertical thalamocortical and corticothalamic projections are sufficient to sustain synchronous oscillations in the gamma range across the entire thalamocortical depth (Lumer et al. 1997).

The notion of resonant modes forwarded by the target article suggests that the frequencies at which coherent activity will be detected in two populations will be variable, depending in part on the delays between the populations. Thus, interactions between brain regions can be expected to occur over a wide range of frequencies. There are several reports of coherent oscillations in theta, alpha, and beta frequencies in recordings from within the brains of animals (Bressler et al. 1993; Murthy & Fetz 1992; Sanes & Donoghue 1993) and humans (Kahana et al. 1999; Towle et al. 1998). Whether these observations reflect the resonant modes of the brain, as suggested by Nunez, can only be determined by further experimental study. However, were this hypothesis verified, it would provide a potential mechanism for solving the binding problem by taking advantage of an intrinsic property of the architecture of connections in the cortex. In this mechanism, the temporal properties of cortical inputs or local cortical activity could determine which resonant modes were activated, effectively specifying the spatial distribution of correlated neural activity throughout the brain. For instance, if beta range resonances were related to corticocortical delays between visual and motor areas, oscillating at beta frequencies could enable visual neurons to selectively activate neurons in motor areas but not other areas of the brain. Experimental studies of visuomotor integration in animals (Roelfsema et al. 1997) and humans (Classen et al. 1998) have shown stimulus-dependent beta coherence rather than gamma coherence. Although we admit this idea is speculative, it would be an efficient solution to the binding problem, with sufficient generality to account for the need to organize neural activity at multiple spatial scales for cognitive function.

In summary, the target article by Nunez provides a theoretical framework for viewing EEG data as a mixture of global and local phenomena. For the experimentalist with an interest in investigating the binding problem, this framework strongly suggests that global EEG rhythms are a reflection of a large-scale mechanism of functional integration. Neuroscience has experienced many rigid notions of brain function that insist on particular frequencies, scales, or directions that were later proven inadequate and revised. As an example refer to the relationship between thalamus and cortex in general: the view of the thalamus influencing cortical activity in a purely feedforward way was gradually replaced by a more balanced one that also took into account corticofugal influences on thalamic receptive fields and timing relations (cf. Contreras et al. 1996; Rauschecker 1998; Woergoetter et al. 1998). Gamma oscillations have helped us recognize the importance of coherence in brain function. We should not allow them to limit our appreciation of brain dynamics.

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Statistical mechanics of neocortical interactions: EEG eigenfunctions of short-term memory

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Abstract: This commentary focuses on how bottom-up neocortical models can be developed into eigenfunction expansions of probability distributions appropriate to describe short-term memory in the context of scalp EEG. The mathematics of eigenfunctions are similar to the top-down eigenfunctions developed by Nunez, despite different physical manifestations. The bottom-up eigenfunctions are at the local mesocolumnar scale, whereas the top-down eigenfunctions are at the global regional scale. Our respective approaches have regions of substantial overlap, and future studies may expand top-down eigenfunctions into the bottom-up eigenfunctions, yielding a model of scalp EEG expressed in terms of columnar states of neocortical processing of attention and short-term memory.

Categorization of experimental spatial-temporal EEG. Many reasonable theoretical studies of synapse-like or neuron-like structures have been tested experimentally. Such studies often fail to address the "spatial-temporal" scales they attempt to describe. Many investigators would like to see more work on experimental designs or tests of local-global interactions correlated with behavioral states at specific scales. For example, if an EEG could rea-

sonably be correlated with a resolution of 3–5 cm within a time scale of 1–3 msec, then experiments should test whether specific states of attentional information processing are highly correlated within this specific spatial-temporal range.

In this context, the work of Nunez stresses resolution of EEG data within specific spatial-temporal scales, giving us candidate data for such correlations. It is most important for researchers to deal with the details of experimental evidence, not just pay homage to its existence.

Theoretical descriptions of spatial-temporal EEG. Nunez's theoretical framework encompasses global and local neuronal columnar activity, giving a primary role to global activity. His work has generated interest from other investigators to take similar approaches to describing neocortical activity (Jirsa & Haken 1996). Other investigators, myself included, assign a primary role to local activity, immersed in global circuitry. In this context, Nunez brings to *BBS* a sound framework in which to further analyze the importance of considering multiple scales of neocortical activity.

Generality of eigenfunction expansion. Here I address how eigenfunction expansions of models of brain function, similar to those performed by Nunez to describe how global models of wave phenomenon can be used effectively to describe EEG, can be applied to probability distributions of short-term memory fits to EEG data. In the following description, emphasis is placed on overlap and collaboration with the work of Nunez, especially in areas where local and global interactions are required to detail models of neocortical interactions giving rise to EEG phenomena.

SMNI description of short-term memory (STM). Since the early 1980s, a series of papers on the statistical mechanics of neocortical interactions (SMNI) has modeled columns and regions of neocortex, spanning millimeters to centimeters of tissue. Most of these papers have dealt explicitly with calculating properties of short-term memory (STM) and scalp EEG in order to test the basic formulation of this approach (Ingber 1981; 1998; Ingber & Nunez 1990). This model was the first physical application of a nonlinear multivariate calculus developed by other mathematical physicists in the late 1970s (Graham 1977; Langouche et al. 1982).

Statistical aggregation. SMNI studies have detailed a physics of short-term memory and of (short-fiber contribution to) EEG phenomena (Ingber 1984) in terms of M^G firings, where G represents E or I, M^E represents contributions to columnar firing from excitatory neurons, and M^I represents contributions to columnar firing from inhibitory neurons. About 100 neurons comprise a minicolumn (twice that number in visual cortex); about 1,000 minicolumns comprise a macrocolumn. A mesocolumn is developed by SMNI to reflect the convergence of short-ranged (as well as long-ranged) interactions of macrocolumnar input on minicolumnar structures, in terms of synaptic interactions taking place among neurons (about 10,000 synapses per neuron). The SMNI papers give more details on this derivation.

In this SMNI development, a Lagrangian function is explicitly defined from a derived probability distribution of mesocolumnar firings in terms of the M^G and electric potential variables, ϕ^G. A mechanical string model, as first discussed by Nunez as a simple analog of neocortical dynamics (Nunez 1989b; Nunez & Srinivasan 1993), is derived explicitly for neocortical interactions using SMNI (Ingber & Nunez 1990). In addition to providing overlap with current EEG paradigms, this defines a probability distribution of firing activity, which can be used to further investigate the existence of other nonlinear phenomena, for example, bifurcations or chaotic behavior, in brain states.

The SMNI calculations are of minicolumnar interactions among hundreds of neurons, within a macrocolumnar extent of hundreds of thousands of neurons. Such interactions take place on time scales of several τ, where τ is on the order of 10 msec (of the order of time constants of cortical pyramidal cells). This also is the observed time scale of the dynamics of STM. SMNI hypothesizes that columnar interactions within and/or between regions containing many millions of neurons are responsible for these phenomena at time scales of several seconds. That is, the nonlinear evolution at finer temporal scales gives a base of support for the phenomena observed at the coarser temporal scales, for example, by establishing mesoscopic attractors at many macrocolumnar spatial locations to process patterns in larger regions.

EEG regional circuitry of STM local firings. Previous calculations of EEG phenomena (Ingber 1985) show that the short-fiber contribution to the α frequency and the movement of attention across the visual field are consistent with the assumption that the EEG physics is derived from an average over the fluctuations of the system. That is, this is described by the Euler-Lagrange equations derived from the variational principle possessed by L_ϕ, which yield the string model described above (Ingber 1988).

Individual EEG data. The 1996 SMNI project used evoked potential (EP) EEG data from a multielectrode array under a variety of conditions, collected at several centers in the United States, sponsored by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) project (Zhang et al. 1995). The earlier SMNI 1991 study used only averaged EP data.

After fits were performed on a set of training data (Ingber 1997), the parameters for each subject were used to generate CMI for out-of-sample testing data for each subject (Ingber 1998). The results illustrate that the CMI give enhanced patterns to exhibit differences between the alcoholic and control groups of subjects.

STM eigenfunctions. The study fitting individual EEG data to SMNI parameters within STM-specific tasks can now be recast into eigenfunction expansions yielding orthogonal memory traces fit to individual EEG patterns. This development was described in the first SMNI papers (Ingber 1981; 1982; 1983).

The clearest picture that illustrates how this eigenfunction expansion is achieved is in Ingber and Nunez (1995) where, within a tenth of a second, there are stable, multiple, nonoverlapping Gaussian-type peaks of an evolving probability distribution with the same STM constraints used in the NIH EEG study above. These peaks can be simply modeled as a set of orthogonal Hermite polynomials.

Expansion of global EEG eigenfunctions into local STM eigenfunctions. In the "classical" limit defined by the variational Euler-Lagrange equations previously described, we have demonstrated how the local SMNI theory reduces to a string model similar to Nunez's global model (Ingber & Nunez 1990). One reasonable approach to developing the EEG eigenfunctions in Nunez's approach is to apply the variational derivatives directly to the SMNI STM Hermite polynomials, thereby yielding a model of scalp EEG that is ultimately expressed in terms of states of neocortical processing of attention and short-term memory.

Conclusion. Nunez has been a key exponent of realistic modeling of realistic neocortex for many years, even when it was not as popular as neural network modeling of "toy brains." In the process of insisting on dealing with aspects of models of neocortical systems that could be experimentally verified or negated, he has contributed to a rich approach to better understanding the nature of experimental EEG.

His approach has led him to stress appreciation of neocortex as functioning on multiple spatial-temporal scales, and he has collaborated with other investigators with different approaches to these multiple scales of interactions. His approach has been to formulate a top-down global model appropriate to the scale of scalp EEG phenomena, which includes some important local mesocolumnar features. This approach has been sufficiently robust to overlap with and enhance the understanding of other bottom-up approaches such as I have described, wherein mesocolumnar models appropriate to the scale of STM are scaled up to global regions appropriate to EEG.

In this commentary, I have focussed on how bottom-up SMNI models can be developed into eigenfunction expansions of probability distributions appropriate to describe STM in the context of EEG. The mathematics of eigenfunctions are similar to the top-down eigenfunctions developed by Nunez, albeit they have different physical manifestations. The bottom-up eigenfunctions are at the local mesocolumnar scale, whereas the top-down eigenfunc-

tions are at the global scale. Future studies may expand top-down eigenfunctions into the bottom-up eigenfunctions, yielding a model of scalp EEG that is ultimately expressed in terms of columnar states of neocortical processing of attention and short-term memory.

NOTE

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Beyond the limits of the brain as a physical system

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Abstract: Nunez's description of the brain as a medium capable of wave propagation has provided some fundamental insights into its dynamics. This approach soon reaches the descriptive limits of the brain as a physical system, however. We point out some biological constraints which differentiate the brain from physical systems and we elaborate on its consequences for future research.

In the early 1970s Paul Nunez pioneered the rigorous application of physical wave propagation theories to brain sciences. In explicitly viewing the brain as a physical medium capable of sustaining spatiotemporal wave dynamics, his description differed distinctly from that of his contemporaries (e.g., Wilson & Cowan 1972; 1973). Physics provides a vast toolbox for treating wave phenomena mathematically, such as dispersion relations, Fourier techniques, coherences, and the like. These techniques have been applied to the description of brain dynamics, in particular revealed by EEG, over the years (Nunez 1981a; 1995) and have provided some understanding of global brain wave phenomena in terms of physical properties of its carrier medium (see sect. 6 of target article), believed to be mainly the neocortex.

How far can we go with this view of the brain as a physical system? This will depend on the questions asked. As long as the questions concern physical properties such as dispersion relations, the ocean metaphor (see target article, sect. 3.3.2) will provide satisfying answers. To understand the brain as a biological system, however, will demand concepts that go beyond physics (Kelso & Haken 1995). We wish to emphasize one of these: spatially distributed information processing. To understand the brain as a biological system, will demand concepts that go far beyond physics (Kelso & Haken 1995). This concept is important on two levels: the first concerns information-processing operations within a cortical area, the second, the nature of processes that link cortical areas. Addressing the first level, Nunez introduces the distinction between local and global dynamics (see sects. 5.2 and 6.13). In a local cortical area, information can be spatially represented as in the columnar structures of the visual system or the tonotopic organization of the auditory system. It can also be spatiotemporally represented by synchronized population codes (e.g., Philips & Singer 1997). This crucial aspect of local neural activity is lost when performing the averaging approximation in section 5.3.2, because the local field loses its spatial resolution and is lumped into one time-dependent, spatially uniform variable. Memory, learning, and sensorimotor processes taking place on this spatiotemporal scale are thus averaged out. If the information handling in the brain is to be addressed in a way that distinguishes it from a mere aggregation of cellular mass, this is surely the place to start.

The second level of information processing occurs on the global scale and poses a major problem and challenge unknown to physical systems. In the latter, the connectivity between elements is translationally invariant and thus the connectivity is independent of a particular location. This is not true for the neocortex in which the intracortical fiber distribution seems to be translationally invariant (that is, the distribution of the actual neuroanatomical fibers), but corticocortically specific pathways project from one area to another (see Braitenberg & Schüz 1991) and thus contribute to a translationally variant fiber distribution. Based on this anatomy and electrophysiological evidence, neuroscientists (see, e.g., Bressler 1995 and references therein) report consecutive activation of cortical areas and develop discrete models of hierarchical information processing streams. On the other hand, the neocortical sheet may be viewed as a continuous medium on a large enough space-time scale and result in spatiotemporal wave phenomena known from continuous systems with translationally invariant, typically nearest-neighbor connectivities. The reality will be somewhere between discrete and continuous, providing a continuous medium with interregional projections serving brain function. Thus the translational variance of the white matter fiber system relates structure to function in biology, and this nature is fundamentally different to physical systems.

Nunez formulates a multiple fiber system in Eq. (9) of the appendix, but assumes each is translationally invariant, that is, dependent on the difference $x - x_1$ rather than x and x_1 independently. This assumption does not suffice for the white matter system, since it implies the same connectivity for each cortical area. In a similar vein, Haken's general treatment of connectivity functions (Haken 1999) refers to translationally invariant connectivities and thus proves the universality of Nunez's global field equations (see sect. 6.12) in the long wavelength limit, but only for this particular class of systems. The introduction of selected interregional projections into the corticocortical fiber system will generally cause the dispersion relations to be nonalgebraic, and wave propagation will depend strongly on selected pathways. These pathways connect to the earlier hierarchical information processing streams but are also an essential determinant of the global wave dynamics.

In Figure 1 we show that local changes of inter-region projections (see Jirsa et al. 1999), for example, realized by synaptic plasticity, can control the global spatiotemporal dynamics. Here the topology of the connectivity of the fiber system serves as a control parameter which may guide the global neural dynamics through a series of phase transitions (different patterns of brain activity). Again, this is fundamentally different from any physical system (at least known to us) and provides a mechanism for learning and memory to alter the brain dynamics globally.

The example in Figure 1 also allows us to clarify some of the dy-

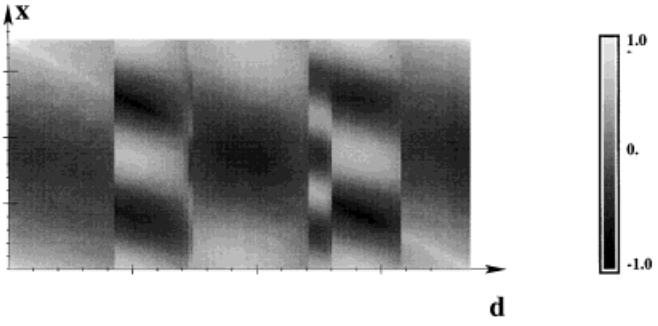

Figure 1 (Jirsa & Kelso). Variation of the spatial structure of neural activity as a control parameter, d, is varied. The one-dimensional spatial distribution of the amplitude of a neural field is plotted over the location x (vertically) for the time point when maximum amplitude occurs. The dynamics is based on the model in Jirsa and Haken (1996) with periodic boundaries. The control parameter is the length d of a pathway connecting two cortical areas. As d varies from zero to maximal length, the neural field dynamics undergoes spatial and temporal reorganization (the latter not shown here).

namical concepts used in Nunez's target article that we feel need to be taken quite seriously if rigorous models are to ensue. As just two points, consider the terms "control parameters" and "state of the system" as used by Nunez (sect. 3.2). Notice that in Figure 1, the control parameter d does not "describe the state of the system." Rather, in these nonlinear dynamical terms, the state is multivalued (consider the bistable coordination dynamics of the Haken et al. (1985) (HKB) model. Control parameters neither prescribe nor describe system "states"; they are simply parameters that move the system through "states." Nunez refers variously to system states, brain states, mental states, sleep states, and so forth. This seems altogether too cavalier. Notice that the states in Figure 1 are those that undergo qualitative change when the control parameter is varied. In truth, you only really know you have a "state" when the system's behavior changes qualitatively. Likewise, you only know what the control parameter is if that is the parameter, which, when varied, causes qualitative change (multistability, etc.).

The considerations in the previous paragraph show some limitations in Nunez's approach to understanding the brain as a physical system. Nunez's work is important in exhausting the limits of the physicalist's approach, but biology introduces new constraints such as translationally variant connection topologies, which are not known to physical systems and require the development of new tools and concepts specifically for the brain. The concepts and tools of dynamical systems are likely to be important in neural modeling (as they are in other branches of science). Experimental neuroscientists will need to understand these concepts if they are to identify control parameters and collective variables characterizing states on any given level of description. This is the key information that "theorists" will need to have if they are to construct serious, neurobiologically plausible models that go beyond the correlations between EEG and "brain states" that Nunez addresses.

Physiological units and behavioral elements: Dynamic brains relate to dynamic behavior

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Abstract: Nunez is to be applauded for putting forward a theoretical brain model. In order to improve any model it needs to be experimentally testable. The model presented in the target article suffers from insufficient clarity as to how new experimental designs could be derived. This is a consequence of neglecting the purpose of the brain, which is to produce effective and adaptive behavior. It might be possible to overcome this drawback by including Hebb-based modeling.

A major problem in the interpretation of EEG/MEG findings has been the lack of a coherent theoretical framework within which to articulate and test the results from experimental studies. Paul Nunez provides an interesting approach for the interpretation and analysis of electromagnetic measures of neural mass activity. This is the more remarkable as reference to dynamical aspects of the signals is usually sparse in ERP/EEG literature. Furthermore, the relation between specific experimental findings and brain theory has been examined only sporadically. This strongly contrasts with the fact that the processes underlying the scalp-recorded voltage modulations remain unclear unless examined on the ground of an appropriate theoretical foundation. What would the main characteristics of such a theoretical account be? We shall confine our comments to two points that may be complementary to some of the main issues raised in the target article.

First, we would like to address the issue of experimental paradigm selection and its consequences for theory-guided predictions on EEG parameters. In the target article and his 1995 book, Nunez describes a number of studies, the results of which can be explained by local/global theory in a post-hoc manner. In addition, several predictions are made for spectral characteristics of spontaneous EEG in distinct brain states such as sleep stages. The target article mentions the fact that the predictions made on the basis of the local equations may be hampered by global effects and vice versa. Nunez acknowledges that his "theory is silent on most cognitive questions because it was developed specifically to describe EEG, not behavioral or cognitive correlates" (sect. 2.7, para. 2). However, without further specification and more precise relation to variables on a behavior or psychological level, this approach seems to have limited applicability for designing meaningful studies of brain functioning. What is needed is a theoretical account of brain-behavior relations in terms of task-specific assumptions and predictions, being embedded in a behavioral theory. Of course, the selection of appropriate algorithms is not trivial, because a number of alternate mathematical models are also able to predict the cortical dynamics as recorded by EEG (e.g., Elbert & Rockstroh 1987; Skarda & Freeman 1987). One example for a theoretical framework that allows both for the construction of experimental paradigms and selection of relevant parameters may be the work by Haken, Kelso, and collaborators, referred to in the target article. Their synergetic approach incorporates predictions for both behavioral and neuronal dynamics during performance of well-defined perceptual and motor tasks (e.g., Kelso et al. 1995). In order to test these predictions, experimental designs have been developed that allow for monitoring phase transitions (i.e., qualitative changes between system states) using behavioral measures such as self-report or electromyogram on the one hand as well as electrocortical recordings on the other. Thus, a dynamic perspective is not only applied to brain parameters, but also to the experimental design.

Second, an extension of the Nunez model might be achieved if our understanding can be integrated regarding how Hebbian cell assemblies are sculptured within a highly interconnected neuropil by the forces of stimulus-evoked activity. These forces include experience-driven synaptic plasticity (synapse formation, spine density, and alterations in dendritic length) and the competition of previously formed cell assemblies. The power of the Hebbian idea derives from the connection between physiological units and behavioral elements. A cell assembly can be spread across large cortical areas (Pulvermüller et al. 1999). The meaning and qualitative nature of an event, an idea, an emotion, or a percept, are reflected in the local topography of its connections and firing patterns, so to speak, in the topographical "Gestalt" of an assembly in its phase space and not in the properties of its parts, cells, or transmitters. A model based on such considerations has been presented by the recent target article of Pulvermüller (1999). The specificity of an assembly is best reflected in the spatial distribution and frequency of fast-changing electrical activities, such as the EEG and event-related components. Meanwhile, a large number of studies have converged to show a strong correlation between high-frequency brain activity and experimental manipulations. The measures used include single-cell recordings, local field potentials, electrocorticogram, EEG spectral power, and EEG coherence (Keil et al. 1999; Pulvermüller et al. 1999; Tallon-Baudry & Bertrand 1999). Nunez's local/global theory could contribute to these findings, providing an approach to quantify and predict interactions between these scales, for example, as proposed in Equation 5 of the target article.

