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Chapter 11

From synchronous neuronal discharges to subjective awareness?

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Abstract: For practical clinical purposes, as well as because of their deep philosophical implications, it becomes increasingly important to be aware of contemporary studies of the brain mechanisms that generate subjective experiences. Current research has progressed to the point where plausible theoretical proposals can be made about the neurophysiological and neurochemical processes which mediate perception and sustain subjective awareness. An adequate theory of consciousness must describe how information about the environment is encoded by the exogenous system, how memories are stored in the endogenous system and released appropriately for the present circumstances, how the exogenous and endogenous systems interact to produce perception, and explain how consciousness arises from that interaction. Evidence assembled from a variety of neuroscience areas, together with the invariant reversible electrophysiological changes observed with loss and return of consciousness in anesthesia as well as distinctive quantitative electroencephalographic profiles of various psychiatric disorders, provides an empirical foundation for this theory of consciousness. This evidence suggests the need for a paradigm shift to explain how the brain accomplishes the transformation from synchronous and distributed neuronal discharges to seamless global subjective awareness. This chapter undertakes to provide a detailed description and explanation of these complex processes by experimental evidence marshaled from a wide variety of sources.

Introduction

Beliefs about the basis of subjective human experience have slowly evolved, from mystical notions of the soul and a disembodied mind to acceptance of the proposal that consciousness must derive from neurobiological processes. After a long reluctance to confront the task, resulting first from the influence of religion and then from the dogmas of behaviorism, a widespread consensus that understanding consciousness is the most important problem of neuroscience is emerging. Not only philosophical interest motivates this endeavor. Adequate anesthesia demands suppression of movement, pain, and awareness during surgery, which anesthesiologists achieve by administering drugs to alter the interactions between brain regions. Among the millions who undergo general anesthesia every year, a substantial percentage manifest post-operative cognitive deficit of unknown origin. Tens of thousands of persons suffer traumatic head injuries in vehicular accidents, and many remain with significant cognitive impoverishment or in long-lasting coma. Psychoactive drugs are administered to millions of patients every year by general practitioners compared to those by psychiatrists. Many of the cognitive and functional disturbances in patients thus medicated can be considered as disorders of consciousness, distorted in a manner which deviates

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consistently from a realistic interpretation of the past and the present, in terms of the patient's life experience, leading to maladaptive behaviors. The deviations may originate from the individual's genetic endowment or vulnerability, activation of episodic memories of traumatic experiences in the past, or some temporary neurochemical imbalances. Regardless of the genesis, their manifestation represents a deviation from the regulatory processes that enable the normal brain to achieve adaptive behavior and a comfortable, tranquil state for the individual.

A self-organizing system may define a "ground state" of the brain. Homeostatic regulation of the ground state is temporarily altered during general anesthesia, may be perturbed persistently in coma, and is often disturbed in psychiatric patients. Return of consciousness after general anesthesia is accompanied by restoration of regulation. Successful treatment of comatose patients and those with neurological and psychiatric disorders may be facilitated by correction of underlying disturbances of regulation. For these practical clinical purposes, as well as because of their deep philosophical implications, contemporary studies of the brain mechanisms that generate subjective experiences are increasingly important. Plausible explanations can be made about the neurophysiological and neurochemical processes that mediate perception, sustain subjective awareness, and create the phenomenon of consciousness. This chapter provides an overview of contemporary studies providing useful insights into these processes. It also presents a radical proposal to resolve the gap between the discrete processes of neuronal interaction and the global experience of consciousness, which is speculative in that it is based on inferences indirectly derived from the inadequacy of connectionist theories rather than upon direct evidence. The following overview provides a synopsis of the major conclusions:

(i) Attributes of complex stimuli are fractionated and projected by the thalamo-cortical relays of the sensory specific "exogenous system" to the basal dendrites of ensembles of pyramidal neurons throughout the cortex, and thus encoded as time series of nonrandom synchronization within dispersed cell assemblies rather than by discharges of dedicated cells. These fragments of sensations constitute islands of local negative entropy.

(ii) Collateral fibers from afferent sensory pathways project to the ascending reticular activating system from which they are distributed as time series of nonrandomly synchronized volleys that are propagated to structures in the limbic system, where they are encoded as episodic memories. Those representations of previous experiences most similar to the momentary present input, which have been stored in the limbic system, are simultaneously activated by associational mechanisms and readout as a time series of nonrandom discharges. This "endogenous" readout is propagated via the nonsensory specific nuclei of the diffuse projection system to the apical dendrites of the cortical sheet of pyramidal neurons.

(iii) Coincidence detection between the converging time series of inputs to basal somatic and apical dendritic synapses of dispersed pyramidal neurons causes enhanced excitability, converting those assemblies that are currently encoding fragments of sensation into fragments of perception, which further increases the local negative entropy. This coincidence integrates encoded sensory information with output of systems encoding expectations, memories, planned actions, interoceptive, affective, and motivational states.

(iv) Integration of these fragments is required to yield a global percept. Modulation of membranes by local field potentials (LFPs) facilitates discharge of excited cells as a coherent cortico-thalamic volley, followed by back-propagated high-frequency reverberating oscillations. Coherent interactions of these cortico-thalamo-limbic-cortical oscillations cause a state transition of the system into resonance, binding these fragments into global negative entropy that creates consciousness, producing a unified perception.

(v) LFP oscillations are homeostatically regulated, controlling local synchrony, regional interactions, and periodic sampling, and defining a "ground state" with maximum entropy. Activity corresponding to this ground state is the most probable in a normally functioning, healthy individual at rest with eyes closed but alert.

(vi) Perturbations of the homeostatic LFP regulatory system alter the normal regulated thresholds that define the ground state. Cyclic fluctuations in these thresholds occur with the diurnal rhythms of sleep. Deviations constituting negative entropy are consistently found during processing of sensory stimulation, cognitive activity, developmental, neurological and psychiatric disorders, seizures, sleep, substance use, coma, and general anesthesia. Shifts from the ground state can be induced by chemicals such as anesthetics or addicting substances and accompany many neurological and psychiatric disorders. Restoration of the normal ground state is accompanied by return of normal consciousness and adaptive behavior.

This theory of consciousness proposes that elements of consciousness are dispersed as negative entropy, within many cell assemblies. Consciousness requires that this dispersed statistically nonrandom activity be transformed into a seamless subjective experience. Connectionistic concepts are inadequate to explain this conversion. The integration of dispersed, local negative entropies into global negative entropy may produce consciousness, an inherent property of an electrical field resonating in a critical mass of coherently coupled cells.