The need for an integration of approaches such as Nunez's and aspects of Hebbian plasticity and self-organization is evident: Any physiological activity has to be nonlinear and nonrandom, because living biological systems can only function if held within certain activity limits through feedback of the ongoing activity. Consequently, cell assemblies, and therefore the EEG and ERP, may have properties of deterministic chaos (for review see, e.g., Elbert et al. 1994). Skarda and Freeman (1987), for instance, have shown

in the olfactory system of the rabbit that chaos becomes more prevalent when there is competition among parts of assemblies, or among several assemblies. Why shouldn't similar mechanisms hold for the human neocortex?

The position of event-related EEG activity in the local/global theory

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Abstract: The theory of local/global neocortical EEG dynamics responds to newly emerging conceptualizations in neuroscience. An extended application of the model to event-related EEG activity composed of distinctive global and local functional epochs with presumably different timing is proposed.

As discussed recently in *BBS* (Gold & Stoljar 1999), current trends in neuroscience philosophy are reflected primarily by the neuron doctrine according to which "emergent properties are high-level effects that depend on lower-level phenomena" (Churchland & Sejnowski 1992). Accordingly, whether and how neurophysiological processes underlie conscious behaviour and mental functions is at present a target field of research. To bridge psychology and neurophysiology, concepts that are integrative and mathematically supported become increasingly important. Theories of brain dynamics based on electroencephalographic (EEG) activity merit special attention because EEG is an integrative bioelectrical signal resulting from the summated coactivation of the neurophysiological substrate (cells and cell assemblies) (e.g., Birbaumer et al. 1990; Steriade et al. 1990; Wright 1997), and it also correlates with cognitive states and functions as assessed at the behavioural level (Berger 1929; Regan 1989; Rugg & Coles 1997). Thus, the EEG appears as a relevant brain signal or code (Basar 1998; Gevins 1998) capable of integrating the now distinct levels of observation of brain functioning: the physiological and the psychological. The model of local/global neocortical EEG dynamics described in the target article hence has a major advantage in responding to newly emerging conceptualizations in neuroscience.

More specifically, a coexistence of local and global processes is proposed. Local (cellular and neural network) processes are assumed to underlie functional segregation based on specific information processing and storage. Global processes support functional integration by sustaining a background environment of standing waves of "synaptic action." EEG dynamic behaviour results from the close interdependence between local and global components. Nunez's conceptual framework can be extended to the following issues:

1. Event-related EEG activity. The local/global model is especially relevant to event-related EEG activity, that is, to bioelectric signals generated during external or internal event processing by the brain. The reasons are the following: (1) Perception and evaluation of each particular sensory-cognitive event is subserved by highly specific functional activation in the sense of both segregation and integration (e.g., Fuster 1999; Gazzaniga 1995; Polich & Kok 1995). Hence, external or internal event processing involves a distinction not only between local and global processes but also between different aspects of the local and global components. (2) Previous studies of event-related potentials (ERPs) and event-related oscillations have consistently demonstrated the functional involvement of EEG responses from various frequency ranges (delta, theta, alpha, beta, gamma) in both sensory and cognitive information processing (e.g., Basar et al. 1997; Bressler 1995; Freeman 1979; Klimesch 1999; Pantev et al. 1994; Pulvermüller et al. 1997; Yordanova & Kolev 1998a; 1998b). Given the association of EEG responses with transient or self-paced rather than steady-state events involving both specific and basic functional mechanisms, applying the local/global model to event-related EEG activity may be most reliable for testing the model strength and may contribute to further the understanding of neocortical dynamics in relation to brain function.

2. Timing of functional epochs. The time dimension is crucial in evaluating local and global neocortical processes as well as their interaction. Local processes emerging from neuronal substrates of microspatial scale are expected to occupy time periods that are considerably shorter than those of global processes (Nunez target article, sect. 5). In addition, the timing of functional epochs with different lengths may partly or fully overlap. The efficiency of appropriate time scaling for distinguishing between different mental states or operations has been validated by time-frequency analyses of ERPs (Demiralp et al. 1999; Kolev et al. 1997; Samar et al. 1995; Tallon-Boudry et al. 1998). The duration and time localization of coherence-producing epochs should vary correspondingly as a function of specific state or processing conditions. Thus, along with the spatial dimension, the temporal dimension might be an influential factor in the application of the local/global model.

3. "Connectivity" in neuroscience. Neocortical dynamics are a target of various approaches. As a consequence, different concepts (local, global, or integrative) are emerging. These start from more or less specific theoretical, methodological, and spatial-scale backgrounds, but converge on a common problem of brain dynamics (e.g., Lopes da Silva et al. 1976; Wright & Liley 1996). For example, the origin of the widely distributed EEG activity induced by (but non-phase-locked to) event delivery is thought to differ from that of the phase-locked EEG arising from localized specific processes (Pfurtscheller et al. 1996; Tallon-Boudry et al. 1998). In contrast, a common origin of the spontaneous and event-related EEG activity has also been suggested, with event-related oscillations resulting from the reorganization (phase-reordering, frequency stabilization, and amplitude enhancement or damping) of the ongoing rhythmic EEG activity (e.g., Basar 1980; 1998; Sayers et al. 1974). Common neural generators represented by small- and large-scale neural assemblies or distributed frequency-specific networks are supposed to give rise to both the spontaneous and evoked oscillations (Basar 1998). Furthermore, to study transfer functions of the brain as a system, resonant frequencies have been evaluated by calculating amplitude-frequency characteristics from event-related EEG signals as a first approximation (Basar 1980; Röschke et al. 1995). These examples illustrate that identical or similar notions and methodologies can be used in specific contexts.

Although the use of multiscale coherence as an indicator of neocortical dynamics in relation to mental functioning is advocated Nunez's local/global model, it is important to recognize how this apparently broad model applies to at least part of the enormous EEG data accumulated to date. The contribution of each integrative theory is based on its specific innovations, but it would be most useful to map existing theoretical and experimental knowledge onto new conceptual frameworks, to establish a common ground for linking models and theories.

Local and global dynamical control parameters are not so easily separated

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Abstract: Hierarchical systems such as cortical tissue will indeed exhibit dynamics that are scale-dependent, but Nunez's conjecture that theoretically independent transfer functions for each level can be specified and then combined ignores the fact that, in cortex, the same excitatory neuronal populations will contribute to both local and global dynamics.

In a comprehensive target article, Nunez argues convincingly that multiple scales are needed to describe the dynamical genesis of brain electrical activity and thus, by inference, brain dynamics and behaviour. Nunez then broadly identifies, on the basis of the characteristic scales of axonal connectivity within cortex, local and global levels, which will in turn distinguish the scale of the respective dynamical processes. This may seem reasonable as a first approximation, but it ignores the intermediate mesoscopic scale contributed by the surface parallel conduction fiber system in the agranular layer (layer I) and obscures the fact that ongoing neural activity, through learning, will modify the functional architecture of cortex such that there may coexist many more than just two interacting, and thus interdependent, scales of activity. Thus, while existing descriptions of cortical architectonics may suggest a relatively discrete collection of spatial scales, there is no necessity that this be functionally respected with ongoing network activity and synaptic modification.

This notion has been elegantly articulated by Freeman (1975) using the notion of hierarchically organised interactive neural sets (K-sets). [See also Skarda & Freeman: "How Brains Make Chaos in Order to Make Sense of the World" *BBS* 10(2) 1987.] Neurons that are members of different KI sets (interactive populations of functionally equivalent neurons sharing a common mode of input) may be members of a single KII set (two interactive KI sets). Thus, two locally defined KI sets may be members of a single globally defined KII set, and hence the properties of these two local sets will help to co-define any emergent global properties. Although Nunez is aware of the oversimplification of positing a distinction between local and global processes, the "meta" formulation (see, for example, the caption of Fig. 4), as specified in Equation (5) and Figure (4), implies that local and global processes can be formulated independently of each other, despite the obvious objection that the constitutive parts of the global whole are predominantly local in character.

Ultimately all neurons in the cortex will be involved in processes of local and global character. This is particularly clear when one notes some important features of the dominant cortical neuronal population – the excitatory pyramidal cells. A single pyramidal cell can form synapses locally via the lateral spread and arborisation of recurrent axonal collaterals as well as by establishing synapses with more distant excitatory and inhibitory cells via the longer range corticocortical fibers. As clearly demonstrated by David Sholl (Sholl 1956), the majority of pyramidal cells in neocortex are of this type. Thus changes in local pyramidal population sensitivity (by whatever mechanism) will give rise to concomitant changes in both the local feedback gain Q and the global "positive" feedback gain B (sect. 5.2, para. 2). Hence it is unclear on what basis Nunez makes the claim that the "control parameters" Q and B can be considered distinct.

Physiological evidence is equivocal on whether long- and short-range excitatory connection strengths can be independently modulated. One possible mechanism is that shunting inhibition, provided by a local interneuron population (e.g., the Martinotti neurons – see Braitenberg & Schuz 1998), applied at some point on the apical trunk of the pyramidal cell, could differentially modulate the relative efficacy of excitatory input from long- or short-range fibre systems, given that long-range connections form predominantly on the apical dendritic tree whereas short-range connections form predominantly on the basal dendritic tree (Braitenberg and Schuz 1998). [See also Braitenberg, Heck & Sultan: "The Detection and Generation of Sequences as a Key to Cerebellar Function, Experiments and Theory" *BBS* 20(2) 1997.] As local interneuron input will probably depend on local circuit activity, however, such a mechanism will only serve to emphasise the problematic nature of attempting to delineate global and local control parameters. Nunez's claim that "the theory contains no 'free' parameters" (sect. 5.3.6, para. 1) and "we appear to know much more about the physiological parameters of the purely global theory" (sect. 6, para. 2) accordingly seems erroneous, given the considerable ambiguity in defining what might be local and global control parameters and also whether it is meaningful to do so.

In a linearized model of electrocortical activity (Liley 1997; Liley et al. 1999), in which both corticocortical and intracortical connectivity between homogeneous populations of inhibitory and excitatory neurons were modeled, two independent "control" parameters were defined, Q_e and Q_i. These correspond to the respective sensitivities of excitatory and inhibitory neural populations to synaptic input and are equivalent to the slopes, at the point of linearization, of the nonlinear functions relating the number of action potential firings per unit time (i.e., firing rate) to the mean soma membrane potential in a locally homogeneous neural population. When modulated independently of each other these control parameters have effects in the linear model that are roughly orthogonal. In this model, increases in Q_e result in reductions in temporal and spatial frequency and damping, whereas augmenting Q_i results in increases in spatial and temporal frequency and reductions in the associated spatial and temporal damping. With auxiliary functions that are linear combinations of Q_e and Q_i, new parameters can be defined that are able to effect approximately orthogonal changes in spatial *and* temporal damping (Q_d) and spatial *and* temporal frequency (Q_f). Thus, changes in the physical scale of the dynamics can be effected by changes in the derivative parameter Q_d, which will necessarily be of global extent because of assumptions about the spatial homogeneity of the linearization (assumed also by Nunez). It is interesting to note that increases in Q_e will correspond approximately to Nunez's "hypercoupled" state whereas increases in Q_i will correspond approximately to Nunez's "hypocoupled" state (sect. 6.3, para. 1). Because changes in Q_e and Q_i are equivalent to changes in excitatory and inhibitory coupling strengths in this model, these predictions admit *relatively* easy verification using glutamate and GABA agonists and antagonists.

Nunez correctly advises caution applying the preliminary modeling attempts to the interpretation of macroscopic electrocortical activity (sects. 2.1, 2.2; sect. 2.7, para. 2), but more might be gained empirically if one realises that a conceptual delineation between local and global control parameters is problematic and needs to be abandoned in favour of a more synthetic approach.

Interscale interactions in cortical neural networks

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Abstract: This commentary focuses on how the large-scale cortical dynamics described in Nunez's target article are related to various phenomena at different scales, both spatial and temporal, in particular, how the brain dynamics measured with EEG could relate to (i) experience and mental state, (ii) neuromodulatory effects, and (iii) spontaneous firing and autogenerated electromagnetic effects.

Paul Nunez brings up the important issue of scale and interscale relations in brain dynamics. In so doing, he links closely to a previous BBS target article by Wright and Liley (1996), although the problems of local-global relations, which are stressed by him, are not necessarily the same as those of the micro-macroscopic relations stressed by Wright and Liley. Another work that connects to these issues is the excellent book, *Neural Organization – Structure, Function and Dynamics,* by Arbib, Erdi, and Szentagothai (1997; see BBS multiple book review of Arbib & Erdi's *Structure, Function, and Dynamics BBS* 23(4) 2000), where several theories and experimental results related to EEG are discussed.

Overall, there is an increasing aspiration to link theory and experiment in neuroscience and also to make neural network models that would be hard to distinguish from what Nunez refers to as

"genuine physiological theory" (sect. 2.1). In our group, we address questions of neural interscale interaction, using both theoretical and experimental techniques (Johansson & Århem 1994; Liljenström 1991; 1995; 1996; Liljenström & Århem 1997; Wu & Liljenström 1994). In particular, we use models of the olfactory cortex and hippocampus to investigate amplification and control of oscillations and fluctuations in these systems, and my comments here relate to these efforts, which complement those of Nunez.

Brain dynamics, as revealed by EEG and other methods, apparently depend on many different factors at different "scales," including the following: (1) mental state and experience dependent activity at a macroscopic/global level, (2) neuromodulation at a mesoscopic/semilocal level, and (3) spontaneous firing and autogenerated electromagnetic field effects at a microscopic level. (Levels are somewhat arbitrary, since processes at the different scales influence each other, and cause and effect cannot easily be separated.)

1. Macroscopic. Since the dynamics of the brain changes continuously and is highly nonstationary, it is not clear what Nunez means by a "fixed state" (sect. 3.2) which would allow EEG to be partly predictable. At the same time, the activity measured with EEG seems to depend critically on processes acting at a much larger time scale, for example, as a result of previous experience or the level of arousal and motivation (Skarda & Freeman 1987). The large variability in cortical-evoked activity (in response to repeated presentations of the same stimulus) seems to depend on the combination of a reproducible stimulus response and a dynamically changing ongoing activity, reflecting varying brain states (Arieli et al. 1996). In addition, the EEG apparently also strongly depends on mental ability, partly of a genetic origin (Cotterill 1998).

2. Mesoscopic. Neuromodulatory effects are acting on a time scale (much) larger than the EEG, as pointed out by Nunez, but they should nevertheless be included as part of the overall global behavior. Neuromodulators, such as acetylcholine and serotonin, diffuse fairly locally and can change the excitability of a large number of neurons simultaneously, as well as the synaptic transmission between them. This can have large effects on the neural dynamics and functions. For example, acetylcholine enhances the persistence of gamma-frequency oscillations in response to stimulation, and it can also induce theta-frequency oscillations (Biedenbach 1966; Bland 1986). These effects are reproduced with our cortical network model (Liljenström & Hasselmo 1995).

Microscopic. Nunez does not discuss EEG in relation to any specific phenomenon at the "microscopic level," such as the spiking of neurons or the interaction between the electromagnetic fields and neural firing patterns. Yet, these problems need to be dealt with in order to get a full appreciation of the EEG method. For example, certain cells seem to have a highly spontaneous random firing, but its relation to the activity at a global scale is uncertain. It is conceivable that such microscopic events can be amplified, under certain circumstances, and in computer simulations we show how "microscopic" fluctuations can induce global synchronous oscillations in cortical networks (Liljenström 1996; Liljenström & Århem 1997).

Whenever an action potential travels along a nerve fiber, or when the potential of a nerve cell changes, an electromagnetic field will induce potential changes in surrounding neurons. Autogenerated fields are sometimes even found to be considerably stronger than needed to affect activity in these regions (Jefferys 1995). Such field effects could mediate fast neuronal synchrony, for example, during epileptic seizures or during population spikes in the hippocampus. In the latter case, thousands of pyramidal neurons fire action potential synchronized within 1 millisecond of each other. This effect must result from a much faster synchronization mechanism than synaptic (or ionic) transmission (Jefferys 1995). Electrical gap junctions could play an additional role in the synchrony and stabilization of cortical oscillations (Peinado et al. 1993). Simulations with electric and electromagnetic field effects clearly show such an increased synchronization of network units, as well as the observed suppression of high-frequency components (Liljenström & Aronsson 1999).

Nunez proposes a nice mathematical framework for the local-global brain dynamics, as measured with human scalp EEG, and provides experimental evidence in support. This is indeed an important step on the way of understanding EEG, while there are obviously many questions not thoroughly dealt with that deserve deeper analysis.

For example, what is the relation between the "macroscopic" EEG and the microscopic firing of action potentials? How do the various frequency peaks in EEG correspond to the firing rate and distribution of interspike intervals? How are the various frequencies, for example, gamma and theta, related phenomenologically and functionally? Is the spatial resolution of scalp EEG adequate, and is coherence a relevant measure for addressing any of these questions? Is it possible to say anything about the microscopic level by regarding synaptic action and action potentials as merely macroscopic field variables?

Without doubt, scalp EEG and coherence measures can be good indicators of brain (consciousness) states, but it is unclear to what extent anything can be said about the functional significance, the underlying mechanisms, or the information processing of the brain. However, it is only with the persistent, combined efforts of theory and supplementary experimental methods that these problems can be resolved.

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From metaphors to equations: How can we find the good ones?

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Abstract: Among the metaphors used in the target article are "musical instruments," "water waves," and other types of mechanical oscillators. The corresponding equations have inertial properties and lead to standing waves that depend on boundary conditions. Other, physiologically relevant quantities like refractory times are not contained in the mechanical oscillator model but occur naturally, for instance, in biological forest fire metaphors.

The metaphors that we find in Nunez's target article (mechanical oscillators, musical instruments, water waves, etc.) have one thing in common: the vibrating systems have mass and therefore inertia. This property alone has fundamental consequences for the solutions that we expect from any model that is based on that metaphor.

Other metaphors like that of a forest fire can lead to equations whose solutions have many similar properties but that result from quite different mechanisms. They can also allow for treating the two subprocesses, burning and growing (polarization and depolarization), with independent time scales. Jung and Mayer-Kress (1995) study a stochastic McCulloch-Pitts neuronal network model that abstracts from details like skull conductivity but is large enough so that boundaries can be assumed to be absorbing. The type of resonance that we discovered is fundamentally different from that of musical instruments with oscillating strings or air columns. We could show that the critical variable is not the shape of the boundary or neocortex but the level of stochastic noise relative to the firing threshold. Close to resonant noise conditions we can observe large scale structures (see Fig. 1) that would be picked up by spatially separated scalp electrodes as coherent oscillations similar to those shown in Figures 1 and 2 of the target article.

Nunez also uses a social communication metaphor with people talking to each other face to face (few-to-few, local) or through

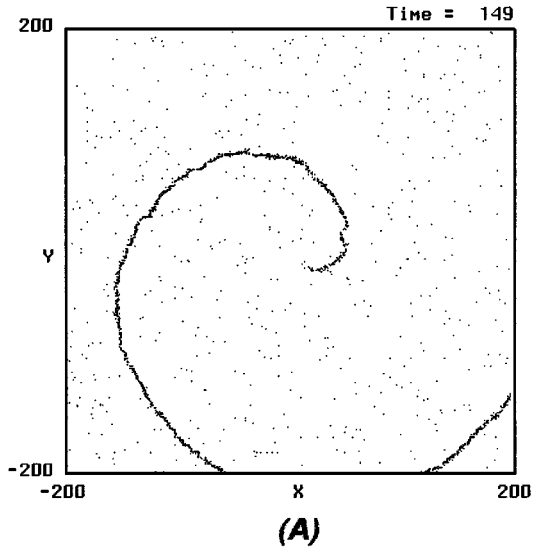

Figure 1A (Mayer-Kress). Resonant stochastic parameters can stabilize large-scale coherent structures in a neural net with absorbing boundary conditions.

mass media (few-to-many, global). Even if we include telephone and fax (few-to-few, global), Nunez misses the most important part in that metaphor, the Internet (many-to-many, global). There are strong indications that global structures like cell assemblies are indeed emerging there (Mayer-Kress & Barczys 1995). Since cell assemblies are defined functionally, it should be possible to observe synchronous EEG γ-oscillation between areas that are associatively related, even if they are spatially very far apart (see Mayer-Kress 1994 for methodology and Fig. 2 for illustration). The prediction was that the oscillations would last only for a few hundred milliseconds and therefore would be washed out in traditional coherence measurements. In two recent articles in *Nature,* this phenomenon has been confirmed (Miltner et al. 1999; Rodriguez et al. 1999).