Fractionation or "local negative entropy" and consciousness or "global negative entropy"

Understanding perception is propadeutic to an understanding of consciousness, since it specifies the content of consciousness. Evidence indicates that perception is compounded of a multimodal representation of momentary exteroceptive and interoceptive stimuli contributed from an "exogenous system" combined with a continuous contextual rendering derived from readout of relevant episodic and short term or working memories and associated emotional coloration contributed by an "endogenous system." Consideration of this evidence has led some to the apt description of consciousness as perception of the remembered present (Edelman, 2001). The "exogenous system" processes information about each sensory modality, continuously fractionating incoming complex, multimodal signals into distinct features that are processed separately. Feature extractors or analyzers exist within multiple anatomically dispersed brain regions, each containing large neuronal networks relatively specialized for extracting distinct attributes of complex stimuli or representing selective aspects of recent or episodic memories. These fragmented multimodal attributes are recombined and placed into the context of past experience to construct perceptions that are the momentary, dynamically changing content of consciousness. This dispersed local analytic information is constantly reintegrated globally by dynamic interactions among regions. For this synthesis to achieve a reliable assessment of reality, certain errors must be avoided. Neurons are unreliable reporters. Neural activity representing information useful for adaptive response to the momentary environment, or "signal," must automatically be segregated from spontaneous neural activity, or "noise." Failure of a "dedicated" cell in a feature detector to respond due to refractoriness should not result in failure of the system to detect the corresponding attribute. Persistent after effects and self-sustained reverberatory activity should be suppressed. Contributions from neuronal assemblies that represent an attribute absent from the exogenous input must be excluded. It sometimes might be advantageous to use a subset of cues to complete the encoding of important but complex stimuli that have only partially been detected. It would be advantageous to automatically attach a valence to the encoded stimuli that reflected their importance. Failure to avoid such errors may result in seizure activity, inappropriate behavior, misperceptions, delusions, or other psychiatric symptoms. How the brain reassembles the fractionated sensory elements from dispersed populations into a global percept, while complying with these requirements, constitutes the "binding problem." How this representation of essentially statistical information is transformed into a personal subjective experience is the problem of consciousness.

This theory proposes that homeostatically regulated thresholds exist in every neuronal population, defining the baseline levels of random synchronization of firing in the ensemble that reflect transactions within the local neural network and inputs from exteroceptors and other brain regions. A local 'ground state' of maximum entropy can be defined as the absence of information or perfect predictability. The regulated thresholds define the range of fluctuation that is most probable in each brain region, within the normal distribution of the resting power spectra of local field potentials and the cross-spectra of interactions between regions. Such power spectra or cross-spectra are mathematical descriptions of the average frequency composition of a time series of voltages, or synchronized deviations from the randomness in spatiotemporal discharge patterns. A temporal sequence of synchronized activation or inhibition of some significant proportion of the cells in any brain region, deviating from the mean values of the distributions that define the ground state, is the neural activity of informational value. Complex, multimodal environmental inputs cause nonrandom, temporal patterns of synchronized activity in extensive networks that deviate from the regulated thresholds, establishing spatially dispersed states of local negative entropy. Evaluation of such spatially dispersed statistical representations by any cell or set of cells so as to uniquely identify the complex inputs from the environment cannot plausibly be envisaged, let alone the transformation of such statistical description into subjective experience by processes restricted to discrete synaptic transactions in dedicated cellular networks. The difficulty of accounting for this transformation has been termed the "explanatory gap" (Levine, 1983). As a solution to this quandary, we have proposed that consciousness may emerge from global negative entropy, integrated across anatomically dispersed neuronal ensembles that are nonrandomly active and electrically coherent in spite of spatial separation, and is a property of an electrical field of information resonating in a critical mass of brain regions (John et al., 2001; John, 2002, 2003, 2004).

Local field potentials (LFPs) are the envelope of the time series of synchronization in ensembles

In parallel with the activity of neural elements, voltage oscillations of LFPs can be observed within the volume of the brain. Like the LFPs, the electroencephalogram (EEG) is the time series of synchronized activity in huge neural ensembles in the vicinity of the recording site. The voltage waves and coherences arise from synchronized excitatory and inhibitory post-synaptic potentials produced by transactions between elements within a local region as well as from interactions among regions, while neuronal discharge is determined by influences impinging upon a single element. These two aspects of brain activity, discrete unit discharges, and potential waves are intrinsic to the principles by which the brain operates. This article proposes specific processes by which slow wave oscillations (1) contribute to the construction and identification of meaningful stimulus attributes from non-random synchrony of neural discharges caused by afferent inputs producing sensations and (2) enable the brain to bind these fragments into meaningful percepts which enter subjective awareness of the individual.

Since single neurons respond erratically, the discharge of an individual neuron does not provide reliable or interpretable information. Then, a question arises: where is the information? Were neuronal activity in a brain region random, the unit discharges would be distributed evenly throughout time, and a macroelectrode recording would be essentially isopotential. A certain level of "self-organizing" synchronization, or coherence, occurs spontaneously among CNS neurons and has also been observed to take place in stimulations of neural tissue in which the elements are weakly coupled (Abeles et al., 1994). As a consequence, the voltages which are recorded from these large neural aggregates approach zero only in slabs of cortical tissue surgically isolated from the rest of the brain (Burns, 1968). Oscillations of LFPs or evoked potentials (EPs) reflect nonrandom neural activity (Fox and O'Brien, 1965). When brain voltages recorded from some brain region depart significantly from the baseline, the local neuronal activity is synchronized or "nonrandom," indicating transactions among brain regions or regional involvement in processing exteroceptive or interoceptive information.

LFPs and multiple unit activity (MUA) are closely related, with multiple unit activity increasing when LFPs are negative. Multiple unit activity and LFPs can be entrained by visual stimuli in the delta, theta, alpha, beta, and gamma ranges (Rager and Singer, 1998). Synchronization is more precise with oscillatory modulation in the beta and gamma range (Herculano-Houzel et al., 1999). Synchronized neural activity in multiple ensembles, rather than the local discharge of dedicated neurons, integrates dispersed fragments of sensation and may be the basis of perception (Nicolelis et al., 1995). fMRI results suggest that recurrent loops across multiple brain areas lead to resonance, which is the neural correlate of conscious vision (Goebel et al. 2001).

Basis vectors of the brain, the ground state, and global negative entropy

Power Spectra

Striking regularities, which may reflect action of a genetically specified homeostatic system common to all healthy human beings, have been found by quantitative analysis of the EEG (QEEG). The power spectrum of the QEEG from every cortical region changes predictably as a function of age in healthy, normally functioning individuals in a resting but alert state (Matousek and Petersen, 1973; John et al., 1980, 1983, 1988). These highly predictable values of the normative age-appropriate power spectra and spatio-temporal organization of EEG patterns define the baseline or "ground state" of brain activity. Under resting conditions, EEG spectra remain within the variance defined by their distributions in normal reference groups. Normative values have been established from age 1 to 95 in large normative studies for numerous parameters, such as absolute and relative power, power ratios (symmetry) and synchrony (coherence) in different frequency bands, within every local region, and between pairs of regions within and across the hemispheres. The specificity and independence from ethnic factors of these descriptors have been established in cross-cultural replications in Barbados, China, Cuba, Germany, Hungary, Japan, Korea, Mexico, Netherlands, Sweden, USA and Venezuela (John and Prichep, 1993). Like the electrocardiogram, these rhythms display extremely high test-retest reliability within the healthy individual across intervals of hours, days, or even years (Kondacs and Szabo, 1999) and have been demonstrated to be clinically sensitive (John and Prichep, 1993; Hughes and John, 1999). This stability, specificity, and sensitivity of the EEG in all healthy human beings from any ethnic background is due to dynamic regulation by complex homeostatic processes that we believe to reflect our common genetic heritage.

Multivariate descriptors

Lawful patterns of covariance of QEEG variables across the whole brain as well as among sets of brain regions have been quantified as Mahalanobis Distances (composite features with inter-correlations removed), which display similar stability and replicability across the life span (John and Prichep, 1993). These multivariate compressions display remarkable specificity and sensitivity to subtle brain dysfunctions (Jonkman et al., 1985). High levels of common mode resonance of the EEG exist over long-range cortical-cortical distances (John et al., 1990).

Spatial principal components

Spatial principal component analysis (SPCA) has been applied to EEGs from large groups of normally functioning individuals, to quantify statistically significant, independent spatiotemporal modes of neuronal interaction across the entire cortex as well as to classify distinctive brain actions of drugs (John et al., 1972). As few as five spatial principal components account for 90% of the variance of the EEG and reveal a high degree of true phase correlation. The complex electrical activity of the brain reflects interactions among a limited number of simultaneously active, well-regulated subsystems, each with its characteristic mode of oscillation and distinctive functional neuroanatomical organization (Duffy et al., 1992; John et al., 1997; Srinivasan, 1999).

Microstates

A variety of evidence, presented below, indicates that information processing in the brain occurs in discrete discontinuous microstates and sampling occurs at a specific rate that is similarly well regulated. Adaptive segmentation reveals that there are a limited number of microstate topographies and they correspond well to spatial principal component loadings (Koenig et al., 2002). Clearly, this regulation requires control of neurotransmitters.

Departures from ground state

Recently developed clinical QEEG instruments reliably monitor the depth of general anesthesia during surgery independent anesthesia. In individual patients, such instruments provide an index of the level of consciousness by continuous quantification of multivariate deviations of brain electrical activity from the ground state defined above independent particular anesthetics agents. The level of consciousness during anesthesia can be accurately predicted by the magnitude and direction of such multivariate deviations, independent of anesthetic agents. When baseline values are restored, consciousness returns (Prichep et al., 2000; John et al., 2001). A wide variety of QEEG and EP monitors of effects of anesthetics on brain activity confirm the high sensitivity of these descriptors (John and Prichep, 2005).

Deficiencies or excesses of any neurotransmitter should produce marked departure from the homeostatically regulated normative EEG spectrum. In fact, consistent profiles of deviation from values predicted by normative databases have been replicably found in large groups of psychiatric patients in conditions such as attention deficit disorder, dementia, head injury, mood disorders, obsessive compulsive disorder, schizophrenia, and a number of other behavioral, developmental, and cognitive disorders (Prichep and John, 1992; Alper et al., 1993), as well as in groups of patients undergoing general anesthesia. The patterns of these deviant values are so distinctive that accurate, replicable statistical classification of patients into different DSM IV diagnostic categories has been accomplished (Prichep and John, 1992; Alper et al., 1993; John and Prichep, 1993; Hughes and John, 1999; John et al., 2001). Further, deviations induced in normally functioning individuals by drugs that are clinically effective for a particular disorder, are opposite from the distinctive deviations found in unmedicated patients with the corresponding disorder, and successful treatment of such patients restores the QEEG to normative values (Saletu et al., 2000). Such observations validate the conclusion that baseline LFP spectra and patterns of covariance are functionally relevant and clinically useful manifestations of processes relevant to consciousness and subjective experience.

Global negative entropy

These normative baselines are considered to be basis vectors describing genetically determined modes of brain electrical organization, or basic ‘‘traits,’’ whose set points determine the origin of a multidimensional signal space. The brain is a self-organizing system that conforms to these genetic constraints. The electrical ‘‘ground state’’ of the brain is defined as a hypersphere around this origin, the surface of which is defined by the variance of the normally functioning human population. Regions within this hypersphere represent a region of maximum entropy in which the range of magnitudes of interactions among functional brain systems can be predicted. Subjectively, we habituate to these states and, therefore, we treat such activity as if it contains no information. The state of the brain can be represented as a ‘‘brain state vector’’ in this multivariate signal space. Excursions of the brain state vector that extend outside the boundaries of this hypersphere constitute negative entropy. Phasic modulations of the fundamental modes reflect the present, momentary sensory, cognitive, and motor states of the individual, as well as transient alterations of consciousness. Tonic or sustained departures from these modes can be considered as deviant or pathophysiological, abundant evidence for which was cited above. Overall momentary deviations from these fundamental modes of synchronization, within and among brain regions, are how information is represented in the brain and are global negative entropy, the content of consciousness.

Origins and functional relevance of rhythmic EEG oscillations

EEG activity has conventionally been described in terms of a set of wide frequency bands, usually defined as delta (1.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz), beta (12.5–25 Hz), and gamma (25–50 Hz). Factor analysis EEG power spectra has found a similar factor structure, suggesting that different functional systems produce these rhythms. The observed predictability of the EEG power spectrum arises from regulation by anatomically complex homeostatic systems involving brainstem, thalamus, and cortex and utilizing all neurotransmitters (Llinas, 1988; Steriade et al., 1990; McCormick, 1992; McCormick, 2002). "Pacemaker neurons" throughout the thalamus interact with the cortex and nucleus reticularis to oscillate synchronously in the alpha frequency range. Efferent projections of these oscillations modulate waves also generated by a dipole layer in widely distributed cortical centers, producing the dominant alpha rhythm. The nucleus reticularis can hyperpolarize the cell membranes of thalamic neurons, slowing this rhythm into the theta range, and diminishing sensory throughput to the cortex. Theta activity is also generated in the limbic system by pacemakers in the septal nuclei, which can be inhibited by entorhinal and hippocampal influences (Buzsaki, 2002). Delta activity is believed to originate in neurons in deep cortical layers and in the thalamus, normally inhibited by input from the ascending reticular activating system (ARAS) and nucleus basalis of Meynert. Delta activity may reflect hyperpolarization and inhibition of cortical neurons, resulting in dedifferentiation of neural activity. Activity in the beta band reflects cortico-cortical and thalamo-cortical transactions related to specific information processing. Gamma activity reflects cortico-thalamo-cortical and cortical-cortical reverberatory circuits, which may play an important role in perception (also see Ribary, this volume). This activity is the topic of intense contemporary investigation, some of which will be discussed below. Sleep-wake cycles depend on interactions involving the pontine and mesencephalic reticular formation, locus ceruleus, the raphe nuclei, thalamic nuclei, and the nucleus of Meynert. As an oversimplification, the neurons of the thalamus manifest two intrinsic states: When hyperpolarized to a certain level, they enter a bursting mode in which they do not relay information to the cortex and other brain regions, and sleep ensues. When in this state, the EEG manifests large delta waves, perhaps reflecting the release of cortical neurons mentioned above, normally inhibited by the influences of the ARAS. For wakefulness to take place, the thalamo-cortical neurons must be restored to a state in which throughput of afferent sensory information to the cortex is again possible. This occurs by cholinergic influences of the ARAS and the nucleus of Meynert, a process that is described below in further detail.

EEG regulation depends upon this extensive neuroanatomical homeostatic system. Structures in this system play an important role in a wide variety of behavioral functions. Thus, behavioral implications are inherent in any detailed evaluation of disturbances from this homeostatic regulation, whether transient as in anesthesia, persistent as in coma, or tonic as in developmental and psychiatric disorders. Major elements of this system, neurotransmitters mediating their interactions and their putative behavioral contributions, are schematized below in Fig. 1.