If mechanical oscillators like the ones described by Nunez serve as heuristic metaphors, then it is not a surprise if equations emerge that represent exactly those mental images. Consider Equation

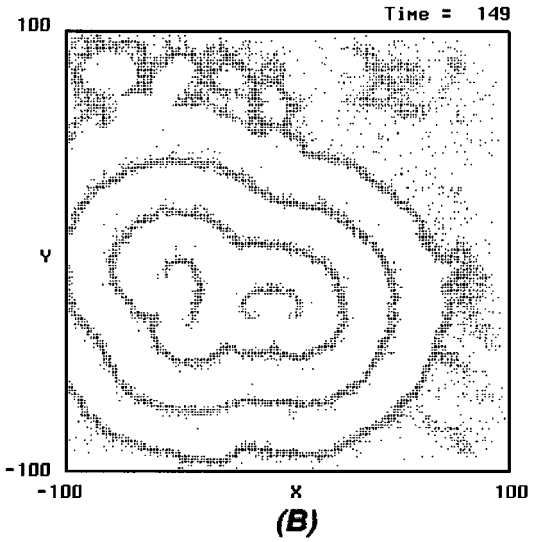

Figure 1B (Mayer-Kress). Slight increase in parameters lead to coherent patterns with decreased average wavelength and increased temporal frequency as measured at a fixed location. (See Jung & Mayer-Kress 1995 for details).

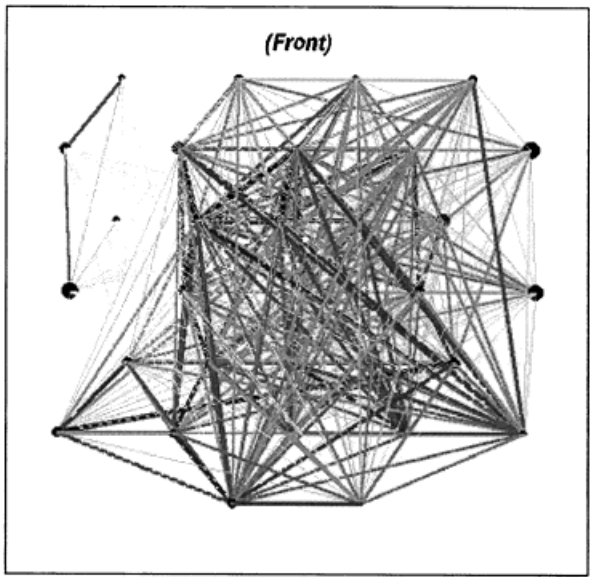

Figure 2 (Mayer-Kress). Frequency (point size) of short-term 40-Hz events at 31 electrodes and frequency (line thickness) of coincidences (simultaneous 40-Hz events between pairs of electrodes). Note that some far apart locations "communicate" much more intensely than some neighboring sites. (See Mayer-Kress 1994 for details; data courtesy of W. Miltner.)

(11.1) in the target article, according to which the number of active excitatory synapses at a specific location x will always increase with the excitatory input it receives from other cortical locations. There are no restrictions to the time variable t, that is, the equation should hold even a few milliseconds after all neurons in the neighborhood of x have fired! According to Nunez, this leads after several mathematical steps to Equation (10), a damped wave equation. Let us construct a special, simple case of Equation (10) for which we can estimate the qualitative behavior of the solutions without having to actually solve the equations. For uniform initial conditions without external input, Equation (10) turns into that of an overdamped mechanical spring. For this initial condition a coherent EEG would be predicted that gradually decays over a span of about five characteristic global delay times τ_g (= 30 to 125 msec). Even for arbitrary high initial values of $F(t = 0)$ (i.e., even if all neurons fire at $t = 0$) we would still find significant synaptic action density after several units of τ_g. In a forest fire framework, however, the activity would stop after only one microscopic time step.

A mechanical metaphor also implies that boundary conditions determine resonance frequencies of standing waves. If we ignore problematic geometric and topological consequences, there seems to be no empirical evidence (in either real brains or realistic simulations) that boundaries are essential for the propagation of brain waves.

Perhaps geometrical parameters of the brain are not responsible for the observed oscillation frequencies and parameters related to the actual physiology are sufficient to produce oscillations in the correct frequency bands. Rennie et al. (1998) found that local feedback determined frequencies of coherent oscillations. In our simple, stochastic McCollough-Pits network (Jung & Mayer-Kress 1995), the coupling between the elements, refractory properties and (surprisingly) the noise amplitude of ambient perturbations were sufficient to produce coherent oscillations in wide frequency bands and even with qualitatively correct dispersion relations.

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Large-scale neocortical dynamic function and EEG: Use of theory and methods in clinical research on children with Attention Deficit Hyperactivity Disorder

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Abstract: We used Nunez's physiologically based dynamic theory of EEG to make predictions about a clinical population of children with Attention Deficit Hyperactivity Disorder (ADHD) known to have neuronanatomical abnormalities. Analysis of high-density EEG data (long-range coherence) showed expected age-related differences and surprising regional specificity that is consistent with some of the literature in this clinical area.

In the target article, Nunez accomplishes his goal of presenting a framework for a physiologically based neocortical dynamic theory (sect. 2.7) to describe EEG. His theory is firmly based on brain anatomy, with local and global neural mass elements (quantified in terms of number of synapses) connected by fibers (specified in terms of length and speed of transmission). He uses this dynamic theory to describe EEG, not behavioral or cognitive correlates (sect. 2.7).

Neuroscientists will probably accept the challenge to test this simplified model of the brain and to identify its limitations and mistakes. This will serve Nunez's stated purposes to develop a theory appropriate for verification and falsification (sects. 3.3.4 and 5) and to provide a useful, semiquantitative environment to discuss the general conceptual framework of neocortical dynamics, not to prove his theory right or wrong (sect. 5.1).

In contrast, clinicians may be tempted to use this oversimplified "grey box" model (sects. 3.1 and 5, Fig. 4) for practical purposes, to better understand abnormal conditions. Our commentary falls in this realm. We will relate data we have collected (Murias et al. 1998) to topics in Nunez's paper and comment on the usefulness of the proposed framework for constraining our interpretations of the literature on the biology of ADHD in children.

Nunez's framework emphasizes "a small part of the brain's dynamic complexity, the very large-scale field of synaptic action density, of which scalp electroencephalography (EEG) is believed to provide a crude measure" (sect. 1). The estimates of synaptic action represent averages over 10 million to 1 billion neurons by each electrode (sect. 1.1), which is assumed to provide unique, not impoverished measures of brain activity.

In our application of these methods, we addressed critical technical issues that Nunez discusses in this paper. We heeded the recommendations (sect. 1.1) for high-density recording (by using a 128-channel electrode array). We followed the suggestion to investigate coherence within a narrow band (sect. 1.2), by focusing on the peak alpha frequency for each subject for eyes-closed resting EEG. We calculated coherence as a function of interelectrode separation (sect. 1.2, Fig. 1) and used a subset of the total (approximately $128 \times 127/2 = 8{,}128$) that were separately by 20 cm or more.

How might Nunez's framework be used to characterize brain differences between ADHD and control children? Recently, anatomical abnormalities have been reported by multiple investigators (see Swanson et al. 1998, for a review). A controversial finding has been reduced white matter in specific anterior and posterior brain regions and in the corpus callosum (Baumgartner et al. 1996; Castellanos et al. 1996; Filipek et al. 1997; Giedd et al. 1994; Hynd et al. 1991). Using Nunez's physiologically based theory, we predicted that coherence estimates would be reduced in ADHD children relative to normal children for specific brain regions with reduced white matter or linked by smaller than normal sections of the corpus callosum.

We compared coherence estimates for groups of frontal and posterior electrodes within and across hemispheres (Murias et al. 1998). The results were surprising and may indeed give some direction to our future research. In current theories of ADHD, a frontal abnormality plays a predominate role. When we used the Nunez framework to investigate this hypothesis, we failed to demonstrate differences in coherence for frontal brain regions in ADHD subjects compared to control children (0.23 vs. 0.21). However, we did demonstrate differences between ADHD and normal children in coherence for posterior brain regions (0.32 vs. 0.40), confirming similar findings based on EEG and implicating posterior brain regions (Brandeis et al. 1998). We interpret that as consistent with some reports of abnormal neuroanatomy in children with ADHD.

Does Nunez's neocortical dynamic theory offer promise for clinical research? Our direction by the theory and application of the methods provided by the framework described by Nunez in this paper was successful in verifying predicted abnormalities (reduced coherence in ADHD children compared to normal children). The anatomical specificity of the findings (posterior rather than anterior) suggests directions of research that may have been given low priority by nonphysiologically based theories of ADHD. This is the mark of a good theory.

Brain function theories, EEG sources, and dynamic states

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Abstract: This commentary discusses three features of the general theoretical framework proposed by Nunez: (1) Functional concepts, such as computation and control, are not foundational. (2) A mismatch between the concept of subcortical input and EEG output is problematic for the input/output operator concept of cortical dynamics. (3) The concept of brain state is relatively static.

The target article by Nunez proposes a theoretical framework for large-scale neural modeling that combines mathematical precision with empirical interpretability. For individual researchers, this can provide a "conceptual incubator" for hatching specific brain theories that are both computable and testable. For the community of experimentally minded brain theorists, the framework, considered via its more abstract aspects, can provide an arena for open competition between theories, because it accommodates distinct branches of theoretical development that are also distinguished by their experimental predictions.

The most abstract conceptions of any theoretical framework (such as this one) are initially justified more by a priori criteria than by a posteriori results. Eventually, a framework for scientific inquiry is judged by the experimental fruitfulness of its best theories; in this regard, Nunez adduces an impressive list of prima facie connections to EEG data (sect. 6). Although these specific connections also deserve attention, I have chosen to focus here on selected abstractions of the general framework, because these "set the stage" for all subsequent developments.

In addition to the a priori criteria of mathematical precision and empirical interpretability, a framework can be evaluated by the criterion of *functional relevance*, with a central role for "the work accomplished" or "the problem solved" by a system. To illustrate, an incomplete framework that conceives computer systems merely as transformers of physical inputs to outputs, and which lacks a concept of general-purpose symbolic computation, cannot explain how computers implement their function.

Nunez addresses the objection that his framework largely ignores the functional issues of brain information processing (sect.

6.13) by conjecturing that "any physiologically based dynamical foundation is likely to provide intermediate- and large-scale constraints on new cognitive models, in a manner analogous to constraints imposed by established physiology at the membrane or neuron level." This perhaps implies that a "cognitive layer" can later be added to the framework, without including computational concepts at its foundations; that is, that biophysics constrains computation, but not vice versa. Although multiscale information processing is later mentioned (sect. 7), the analogy also suggests that physiology is separable from computational functionality at the neuron and membrane levels. By omitting information processing concepts at its foundations, the framework leans by default toward a view of computation and control as functions that emerge "on top of" biophysics. By contrast, a broader framework for "computational biophysics" would integrate information processing concepts with spatiotemporal biophysical ones at its core; this would permit neurons and specialized membrane patches to be viewed as computational or control systems in their own right (e.g., Koch 1998). To suggest a point of departure, an objective function (e.g., coherent infomax per Phillips & Singer 1997) can provide a framework for computational function with precision comparable to the Nunez's biophysical framework. Then the integration task becomes one of constructing a common framework that treats spatiotemporal biophysical systems *as* objective-optimizing information systems, and vice versa.

The starting point for the biophysical framework proposed by Nunez is Eq. (1), which expressed the abstract notion of a mathematical operator that models the transformation of spatiotemporal input to spatiotemporal output (sect. 3.1). A theory of neocortical dynamics is identified with a mathematical operator (sect. 3.3), which produces spatiotemporal scalp potential output sampled by EEG measurements (sect. 3.3.1) from the largely unknown spatiotemporal input of subcortical structures (sect. 3.3.2 and Fig. 4). Thus, cortex is conceived primarily as a transformer of subcortical input to EEG output. More exactly, the "actual" output of cortex – such as dura potential, cortical current density, or synaptic action – generates the observed scalp EEG (sect. 4.2). "Actual" here may simply mean "in or near the surface of cortex" because, clearly, the framework does not propose that the cortex *functions* to produce these biophysical epiphenomena, whether in cortex or at the scalp. Thus, the essential attribute of output in this framework remains its connection with *observed data.* However, if this interpretation of output is correct, then the framework uses a completely different criterion – presumably anatomical connections – to identify input, which is *largely unobserved.*

The mismatch between unobserved/functional input and observed/nonfunctional output appears especially problematic because cortical dynamics are characterized in the framework precisely as a relational term between inputs and outputs. The subcortical inputs, by virtue of their anatomical connections, are presumably functional to the cortical system. However, without evidence to the contrary, the source-of-EEG outputs are presumably nonfunctional, even though EEG sources can be *signs* of functionally relevant brain activity. By contrast, note that cortically controlled behavioral output is intrinsically functional and also observable, both by scientist and by cortex (from different points of view). Except in biofeedback situations, cortex does not attempt to control EEG sources *per se,* even though these might reflect, for example, the control of one part of cortex over another part or their mutual coordination, and so on.

The mismatch problem just discussed can perhaps be alleviated by adopting a state-space approach to dynamic systems in place of the input/output operator approach. *State* in the Nunez framework is identified with relatively slow-changing (quasi-static) control parameters of the cortical input/output operator (sect. 3.2). However, in the (deterministic) state-space approach, "A *state* is some compact representation of the past activity of the system complete enough to allow us to predict, on the basis of the inputs, exactly what the outputs will be, and also to update the state itself." (Padulo & Arbib, 1974, p. 21) State in this conception spans the full dynamic range, from quasi-static to sub-millisecond. EEG sources (system outputs) can be obtained as a macroscopic projection function of the current brain state. State, rather than observable output, has intrinsic dynamic (and putative functional) significance. A brain state transition operator transforms dynamic states to states, under the functional influence of system inputs. Consequently, emphasis shifts from input/output operators toward self-reflexive operators conditioned by input. Thus, translation of the local/global theory of Nunez to the dynamic state-space formulation might be particularly beneficial because his special theory already is dominated by intra-cortical interactions.

Two compartmental models of EEG coherence and MRI biophysics

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Abstract: Studies have shown that as MRI T2 relaxation time lengthens there is a shift toward more unbound or "free-water" and less partitioning of the protein/lipid molecules per unit volume. A shift toward less water partitioning or lengthened MRI T2 relaxation time is linearly related to reduced high frequency EEG amplitude, reduced short distance EEG coherence, increased long distance EEG coherence, and reduced cognitive functioning (Thatcher et al. 1998a; 1998b).

There is considerable experimental support for the existence of traveling and standing EEG waves, and the quantitative description in the Nunez target article is very powerful and useful. There is also strong experimental support for EEG coherence to be partly explained by short and long distance connection systems that are at times competitive and/or cooperative and in which the short distance connections have a different genetic inheritance in comparison to the long distance connection system (Thatcher 1998; van Baal 1997). Recently, our laboratory has tested the local/global wave models of EEG by correlating the scalp EEG amplitude, coherence and phase with the T2 relaxation times of volumes of the brain interior to the skull (Thatcher et al. 1998a; 1998b). We found a systematic linear relationship that is best described by two oppositely signed linear equations, one for short interelectrode distances (e.g., 3 to 7 cm) and one for the long interelectrode distances (e.g., 18 to 28 cm).

Real brain waves

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Abstract: Metaphors, particularly the implicit ones, constrain imagination. If we think of the brain as a collection of centers of cognitive activations, lighting up on demand, then this becomes all we can imagine. By thinking of the cortex as propagating its functional work through physical waves, Nunez offers us a new, rich model for distributed representation. Now let's add real anatomy.

What if brain waves were actually *waves?* Waves of electrical excitement, washing over the surface of the cortex, like the seas, rollers, and ripples that play over the surface of the Pacific? If this were true, then a physicist could describe the brain's activity as a series of perturbation events, together with the dispersion relations that propagate those events through the dispersive medium.

A psychologist, linguist, or educator might argue that a theory

of brain waves *per se* is misdirected science, just the kind of thing we might expect from a physicist. Even if it were possible to explain brain waves with a physical theory, such a theory could end up telling us nothing about the brain's mental activity. In fact, if Nunez is right about his standing waves and boundary conditions within the dispersive relations of the prolate spheroid, then we might be forced to conclude that brain waves are so far removed from the brain's functional work that the critics have been right all along. Brain waves are indeed the empty content of neurophysiology, proved at last to be the epiphenomenal wiggling of the jello brain.

On the other hand, because each region of cortex contains billions of neurons, maybe we need a continuous field theory to capture the functional properties of activity propagation through the neuropil. Certainly we need ways of modeling massive cell assemblies through the kind of statistical mechanics that can address each element's influence on its thousand or so neighbors. In trying to understand such a system as the mammalian cortex, we have precious little in our analytic toolkit, except for the specifics of the conduction time constants and the specifics of the connectivity. Nunez's first pass model of cortical dynamics gives us a way to think about the first of these – how a certain range of neuronal time constants could play out across a massive network. To become more than a conceptual exercise, a cortical field theory will need to address the second as well – how actual connectivity patterns of the mammalian cortex give structure to network oscillations that are anatomically possible. For the neurophysiologist, the anatomy provides the physical basis upon which theories must rest.

The mammalian cortex has indeed given rise to massive neural populations, but through a history of network differentiation that has left a highly ordered structure of connectivity. Evolving first from the primitive general cortex associated with the hippocampus and olfactory bulb, the cortex gave rise to successively more differentiated regions for sensory neocortex, so that each sensory modality of the primate brain contains five rings of increasing network articulation (Mesulam 1985; Pandya et al. 1988). The pattern of thalamic connectivity co-evolved with the cortex, with the primary thalamic sensory input shifting from primitive cortex toward the most recently differentiated sensory isocortex. The pattern of corticocortical connectivity also changed with each ring of evolutionary differentiation, from global, indiscriminant connectivity across the entire primitive cortex to highly isolated local connectivity for the most recently differentiated sensory isocortices (Pandya et al. 1988).

The result of mammalian evolution is therefore a highly ordered network architecture, not a diffuse neuropil, and a useful theory (for function or for brain waves) must reflect this order. For motor control, the cortex has evolved to entrain not only the thalamic oscillators, but the control loops of the cerebellum and basal ganglia. The time constants that play across motor cortex – for controlling thoughts as well as actions – therefore reflect this highly specific architecture. When the brain's oscillations become dysfunctional, and break into motor control in the form of pathological tremors, these movement waves reflect the brain's highly evolved anatomy. Some tremors reflect the loops and delays of corticocerebellar networks, whereas others reflect those of the reentrant cortio-striatal-pallidal-thalamo-cortical circuits.

Waves thus take shape in their media, and in the brain the medium is the connectional anatomy. To understand temporal brain dynamics of the cortex, we must look to the specific time constants of the highly ordered subcortical anatomy of the progressively evolved vertebrate brain, not the diffusion of a prolate spheroid. We can be grateful to a physicst for teaching us brain researchers a linear algebra for modeling interactive population dynamics. But to craft equations that look like brains, we'll have to get a little more real.

EEG frequency and the size of cognitive neuronal assemblies

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Abstract: We have performed a set of experiments that correlate EEG spectral parameters with cognitive functions. The tasks (visual perception, supramodal object recognition, short-term memory) were chosen so that the cortical area involved extended over different length scales. The extent of the cognitive neuronal assemblies correlated inversely with the frequency where EEG synchronization was found. This provides a further relation between experiment and the theory put forward in the Nunez target article.

An important basis for judging the comprehensive theory presented by Nunez is of course its relation to experimental results. We present here a series of three human EEG experiments that lead us to infer an inverse relationship between the size of an active neuronal assembly and the frequency of interactions. The neuronal assemblies of interest, however, are not defined on anatomical grounds but are recruited according to cognitive demand.

The first experiment (von Stein et al. 1995) was inspired by the reports on synchronized neuronal assemblies in cat primary visual cortex (Singer & Gray 1995). To reproduce these results, one must take into account the large amount of averaging that occurs between the electrical activity of single neurons and the potential recorded on the scalp. We proposed that, if the coherency within a stimulus is translated into coherent neuronal firing, then increasing the coherence with a stimulus should increase the amount of coherent neuronal activity, and this change might be measurable with macroscopic scalp EEG electrodes. In the experiment, human subjects fixated on 16 types of parallel grating stimuli with different numbers of bars per degree of visual field. Scalp EEG was recorded from 19 electrodes placed close to primary visual cortex against a digitally linked ear reference. Average power was computed in five frequency ranges. As a main result, power in the highest frequency band (24–32 Hz gamma) increased with the number of bars per degree. To control whether this only reflects an increase in the number of generators, short sections of the bars were tilted, thereby disturbing the coherency of the stimulus. For a fixed number of bars, the power in the gamma band fell with the number of tilted sections. Along with several others in the literature, this experiment shows that neuronal assemblies confined to primary visual cortex synchronize their activity in the gamma frequency range.