The following explanation is an oversimplification for heuristic purposes. Assume that a subject is drowsy, with an EEG dominated by slow waves, perhaps in the theta frequency range, indicating dedifferentiation and increased synchrony of cortical neurons disengaged from information processing. This slowing of the alpha rhythm arises from hyperpolarization of the alpha pacemakers, reflecting GABAergic inhibition of thalamic pacemakers by the nucleus reticularis that can be initiated by glutaminergic influences from the cortex.

Activation of the mesencephalic reticular formation by altered environmental stimuli results in inhibition of the nucleus reticularis by cholinergic and serotonergic mediation via the ARAS. This inhibition by the ARAS releases the thalamic cells from inhibition by the nucleus reticularis, and flow of information through the thalamus to the cortex is facilitated. The dominant activity of the EEG becomes more rapid, with return of alpha and higher frequency beta activity, reflecting differentiation of

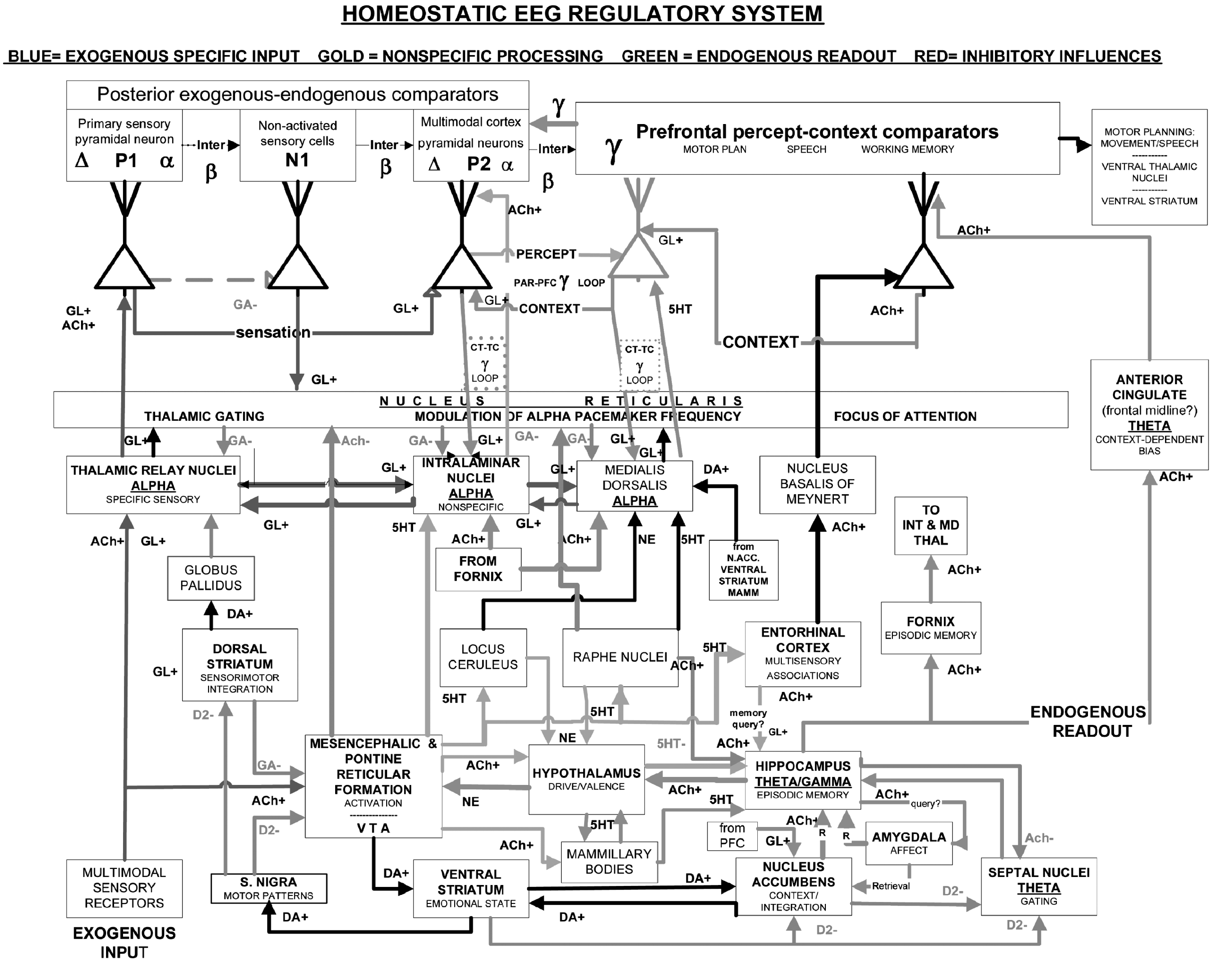

Fig. 1. Oversimplified scheme of the neuroanatomical structures and neurotransmitters comprising the homeostatic system that regulates the electrical rhythms of the brain. The diagram assigns putative roles in the generation of EEG oscillations in the delta, theta, alpha, beta, and gamma frequency ranges and to components of event related potentials. Elements of the exogenous system processing sensory specific inputs are encoded as blue, elements performing nonsensory specific processing are encoded as gold, inhibitory influences are encoded as red, and endogenous processing of readout from the memory system is encoded as green. The behavioral functions that various regions are believed to contribute to are tentatively indicated for some of these brain structures (see text for details). See Plate 11.1 in Colour Plate Section.

cortical neurons and resumption of cortical-cortical interactions. However, as an alternative result of cortical influences, dopaminergic striatal projections can inhibit the mesencephalic reticular formation, enabling differential inhibition of thalamic neurons by the nucleus reticularis to occur. These interactions between the ARAS, nucleus reticularis, and the thalamo-cortical relay neurons provide a mechanism whereby the brain dynamically filters and selects permissible stimuli to reach cortical centers. The flux of activity through these pathways constitutes a temporal pattern of synchronized input from the exogenous system to the axosomatic synapses of cortical pyramidal neurons in lower layers of the cortex.

In parallel, collateral pathways from the mesencephalic reticular formation enter the limbic system, which is intimately involved in the storage and retrieval of memories and contributes hedonic valence and emotional tone to the momentary brain state. Influences from the limbic system impinge upon the cortex via nonsensory specific pathways, and are the major input from the endogenous system to the apical dendrites of cortical sheet of pyramidal neurons, in upper layers of the cortex. An entorhinal–hippocampal–septal circuit is involved in the storage of episodic memories. Affective valences are attached to these episodic memories by associative linkages with other limbic regions. Septal–hippocampal interactions modulate the activity of circuits that generate EEG rhythms in the theta band projected to the cortex via the cingulate gyrus and the medialis dorsalis nucleus of the thalamus. When this circuit is activated, gamma oscillations arise in the hippocampus, become phase locked to the theta activity, and are projected to the cortex. Thus, cortical theta may reflect either underactivation of the ARAS or activation of affective states, memories, or related cognitive processes.

These reciprocal cortical–subcortical interactions can diminish, modulate, or actually block the flow of sensory information to the cortex and, together with the contribution from the limbic system of retrieved memories most relevant to the current environment, play an important role in focusing attention and can have a decisive influence on selective perception. This continuous interaction between the exogenous and endogenous systems constructs the "remembered present." In view of the dependence of both systems upon the delicate balance and relative abundance of multiple neurotransmitters, the relevance of these interactions to psychiatric disorders becomes self-evident.