A second experiment addressed the recognition of daily objects (von Stein et al. 1999). The objects were not only visual features but entities familiar to all sensory modalities. Whereas neuronal synchronization has often been documented in response to visual stimuli, to auditory stimulation, and in the sensory-motor areas, few studies have shown interactions between neurons from different modality-specific areas. Each object was presented in three modalities: as spoken word, written word, and picture. During presentation and during free fixation as a baseline, EEG was recorded with the 19 electrodes of the 10/20 system; power and spectral coherence were computed in five frequency bands; and the spectral parameters of the baseline-EEG were subtracted from those corresponding to object presentation. The aim was to find changes in spectral parameters that were consistent in all three modalities of presentation. As the main result, a consistent increase of coherence occurred between temporal and parietal electrodes in all three stimulus conditions. Interestingly, there was no such consistent pattern in the power of individual electrodes, implying that there are no local assemblies responsible for supramodal representation. Modality-independent processing of objects seems to induce synchronization of activity between temporal cortex and parietal cortex. This makes an activation of one

specific cortical area unlikely. Rather, member neurons of an assembly distributed over different adjacent areas synchronize their activity. This synchronization took place in the 13–18 Hz beta range.

In a third experiment, we investigated cortical synchronization during working memory tasks (Sarnthein et al. 1998). Working memory is typically defined as the ability to keep events actively in mind for short periods of time, and it is based on a neuronal circuitry involving prefrontal cortex and posterior association areas. Subjects were presented with two sets of stimuli, which they had to retain in short-term memory for an interval of 4 s. One set of stimuli addressed the verbal memory system and the other activated visuospatial working memory. During the baseline condition, subjects fixated the dark computer screen as in the retention interval, except that no stimuli had to be kept in memory. As in the second experiment, EEG was recorded with the 19 electrodes of the 10/20 placement; power and spectral coherence were computed in five frequency bands; and the spectral parameters of the baseline-EEG were subtracted from those corresponding to the task conditions. To exclude unspecific arousal of the brain during the retention interval, we considered only those changes from baseline to be relevant for working memory retention which (i) distinguished retention from perception and (ii) were reproducible between the two types of tasks. As a main result, coherence increased between electrodes over prefrontal cortex and posterior association cortex during the retention interval. This suggests that synchronized neuronal activity occurs between prefrontal and posterior regions, which are maximally separated in the cortex. The frequency range of this synchronization was the 4–7 Hz theta range.

Taken together, we found fast (gamma) synchronization during local visual processing, beta synchronization between neighboring temporal and parietal areas during semantic integration, and slow frequency (theta) interactions between largely separated frontal and posterior areas during working memory retention. This group of experiments suggests that the frequency synchronization in a neuronal assembly is inversely related to the size of the assembly. Note that in our case assemblies are not rigid as in anatomy but functionally recruited according to the cognitive task. It therefore seems that the inverse relationship between the oscillation frequency f and the system's scale factor R (cm) in Eq. (8) may be applicable in a more general way.

Developing testable theories of brain dynamics: The global mode theory and experimental falsification

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Abstract: The development of theories of global cortical dynamics, using linear wave theory, owes much to the pioneering work of Nunez. His work leads to clear predictions on relations of brain size, axonal conduction velocity, and the frequencies of the cerebral rhythms. These predictions do not appear to be fulfilled, but their falsification constrains the range of parameters applicable in further formulations.

As a pioneer in the field of brain dynamics, Nunez was one of the first to bring wave theory to bear upon brain mechanisms. He also recognised that linear wave techniques might be used to address brain modelling problems at the global level – particularly with regard to the origin of the cerebral rhythms.

The utility of linear wave analyses for addressing the dynamics of the brain is still not adequately recognised. Even among those who use a dynamic conception of integration in the nervous system, few recognise that the interaction of billions of neurones invites the application of continuum formulations dealing with statistical, and essentially linear, properties over considerable epochs and spatial extents of the cortex. Thus, despite the extreme nonlinearity of neural elements, it is possible to apply small perturbation approximations and thus utilise classical linear wave methods. More complex dynamics may then be considered as bifurcations between approximately linear domains.

It is by use of these mathematical techniques that Nunez has been able to predict that a component of the great cerebral rhythms depends for its origin on the occurrence of modes of resonance of the cerebrum. That is, he concludes that the cerebral rhythms arise as standing waves generated by interference of travelling waves of mean dendritic depolarisation. If the size and shape of the brain and the velocity of axonal conduction is known, this leads to precise predictions regarding the frequencies of the cerebral rhythms.

In the present paper, Nunez makes relatively scant mention of this prediction, which has dominated much of his earlier work. Nonetheless, I want to focus on this aspect.

It presently appears unlikely that standing waves contribute in any significant way to the occurrence of the cerebral rhythms. However, such is the clarity of Nunez's general theory that the failure of his prediction itself casts light on alternate directions for brain modelling.

The principal reason for rejecting any important role for standing waves, as described by Nunez, is that power spectra of the EEG and ECoG from mammalian species of greatly different brain size appear essentially identical. In our laboratory, we have access to human EEG; rat, cat, and rhesus monkey ECoG; and foetal sheep ECoG, recorded in a wide variety of states, from extremely alert to asleep. We are not able, on the basis of the spectral content observed in comparable conditions of arousal, to distinguish the species of the animal with any degree of confidence at all. Such subtle markers of species evident in the spectral content do not feature large changes in the center frequencies of the cerebral rhythms. Perhaps most strikingly, the spectral content of ECoG from the foetal sheep (both sleeping and waking) changes very little at all during maturational changes (Sergejew 1999). Foetal maturation includes myelinisation in the corticocortical system, which produces drastic changes in the axonal conduction velocities, upon which the frequencies of the cerebral rhythms are predicted to depend. While it may be argued that these findings are not conclusive evidence for the absence of global standing waves in all conditions, they give a strong indication that global modes play little, if any, part in most EEG recordings.

However, we can consider those assumptions of the theory which determine the occurrence of standing waves. The most crucial property upon which global resonances depend is the selection of values for Nunez's control parameter B, which directly regulates the spatial damping of travelling wave – and the relation of this parameter to other static parameters within his models. Nunez selects parameter B to produce low spatial damping, which thus permits strong propagation of travelling waves. Brain size and velocity of conduction then determine the exact frequencies at which resonances will then emerge (see Nunez 1995 and earlier works). With high spatial damping, such resonances cannot develop.

An important secondary factor is that Nunez generally treats dendritic delays as small compared with axonal delays. This has the effect of lowering the predicted spatial damping of the waves – yet a good deal of physiological data is in contradiction to this assumption (e.g., Thomson 1997). My colleagues and I have been developing formulations similar in basic mathematical form to Nunez, but which do not share his assumptions about the operating range and ratios of parameters. This leads to prediction of highly spatially damped waves. (Rennie et al. 1998; Robinson et al. 1997; 1998; Wright 1999; 2000). These give an account of the origin of cerebral rhythms in terms of thalamocortical interactions and synaptic feedback mechanisms. They are also able to account for such phenomena as synchronous oscillation without the need to appeal to standing waves as a mechanism of zero-phase lag between widely separated sites.

In turn, these models make other predictions that are beyond the range of this commentary to consider. Suffice to say that the class of models that Nunez has pioneered (along with Freeman, Lopes Da Silva, Wilson & Cowan, and others) is now leading to a range of related models. Members of this family of models can compete with each other in experimental tests. This healthy state of affairs is surely to be welcomed.

Author's Response

Neocortical dynamic theory should be as simple as possible, but not simpler

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Abstract: EEG and synaptic action fields provide experimental and theoretical entry points into brain complexity. Such entry is distinguished from the core system of cell assemblies assumed to underlie cognitive processing. The global theory of synaptic action predicts several new properties of EEG, providing limited penetration into brain complexity.

R1. General conceptual framework

The title of my Response paraphrases Einstein's famous advice suggesting moderate and selective use of Occam's razor. The target article is aimed at a broad audience forcing some oversimplification. Commentary is cited according to Table R1 and organized according to section R1 general framework issues, section R2 theoretical models, section R3 miscellaneous challenges, and section R4 summary comments. I have borrowed the phrase "entry points" from several commentators and biologist Edward Wilson (1998) who describes reductionism as "the search strategy employed to find points of entry into otherwise impenetrably complex systems . . . The love of complexity without reductionism makes art. The love of complexity with reductionism makes science."

EEG, MEG, MRI, and PET are experimental entry points to complex brains. Synaptic action fields provide theoretical entry points. Much confusion may be avoided by clearly distinguishing entry points from the core cell assemblies in Figure R1, which summarizes the general conceptual framework advocated by the target article. Solid lines for boxes and arrows refer to cell groups and interactions that are relatively well understood, at least in general outline. Dashed lines indicate poor understanding. Most of my comments concerning EEG also apply to MEG, so I generally avoid the cumbersome label EEG/MEG. I also mean for "EEG" to encompass event-related potentials (ERPs).

R1.1. Synaptic action fields. The *synaptic action fields* (Figs. 4 and R1) are defined simply in terms of number densities of active excitatory and inhibitory synapses, independent of their functional significance. Thus, *cell groups 1* and *2* and *cell assemblies* of Figure R1 are subsets of the synaptic action fields. These subsets may or may not overlap, but all are embedded within synaptic action fields. To use a sociological metaphor, the synaptic action fields form a "culture" composed of various sub-groups at multiple scales of neighborhoods, cities, nations, and so forth.

Keil & Elbert, Pflieger, and **Tucker** question the relevance of "field concepts" to cognitive science, modeled here in terms of traveling and standing waves. Other commentaries appear generally comfortable with brain fields of various kinds and scales. But **Freeman & Kozma** point to the enormous differences between simple physical waves (e.g., my metaphorical ocean waves) and putative brain

Table R1. *Organization of specific responses*

Section	R1.1	R1.2	R1.3	R1.4	R1.5	R1.6	R1.7	R2.1	R2.2	R2.3	R2.4	R2.5	R2.6	R2.7	R3.1	R3.2	R3.3	R3.4	R3.5	R4
Andrew		A	A		A			A		A	A		A	A						
Daffertshofer									D	D							D			D
Freeman	F	F	F	F				F	F									F	F	
Greenblatt							G							G						
Habeck			H		H		H		H		H			H					H	
Ingber	I	I	I				I		I		I			I		I	I		I	I
Jirsa	J		J						J							J	J			J
Keil	Kl	Kl	Kl								Kl							Kl		
Kolev	Kv	Kv	Kv				Kv													
Liley	Ly								Ly	Ly	Ly						Ly			Ly
Liljenström		Lm							Lm							Lm	Lm		Lm	
Mayer-Kress	MK							MK							MK				MK	
Murias						M														
Pflieger	P	P					P				P					P		P		
Thatcher		Th		Th		Th	Th				Th			Th						
Tucker	Tu	Tu						Tu												
von Stein			vS		vS									vS						
Wright	W									W	W	W								W

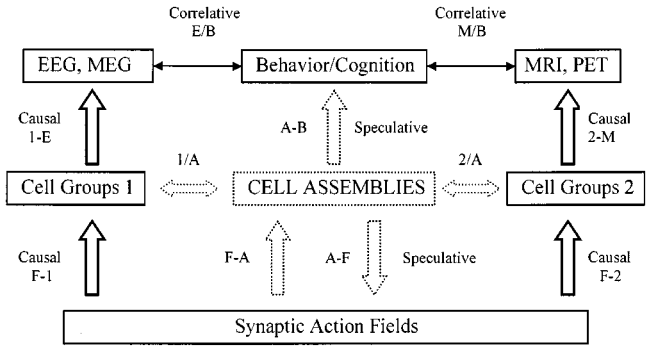

Figure R1. Double arrows indicate established correlative relationships between behavior/cognition and EEG, MEG, MRI, or PET. Excitatory and inhibitory *synaptic action fields* are defined simply in terms of numbers of active synapses per unit volume of cortical tissue, independent of functional significance. *Cell Groups 1* and *2* are embedded within this larger category of active synapses. Synaptic action causes current sources in Cell Groups 1 generating EEG and MEG. Synaptic action also causes metabolic activity in Cell Groups 2 measured by MRI and PET. Putative *Cell Assemblies* and Cell Groups 1 and 2 may or may not have substantial overlap. Causal and correlative (may or may not be causal) interactions are indicated by hyphens and slashes, respectively.

waves, perhaps implying that the word "wave" is inappropriate for multi-scale, nonlinear dynamics. **Ingber**'s fields involve probability of neural firing at overlapping microscopic and mesoscopic scales. His statistical mechanics of neocortical interactions bears a complementary relationship to the macroscopic theory of the target article, analogous to the relationship between the classical kinetic theory of gasses and fluid mechanics. **Jirsa & Kelso** see severe limits on future descriptions of the brain as a physical system, since macroscopic field variables may average out memory, learning, and sensorimotor processes. **Liley** points out that the same neural population often contributes to both local and global dynamics. He advises a more complete synthesis of local and global models. **Wright** concludes that control parameters (e.g., the global B discussed here) in genuine brains are such that traveling neocortical waves are strongly damped, implying that standing wave phenomena do not influence experimental data.

The synaptic action fields may be defined either as active synapses per unit volume (excitatory and inhibitory) or, given the columnar structure of neocortex, as the numbers of active synapses per unit area of neocortical surface. The introduction of synaptic action fields is motivated by their causal connection to EEG (paths F-1 and 1-E in Fig. R1). A minicolumn of human neocortex contains about 100 pyramidal cells and a million synapses (Mountcastle 1979). There are perhaps six excitatory synapses for each inhibitory synapse, at least in mouse (Braitenberg & Schüz 1991). If, for purposes of discussion, we assume that 10% of all synapses are active at any given time, the excitatory and inhibitory synaptic action densities are about 85,000 and 15,000, respectively, per minicolumn area. Synaptic action is defined independently of its functional significance for brain processing. **Pflieger, Keil & Elbert, Kolev & Yordanova** and **Tucker** apparently see this as a drawback. **Jirsa & Kelso** imply that synaptic fields are useful in the short run, but should soon be replaced by more biologically relevant concepts. I argue that conceptual separation of (functionally irrelevant) synaptic fields from cell assemblies will be useful at least as long as EEG is important.

EEG frequencies below about 50 to 100 Hz are believed to be essentially the modulation frequencies of synaptic action fields around their background levels (Nunez 1995). Higher frequencies appear to be low pass filtered at cellular levels due to capacitive-resistive membrane properties. Thus, macroscopic synaptic action fields are natural variables to explain scalp potentials. **Freeman & Kozma, Ingber, Jirsa & Kelso, Keil & Elbert, Mayer-Kress, Pflieger,** and **Tucker** describe various ways that such macroscopic field descriptions must fall short of describing the most interesting brain processes. I agree. But, these macroscopic field descriptions are required to maintain contact with macroscopic measures like EEG and MEG; at least until new variables with equally robust connections to such data are developed. I disagree with **Jirsa & Kelso** that we are near exhausting the limits of a physical approach to brain dynamics. But, I concede that that new theories of behavior and cognition, for example, within the confines of the cell assembly box in Figure R1, may be quite distinct from known physical systems. New variables used to describe such "networks" must explain data if they are to represent genuine science. If such data include EEG, separate theories will be required to relate the new variables either to synaptic fields or to alternate measures closely aligned with scalp data.

I do not imply that EEG and synaptic field dynamic behavior are necessarily similar. Quite the contrary, the most complicated synaptic field dynamics (all but the low end of the spatial frequency spectrum) are never recorded on the scalp because of spatial filtering by the volume conductor (sect. 4.2).

R1.2. Behavior and cognition is correlated with EEG measures. There is a general concern on the part of **Keil & Elbert, Kolev & Yordanov,** and **Tucker** with my neglect of cognitive models, especially their putative connections to cell assemblies and ERP data. For example, Keil & Elbert suggest the inclusion of Hebb-based modeling and Pflieger advises adding a cognitive layer to the conceptual framework. Tucker reminds us that the brain is a highly ordered network architecture, not a diffuse neuropil and a useful theory must reflect this order.

These objections are answered using a distinct conceptual separation of synaptic action fields (supporting wave phenomena), cell groups 1 (producing EEG current sources), and putative cell assemblies believed to underlie cognition and behavior, as indicated in Figure R1. To address additional questions concerning relations to MRI and PET raised by **Freeman & Kozma, Thatcher et al.** (and by implication several other commentators) and to broaden the conceptual framework, I have included a box for cell groups 2 in Figure R1. The correlative relation between EEG and cognition (E/B) shown in Figure R1 can occur two general ways.

1. Cell assemblies can produce output that makes direct synaptic contact on cell groups 1 (1/A). Or, cell groups 1 and cell assemblies may substantially overlap. In either case, the connections (1/A) and (A-B) provide plausible physiological mechanisms to produce observed cognitive correlations (E/B).

2. Even if no direct interactions (1/A) occur, cell assemblies can influence synaptic action fields (A-F), which in turn influence cell groups 1 (F-1). This can occur by serial

synaptic connections (A-F), or possibly by the kind of local/global resonance field interactions (A-F) conjectured in section 7 and emphasized by **Andrew.**

Many EEG scientists appear to assume that cell groups 1 and cell assemblies (responsible for particular cognitive events under study) overlap substantially, or are perhaps even identical. Other scientists working with MRI may conjecture substantial overlap of cell assemblies with cell groups 2. In section R1.4, I suggest that for either measure, such overlap may be lower than is generally assumed, for example, in the context of currently popular EEG/MRI co-registration methods.

Tucker's apparent concern is that I am replacing cell assemblies with synaptic wave fields, for example, "we might be forced to conclude that brain waves are so far removed from the brain's functional work that critics have been right all along. Brain waves are indeed the empty content of neurophysiology, proved at last to be the epiphenomenal wiggling of the jello brain." But, my purpose in the target article is not to downgrade the importance of cell assemblies. Rather, I suggest a useful separation of neural processes that are somewhat known (interactions F-1 and 1-E) from processes that are very poorly understood (interactions A-B, F-A, and A-F). The synaptic wave fields are theoretical entry points to cell assemblies.

Better cognitive theories, with closer connections to data, are more likely to be developed if cell assemblies are viewed in the context of the multiple interaction mechanisms of Figure R1. **Keil & Elbert** cite a recent target article by Pulvermüller (1999) suggesting that cell assemblies can be widespread and "the meaning and qualitative nature of an event, an idea, an emotion, or a precept are reflected in the local topography of its connections and firing patterns." I find this idea compelling. I only suggest that if EEG is to provide supporting data, the known physiological processes of Figure R1, including nonspecific synaptic action fields, provide a useful avenue for experimental verification. In this manner, the intimate relationship between the brain medium and the dynamics may be more brightly illuminated (**Freeman & Kozma**).

Tucker is concerned that my characterization of EEG in terms of waves will provide ammunition to those who charge that EEG is only an epiphenomenon, far removed from brain function. **Liljenström** questions the functional significance of EEG. The epiphenomenon charge might originate from a belief that there is no overlap of cell groups 1 with cell assemblies in Figure R1. But, if true, the connections (1/A), (A-F), or both must be intact in many cognitive, behavioral, and clinical studies, as evidenced by the well-established correlative connections (E/B). This experimental evidence fully discredits the epiphenomenon charge. Cognitive scientists become vulnerable to such criticism only when they oversell the putative overlap between cell groups 1 (or cell groups 2) and cell assemblies since such overlap is not essential to the correlation (E/B).

R1.3. Connections of cognition and behavior to neocortical dynamic theory. There is agreement on the part of **Keil & Elbert** with my characterization of the work by Haken, **Jirsa & Kelso** and collaborators, as a good example of incorporating predictions of both behavioral and dynamical measures, that is, modeling interactions (F-A), (A-F), and (A-B) for a simple motor task. Perhaps they fail to appreciate that the theoretical model used to make the experimental predictions grew out of earlier theoretical work on dynamic fields by Jirsa and Haken (1996; 1997). This work combined the global field theory of Nunez (1972; 1974a) with the local field theory of Wilson and Cowan (1972; 1973). The purely dynamical foundation provided by these five scientists was accomplished independently of cognitive science, but was essential for later development of a physiologically based model for behavior. This illustrates why I suggested that brain science mimic some of the proven methods of physical science.

Another example for which cognitive and behavioral measures overlap dynamic theory is provided by **Ingber**'s theoretical identification of multiple, stable firing patterns used to store the "memory" of neural activity that gave rise to the patterns in the first place. These theoretical patterns are candidates for (spatially distributed) human short-term memory. Several such patterns can persist simultaneously within the same neural population so several short-term memories can be stored simultaneously. Ingber emphasizes the importance of establishing robust connections between his statistical theory and variables (EEG, ERP, etc.) that may be measured at other spatial and temporal scales.

Von Stein & Sarnthein provide three additional examples of cognitive/behavior and dynamic overlap. First, they find that EEG power at higher frequency increases with the spatial frequency of visual stimulus. Although the physiological basis for this effect is unknown, it is worth noting that higher temporal frequencies are generally expected in wave media driven with input functions of higher spatial frequencies (Nunez 1995), in accordance with wave dispersion relations. To the extent that spatial frequency of visual stimulus reflects spatial frequency of cortical input function, this result is consistent with the global theory of the target article.

Von Stein & Sarnthein's second experiment involved increased beta coherence between temporal and parietal cortex during spoken words, written words, and pictures. A plausible conjecture involves formation of a supermodal cell assembly, which also has sufficient overlap with cell groups 1 of Figure R1 to allow measurement of increased scalp coherence. As in the case of all scalp data in the beta frequency (or higher) range, possible muscle artifact contamination must be eliminated to confirm these results.