The "microstate" — temporal parsing of brain fields

Although subjective time is experienced as continuous, "brain time" is in fact discontinuous, parsed into successive "perceptual frames" that define a "traveling moment of perception" (Allport, 1968; Efron, 1970). Sequential events within this brief time interval will be perceived as simultaneous, but are perceived as sequential if separated by a longer time. The duration of the perceptual frame in different sensory modalities is about 75–100 ms. The most familiar example of discontinuous sampling is the apparent stability of a movie viewed at about 64 frames per second. Examination of the momentary voltage maps on the scalp reveals a kaleidoscope with positive and negative areas on a field or "microstate," which persists briefly and changes continuously (Lehmann, 1971). Computerized classification of sequences of microstates in 500 normal subjects, aged 6–80 years, yielded the same topographic patterns in every individual, with 4–5 basic fields accounting for about 85% of the total spatiotemporal variance of the EEG with approximately equal prevalence. The mean microstate duration slowly decreased during childhood, stabilizing for healthy young adults at about 82 ± 4 ms (Koenig et al., 2002). The stability of these microstate topographies and their mean duration across much of the human life span, and their independence from ethnic factors, supports the suggestion of genetic regulation. The topographies of these momentary fields closely resemble those of the computed modes described in the spatial principal component studies cited above, indicating that the spatial principal component loadings are not a computational artifact. While these normative modes of regional interaction are statistically independent, they may overlap in time with different weightings. Different microstates seem to correlate with distinctive modes of ideation (Lehmann et al., 1998). The transition probabilities from one microstate to another are apparently altered during cognitive tasks (Pascual-Marqui et al., 1995) and in schizophrenia (Streletz et al., 2003).

The correspondence between the experimentally obtained durations of each subjective episode and the mean duration of microstates suggest that a microstate may reflect a "perceptual frame." Recent functional brain-imaging evidence has led to similar proposals that consciousness is discontinuous and is parsed into sequential episodes by synchronous thalamo-cortical activity (Llinas and Ribary, 1993; see Ribary, this volume). Asynchronous, multimodal (Zeki, 2000) sensory information may thereby be integrated into a global instant of conscious, apparently simultaneous multimodal experience.

Introspection reveals fading, but persistent recollection of the recent past that coexists in subjective continuity with the momentary present. A degree of constancy must persist across a sequence of perceptual frames, analogous to a moving window of time much longer than the momentary persistence of a microstate. Conversely, humans can make temporal discriminations much faster than these estimates of perceptual frame duration. The brain's sampling algorithm must somehow reconcile the 80 ms microstate duration with millisecond discriminations as well as persistent recent memories. This implies that afferent input in any modality is mediated in parallel by many multiplexed channels. Sequential events within a single such channel are combined into a corresponding perceptual frame. Subsets of channels must be integrated in receiving areas as a ''standing spatiotemporal wave'' of synchronized activity, like an interference pattern persisting through the integration period across serial microstates. Adaptive behavior requires that information in the immediate perceptual frame be continuously evaluated in the context of recent and episodic memories as well as evaluation of emotional and motivational valence relevant to the immediately preceding frame. Coincidence detectors of the differences in local non-randomness across successive microstates might provide a priority interrupt signal that serves to close the integration period arbitrarily, abruptly resetting the timing and opening a new frame.

The sustained persistence of microstates, as well as many behavioral measures, is difficult to reconcile with the brevity of neural transactions. Some reentrant or reverberatory brain process must sustain cortical transactions as a ''smoothed'' steady state, independent of the activity of individual neurons. Temporal extension of neural activity has been considered critical for binding, and NMDA has been proposed to play an essential role in this regard (Flohr, 1998). It may be relevant that EPSP–IPSP sequences ranging from 80 to 200 ms are omnipresent in mammalian forebrain neurons (Purpura, 1972), comparable to the long-persistent, post-synaptic depolarization displayed by NMDA receptors.

A comparator constructs perceptions from sensations

Not only is brain processing of information discontinuous, parsed into successive frames that are subjectively continuous, but the content of each frame appears to be constructed from interaction of two separate systems. The phenomenon of ''backward masking'' or metacontrast, the ability of a later sensory input to block perception of a prior event (Alpern, 1952), suggests that two different processes representing independent inputs to a comparator are required for conscious perception. This interaction is constantly ongoing and, like any good computer operating system, is transparent to the user, the self.

The existence of this combinatory process was initially inferred from the results of animal experiments, in which electrical activity was recorded from electrodes that were chronically implanted into multiple brain regions while the animals learned discriminative behaviors. These electrodes were implanted in pairs with closely spaced tips separated by 1 mm, enabling ''bipolar'' recordings from well-localized ensembles. The differential cues were ''tracer-conditioned stimuli'' consisting of auditory or visual stimuli presented at two different specified repetition rates. Appearance of EEG activity at the tracer-conditioned stimuli frequency in bipolar recordings in any region was interpreted as ''labeled response,'' indicating local participation in processing the tracer-conditioned stimuli and in mediating the behavior. When cats learned to discriminate among several visual and auditory differential-conditioned stimuli, marked changes were observed during training in the anatomical distributions of labeled activity. Initially, labeled activity appeared in only a few regions, but as learning progressed, labeled responses began to appear in wider regions of the brain. Anatomical spread of labeled activity gave direct insight into the establishment of extensive brain networks during learning. More unexpected was the observation that when errors were performed, labeled responses in some brain regions corresponded not to the physically presented tracer-conditioned stimuli, but rather to the frequency of the cue appropriate for the behavior that was actually performed. These results showed that the brain could store a distinctive temporal pattern of synchronized discharges in a representational system and release that pattern from memory on a subsequent occasion, when cues were misperceived.

Further experiments examined averaged event-related potential (ERP) waveshapes elicited by the tracer-conditioned stimuli. Initially, ERPs displayed only a primary positive component at early latencies. As the conditioned response was successfully established, a later primarily positive component appeared, implying that a second set of inputs was reaching those regions, but was manifested only in those trials in which appropriate behavior ensued. When differentiated behavioral responses became firmly established, requiring discrimination between visual or auditory tracer-conditioned stimuli at two different repetition rates, the ERP waveshapes elicited by the two tracer-conditioned stimuli developed distinctively different late components. Waveshapes acquired distinctive morphology to different cues and became similar in bipolar recordings from multiple nonsensory- and sensory-specific regions. It was proposed that perception, i.e., accurate interpretation of inputs from the environment, required coincidence detection between activity in sensory-specific and sensory-nonspecific systems (John, 1968).

Evidence of contributions to the comparator by a time series released from the hippocampus

A series of experiments were performed in such differentially conditioned cats, recording from multiple movable arrays of closely spaced microelectrodes chronically implanted in different brain regions, in addition to 24 fixed electrodes usually arranged in bipolar pairs sampling 12 other neuroanatomical structures that varied from animal to animal. Post-stimulus histograms were examined, showing the average temporal firing patterns of single and multiple units as well as LFPs and ERPs simultaneously elicited by different tracer-conditioned stimuli were examined. Recording simultaneously from all bipolar electrode pairs and moving the microelectrodes 0.1 mm every week, extensive brain regions were surveyed as different behaviors were performed to randomized presentations of the two tracer-conditioned stimuli. These experiments yielded some salient findings: (1) Although single tracer-conditioned stimuli presentations from several neurons in the same neighborhood elicited firing patterns that were highly variable and very different for each cell, after several hundred presentations almost identical post-stimulus histograms were obtained from every cell; (2) The post-stimulus histograms of single neurons during large numbers of tracer-conditioned stimuli presentations slowly converged to the post-stimulus histograms of multiple unit activity from the local neural ensemble that was rapidly elicited during a small number of presentations; (3) The ERPs recorded from any region were the envelope of the post-stimulus histograms from multiple units in that region, and remained very similar as the microelectrodes traversed through extensive intracerebral distances (3–4 mm); (4) Different distinctive ERP waveshapes and post-stimulus histograms contours were elicited by different behavioral cues, but the time series of nonrandom synchronization of neuronal firing was very similar in different brain regions; (5) The ERPs and post-stimulus histograms throughout such extensive traverses of the sensory-specific lateral geniculate body (a thalamo-cortical relay nucleus) and in the contralateral non-sensory-specific dorsal hippocampus displayed very similar post-stimulus histograms and ERP waveshapes; (6) The distinctive time series of neuronal discharges were present in the thalamo-cortical relay nucleus, but absent from hippocampus when correct responses failed to occur, and the thalamo-cortical relay nucleus and hippocampus displayed very disparate waveshapes in response to novel stimuli; and (7) Similar ERP waveshapes were recorded simultaneously from bipolar electrode derivations in many other brain regions (John and Morgades, 1969a, b; John, 1972).

These results and those of subsequent studies suggested that activity of an individual element was informational only insofar as it contributed to the population statistics. The time series of voltages comprising an EEG or ERP waveshape recorded from a brain region closely corresponded to the temporal pattern of synchronized firing among the neurons in the local ensemble. Storage of an episodic memory appeared to establish a system that displayed distinctive temporal patterns of nonrandom activity synchronized across widely dispersed regions of the sensory cortex appropriate to the modality of the cue, the corresponding thalamo-cortical relay nucleus, the intralaminar nuclei, the mesencephalic reticular formation, and the hippocampus. When novel stimuli at an intermediate rate midway between the two tracer frequencies were randomly interspersed into a series containing the two tracer-conditioned stimuli, "differential generalization" occurred and the animal performed one or more differentiated, conditioned responses. When differential generalization occurred, both the ERP waveshapes and post-stimulus histograms firing patterns elicited by the neutral cue corresponded to those distinctive for the tracer-conditioned stimuli appropriate for the behavior that was subsequently performed. The retrieval of a particular episodic memory seemed to be related to the readout of the corresponding distinctive time series of synchronized discharges from an endogenous system, concordant with a similar time series of synchronized discharges in the exogenous pathways. When ERP waveshapes recorded during behavioral errors of omission were subtracted from ERP waveshapes when behavioral response was correct, the resulting "difference waveshape" was essentially identical, with simultaneous peak latencies, in cortex, intralaminar nuclei, mesencephalic reticular formation, and hippocampus, but substantially delayed in the thalamo-cortical relay nucleus. The "difference waveshape" was interpreted to be the time series of the "readouts" released when a neutral stimulus elicited differential generalization. The delay in the corresponding thalamo-cortical relay nucleus (lateral geniculate body) was interpreted to mean that a memory system imposed a selective filter on the sensory nucleus processing incoming visual information (John et al., 1969, 1972, 1973; Ramos et al., 1976). Readout waveshapes in sensory-specific brain regions could be released by tracer stimuli of several sensory modalities; during differential generalization, the same cue distinctive ERP waveshapes were elicited in the medial geniculate body (a supposedly specific "auditory thalamo-cortical relay" nucleus) by novel visual as well as auditory tracer-conditioned stimuli (Thatcher and John, 1977).

These results led to an hypothesis that information was encoded statistically by the time series of nonrandomly synchronized neural activity within neuronal ensembles in various brain regions, rather than by synaptic changes in specific neurons in dedicated pathways. This idea was tested experimentally using electrical stimulation of brain regions to artificially produce nonrandom neuronal discharges. Independent of the region, it was shown that brain stimulation could achieve complete differential behavioral control, parametrically proportional to the amount of current delivered. Efficacy depended upon current strength rather than locus of stimulation, and regions differed only with respect to the amount of current required to achieve behavioral control (Kleinman and John, 1975). When two patterned pulse trains were delivered out of phase to arbitrarily selected pairs of brain regions, behaviors appropriate to the global temporal sum of the two electrical patterns were performed; simultaneous recordings suggested that integration between the two pulse trains took place in the intralaminar nuclei. Synchronized activation in arbitrarily selected pairs of brain regions was integrated and incorporated by the brain into a single cue that could guide adaptive behavior. Such arbitrarily placed pulses of electric current cannot be presumed to activate dedicated brain circuits selective for different behaviors.

Different geometric forms elicited different ERP waveshapes in humans, which displayed "size invariance;" the same basic waveshape was elicited by a geometric form independent of its size (John et al., 1967). When a series of numbers or letters were presented to human subjects, a vertical line elicited markedly different ERPs on the parietal cortex, when perceived as the letter "i" imbedded in a letter sequence or as the number "1" in a number sequence. However, ERPs from the visual cortex were identical under the two different conditions (Thatcher and John, 1977). Such findings suggest that information about a complex stimulus is represented by a distinctive spatiotemporal pattern of discharges coherent across a dispersed set of regions, which is encoded by a limbic memory mechanism that can reproduce the specific time series and propagate it effectively to other brain regions.

The chronometry of consciousness

Psychophysiological research has established that latencies of ERP components are correlated with information processing, and successive peaks correspond to (a) sensory activation, (b) detection of sensation, (c) perceptual identification of the information, (d) cognitive interpretation of the meaning of the input, (e) linguistic encoding of that concept, and (f) organization of adaptive reactions.

Sensory activation

In a cognitive auditory task, evoked gamma oscillations (40–45 Hz) phase-locked between vertex and posterior temporal scalp regions have been detected as early as 45 ms (Gurtubay et al., 2004). In recordings restricted to lower frequencies, the earliest components of scalp-recorded ERPs appear as a surface negativity (N1) at about 60–80 ms and a positivity (P1) at about 100 ms. These components have been localized by imaging methods to the primary cortical sensory receiving areas of the corresponding modalities. The later peaks are task-dependent and localization of their sources is still a subject of investigation (Gazzaniga et al., 2002).

Detection of sensation

In an attempt to establish the minimum duration of a stimulus for it to be detected, Libet (1973, 1982, 1985) studied the experiential consequences of series of electrical stimuli delivered directly into the brain of conscious human subjects, as well as other stimuli of varying duration. A debate still rages about the interpretations of those experiments, indicated by a special issue of a leading journal recently devoted to this topic (Baars et al., 2002). In brief, evidence suggests that although a person may not yet be aware of a stimulus, it has already been detected by the brain by about 80–100 ms. Intracerebral recordings from multiple sites suggest that initial visual processing may occur exclusively in the visual association cortex from approximately 90 to 130 ms (Halgren et al., 2002), an estimate concordant with the observed average duration of a microstate discussed above.