Von Stein & Sarnthein's third experiment suggests that the synchronization frequency in a cell assembly is inversely related to its size. This effect might be predicted by nearly any model in which cortico-cortical fibers dominate both coherence and time delays, for example, the purely global theory outlined in the target article. By contrast, size may not matter in purely local theories with only local delays, for example, PSP rise and decay times. The scale factor R in Equation (8) refers to the entire neocortex, not cell assembly size. However, if cortico-cortical axons provide the dominate interaction mechanisms and propagation speed is finite, larger cortical assemblies might be expected to produce longer delays and lower coherent frequency bands. If substantial local delays also occur, the size effect may be measurable only for assemblies larger than some minimum size. If, for example, local delays are in the 10 msec range and cortico-cortical propagation speed is in the 7 msec range, the local and global time scales are equal for pyramidal cell separations of about 7 cm. Thus, significant size effects can perhaps be studied experimentally in cell assemblies of di-

ameter larger than about 7 cm, for example, the inter-lobe coherence estimates of Sarnthein et al. (1998).

This oversimplified picture of size effects is clouded by the possibility that slow interactions, for example, by means of unmyelinated intracortical fibers over short distances, may operate on approximately the same time scale as fast interactions over large distances, as suggested by **Ingber** and implied by **Liley.** Most intracortical fibers are shorter than one mm and even the relatively long surface parallel axons of cortical Layer I are shorter than 1 cm (Eccles 1984). The wide range of neocortical interaction scales suggests that coherence (and effective correlation length) may depend strongly on spatial measurement scale (Nunez 1995). For example, one might conjecture moderate 10 cm-scale coherence, 1 mm to 1 cm-scale incoherence, and 0.1 mm-scale high coherence acting simultaneously in the same tissue mass. But, whether or not a coherence-size effect is sufficiently robust to measure at a particular scale can only be answered experimentally.

Habeck & Srinivasan cite Singer's (1999a; 1999b) work indicating that coherent gamma band activity is related to a number of cognitive processes in animals. Singer apparently postulates that gamma band coherence is a means by which brains solve the binding problem. Habeck & Srinivasan support the importance of coherence to binding. But, they point out that the assumption of connections between cognition/behavior and exclusively gamma band coherence is not well justified. For example, binocular rivalry experiments (with dissimilar objects presented to the two eyes) have shown substantial increases in intrahemispheric and interhemispheric (high, driven) theta coherence during periods of perceptual dominance (conscious perception of a single object) (Srinivasan et al. 1999). **Von Stein & Sarnthein**'s commentary and section 1.2 provide additional examples. Habeck & Srinivasan suggest that dynamic patterns of cell assemblies may be reflected over a large part of the measurable EEG spectrum. **Andrew, Freeman & Kozma,** and **Kolev & Yordanova** make similar points about the importance of broad frequency ranges to cognition. I agree. Cognitive scientists should avoid "gamma traps," where ability to record gamma activity from the scalp becomes a test of scientific merit.

An additional conjecture is that cell assemblies are organized in hierarchical structures such that super-assemblies (e.g., full neocortex), assemblies, sub-assemblies, sub-sub assemblies, and so on, function simultaneously. This picture comes close to **Ingber**'s work if we interpret cell assembly formation in terms of overlapping probability distributions of neural firing patterns. Such hierarchical super-assemblies might simultaneously produce coherent activity at different frequencies, with coherent frequency band partly dependent on hierarchical level (e.g., size). However, any particular experiment is sensitive only to a limited range of spatial and temporal scales, thereby requiring many kinds of studies to obtain anything approaching a comprehensive picture of the underlying dynamics.

Freeman & Kozma's model emphasizes self-organizing dynamics of neural populations within olfactory systems. Phase transitions in the dynamics occur to accommodate changed external conditions in a manner perhaps similar to experiments on the dynamics of motor control (**Jirsa & Kelso**). They suggest that strong non-linear effects (e.g., multi-scale interactions, chaos, self-organization, phase transitions) are the essence of adaptation through perception and learning. Freeman & Kozma's ideas are also consistent with cell assemblies, but the detailed nature of these cell assemblies is, of course, model dependent. I agree with the general thrust of this work. However, there are important differences in details between Freeman & Kozma's work and the quasi-linear local/global theory. These differences involve presumed autonomy of mesoscopic brain systems, axon propagation, and boundary conditions.

R1.4. Cell groups 1 and 2 may or may not overlap. The definitions of synaptic action fields are independent of their possible participation in cell groups 1 and 2 of Figure R1. EEG and MEG are generated mainly by current sources in cell groups 1. The "source strength" of a volume of tissue is given by its dipole moment per unit volume (Nunez 1981a; 1995)

$$\mathbf{P}(\mathbf{r}, t) = \frac{1}{\Theta} \iiint_{\Theta} \mathbf{r}_1 s(\mathbf{r}_1, t) \mathrm{d}\Theta \qquad \text{(R1)}$$

Here Θ is the tissue volume element, $s(r_1,t)$ is the local volume source current (microamperes/mm^3) near membrane surfaces, and r_1 is the vector location of sources within Θ, as shown in Figure R2. Because of cortical morphology (columnar structure) and physiology (high correlations between mesoelectrode recordings taken normal to minicolumn axes), it is convenient to think of the volume elements Θ as minicolumns (diameter $\approx$ 0.03 mm, height $\approx$ 3 mm). The sources $s(r_1,t)$ are generally positive and negative due to local inhibitory and excitatory synapses, respectively. In addition to these active sources, the $s(r_1,t)$ include passive membrane current required for current conservation. Dipole moment per unit volume $P(r_1,t)$ has units of current density (microamperes/mm^2). For the idealized

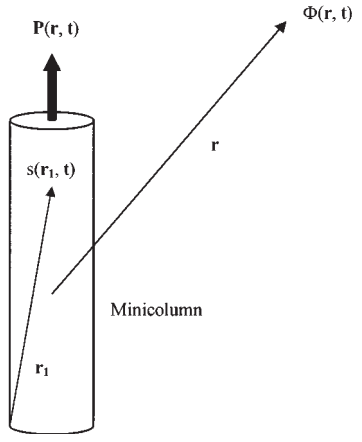

Figure R2. A neocortical minicolumn with approximate dimensions of 3 by 0.03 mm is shown. The minicolumn has been proposed as a basic functional unit of neocortex (Mountcastle 1979; Szentagothai 1979). Minicolumns are defined by the characteristic lateral spread of axons of inhibitory neurons; each contains about one hundred neurons and a million synapses. Vector dipole moment per unit volume P(r, t) is defined at the minicolumn scale for convenience, independent of morphology. P(r, t) is the "source strength" of the minicolumn, which depends on the magnitude and distribution of volume current sources $s(r_1, t)$ within the minicolumn. These sources result from synaptic action at membrane surfaces. Scalp potentials $\Phi(r, t)$ are generally due to the weighted integral of P(r, t) over the entire cortex.

case of sources of one sign confined to a superficial cortical layer and sources of opposite sign confined to a deep layer, $P(r_1,t)$ is roughly the diffuse current density across the minicolumn (Nunez 1981a; 1990; 1995). This corresponds roughly to superficial inhibitory synapses and deep excitatory synapses. More generally, minicolumn source strength P(r,t) is reduced as more excitatory and inhibitory synapses overlap along minicolumn axes. However, such complications are fully consistent with equating "source strength" to dipole moment per unit volume, Equation (R1).

The neocortical surface may be viewed as a large dipole sheet of perhaps 1,500 to 3,000 cm^2 over which the function P(r,t) varies with cortical location r, measured in and out of cortical folds. In limiting cases, this dipole layer might consist of only a few discrete regions with large P(r,t), for example, "focal sources." More generally, P(r,t) is distributed over the entire folded surface. Scalp potentials are believed generated by the summed activity of P(r,t) from all upper regions of cortex, plus much lesser contributions from deep sources, as depicted in Figure R2. Magnetic fields are believed to be generated mainly by intracellular currents; however such currents are simply related to $s(r_1,t)$ by current conservation. Cell groups 1 have the following properties (Nunez 1981a; 1995):

1. Cells are close to scalp surface. EEG and MEG favor neocortical gyri and sulci sources, respectively.

2. Cells are aligned in parallel to encourage large extracranial electric and magnetic fields due to linear superposition of fields of individual current sources. Thus, minicolumns aligned in parallel and synchronously active make the largest contribution to scalp potentials. For example, 1 cm^2 of a cortical gyrus contains about 110,000 minicolumns, approximately aligned. If 1% of the minicolumns produce synchronous sources P(r,t) and the other 99% produce sources with random time variations, the 1% "synchronous minicolumns" contribute about three times as much to scalp potential as the 99% "random minicolumns."

3. As a "rule of head," about 6 cm^2 of cortical gyri (700,000 minicolumns or 70,000,000 neurons forming a dipole layer) must be "synchronously active" (in a crude sense determined from ECoG recordings) to produce scalp potentials that may be recorded without averaging (Ebersole 1997; Nunez 1995). In the case of dipole layers partly in fissures and sulci, somewhat larger areas are required. The contribution of action potential sources to extracranial fields appears to be small due to multi-directional axon geometry and asynchronous timing of firings. However, addition of action potential sources of EEG would have minimal effect on the framework outlined here.

Freeman & Kozma and **Thatcher et al.** raise the important issue of connections between EEG and MRI (including fMRI) or PET. Cell groups 2 are responsible for metabolic or hemodynamic signatures and may be anywhere in the brain. Typically, they show small percentage increases in activity in one brain state relative to a control state; they are "tip of the iceberg" measures of brain function. This metabolic or hemodynamic activity is believed to originate mainly from neurotransmitter action at synapses. If enough cells within a voxel act consistently over long enough times, MRI or PET may show a voxel "hot spot" with brain state change. Cell groups that are much smaller than voxels and act independently of contiguous cell groups will generally not show up in the image.

EEG, MEG, PET, and MRI are selectively sensitive to different kinds of brain activity. In particular experiments and/or brain states, cell groups 1 and 2 may show substantial overlap. However, there is no requirement that these disparate measures must generally agree. For example, a large number of excitatory and inhibitory synapses might be simultaneously active in a brain region lacking morphology favorable to large dipole moment generation (e.g., "closed fields" from structures like hippocampus). In this case, essentially no extracranial electric and magnetic fields will be recorded from the neural structure. Such regions could, however, produce large signatures in MRI or PET. Alternately, cell groups may form for periods too short to be imaged by MRI or PET, but may show up in EEG because of its much better temporal resolution.

R1.5. Cell assemblies. As defined here, "cell assembly" or "neural network" may indicate a group of neurons or neural masses (e.g., minicolumns, cortico-cortical columns, macrocolumns, etc.) for which correlated activity persists over substantial time intervals (say at least several 10s of milliseconds). Such correlated activity is widely believed to underlie behavior and cognition in some largely unknown way. Cell assemblies involving contiguous neural structures may occur more readily. However, assemblies may also involve cortical regions separated by large distances (e.g., 10 to 20 cm), as suggested by the experiments cited by **Andrew, Habeck & Srinivasan, von Stein & Sarnthein,** Silberstein (1995a), and Gevins and colleagues (reviews by Gevins & Cutillo 1986; 1995). The extreme interconnectedness of brains seems to encourage such widely distributed assemblies. For example, mainly because of the large density of cortico-cortical fibers, the typical "path length" between any two cortical neurons is only two or three synapses (Braitenberg & Schüz 1991).

As envisioned here, cell assemblies may overlap so that, for example, a single minicolumn may be simultaneously part of several assemblies that perhaps operate in different frequency ranges. Cell assemblies may also have hierarchical structure so that, for example, the 100 neurons in a minicolumn, the 100 minicolums in a cortico-cortical column, and (say) 1,000 cortico-cortical columns in remote cortical regions (connected by specific cortico-cortical fibers) may simultaneously form temporary cell assemblies at different spatial scales.

The simple definition of synaptic action fields proposed in the target article ignores cell assemblies or neural networks embedded within synaptic fields, achieving a useful separation of partly known and unknown physiology. Synaptic action fields cause current sources in cell groups 1 that generate EEG, irrespective of whether such cell groups are part of cell assemblies associated with behavior/cognition. Large scalp potentials occur because columnar dipole moments are lined up in parallel and synchronously active. There are many details to be discovered. However, the general causal connections F-1 (synaptic field-cell group 1) and 1-E (cell group 1 sources-EEG/MEG) of Figure R1 rest on relatively solid theoretical and experimental ground (Nunez 1995).

The synaptic synchrony requirement for large scalp potential production may also favor the recording of synaptic sources that are parts of cell assemblies. However, other source properties, apparently unrelated to functional cell assembly formation, are also important for large scalp potentials, including dendrite orientation and source depth.

The issues of overlapping and hierarchical cell assemblies further complicate the picture. Thus, there may be minimal justification in assuming that EEG primarily records cell assembly or neural network activity (the 1/A, 1-E path in Fig. R1) More likely, EEG originates with a mixture of cell assembly and non-cell assembly synaptic action, that is, cell groups 1 only partly overlap the cell assemblies responsible for the specific cognition/behavior under study. But, even if no overlap between cell groups 1 and cell assemblies occurs, correlations between EEG and behavior/cognition (E/B) can occur as a result of the paths (F-1, 1-E) and (F-A, A-B). The local/global model outlined in the target article addresses the binding problem (sect. 7) by suggesting that remote cell assemblies having no overlapping cells may become synchronized (e.g., phase locked) through resonant interaction (F-A) with global synaptic action field. This putative binding mechanism is described by **Andrew** and in Nunez (1995, pp. 694–98).

R1.6. Clinical applications within the conceptual framework. Clinical neurologists and psychiatrists deal with complex brain systems and are often faced with critical decisions based on very minimal information. Sound clinical work requires an operational conceptual framework. It is perhaps naïve to expect any mathematical theory of brain dynamics to have substantial short-term impact on clinical practice. However, **Murias & Swanson** demonstrate that mathematical models can be useful vehicles to demonstrate (and make explicit) critical aspects of a conceptual framework, especially when models are closely related to experimental measures. They carried out high resolution EEG studies of ADHD in children, with experimental details based on such framework and report lower posterior coherence in children with ADHD than normals.

Thatcher et al. (1986) and **Srinivasan** (1999) also studied EEG coherence in children. One rationale for clinical studies of EEG coherence is that disease states may involve abnormalities in the cortico-cortical axons themselves (e.g., demyelination reducing axon propagation). Another possibility is abnormal synaptic strengths of cortico-cortical axons on target neurons (e.g., positive feedback gains, partly determined by global parameter B) due to defective neuromodulatory systems (Silberstein 1995b). Since cortico-cortical axon myelination takes place throughout childhood (and beyond), I suspect many developmental diseases may be studied productively with combined MRI and EEG coherence measures.

Thatcher et al. cite data for closed head injury patients indicating that MRI, EEG, and neuropsychological measures were significantly correlated. Increased T2 relaxation times in cortical gray matter and white matter were correlated with a shift in relative EEG power to lower frequencies and reduced cognitive performance (Thatcher et al. 1998a). Thatcher et al. (1998b) also found that increased T2 times were also correlated with long-range (28-cm) coherence increases and short-range coherence decreases. Thatcher et al. (1998a; 1998b) list several possible gray and white matter mechanisms that may cause these effects. Generally, these data are consistent with the idea that head injury somehow damages the ability of brains to form local cell assemblies within the global synaptic action field environment of Figure R1.

The work of **Murias & Swanson** and **Thatcher et al.** illustrate nicely how consideration of neocortical dynamic theory can lead to testing of new clinical strategies, even when such theory is speculative. The general conceptual framework summarized in Figure R1 can perhaps suggest new clinical treatments. For example, the top-down synaptic action field-cell assembly interactions (F-A) provide (speculative) motivation to consider several nontraditional clinical approaches. Possible examples are biofeedback and brain electrical stimulation in normal EEG frequency ranges at low current densities well below seizure threshold. Apparently, diffuse current densities of about 1 ma/cm^2 (about 300 times larger than that of spontaneous EEG) are required to excite nervous tissue (Myklebust 1985; Nunez 1995). Stimulation with brain current density in the general range of natural EEG electric fields might be tried for relative long periods (e.g., hours) in an effort to encourage production of normal EEG in (say) deep coma patients, perhaps by top-down stimulation of the appropriate neuromodulatory systems. Although such methods may have low success probability, they appear harmless and easy to implement. Application to patient populations not responsive to conventional treatments may be justified. The purpose of this clinical speculation is not to suggest specific clinical treatments (for which I am unqualified), but rather to propose new alliances between dynamic theory and clinical practice (Pilgreen 1995).

R1.7. Event related potentials. It is suggested by **Kolev & Yordanova** and **Pflieger** that the target article severely neglects the traditional ERP literature. ERP methods typically adopt methods of experimental psychology. Cognition is viewed as a sequence of processes in which stimulus information is encoded, compared with memory and acted upon (Gevins & Cutillo 1986; 1995; Thatcher & John 1977). The averaged evoked (or event related) potential is assumed to consist of spatially and temporally overlapping waveforms generated by different neural systems. These components are extracted from spontaneous EEG by averaging scalp potentials over evoked stimuli. My view of ERP and its relationship to neocortical dynamics follows.

1. The ERP averaging paradigm is relatively simple to understand and made compatible with traditional experimental psychology. From the perspective of Occam's razor, ERPs make good scientific sense, especially as entry points or precursors to more sophisticated methods. Many robust correlations between cognition/behavior and amplitude/latency of ERPs have been established over the past 35 years (E/B in Fig. R1).

2. Over the past 15 years, Gevins and colleagues (Gevins & Cutillo 1995) have developed high spatial resolution methods to measure spatial covariance patterns over widespread scalp locations associated with cognitive tasks. These time-delayed correlation coefficients are the time domain analog of (frequency domain) coherence. The covariance patterns are strongly suggestive of formation of widespread cell assemblies. For example, scalp sites are correlated over large distances with many delays in the 30 to 80 msec range. With visual stimuli, frontal and central sites typically lag posterior locations. These data are roughly consistent with anterior/posterior propagation times along myelinated cortico-cortical axons in the 20–30 msec range, although intracortical and thalamocortical relays may also contribute. Formation of cell assembly covariance large enough to measure from the scalp may require several relay times.

3. The design of ERP studies often involves compromise

between good engineering and obtaining specific cognitive measures. Unfortunately, many cognitive scientists have opted for a preferred cognitive paradigm while ignoring or misinterpreting critical technical issues. As a result, problems associated with reference electrode, volume conduction, muscle artifact, and so on have limited reliable interpretations of ERPs (Gevins & Cutillo 1986; 1995; Nunez 1981). There is a tendency to oversell the overlap between cell groups 1 and cell assemblies, often based on dubious interpretation of volume conduction. For example, many studies have assumed that an ERP waveform from a "recording electrode" mainly reflects neural activity underneath that electrode. This ideal is only approached with high resolution EEG using 64 to 131 or more electrodes and accurate algorithms, providing spatial resolution in the 2 to 3 cm range. The usual 10/20 system yields very poor spatial resolution, roughly in the 6 to 10 cm range (Nunez 1981a; 1995), with additional interpretation problems owing to reference electrode effects.

4. From the strictly dynamic perspective (ignoring cognition), traditional ERPs contain useful information. However, the simple averaging procedure may eliminate a large portion of potential information in the signal, as suggested by **Ingber.** I also agree with **Kolev & Yordanova** that there may be substantial overlap of tissue generating spontaneous EEG and ERP's. This is suggested by studies of the timing of stimuli in relation to phase of the on-going EEG by Basar (1980; 1998) and others. If the overlap is substantial, treatment of EEG as uncorrelated "noise" in ERP studies is not valid. More accurate interpretations of ERP data are badly needed, especially for data with very robust connections to behavior/cognition. The E/B correlations of Figure R1 can occur in several different ways.

5. Steady state evoked potentials or magnetic fields ("steady state probe technology" or "frequency tagging") have several advantages over traditional (transient) ERPs. Subjects are typically presented with sinusoidal visual flickers of fixed frequency superimposed on task-related images. The task/nontask EPs are measured in the narrow frequency band centered on the stimulus frequency. Because artifact (especially muscle) is mostly broad band, the narrow band signal to artifact noise can be made very high (Regan 1989; Silberstein 1995a). Robust amplitude, phase, and coherence measures of cognitive tasks have been demonstrated (Silberstein 1995a; Silberstein et al. 1990; Srinivasan et al. 1999). These task-related changes to visual input have been recorded at many scalp locations including frontal and prefrontal regions far from primary visual cortex.

6. Mathematical models should be used to test the relative efficacy of transient and steady state probes of the dynamical properties of nonlinear systems. Such models can also test data analysis methods, for example, beyond simple averaging with ERP. Given our very limited understanding of physiological mechanisms, a range of models should be employed, including models with spatial extent (Nunez 1995). Coupled nonlinear oscillators and physiologically based theory (e.g., outlined in the appendix) might be employed. In a related example, the driven linear string/nonlinear springs system (Ingber & Nunez 1990) provides a metaphor for top-down and bottom-up interactions between local and global processes. In states of local dominance, the system approximates the well-known Duffing oscillator exhibiting transitions between periodic and chaotic behavior as control parameters are varied (Ueda 1980). But, such dynamics may be substantially modified top-down by the global influences (stretched string), believed to be somewhat analogous to long-range cortico-cortical interactions (Nunez 1995; Nunez & Srinivasan 1993; Srinivasan & Nunez 1993). Furthermore, influences of spatial filtering on measured variables may be estimated. Such simulations can address concerns about ERP and other data analysis methods expressed by **Greenblatt, Ingber, Kolev & Yordanova,** and **Pflieger.** At the very least, they can serve to eliminate methods that are obviously flawed for a wide range of simulated data having some common ground with EEG.

R2. Model-specific issues

I begin this section with yet another metaphor, but the reader is reminded that metaphor is used only to describe (qualitatively) genuine physiologically-based mathematical theory.

R2.1. Brains of air and glass: Resonant interactions between brain fields and networks? We are reminded by **Freeman & Kozma** of the vast differences in complexity between physical waves (e.g., my simple ocean wave metaphor) and propagating fields in neural tissue. They say that, unlike oceans, neural tissues are not passive media, rather critical interactions take place between the fields and the medium through which they propagate, for example, fields may cause phase transitions (believed to correspond to brain state changes). I agree; such processes are represented by interactions F-A and A-F in Figure R1. However, much of physics involves interactions between wave fields and matter so I would not make distinctions between physical waves and neural mass action on this basis.

The simple ocean wave metaphor was chosen to allow visualization of frequency-wavenumber spectral analysis, wave dispersion, experimental relationships between long and short wavelength EEG phenomena, and the effect of sensor size. But, ocean wave metaphors are inappropriate to describe brain dynamics itself. Examples of important physical wave-media interactions include propagation of electromagnetic waves through electrically conductive media (e.g., cooking in a microwave oven, resonant interactions in the ionosphere), proton spin resonance in MRI, microwave spectroscopy, and so forth. In molecular microwave spectroscopy, incident waves are absorbed in narrow frequency bands (the rotational or vibrational resonant modes of molecules analogous to interactions A-F and F-A in Fig. R1). The microwave absorption spectra provide signatures for molecules present in the sample.

By contrast to electromagnetic waves, sound waves have underlying physical structure. In this sense they provide a better metaphor for synaptic fields. A metaphor that roughly describes the putative local/global brain processes of section 5.3.6 and Figure 7 involves sound in an opera hall (neocortex/cortico-cortical axons). External noise sources (subcortical input) replace opera singers (pacemakers). Global sound resonance occurs at multiple frequencies (fundamental and overtones) depending on sound speed (cortico-cortical axons propagation speed) and hall size and shape. To avoid the (physiologically unrealistic) reflective boundary conditions at the walls of a normal hall, let the opera hall take the shape of a torus or spherical shell with sound absorbing walls. The external sound sources cause

traveling waves in the air that interfere because of the periodic boundary conditions due to the hall's shape. Thus, certain spatial wavelengths (and corresponding temporal frequencies) dominate the sound field. These are the "normal modes" of the hall, the resonant frequencies of air pressure modulations around background pressure (synaptic field modulations).

The imagined opera hall contains many water glasses of different sizes and shapes (local and regional networks) that vibrate when driven by global sound waves at glass resonant frequencies. Valves (neurotransmitters) control the amount of water in each glass, thereby controlling local resonant frequencies. Sensors on an outside wall of the hall (scalp electrodes) record only the long wavelength part of the internal sound because of wall properties (CSF, skull, scalp) and physical separation of sensors from air molecules. A purely global opera hall theory (the purely global theory of the target article) might attempt to predict resonant frequencies of air pressure modulations around background pressure (synaptic field modulations), by ignoring influences of the internal glass structures.

In the next approximation, an oversimplified local/global theory of the opera hall might attempt to add some of the effects of air-glass interactions. For example, to generally predict that each water glass responds to air waves at its particular resonant frequency (interaction F-A in Fig. R1). Furthermore, the resonating glasses modify the air waves (interaction A-F in Fig. R1 and waveform in Fig. 7). In this manner, widely separated glasses with at least one resonant frequency in common can become parts of the same network if driven by a sound wave field containing substantial power in a matching frequency band. A particular glass having several resonant frequencies could easily participate simultaneously in multiple networks. Adding water to a glass changes its resonant frequencies so that it participates in a different collection of networks, perhaps contributing to a global phase change (brain state change).

This "binding by resonance" might offer some advantages over physical connections, as considered briefly in section 7 and in the context of event related desynchronization by **Andrew.** A physiological and mathematical basis is outlined in Nunez (1995, pp. 694–98). A similar idea was developed by Hoppenstead and Izhikevich (1998), who found that synaptic connections between cortical columns in their model did not guarantee substantial interactions. Rather, columns interacted strongly only when certain conditions on their resonant frequencies were met.

I have used the opera hall metaphor to clarify the local/global theory outlined in the target article. However, this theory was derived from physiology/anatomy not metaphor, as charged by **Mayer-Kress** and **Tucker.** The synaptic fields are not metaphors; they are genuine macroscopic physiology, closely connected to measured scalp potentials, as depicted in Figure R2. A legitimate question is whether the oversimplified physiology/anatomy used to develop the global theory of synaptic field modulations is adequate as a first approximation. This can only be answered experimentally.

R2.2. Does the most complicated mathematics win the game? To make the opera hall metaphor more realistic, replace the water glasses by complex networks of test tubes and beakers connected by glass rods that fill a substantial part of the space in the opera hall, for example, the chemistry lab from hell. Hierarchical interactions were discussed qualitatively in the target article and emphasized by **Freeman & Kozma, Ingber, Jirsa & Kelso, Habeck & Srinivasan, Liley, Liljenström,** and early discussions of K-sets by Freeman (1975) that influenced my thinking at the time. To include hierarchical interactions in the opera hall metaphor, imagine rods inside tubes inside small beakers inside larger vessels with overlapping structures (cortical columns at various scales). One can imagine progressively more complications of opera hall glass networks. But, if an important source of experimental data for this system is externally measured sound, the idea of macroscopic waves should be maintained, despite the enormous complexity of dynamics within the glass networks. For similar reasons, I believe we must retain synaptic field concepts as long as EEG is an important data source, even if networks believed to underlie behavior and cognition become known. Separation of synaptic field and network concepts, even when they interact strongly and the separation is somewhat artificial, helps to simplify a very messy picture. I am no where near ready to abandon this separation, as proposed by Liley.

Several commentators chided me for omitting important features of nonlinear dynamical systems with my crude, quasi-linear approximations outlined in the Appendix. These criticisms provide fertile ground from which new and improved theories can grow. **Jirsa & Kelso** discuss specificity of cortico-cortical connections, for example, these fibers are inhomogeneous and anisotropic. The cortico-cortical fibers may be considered both carriers of synaptic wave fields and parts of specific networks, for example, the regional networks considered by Silberstein (1995b). The approximations used in the target article are discussed in more depth in Nunez (1995). Generally, I argued that connection specificity is scale-dependent so that, for example, connection specificity at mm scales does not preclude approximate homogeneity at cm scales appropriate for the global theory. However, I welcome the introduction of selective interareal projections to global theory by Jirsa et al. (1999).

Daffertshofer et al., Freeman & Kozma, Ingber, Jirsa & Kelso, and **Liley** argue that nonlinearity, stochasticity, self organization, and temporal and spatial scale interactions are vital issues in brain dynamics. I agree that these issues plus additional, as yet undiscovered, effects can have profound influences on brain dynamics. My main concern is that, ideally, thought experiments should drive theoretical development. Robust contact with experiment is more important to genuine theory than mathematical sophistication. Scientific merit is often inversely proportional to mathematical complexity (and sometimes even mathematical sophistication). If brain states exist in which such "vital" dynamical issues can be neglected by a theory, and the theory can still make valid experimental predictions, then the simple theory should probably be exploited first. If partly successful, such oversimplified theories can provide groundwork for later, more accurate theories.

There is perhaps some tendency for scientists with strong mathematical training, but minimal experience with genuine theory and/or experimental science, to skip too many preliminary steps, whereas series of small steps have typically characterized successful physical theories. Many physical examples of such progression from the simple to complex come to mind. Special relativity (mathematics limited to high school algebra) followed ten years later by general

relativity is one example. Another is boundary layer theory, which artificially divides fluid flow near an object (e.g., pipe wall, airplane wing) into linear and nonlinear regions, thereby overcoming formidable mathematical obstacles to successful theoretical prediction. For similar history to be repeated in theoretical brain science, close collaboration between neurophysiologists, cognitive scientists, clinical scientists, physicists, engineers, and others will be required, with experimentalists and theoreticians acting to limit each other's excesses.

Liljenström raises the important question of relationships between neuron firing rates/interspike intervals (measured at small scales) and EEG frequency spectra (or macroscopic synaptic fields). High firing rates of excitatory neurons probably increase the modulation depth (and EEG magnitude) of synaptic action fields. The effect on EEG frequency spectra is more complicated. However, the purely global theory of the target article suggests that moderate increases in firing rates do not affect EEG frequencies, but very high excitatory firing rates generally cause reduction of EEG frequencies since frequency is predicted to decrease with increased amplitude at large amplitudes, as discussed in section 6.8. But, Liljenstrom also implies that small-scale variables like firing rates of single neurons are more "real" than macroscopic scalp fields. I contend that variables at all scales are important; the scale of the experimental data dictates the variables chosen in any particular theory. While establishing cross-scale connections is important, most of the available data correlated with human behavior and cognition is recorded at macroscopic scales.

Freeman & Kozma emphasize the importance of chaotic attractors. I agree that systems with large numbers of degrees of freedom often exhibit sensitivity to initial conditions and system parameters; they are chaotic in this sense. But, this was appreciated by complex system scientists (but not appreciated by many others) long before the modern interest in low-dimensional chaos (see Feynman 1963, for example). As far as I am aware, the distinction between chaos and "quasi-periodic" dynamics in systems with many degrees of freedom (that may actually look very different from periodic dynamics) is blurred. Systems for which spatial extent has important influence (as opposed to simple networks) have large (theoretically infinite) numbers of degrees of freedom. The words "periodic" and "chaotic" are not antonyms.

R2.3. Free parameters of physiological parameters? Disappointment is voiced by **Daffertshofer et al.** because the physiological parameters of the global theory are not known more accurately. They imply that my estimates for characteristic fall-off distances in densities of excitatory and inhibitory fibers are arbitrary. This is incorrect. The cortico-cortical fiber systems are now known to be exclusively excitatory (Braitenberg 1978; Braitenberg & Schüz 1991; Szentagothai 1979) so excitatory fiber systems clearly have much longer range. Fiber system ranges were estimated from these anatomical data in Nunez (1995). Cortico-cortical fibers were expressed in terms of multiple long-range systems with different exponential fall-off parameters (the λ_j in Eq. 9 of the Appendix). I showed that large-scale activity (small wave numbers k) could be expressed in terms of the only the smaller λ_j (longest fibers), with large λ_j (excitatory intracortical and short cortico-cortical fibers) incorporated within the global control parameter B (Nunez 1995, pp. 488–94 and Eq. 11.12). Because many homogeneous and isotropic distributions can fit exponential sums, I regard this step as an important generalization. The effects of multiple cortico-cortical fiber systems were simulated, leading to multiple branches of dispersion relations (Nunez 1995, pp. 498–506 and Figs. 11–15 and 11–16).

The fall-off of human cortico-cortical fibers was also expressed as the product of squared distance and exponential, matching (scaled up) data on mouse cortico-cortical fibers (Braitenberg & Schüz 1991; Nunez 1995, pp. 506–11 and Eq. 11.33). The mouse data are the only quantitative data on cortico-cortical fiber distributions that I have found. I also studied effects of distributed axon velocity (Nunez 1995, pp. 511–17). The net result of these studies is that semi-quantitative predictions of the global theory are relatively robust with respect to these complications of the physiology and anatomy. Haken (1999) added nicely to this work by obtaining analytical solutions for dispersion relations corresponding to different functional forms of cortico-cortical fall-off in one, two and three dimensions for the case of a single fiber system with delta function velocity distribution.

Daffertshofer et al. suggest that the global theory should be more firmly rooted in genuine anatomy and physiology, citing Haken (1999). This same idea was the basis of my discussions with **Jirsa** (circa 1994–96) while he completed his Ph.D. work under Haken. Thus, the advice of Daffertshofer et al. has now completed a path of "circular causality." More detailed physiological and anatomical connections to theory are discussed in my book (Nunez 1995), but were omitted in the target article because of space limitations. Such connections will require continual re-evaluation into the foreseeable future.

Liley challenges my claim that the parameters of the purely global theory are much better known than parameters of local theories, thereby allowing experimental connections to globally coherent activity. But we are able to obtain crude estimates of the limit cycle mode frequencies from Equation 8 even though the nondimensional global feedback gain parameters b_{nm} (or more simply B) are unknown (sect. 6.1). The reason is that velocity and size parameters are known approximately and can be measured more accurately in independent experiments. Frequency estimates are approximately independent of B over a wide range of this parameter. Furthermore, since B is physiological, it must fall within a limited range. It cannot be negative or complex, for example. Crude estimates of B based on cell physiology were outlined (Nunez 1995, pp. 492–94, 498–505), suggesting that B is roughly in the range of one to ten. Although such physiology is not currently known in sufficient quantitative detail to take this estimate very seriously, the estimation exercise shows that accurate estimates may be possible in the future. After all, one motivation for theory development is to motivate physiologists to make such quantitative estimates. Section R2.5 provides more predictions of the global theory.

Andrew suggests that local (Q) and global (B) feedback gain parameters change in opposite directions based on differential actions of neurotransmitters and fiber systems (long and short range) at different cortical depths, as tentatively proposed by Silberstein (1995a). **Liley** suggests that the local (Q) and global (B) feedback gain parameters are not independent. But, given the uncertainties in neuro-

chemistry, neuroanatomy, and neurophysiology, we should assume that these parameters can change either together or independently until new data prove otherwise.

Liley cites his new model (with Cadusch and **Wright**) that includes both intracortical and cortico-cortical interactions. This model appears to have much in common with the local/global theory outlined here, so I regard it as more complementary than competing. I encourage Liley's suggestions for checking this model with experiments involving neurotransmitter action. But **Andrew**'s studies remind us of the advantages of separating local and global effects in theoretical models. He was able to distinguish coherent alpha rhythms for Rolandic mu rhythms with nearly the same frequency, and to record global/alpha rhythm simultaneously with 40 Hz local supplementary motor rhythms. I find these data to be more easily visualized in the context of distinct local and global processes, even though they are not fully independent.

R2.4. New experimental predictions. Theory should be judged more on its predictive ability than its capacity to explain existing data, **Keil & Elbert** and **Pflieger** suggest. I mostly agree, but their commentaries appear to underestimate the established predictive success of the purely global theory, which ignores local contributions. Section R3.5 clarifies the chronology of the global theory's predictions of subsequent experiments. Here I suggest new experiments to test the global theory.

Consider first experiments involving changes in the putative global mode frequencies in Equation 8 due to changes in cortico-cortical axon propagation speeds. Propagation speeds are increased with axon myelination during maturation as discussed in sections 6.7, R2.5.1, and by **Wright.** Axon speeds are reduced by demyelinating diseases like multiple sclerosis. Incomplete myelination in patients and children (or even healthy adults) can be estimated with MRI (**Thatcher et al.**). These data can be compared to EEG coherence studies (Srinivasan 1999). Experiments using controlled changes in axon propagation speeds by controlling body temperature might also be considered. Note that increasing body temperature in hot baths worsens symptoms of multiple sclerosis patients and was a standard clinical test for this disease before development of MRI.

Axon propagation speed can be estimated independently from progressive anterior/posterior phase changes in EEG (e.g., eyes closed alpha rhythm or steady state visually evoked potentials) as described by Burkitt et al. (2000), section R2.6 and by **Andrew.** Equation 8 predicts that each EEG limit cycle mode frequency is proportional to characteristic axon velocity (a weighted average over different cortico-cortical axons), provided that feedback gain parameters (Q and b_{mn}) are fixed. Perhaps the Q and b_{mn} (or B) parameters may be relatively constant for constant "brain state" (resting alpha rhythm), while body temperature is changed. This conjecture can be partly verified by checking that EEG amplitude is fixed while axon speed varies. Many experiments of this general kind appear practical. Maturation studies are probably more difficult since velocity v and the Q and b_{mn} parameters may all change, making quantitative prediction difficult. For fixed local Q and global control parameters b_{nm} (or B) the measured changes in mode frequency Δf_{nm} due to changes in propagation speed Δv are predicted to be

$$\frac{\Delta f_{nm}}{f_{nm}} = \frac{\Delta v}{v} \qquad \text{(R2)}$$

This section may motivate new experiments to test the global theory, and some discussion of methods to detect small frequency changes is appropriate. If long records of human alpha rhythm are subjected to Fourier analysis, peak power histograms based on perhaps 4 to 10 second epochs may be constructed (0.1 to 0.25 Hz frequency resolution). That is, each epoch is characterized by a single frequency component that best describes the frequency of that epoch. The spread in such peak power frequencies at each EEG electrode is believed due to a combination of nonstationarity and multiple alpha modes (Nunez 1981a; 1995). These contributions are not easily separated. But, frequency differences between brain states may be quantified by estimating clusters of peak power frequencies, as opposed, for example, to comparisons between power spectra averaged over both time and electrode locations. For example, such clusters might be separated by global changes in myelination between populations (e.g., in children) or by anterior/posterior differences that may be imaged with MRI (**Thatcher et al.**). More sophisticated statistical tests are available, but the simple approach should be intuitive and useful for preliminary analyses.

Consider another class of experiments where brain state is altered by drugs (e.g., alcohol) while axon propagation speed is held fixed. A plausible conjecture is that drugs measurably alter the global feedback gain parameters b_{nm} (or B). To keep things simple, assume one-dimensional anterior/posterior wave propagation with mode-independent feedback gain parameters so that the $b_{nm} \to B - 1$. Equation 26 for the case of uncoupled modes of synaptic action fields has the perturbation solution given by Equation 8, valid only for $B \cong 2$. However, numerical solutions of Equation 26 for a range of lower modes (n) show that Equation 8 provides an accurate semi-quantitative idea of the behavior of Equation 26. That is, each limit cycle mode n oscillates with approximately constant frequency ($v/2\pi R$) for all small to moderate B (somewhat larger than 2). Mode amplitude is proportional to $(B - 2)^{1/2}$. When a critical value $B \cong 1+(n/\lambda R)^2$ is reached, mode n undergoes a Hopf bifurcation (limit cycle to stable point) and no longer contributes to oscillatory dynamics. Such increases in B also cause higher modes to increase in amplitude and eventually to undergo sharp reductions in frequency and finally drop out of the dynamics. Qualitatively similar behavior has been observed with increases in inspired concentrations of halothane anesthesia (Nunez 1981a; 1995).

Equations 8 and 26 or 30 may be used to predict (crudely) measured changes in (alpha) frequency Δf_n and synaptic action amplitude $\Delta\Phi_n$ due to changes in control (feedback gain) parameters ΔB. Taking partial derivatives of f_n and Φ_n with respect to B yields a rough estimate of the relationship between $\Delta\Phi_n$ and Δf_n due to an unknown change ΔB in control parameter B:

$$\frac{\Delta\Phi_n}{\Phi_n} \cong \frac{1+(\frac{n}{\lambda R})^2 - B}{B-2}\left(\frac{-\Delta f_n}{f_n}\right) \qquad \text{(R3)}$$

Here R is characteristic brain size (e.g., square root of neocortical surface area) and λ is a measure of assumed exponential fall-off in cortico-cortical fiber density. From Equa-

tions 8 and 30 and numerical solutions of Equation 26, the feedback gain parameter associated with each oscillatory spatial mode n must lie in the approximate range

$$2 \le B \le 1 + (\frac{n}{\lambda R})^2 \qquad (R4)$$

Equation R4 is exact for the perturbation solution Equation 30, but numerical solutions of Equation 26 show that somewhat larger B's are allowed before mode *n* undergoes Hopf bifurcation. Equation R3 predicts that increased amplitude of mode n will occur with decreased frequency. Based on the anatomy of cortico-cortical fibers, λR appears to be of the order of one (perhaps 0.5 to 1.5). Because of spatial filtering by the volume conductor, only the lowest spatial modes can be recorded on the scalp. Thus, for raw EEG data (excluding dura image or spline Laplacian estimates), the dominant mode numbers appear to be in the approximate range $1 \le n \le 3$ or 4 (Nunez 1995). The spatial anterior/posterior mode n associated with each frequency f_n can be estimated independently from spatial EEG spectra (one reason for considering one-dimensional modes first).