Mismatch negativity

A series of experiments (Naatanen et al., 1987, 1993, 2004) have established that as soon as a stimulus registers in the brain, a memory trace appears to be established that compares subsequent events to a representation of the previous event. This dynamic "echoic trace" appears to last for about 10 s (Sams et al., 1993). When the second element of a pair of sensory stimuli differs from the first, an enhancement of the ERP excursion from the second negativity (N2) to the second positivity (P2) takes place. The amplitude N2P2 is considered to be a measure of attention, referred to as mismatch-negativity (MMN). This process appears to be "preconscious." A critical set of experiments is relevant here (Libet et al., 1979). Essentially, a complex set of observations was interpreted to show that conscious awareness of a neural event is delayed approximately 500 ms after the onset of the stimulating event, but this awareness is referred backward in time relative to that onset. Cotterill (1997) proposed a neural circuit to account for this "backward referral" namely, the "vital triangle," which was further elaborated by Gehring and Knight (2000) in a study of human-error correction. These authors propose that a model of the original event is stored in the dorsolateral prefrontal cortex and is compared to the subsequent event. The existence of MMN suggests that a model of the recent past is continuously compared with the present and, together with other evidence, has led Edelman (2001) to refer to consciousness as "the remembered present."

Perceptual awareness

Numerous reports from intracerebral as well as scalp recordings from conscious human subjects indicate that a burst of phase-locked activity appears between the parietal and prefrontal cortex from about 180–230 ms after presentation of a stimulus to a subject engaged in performing a cognitive task (Desmedt and Tomberg, 1994; Tallon-Baudry et al., 1997; Tallon-Baudry, 2000; Varela, 2000). In posterior temporal regions, phase-locked as well as non-phase-locked gamma oscillations at about 200 ± 23 ms at 43 Hz have been observed by Gurtubay et al. (2004). Results in studies already cited above, in which intracerebral recordings were obtained from multiple implanted electrodes in occipital, parietal, Rolandic, and prefrontal sites during working memory tasks, suggested that the results of initial perceptual processing from approximately 90 to 130 ms after stimulus presentation were projected from the visual association cortex to prefrontal–parietal areas from approximately 130 to

280 ms (Halgren et al., 2002). On the basis of such findings, and from results cited in the next section, we propose that the neurophysiological processes that generate the second positive component of the ERP, P2, at about 200 ms represent the neural correlates of awareness.

Cognitive interpretation

The most studied electrophysiological correlate of human cognitive processes, the so-called P300 (Sutton et al., 1965; Donchin et al., 1986), has been investigated in thousands of experimental studies since first reported. This process is actually composed of an early event, referred to as P3A, that appears over anterior brain regions at about 225–250 ms and a later component, or P3B, that appears more prominently over posterior brain regions at about 300–350 ms, after an unexpected "oddball" or "target" event occurs in a series of common events. Intracerebral recordings have established that target-evoked P3-like components were most frequently recorded from medial temporal and prefrontal sites (Clarke et al., 1999). In an auditory oddball task, 33–45 Hz oscillations phase-locked between midline and frontal, central, and parietal regions in the 250–400 ms latency domain were found only after the target stimuli (Gurtubay et al., 2004).

Haig (2001) studied gamma synchrony in schizophrenic patients and normal controls using an oddball paradigm. This author found early- and late-gamma band phase synchrony (37–41 Hz) associated with the components N1 and P3 components elicited by the "target" stimuli. He proposed that gamma synchrony served to index the activity of integrative cognitive networks and suggested an impairment of brain integrative activity in schizophrenic illness. Spencer et al. (2003) have further studied neural synchronization in schizophrenic patients and matched normal controls discriminating between illusory square and control stimuli. These authors hypothesized that illusory square stimuli presumably synchronize neural mechanisms that support visual feature binding. They reported that compared to the matched controls, using complex wavelet analysis of the EEG, responses of the schizophrenic patients relative to the stimulus onset demonstrated (1) absence of the posterior component of the early visual gamma (30–100 Hz) response to the Gestalt stimuli, (2) abnormalities in the topography, latency, and frequency of the anterior component, (3) delayed onset of phase coherence changes, and (4) a pattern of interhemispheric coherence decreases in patients that replaced the pattern of anterior–posterior coherence increases displayed in the responses of control subjects. In a related subsequent study using a similar experimental paradigm, both healthy controls and schizophrenic patients displayed a gamma oscillation that was phase locked to the reaction time, presumed to reflect conscious perception of the stimulus (Spencer et al., 2004). Reaction time was slower in the patients, and further, the frequency of this oscillation was lower in patients than in the controls. This was interpreted to reflect a lower capacity of schizophrenic brains to support high-frequency oscillations. The degree of phase locking was correlated with visual hallucinations, thought disorder, and disorganization in the patients, as assessed by their performance on the positive and negative syndrome scale and separate scales for the assessment of positive and of negative symptoms. They interpreted their findings as an evidence that although the schizophrenics could perform the task, the interactions within the neuronal networks engaged in detection of the target were poorly organized and proceeded at a slower rate.

Semantic encoding

Evidence has accumulated confirming that a late negative component of ERPs, termed the N450, is correlated with the operations performed during semantic encoding (Kutas and Hillyard, 1980; Hillyard et al., 1985; Donchin et al., 1986; Hillyard and Mangun, 1987). This finding is mentioned here only for the sake of completeness, but does not directly pertain to the model being proposed.

In summary, this body of data suggests that short latency contributions to the ERP appear to arise from inherent sensory encoding processes, while later contributions to the ERP appear to arise from working memory and an experientially dependent memory system, and further suggests that perception requires the interaction between two systems, the exogenous sensory-specific system and the endogenous nonsensory-specific system.

Coincidence detection between exogenous and endogenous activity

Direct electrical stimulation, phase-locked to a peripheral stimulus to block the primary component of the ERP in cortical sensory receiving areas, had little effect on behavioral accuracy in trained cats, but greatly decreased performance when delayed to block the secondary nonsensory-specific component. Such results led to the proposal that coincidence at the cortical level between exogenous input of information about the environment and endogenous readout of relevant memories, detected by a neuronal comparator at the cortical level, identified the informational significance of the stimulus and was critical for perception (John, 1968). Similar hypotheses were proposed by other investigators (Sokolov, 1963). Subsequently, in awake neurosurgical patients, Libet (1973) stimulated the cortex electrically to coincide with the time of arrival of the nonsensory-specific, secondary component of the EP waveshape, usually present in the response of the somatosensory cortex that was evoked by a mild electrical shock to the wrist, and found that such time-locked brain stimulation could block subjective awareness of the wrist shock. Similar findings during brain surgery were reported shortly thereafter by Hassler (1979) who recorded the cortical evoked responses to mild wrist shock, and electrical shock to the sensory-specific ventrobasal nucleus and the non-sensory-specific nucleus centralis lateralis. The waveshape of the cortical response evoked by wrist shock consisted of an early component like the response to the ventrobasal nucleus alone and a later component like that to the nucleus centralis lateralis alone. Hassler then showed that the perception of wrist shocks by a patient could be blocked by later stimulation of the nucleus centralis lateralis in the thalamus, appropriately delayed to disrupt the late cortical response. In comatose patients, presence of early but not late components of multisensory evoked potentials has been used to stage severity of traumatic brain injury (Greenberg et al., 1981) (see Guerit this volume). The return of late evoked potential components is predictive of recovery from coma (Alter et al., 1990). Such data indicate that a comparator between exogenous sensory-specific and endogenous non-sensory-specific systems is essential for sensations to be perceived and is reflected in late ERP components.