Ideally, Equation R3 may be used to estimate the feedback parameter B directly from scalp EEG data since we expect scalp potential amplitude to increase with modulation depth of synaptic action Φ_n for long wavelength modes (small *n*). For example, a subject might be given progressively larger dosages of a drug on different days that increase alpha amplitude and reduce frequency. Suppose each dosage corresponds to a different B parameter. Thus, each dosage is predicted by Equation R3 to cause changes in the ratio of amplitude to frequency ($f_n \Delta\Phi_n / \Phi_n \Delta f_n$). Equation R3 provides a family of curves, one for each (n/λR). Experimental plots of this ratio versus dosage can then provide estimates of both (n/λR) and B for different drugs and dosages by comparison with the family of theoretical curves. Since *n* can be estimated independently with frequency-wavenumber spectra and λR may be estimated independently from anatomy, rough checks for parameter self-consistency are possible.

The predictions of Equations R2 and R3 apply only to globally coherent EEG for which local effects are negligible to first approximation. Also, they are based on the quasi-linear solution in the Appendix for which coupling between spatial modes is neglected. One may postulate, for example, that the crude quasi-linear approximation has some predictive value in light to moderate depths of some anesthesia states, but fails for deep and/or other kinds of anesthetics. Of course, new experiments may show that Equations R2 and R3 have no predictive value beyond the experiments outlined in section 6. Failure to predict the outcome of a particular experiment has several possible interpretations:

1. Local effects cannot be neglected, even in states of apparent global coherence.

2. Mode coupling effects are too strong; the quasi-linear approximations leading to Equations 26 and 8 are invalid. Strong mode coupling is associated with fully nonlinear processes that may dominate the dynamics of some brain states as emphasized by **Daffertshofer et al.** and **Ingber.**

3. Phase velocities measured from scalp data are substantially influenced by intracortical delays, for example, a combination of unmyelinated axon delays and synaptic delays. Sections 7, R1.3, and **Ingber** speculate that cortico-cortical and intracortical signal propagation across the brain may occur on the same time scale. **Liley** emphasizes layer 1 axon propagation.

4. The global theory is fundamentally wrong, in which case the experimental connections of section 6 would probably be interpreted as unlucky coincidences.

Regardless of outcome, the reader will perhaps appreciate that a falsifiable theory has been proposed in the target article.

R2.5. Does size count? A number of studies are referred to by **Wright** involving EEG recorded from cortex (ECoG) of different sized animals in which no apparent relationship between frequency and brain size (parameter R) is observed. He concludes these data show that propagating neocortical waves must be strongly damped so standing waves are not formed by interference of traveling waves, as proposed in the target article. To see why the animal data neither refute nor support standing waves in humans, some details of theory and experiment are required.

The theoretical prediction of a negative correlation between brain size and global mode frequencies, for example by Equation 8, was based on the following approximations:

1. The brain state under study is dominated by global dynamics, or perhaps only the low end of the spatial frequency spectrum (e.g., recorded on the human scalp) is dominated by global mechanisms.

2. Cortico-cortical interactions have a substantial influence on neocortical dynamics compared to thalamocortical interactions.

3. Cortico-cortical axon diameters, axon length distributions, and control parameters, for example, in Equation 8 are constant across subjects (or species in the case of Wright's arguments).

The experiments with different species did not test theoretical prediction of a size-frequency correlation in humans because:

1. The animal data were recorded intracranially so that the severe spatial filtering of human scalp recordings did not occur. The size/frequency prediction applies only to low spatial frequencies, such that dominate wavelengths are in the general range of brain size (e.g., the scale R in Eq. 8).

2. The proportion of cortico-cortical fibers entering (or leaving) the underside of neocortex that originate (or terminate) in other cortical regions becomes progressively larger as a mammal moves up the phylogenetic scale (Braitenberg 1977; 1978; Katznelson 1981; Nunez 1995). In rat, perhaps 50% of entering (or leaving) axons are cortico-cortical. In humans, more than 95% are cortico-cortical; less than 5% are thalamocortical. These data imply that putative standing wave phenomena, due mainly to cortico-cortical propagation, should make much larger contributions in humans than in lower mammals. The global theory predicts that, other parameters being equal, human brains are able to produce larger B (or the b_{mn}) parameters in some states, allowing for weakly damped traveling waves in neocortex and more dominant global dynamic behavior of EEG. One may speculate that this global aspect of brain dynamics is an important part of being human (Nunez 1995).

3. If axon diameter in different species were proportional to brain size, the global theory (e.g., Eq. 8) predicts no size effect. This is because predicted limit cycle frequencies are proportional to speed/size (v/R), and action potential propagation speeds in myelinated axons are proportional to axon diameter. As far as I have been able to de-

termine from the anatomy literature, there is no systematic relation between axon diameter and brain size across mammalian species. In imagined experiments designed to test the size hypothesis across species, either axon diameter distribution or cortical wave propagation speeds require independent measurement.

4. The size prediction applies only to globally coherent EEG with peaked frequency spectra, as in the example of the resting human alpha rhythm. The high long-range human alpha coherence occurs only in a narrow frequency band ($\cong$ 1 to 2 Hz) and with subjects fully relaxed, as demonstrated in Figures 1 and 2. The published animal studies often exhibit spectra that look like l/*f* noise, although spectral peaks are also observed in some behavioral states. However, ECoG coherence is rarely measured. When measured, it typically falls to near zero at distances greater than a few cm, in sharp contrast to scalp-recorded human alpha. But again, it is the long wavelength part of EEG (e.g., space averaged by the volume conductor) that should be most strongly influenced by boundary conditions, resulting in standing waves.

5. The fundamental and overtone frequencies predicted by the global theory are much higher in non-human mammals, for example, perhaps 30 to 40 Hz and higher in dogs, cats, and sheep, with the idealized assumption that these species have the same cortico-cortical propagation speeds and other control parameters as humans. In some animal experiments, low pass filters were used to remove such fast activity so that checking published experiments against global theory is not possible.

R2.5.1. Maturation of ECoG in fetal sheep. The study of fetal sheep in pre- and post-myelination stages of maturation by Sergejew (1999, cited by his dissertation supervisor, **Wright**) is the only animal study of which I am aware that was designed to test for putative global resonance contributions to ECoG. Thus, it is apparently the only study where some measure of control of confounding influences was achieved. Sergejew presented evidence that callosal axon propagation speed increases from the 1 m/sec range in early gestational ages (up to about 10 days before birth) to perhaps 9 m/sec in later stages, perhaps 30 to 60 days after birth when the adult speed is achieved. The purely global theory, equation 8, predicts increases in frequencies of putative coherent global modes in this same range as cortico-cortical axon speed v increases due to myelination. I congratulate these scientists for undertaking these difficult experiments and hope others will follow up with further efforts to test the global mode hypothesis. However, I do not agree with Wright and Sergejew that their results refute the importance of global influences (e.g., standing waves), especially in humans. The issue for sheep is also unclear because of the following extension of issues raised above in connection with other animal studies:

1. ECoG in fetal sheep were recorded at early (50 days before birth) and "late" (10 days before birth) stages of maturation. Based on Sergejew's cited references, this period is clearly not appropriate for observation of large changes in callosal axon velocities (which occur mostly in the 30 days after birth), but technical limitations apparently prevented later recordings. Sergejew argued that cortico-cortical myelination should occur well before callosal myelination so large changes in cortico-cortical axon speed could be expected over the period studied, 50 to 10 days before birth. This (part) conjecture that cortico-cortical myelination is nearly complete 10 days before birth requires closer scrutiny. For example, myelinogenesis of human cortico-cortical axons apparently continues after callosal myelination is complete (Yakovlev & Lecours 1967). Another issue is that the callosal axon velocity measurements cited by Sergejew were obtained by electrical stimulation of homologous cortex. As such, they probably represent propagation along the fastest (myelinated) callosal fibers. These data do not yield the fraction of myelinated axons in the population.

2. In the global theory, cortico-cortical connections with relatively high feedback gains are required to produce globally dominant EEG. That is, the parameter B or the b_{nm}'s in Equation 8 should be relatively large, implying some minimal maturity of neocortical synaptic contact. Even if cortico-cortical axon myelination was complete 10 days before birth, synaptic contact of these axons with target cortical cells evidently lacked sufficient strength to produce important global ECoG effects. But this result does not show that such feedback may not be much stronger in more mature sheep, in different brain states, and/or in humans.

3. In Sergejew's study and the cited references, the early period was characterized by "high voltage slow activity" (HVS), dominant frequencies below about 3 Hz with peak at perhaps 2 Hz, looking roughly like l/*f* noise). The late period involved apparent state changes between HVS activity (l/*f* spectra similar to early period, but with larger amplitude) and "low voltage fast activity" (LVF, broad spectra with substantial power up to perhaps 30 Hz, with weak spectral peaks near 2 and 12 Hz). Thus, the relative ECoG power shift to higher frequencies was qualitatively consistent with increased axon speed during maturation, perhaps lending some weak support to the global theory.

4. No sharp spectral peaks were observed in either the early or late periods, suggesting that global resonances (standing waves) made minimal or perhaps no contribution to the ECoG, which was probably dominated by local effects as suggested by **Wright.** But, it is still possible that the observed increase in spectral peak from 2 to 12 Hz partly reflected a transition from nonmyelinated to myelinated axons. In this case the persistence of the 2 Hz peak into late periods might simply be the result of incomplete myelination or the continued importance of local contributions to the ECoG, in a manner similar to the arguments for combined local/global effects in sections 5.2 and 5.3.6. The fact that most sheep ECoG power occurred at frequencies much lower than expected by naïve extrapolation of human alpha to a much smaller brain may be partly due to the state(s) of the fetal brain under study, for example, "fetalosleep."

5. Future studies along these lines should consider increases in long-range (up to brain size) coherence and sharpness of putative resonance peaks with myelination. The predicted global resonance effect is closely associated with strong cortico-cortical feedback gains that are expected to increase long-range coherence. Since maturation may be associated with both cortico-cortical axon myelination and increased synaptic strength of these axons on cortical target cells (perhaps causing increases in both B and Q parameters), increases in coherence should occur along with increases in frequency. Relatively sharp spectral peaks rather than the broad spectral ECoG's often observed in fetal sheep and other nonhumans, are better candidates for standing waves.

R2.6. Do human neocortical waves exist? If so, are they strongly damped? It has been known for some years that steady state visually evoked potential (SSVEP) can produce progressive posterior-to-anterior phase shifts along the scalp (see review by Burkitt et al. 2000). For example, Reginald Bickford did these experiments at UCSD while I was there in the 1970s. In some very good subjects, the progressive phase shift across eight bipolar channels was obvious from the raw paper trace. One interpretation of these data is that of waves traveling from primary and secondary visual cortical areas to frontal cortex. Estimates of phase velocity in the literature have varied widely, mainly because of distortion due to volume conduction and reference electrode effects. However, the use of close bipolar electrodes eliminates most of these problems and consistent phase velocity estimates from driving at the peak alpha frequency were found to match cortico-cortical axon velocities as discussed in section 6.5. Because of differences in visual pathways to neocortex (spatial properties of input function), discussed in Silberstein (1995a) and Burkitt et al. (2000), a checkerboard pattern stimulus was predicted to be better able to produce traveling waves, whereas a uniform flicker was thought to be better able to produce standing waves. These predictions were largely verified by the experimental phase structure evoked by stimuli at the subject's peak alpha frequency. **Andrew** also cites alpha phase velocities of 9–10 m/sec (fissure corrected), roughly consistent with a few estimates that I obtained (Nunez 1981a) using frequency-wave number spectra.

My group in New Orleans received several separate sets of data from the Melbourne group and carried out an independent study of phase velocity (Nunez 1995). Whereas Burkitt et al. (2000) obtained high frequency resolution (0.003 Hz) by Fourier analysis of 5-min periods of SSVEP data, our estimates were based on the phases of single cycles. The two reasons for changing the analysis method were (1) application to spontaneous alpha rhythm that typically exhibits a nonstationary drift in peak frequency of $\pm$ 0.5 Hz, essentially negating the advantage of high frequency resolution of SSVEP data; (2) obtaining an alternate way to judge the statistical significance of the traveling wave hypothesis. The SSVEP stimuli were uniform flicker and had integer frequencies varying from 9 to 13 Hz. The spontaneous data were resting, eyes closed alpha rhythm. The following questions were asked of the data:

1. Is there strong evidence for traveling waves? SSVEP data were digitized at exactly 16 samples per stimulus cycle to accurately estimate single-cycle Fourier coefficients. Single cycle epochs were 77 to 111 msec in length, depending on SSVEP frequency or peak alpha frequency. Eight bipolar channels along a line just to the right of the midline were followed. A single cycle epoch was defined as "traveling back to front" if linear regression analysis of the phase of the cycle versus posterior-anterior distance produced a linear correlation coefficient greater than 0.834 ($p < 0.01$). A similar criterion was used to define "traveling front to back." The percentage of cycles that satisfied these criteria was about 8% for each direction. The alpha rhythm data also yielded about 8% traveling waves in each direction. The number of cycles expected to satisfy these criteria by pure chance is lower than 1%. This was verified by using the same sets of phases with random electrode positions in a separate linear regression study, for which the number cycles passing the $p < 0.01$ criterion was about 0.1%. A plausible interpretation of these results is that most cycle epochs involved a mixture of traveling waves in different directions, but that 16% of the epochs traveled in a consistent direction across the array. Waves traveling in opposite directions are expected to interfere and form standing waves. The near equality of numbers of epochs traveling in either direction with a diffuse flicker stimulus is consistent with the Burkitt et al. (2000) study showing that this stimulus was most efficient in producing apparent standing waves (based on much longer EEG records).

2. The phase velocity estimates at the scalp were mostly in the 2 to 6 m/sec for the SSVEP and 3 to 6 m/sec for alpha rhythm. These estimates translate roughly to 4 to 12 m/sec along the folded cortical surface, compared to estimated cortico-cortical propagation speeds in the 6 to 9 m/sec range, again roughly consistent with the findings of Burkitt et al. (2000).

R2.7. Zero phase lag. New evidence for standing waves. The possible importance of global resonant modes of standing brain waves is acknowledged in various contexts by **Andrew, Greenblatt, Habeck & Srinivasan, Ingber, Thatcher et al.,** and **von Stein & Sarnthein.** Our team in Melbourne is currently studying 131-channel alpha rhythm, recorded in several brain states. If short epochs of data ($\approx$ 100 msec) exhibit evidence of waves traveling in different directions (sects. 6.4, 6.5, and R2.6) and EEG dynamics depends partly on global (periodic) boundary conditions (sects. 6.7, R2.1, R2.5), longer epochs should exhibit interference patterns caused by the interaction of traveling waves.

Figure R3 shows phase patterns of resting alpha rhythm for two subjects (rows 1 and 2) at their peak alpha frequencies (10 and 12 Hz, 1 Hz bandwidth) for three successive 20-second periods (Wingeier et al. 1999). These plots were constructed by transforming raw data (referenced to the digitally average potential of the two ears) to obtain estimates of dura potential. This high resolution procedure removes reference electrode and volume conduction effects. It also filters out long wave dynamic activity not easily distinguished from volume conduction (roughly the $n = 0$ and 1 anterior/posterior modes, refer to Nunez 1995). Each plot in Figure R3 is based on Fourier transforms of overlapping one-second epochs. Phase was rotated so that Cz was defined as having zero phase for each epoch. (Without such rotation, "phase" is just determined by choice of epoch division.) Cosine of phase is plotted. Centers of contiguous white and black regions are 180 degrees out of phase. Alternating regions of the same color with zero phase lag are shown.

The phase plots appear to be the interference patterns of standing waves predicted by the global dynamic theory. Correlation coefficients between successive phase plots were obtained by point by point comparison of estimated phase at each of the 131 electrode locations. The plots demonstrate "quasi-stable spatial structure," for example, correlation coefficients between three successive (20-sec) phase patterns are $0.6 < r < 0.7$ (Subject BW, row 1) and $0.2 < r < 0.3$ (Subject CV, row 2). By contrast, the equivalent correlations, obtained from simulations of uncorrelated sources in a concentric spheres model and passed through the dura imaging algorithm, were near zero as expected. Earlier studies of steady state visually evoked po-

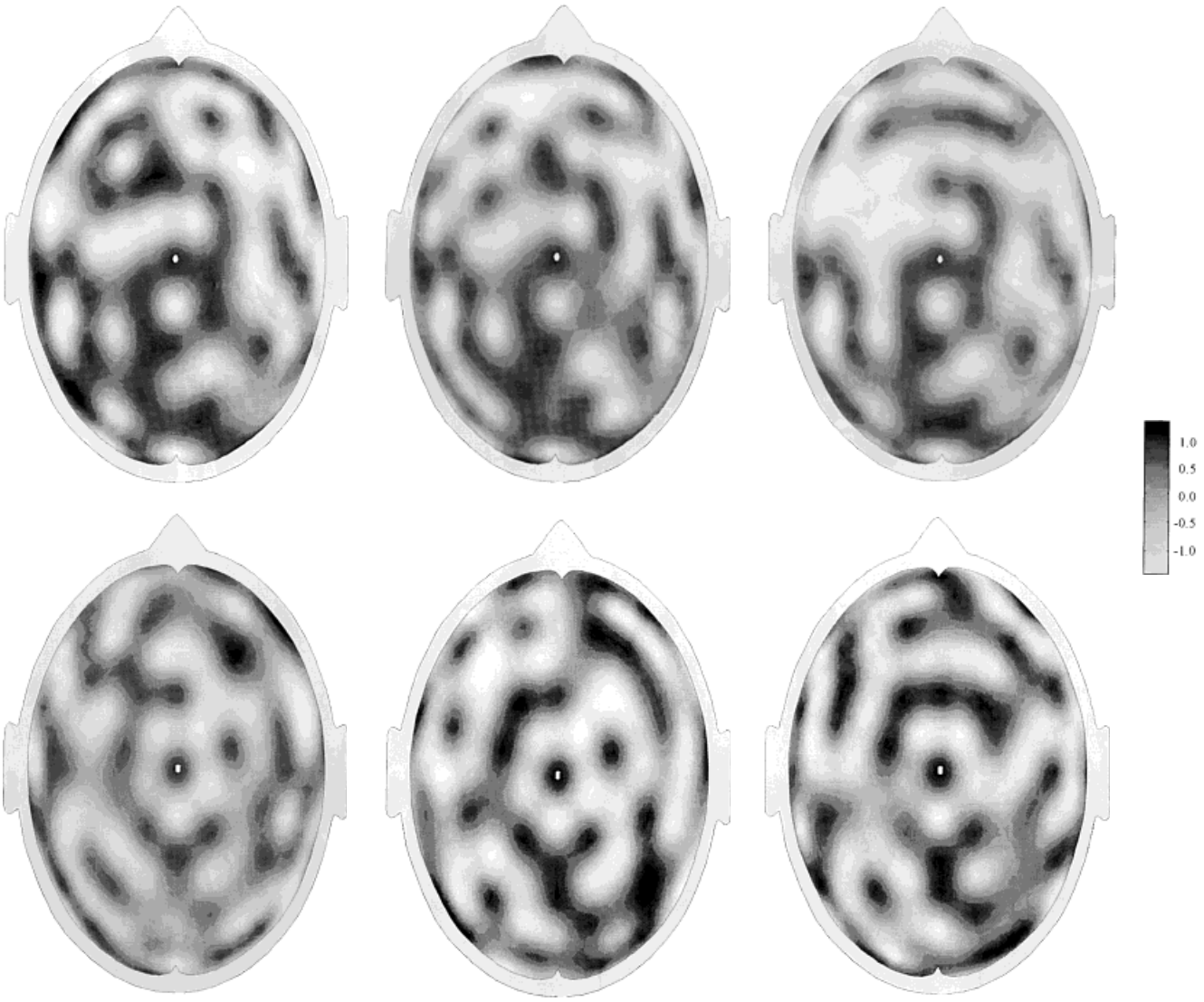

Figure R3. The phase structure of human alpha rhythm on the dura surface is estimated using high resolution EEG. Subject BW (row 1) is a healthy 25-year old male engineering graduate student. Subject CV (row 2) is a healthy 22-year old female psychology graduate student. Resting EEG was recorded with eyes closed using 131 channels referenced to the digitally averaged potential of the ears. Data were passed through the Melbourne dura imaging algorithm based on a three concentric spheres volume conductor model of the head. The algorithm spatially band passes raw data, providing dura potential estimates very similar to estimates obtained with the New Orleans spline-Laplacian (which is based on an entirely different algorithm; Nunez et al. 1997; 1999). Cosine phase (with respect to C_z, white dot) at each subject's peak alpha frequency (BW 10 Hz and CV 12 Hz) is plotted for three successive 20-second epochs. The centers of adjacent white (cosine phase = −1) and black (cosine phase = +1) regions are 180 degrees out of phase. Frequency resolution (bandwidth) for phase estimates is 1 Hz.

tentials with 64 electrodes showed that phase structure is a sensitive a function of 1 Hz changes in driving frequency (Nunez 1995). Thus, phase structure is apparently not fixed by brain anatomy, for example, fissures and sulci, although anatomy probably influences phase structure.

The phase plots in Figure R3 were obtained from spatially (broad) band pass filtered data (dura imaging). Such filtering with high resolution EEG is required to eliminate reference electrode and volume conduction effects at low spatial frequencies and some (typically small) power at spatial frequencies believed too high to originate from inside the cranium (Nunez 1995). We cannot say at this time whether propagation along intracortical fibers, corticocortical fibers or both are responsible for the apparent interference patterns. More generally, we are considering new tests to confirm or refute the standing wave interpretation. However, the evidence for standing neocortical waves appears to be growing, regardless of underlying physiological mechanisms.

R.3. Miscellaneous challenges

R3.1. Tissue depleted of action potentials? It is suggested by **Mayer-Kress** that Equation 11.1 of the Appendix cannot be valid after all neurons in the neighborhood of location x_1 have fired, and that Equation 10 of the Appendix is that of an overdamped oscillator. Both claims are incorrect. As indicated in Figure 4 and Equations 13 or 14 of the Appendix, the action potential field G is coupled to the excitatory synaptic action field F. That is, Equations 11.1 and 10 each involve the two dependent variables G and F so an ad-

ditional equation is required for solution, for example, Equations 13 or 14. F is a population density, so action potential firings in the neural tissue mass at location x_1 are continually replenished as a result of synaptic input from other cortical regions. If Mayer-Kress's interpretation were correct, the solutions shown in Figures 6 and 7 could not have been obtained; in fact a large part of the target article would be negated.

R3.2. Brain states. Jirsa & Kelso find my use of "brain state" to be too cavalier. They are correct, but I am unrepentant. The trouble occurs because science has this one expression to describe many disparate conditions. I don't think "brain state" can be defined rigorously without specifying both the temporal and spatial scales of a particular experiment or theory. Attention or short-term memory (seconds), sleep stages (minutes), awake/sleeping (hours), healthy/pathological (years) are all legitimate "brain states," as this term is used by neuroscientists. Furthermore, one can speak of the "state" of a neuron, column, neocortex, or entire brain. Perhaps this is unfortunate, but I do not think cleaning up the offensive language is nearly as easy as Jirsa & Kelso imply. The brain is clearly a system with microstates within mesostates with macrostates (in both time and space). One scientist's qualitative change in dynamic properties may be of no direct interest to another scientist working at a different spatial or temporal scale, either experimentally or theoretically.

Similarly, **Liljenström** and **Pflieger** ask what I mean by "fixed state" since brain dynamics changes continuously. Liljenström points to influences of processes acting over much longer time scales, for example, previous experience, motivation, and so forth. Again, "fixed brain state" has meaning only in the context of a particular experiment or theory. In the EEG study described in section 1 of the target article, "cognitive state" was alternated with "resting state," defined only by the subject's behavior. These are states defined behaviorally at the spatial scale of one brain and time scale of one-minute. They result from long time scale motivations of scientist and experimental subject to produce good science, partly defined by social dynamics at the spatial scale of many brains. The main question asked of the EEG data was whether one measure of EEG dynamics (coherence patterns) changed consistently with behavioral state change. The experimental answer was "yes."

In theoretical models, "state changes" typically occur in two ways. Either the equation parameters change or an input function changes in a manner that causes the qualitative changes in dynamic behavior that **Jirsa & Kelso** describe. In simple systems with few degrees of freedom typically studied in great detail by mathematicians, "state" can often be defined unambiguously. For example, transition from periodic to chaotic states of the driven Duffing oscillator can be induced by small but selective changes of either amplitude of the driving function or the damping parameter (Ueda 1980; also see review by Nunez 1995). However, nonlinear physical systems with many degrees of freedom can exhibit qualitative changes at one scale that may or may not be observed at other scales. For example, microscopic transition from periodic oscillations to chaos may be irrelevant to macroscopic measurements.

In the limited context of the quasi-linear (one dimensional) global model with mode coupling neglected, one may tentatively define a "state change" when the feedback gain parameters B approaches $1 + (n/\lambda R)^2$. For larger B, the *n* th limit cycle mode drops out of the dynamics (Hopf bifurcation) while higher modes decrease in frequency and increase in amplitude. The expression "brain state change" is appropriate if this parameter change corresponds to a substantial behavioral change in genuine brains, for example, transition from waking to sleeping. If not, then "state change" may be too strong, but I claim that such choice of terminology depends on the experiment being modeled.

Pflieger cites the deterministic state-space definition of Padulo and Arbib (1974), "A state is some compact representation of the past activity of the system complete enough to allow us to predict, on the basis of inputs, exactly what the outputs will be, and also to update the state itself." This definition and the state-space approach have been applied to electric circuits, artificial networks, and other relatively simple dynamical systems. But, they are probably of little use for either theoretical or experimental studies of genuine complex systems. In such systems, we typically have knowledge of only a few of the many dependent variables required for anything approaching a full description. Furthermore, brain system inputs are mostly unknown. Thus, (typically crude) theoretical predictions of future states must be based on stochastic variables (**Ingber**) and/or semi-heuristic theory like that promoted in the target article.

R3.3. Synergetics. The famous field of synergetics, developed by physicist Herman Haken (1983), is based on the idea that complex systems (from disparate scientific fields) form macroscopic "ordered" structures by cooperation of small-scale elements. It was applied to neuroscience by Haken, **Jirsa & Kelso,** and colleagues. Synergetics is both semi-heuristic and stochastic. It aims to compress the effective number of degrees of freedom in complex systems to a few "order parameters" (actually variables) that adequately approximate system dynamics at large scales. The order parameters "enslave" (top down) individual parts of the system, which, in turn, generate the order parameters. This is Haken's "circular causality," consistent with the interactions F-A and A-F in Figure R1. In neocortical dynamic theory, the time dependence of large scale spatial patterns of synaptic action fields (e.g., spatial modes or eigenfunctions) might be order parameters that enclave cell assemblies (e.g., by direct synaptic contact or by resonant interaction), which in turn, influence synaptic action fields (Haken 1999). The synaptic action in cell groups 1 and 2 and the cell assemblies in Figure R1 are embedded within the synaptic action fields.

Calling on the sociological metaphor, individual humans and groups of humans are embedded within cultures that exhibit macroscopic variables (order parameters) associated with nationalism, religion, family structure, economic activity, and so forth. These order parameters act on individuals and social groups ("enslave," top down) that, in turn, produce the order parameters (bottom up). Tractable models of complex systems must focus on a relatively small number of order parameters. The choice of order parameters is typically based on some combination of guesswork and small-scale theory matched with experimental data recorded at the same scale (typified by the work of **Freeman** on various "K sets"). Such models are ultimately judged by their ability to predict outcomes of new experiments at larger scales. The field of synergetics addresses

important issues of spatial and temporal scales raised in the target article and by **Daffertshofer et al., Ingber, Liley,** and **Liljenström.**

Jirsa & Kelso say that my work is an important stepping stone in exhausting the limits of a physicalist's approach. I strongly disagree. True, biological systems are likely to introduce many new properties and constraints not known in physical systems, providing substantial challenges to mathematical physicists and other theoreticians. However, future brain models are likely to retain many important aspects of complex physical systems like hierarchical and non-local interactions. Furthermore, any new theory must maintain close contact with experimental data recorded at specific temporal and spatial scales. As far as I am aware, the scientists with theoretical training to successfully model (hierarchical) complex systems are mostly limited to certain branches of physics and engineering. Hopefully, such education will soon be extended to new generations of theoretical neuroscientists, with substantial training in both mathematical theory and neuroscience. These new cognitive-neurophysicists will select a handful of ideas from each field, purging much of today's parochial baggage.

Daffertshofer et al. point out that nonlinear effects are essential for theoretical modeling of phase transitions (describing brain state changes), emphasizing the enormous reduction in effective degrees of freedom due to enslavement of small scale systems. They are right in this regard. However, they state incorrectly that I have assumed that linear models can address all qualitative aspects of brain activity. Even in my most linear moods, I have never taken this extreme position. Rather, I have suggested that linear and quasi-linear models may provide theoretical entry points to complex systems. **Jirsa** and Haken (1997), **Kelso** et al. (1999) and Haken (1999) have nicely exploited such quasi-linear "entry" to develop deeper penetration into brain complexity with nonlinear theory of neocortical phase transitions.

R3.4. Genuine theoretical predictions or just prima facie connections to existing data? It is correctly pointed out by **Pflieger** and **Keil & Elbert** that theory should be judged by its ability to predict the outcomes of new experiments rather than simply explaining existing data. But, they suggest that I have mainly provided prima facie experimental connections. This is largely incorrect. The global theory outlined here was first presented at the American EEG Society Meeting in Houston (Nunez 1972). The manuscript was submitted about the same time, and rejected after seven months delay by the *Biophysical Journal.* A slightly modified version was finally published in *Mathematical Biosciences* (Nunez 1974a). Four complementary features of this work (taken together) distinguish it from all other neocortical theory published before 1996 (except for Katznelson's solutions for brain waves in a spherical shell, 1981; 1982): (1) field theory rather than a network theory, that is, follows synaptic action in macroscopic tissue volumes rather than firings of individual neurons (**Freeman**'s "mass action"), (2) largely based on delays due to axon propagation rather than local synaptic delays, (3) substantially influenced by global (periodic) boundary conditions (explicit in Katznelson's solution for spherical geometry, implicit in my one-dimensional solution), (4) Formulated specifically to explain the long wavelength EEG recorded on the scalp.

The theory had some minor early success in predicting a positive correlation between frequency and wave number within the alpha band (Nunez 1974b) and a negative correlation between brain size and alpha frequency (Nunez et al. 1977). When the theory was developed in 1972, the numerical dominance and axon propagation speeds in human cortico-cortical axons were unappreciated by nearly all physiologists and anatomists. The original global EEG theory was based on unknown axon velocity distributions. This was a guess based mainly on EEG observations and my ignorance of physiology and anatomy known at that time (I was new to the field). It was not until Katznelson reviewed the literature in 1978–79 (as part of his Ph.D. research) that we realized that the 10 Hz alpha frequency predicted cortico-cortical axon propagation speeds within the range of experimental and theoretical uncertainty. This motivated Katznelson (1981; 1982) to obtain a solution to my "brain wave equations" for the case of waves in a spherical shell. I obtained some early phase velocity estimates in a few subjects that matched cortico-cortical propagation velocities reasonably well (Nunez 1981a). Only in the past few years have fully convincing estimates of EEG phase velocities along the human scalp surface been obtained for SSVEP and alpha rhythm (Andrew 1997; Burkitt 1996; Burkitt et al. 2000; Nunez 1995; Silberstein 1995a), providing additional support for the global theory.

Katznelson's solution for brain waves in a spherical shell (Katznelson 1981; 1982) and **Ingber**'s studies of effects of long range interactions on his statistical theory (Ingber 1982; Ingber & Nunez 1990) acknowledged the importance of delays in axon propagation. However, every other neocortical dynamic theory (of which I am aware) published before Jirsa and Haken (1996; 1997) and Robinson et al. (1997) either omitted cortico-cortical interactions or assumed infinite propagation speeds. For example, Wilson and Cowan's seminal paper (1973) was generally sophisticated in both mathematics and physiology. However, they were evidently unaware of both the numerical dominance of human cortico-cortical fibers (compared to thalomocortical fibers) and the importance of finite axon propagation speeds, reflecting the state of neuroscience at the time. We now know that anterior/posterior delays along cortico-cortical axons can be 20–30 msec or longer. Neglect of these delays by EEG theory is apparently justified only if cortico-cortical synapses are sufficiently small in number and/or strength, as suggested by **Wright.** Again, I emphasize the large potential differences in cortico-cortical coupling between human and lower mammalian brains.

R3.5. Artificial neural networks: Science or computer games? I mean this provocative subtitle to apply to extra-physiological models of "brains," not genuine neural systems or applications to computer design where they are more appropriate. **Mayer-Kress** shows spatial patterns produced by an artificial McCulloch-Pitts neural network. His Figure 2 labels nodes in the network as "electrodes," implying some imaginary connection to experiment. I don't doubt that such artificial networks can produce interesting dynamics, for example, coherent activity and relations between temporal frequency and spatial wavelength shown in Figure 1. But what experiment does he have in mind, for example, what is the size and location of the imagined electrode needed to measure such activity (if any)? Some physicists and many mathematicians appear to regard such issues

as peripheral to theory. I suggest they are central. Just to mention one issue, all electrodes spatially filter experimental data, either because of their non-zero size or because of volume conduction and physical separation in the case of scalp electrodes, as discussed in section 4.2. Any genuine experimental prediction must depend partly on this filtering.

Because measured brain dynamics is clearly very scale-dependent (as observed and anticipated by genuine physiological theory), perhaps **Mayer-Kress**'s network can be modified by interpreting individual units as macrocolumns rather than neurons, with suitable modifications of both units and connections between units. **Ingber** (1992) has published one approach to this neural net scaling issue. When such scale changes are implemented in theory, it must be remembered that interconnection density is very scale dependent as the brain's hierarchy is crossed from neuron to minicolumn to cortico-cortical column to macrocolumn to lobe (Nunez 1995).

I am more optimistic about networks that attempt to mimic the genuine physiology/anatomy of specific brain structures and address questions of interscale interactions, for example, the models of olfactory cortex and hippocampus discussed by **Liljenström** or the early visual system model (Lumer et al. 1997) cited by **Habeck & Srinivasan.** Also noted is the mesoscopic model of **Freeman** (and several colleagues over the years) of the olfactory system that is closely related to experiments carried out at smaller scales. I try to keep an open mind about artificial neural networks, but point to the following issues.

Suppose an artificial neural net contains a few hundred to a few million model neurons, corresponding roughly to neural tissue at minicolumn to macrocolumn scales. For purpose of argument, suppose further that the model neurons accurately represent genuine neurons (a generous assumption). Then one can imagine such networks making predictions of experiments with small intracranial electrodes. However, at least two serious problems are evident if such networks are to model neocortical tissue. First, network predictions apply only to autonomous tissue, which is hard to justify in genuine brains. Verifying such networks with neural tissue provides experimentalists with a difficult job, for example, isolating tissue mass from synaptic input while maintaining blood supply. The next problem is more fundamental. A network of N neurons must contain at least $N(N-1)/2$ connection parameters (although many may be zero in a sparse network). Unless such parameters are aligned with genuine physiology, experimental predictions may not mean much. Perhaps many net connections can be eliminated through application of stochastic algorithms, but the number of remaining parameters may still be large.

R4. Summary: Rabbits, foxes, chaos, and the unbinding problem

Ecological system models are interesting to mathematicians and dynamical scientists. I often introduce them in biomedical engineering classes because they provide convenient, easily understood analogs to engineering and physiological systems. Simple predator-prey equations can yield point, limit cycle, and chaotic attractors. However, connecting mathematical ecology to genuine experimental data has proven far more difficult. It is easy to see why. Rabbits reproduce and provide meals for foxes; plausible equations are easily derived and solved. But rabbit-fox systems are not isolated from their environment. Each external influence requires new parameters that must be determined experimentally, additional coupled equations, or both. Where should we truncate the potentially large set of equations containing a myriad of unknown parameters? This is a central issue for modeling complex systems. For example, the three Lorenz equations (1963) that ignited the modern science of chaos were obtained by extreme truncation of an infinite set of coupled equations. Lorenz presented them for their interesting chaotic properties; he was well aware that they are not able to model accurately the genuine fluid system that spawned them (Nunez 1995; Tabor 1989). Suppose chaos is discovered in some model system represented by a truncated system of equations. How important is this chaos to macroscopic measurements made on the genuine system with unknown external influence? I suspect that for many systems, such low-dimensional chaos is of no practical consequence at all, as suggested by models of simple mechanical systems with added noise (Ingber et al. 1996) or deterministic global (top down) influence (Nunez & Srinivasan 1993; Srinivasan & Nunez 1993).

Models of brain dynamics face the same problem of system autonomy. From a strictly dynamical viewpoint, there is no brain "binding problem." Rather, there is the "unbinding problem." One mm^3 of cortical tissue contains more than 1 km of axon length providing for very dense intracortical interactions at sub-mm to cm scales. Human neocortex is also interconnected by 10^{10} cortico-cortical fibers so that any two cortical neurons are separated by no more than two or three synapses (Braitenberg & Schüz 1991). Yes, cortico-cortical fibers exhibit connection specificity at mm scales so that tissue mass X may not connect directly to tissue mass Y, as emphasized in anatomical/physiological publications. But X is connected to some other neural mass Z, which, in turn, connects to Y. So generally, we should expect interactions between X and Y whether or not they are directly connected. For me, it is remarkable that portions of neocortical tissue are able to preserve (e.g., by lateral inhibition) some measure of autonomy within this highly interconnected environment.

Classical statistical mechanics, developed largely in the nineteenth century by J. Willard Gibbs (Tolman 1938), models complex systems close to equilibrium. The many dependent variables (e.g., gas molecules, species populations, etc.) in complex systems are treated stochastically. Equations for the dependent variables are replaced with a single equation (Liouville's theorem) for a probability density function that describes evolution of the state of the system with time (Haken 1983; Nunez 1995). For example, at any given time, the probability density function might yield the (joint) probability that rabbit and fox populations fall within specified ranges. Classical statistical mechanics represents one of history's foremost intellectual achievements. It forges connections between microscopic variables (positions and velocities of gas molecules) and macroscopic measurements (temperature, pressure). It provides foundation for modern methods that treat complex systems far from equilibrium. Several colleagues, bemoaning publication of vapid computer simulations, have remarked how fortunate we are that Gibbs had no option to develop computer simulations of interacting molecules.

Several theoretical approaches to the brain "unbinding

problem" are evident. One is application of modern methods of statistical mechanics, developed to treat open systems far from equilibrium (Graham 1978; Haken 1983; Ma 1976; Prigogine & Stengers 1984). Modern methods treat unknown external influences as added noise (transforming Liouville equation to Fokker-Planck equations). In addition, spatial scales are crossed using coarse-grained probability density functions of macroscopic variables. In a metaphorical ecological system consisting of many plants and animals, we might replace probability functions for species by probability functions for families, for example. This is essentially the approach (bottom up) to neocortical dynamics developed by **Ingber** over the past 20 years. He derives mesoscopic probability density functions of neural firing patterns from microscopic variables. Ingber has also applied these same general methods to nuclear physics, social systems, optimization, and financial markets.

Another (bottom up) approach to brain dynamics is represented by **Freeman** and several colleagues, developed over the past 40 years. **Wright** and **Liley**'s earlier publications are in this same general category, although later work (Liley 1997; Liley et al. 1999; Robinson et al. 1997; 1998a; 1998b) has moved in the direction of field theory. Freeman's current mesoscopic model of the olfactory system consists of about 100 coupled, first order equations. In my view, the most substantial virtues of this work are:

1. The model was partly checked by recording action and dendritic potentials at many locations within the bulb.

2. The current mesoscopic model of the olfactory system (a "KIII set") was constructed (bottom up) from physiological experiments on smaller tissues and simpler subsystem models ("KO, KI, etc. sets"). This work included cutting the lateral olfactory tract, thereby isolating the olfactory bulb from olfactory cortex. This is possible because input and output fibers enter each side of the bulb, as opposed to mixed input/output from the underside of neocortex.

The relative isolation of the olfactory system appears to provide important justification for approximating it as an isolated system (with sensory input), although I doubt this issue is fully settled.

The third approach is that of (top down) macroscopic field theory, discussed in the target article and by **Daffertshofer et al., Liley,** and **Jirsa & Kelso.** The three approaches have substantial overlap as suggested by Figure R1. The issues of autonomy and model overlap can be described in the context of an imagined perfect model of the human visual system, say LGN, primary visual cortex, and perhaps a few secondary cortical regions. Given known visual input, how well can this system be expected to predict the spatial-temporal properties of evoked scalp potentials? My guess is that the putative model might accurately predict transient evoked potentials within a few 10s of msec of the stimulus. But, at some later times the effects of feedback from cortical (and other) regions outside the visual system (interaction F-A of Fig. R1) might progressively degrade accuracy until recorded potentials had no more connection to input. I conjecture that this (endogenous) extra-visual system influence might be much more important in humans than in lower mammals, partly as a result of higher density of cortico-cortical fibers.

For steady state evoked potentials (SSVEP), "perfect" model accuracy might be a sensitive function of driving frequency. From the perspective of a visual system with "regional resonances" (Silberstein 1995a) and neocortical global resonances, we might expect substantial extra-visual system influence at global resonant frequencies, as emphasized by **Andrew.** But, such external influence on the visual system might be small when SSVEP frequencies match (regional) resonance frequencies of the visual system, but fail to match global resonance frequencies. This conjecture follows from the idea of inefficient coupling between regional and global dynamics when corresponding resonant frequencies fail to match. The conjecture is subject to experimental tests. We may, in fact, have some direct evidence to support this idea since propagation of visual input across the scalp to frontal cortex is robust near alpha frequencies, but appears (in preliminary studies) to be much less predominant at gamma frequencies.

In summary, each approach to dynamic modeling has its own regions where experimental connections are possible. Top down models may suffer from superficial treatment of local and regional processes, for example, cell assemblies. Bottom up models may neglect critical global influences and be difficult to connect to spatially filtered scalp data. To overcome these barriers, future studies should identify robust relations between disparate dependent variables derived by different theories and modify theories to forge new experimental connections. New cycles of theory and experiment should occupy brain scientists productively into the foreseeable future.

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Letters "a" and "r" appearing before authors' initials refer to target article and response, respectively

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