Recent research has described a priming mechanism, whereby top-down influences have a priming effect on bottom-up signals. The electrical activity of the major output neurons of the cortex is strongly influenced by the laminar distributions of synaptic activity. Vertically aligned sheets of pyramidal neurons have basal axosomatic synapses in layers 4–5 in the neocortex, which receive exogenous inputs about complex environmental stimuli from sensory-specific afferent pathways. Apical axodendritic synapses of these pyramidal cells are in layer 1, and receive endogenous input via the non-sensory-specific projection system of the thalamus. Using direct electrical stimulation of pyramidal neurons with micropipettes, it has been demonstrated that pyramidal neurons act as comparators, detecting temporal coincidence of inputs to apical and basal synapses (Larkum, 1999). Direct stimulation of either apical or basal synaptic regions alone caused a sparse axonal discharge of the pyramidal neuron. However, concurrent stimuli delivered to both apical and basal regions within a brief interval elicited clearly enhanced firing of the neuron, with a back-propagated discharge in the gamma frequency range (~50 Hz). Thus, "top-down" axodendritic signals may modulate the saliency of a "bottom-up" axosomatic signal, changing the neuronal output from one or a few spikes into a burst (Siegel et al., 2000). It has been suggested that local rhythmic oscillations may cause subthreshold membrane fluctuations that play a possible contributory role in this process (Engel and Singer, 2000). The somadendrite interactions seem to depend critically upon frequencies of back-propagation between 20 and about 70 Hz, which is the beta and gamma range.

A more recent experiment extended this observation in a very important way, using voltage-sensitive dyes to achieve visualization of cellular activation in brain slices oriented so as to include regions of the thalamus and their projections to the cortex. Direct electrical stimulation by micropipettes placed upon a specific thalamic relay nucleus (ventrobasal thalamic nucleus) caused a visible moderate activation in layer 5 of the corresponding sensory cortex. Direct stimulation of a nonspecific nucleus of the diffuse projection system (nucleus centralis lateralis) caused a visible moderate activation in cortical layer 1. When the ventrobasal, nuclei and centralis lateralis were stimulated concurrently (i.e., when the simulated inputs from the exogenous and endogenous systems were coincident), cortico-thalamic activity was markedly enhanced, with a synchronized strong discharge back to the thalamic regions from where the stimuli had originated. Most important from the theoretical viewpoint advanced, when both regions were subjected to a train of pulses at 50 Hz, there was markedly stronger and more widely spread activation of the cortical regions containing Layers 1 and 5. A volley of cortico-thalamic activity at gamma frequency was transmitted to the thalamic regions where the stimulating pulses had been initially delivered, that was back-propagated to the cortical regions where coincidence had occurred. Thus, a reverberating cortico-thalamo-cortical loop was established (Llinas et al., 2002).

Such an evidence shows that influences from inputs to the upper levels can dominate the effects of feedforward sensory input arriving at basal levels. The precise effect of these interactions upon the firing patterns of the pyramidal neurons depends upon the duration and timing of the inputs to the different levels. The spatio-temporal configuration of corticofugal and cortico-cortical projections from this coincidence detection system may be strongly dependent upon the concordance between the two time series converging thereupon from the exogenous and endogenous systems. The critical time interval within which such interaction can occur probably varies as a function of the level of arousal, but the present results provide an initial approximation for the pertinent time intervals. While this neural enhancement process has thus far only been shown to operate at intervals on the order of tens of milliseconds, some findings (Flohr, 1998) suggest that delays on the order of a 100 ms or more involving the NMDA receptor may serve as a local binding mechanism for a combination of specific and nonspecific inputs. It must be emphasized that this synthesis of percepts from the interaction between the past and the present is mediated by a wide variety of neurotransmitters. Adaptive brain functions are critically dependent upon the availability of these substances and the processes that control their synthesis and metabolism, a topic beyond the scope of this article.

The evidence suggests the existence of a distributed coincidence detection system that is dispersed throughout the cortex. This system serves as a comparator between present multimodal, exogenous input from the environment and input from a ‘‘hedonic system,’’ which integrates endogenous activity reflecting present state, working memory, relevant episodic experience, motivation, and idiosyncratic individual values. The readout from the value system could arise from mechanisms generating experiential associations activated by collateral inputs from the just previous complex sensory stimuli. In a sense, this can be envisaged as a process enabling the past to ‘‘leapfrog’’ into the future. The hypothesized system of coincidence detectors might act as a filter, segregating random neural ‘‘noise’’ or unimportant elements of the complex stimuli from enhanced neural discharges that are thereby recognized as ‘‘signal’’ of informational value.

Contribution to perception of endogenous readout from memory

According to the model herein proposed, activity in a spatially dispersed sheet of neurons encoding attributes representing fragmented sensations would be enhanced, by coincidence between exogenous and endogenous inputs, to become fragments of perception. Outputs from this multimodal comparator converge as ongoing synchronous cortico-thalamo-cortical loops engaging regions of thalamus and cortex in coherent reverberation in the frequency range of the gamma rhythm (25–50 Hz), binding the distributed fragments into a unified percept. Such reverberation has been proposed by some to play an essential role in perception (Ribrary et al., 1991; Llinas and Ribary, 1993; Rodriguez et al., 1999; Varela, 2000; Lachaux et al., 2000; John et al., 2001; Llinas et al., 2002) and is hypothesized to be reflected by the induced long-distance synchronization of gamma oscillations (Pantev, 1995; Rodriguez et al., 1999; Varela, 2000). These ideas are consonant with the experimental evidence and theoretical proposals by Basar and his colleagues that oscillatory systems at various frequencies, but particularly in the gamma range, act as resonant communication systems through large populations of neurons (Basar et al., 2000).

Perception is an active process, modulated strongly by endogenous influences representing readout of the relevant recent and episodic past and present states, which place the immediate environmental input into context and enable the individual to generate predictions and expectations about future stimuli. This process is envisaged to occur continuously in multiplexed channels, such that the past and the present are inseparably merged in every update of the microstate or perceptual frame. An ERP can be conceptualized as an approximation of one cycle of the construction of a frame, extracted from one channel by repetitive phase-locked sampling of the continuously ongoing process.

The sequential steps in this process of construction of perception can be inferred from ERP research and is based upon our knowledge of "mental chronometry" summarized above. In Fig. 1, the endogenous retrieval system was schematized by the green arrows indicating interactions between particular brain regions. The exogenous–endogenous interactions that comprise this process are schematized in Fig. 2, and are hypothetically conceptualized to operate in the following manner:

$f(t_0)$. Inputs from multimodal sensory receptors activated by a complex environmental scene are encoded as time series, $f(t_0)$, of nonrandomly synchronized discharges in multiplexed parallel channels of afferent pathways, projecting to sensory-specific thalamo-cortical relay nuclei of every sensory modality.

$f(t)$. At time t, volleys of synchronized outputs from multimodal sensory-specific thalamo-cortical relay nuclei reencode $f(t_0)$, and are propagated as a modified time series, $f(t)$, of non-randomly synchronized exogenous inputs to the lower layers of the sheet of pyramidal neurons dispersed throughout cortical ensembles of feature detectors. Activation of basal synapses of pyramidal neurons in cortical Layer 5 causes the positive ERP component P1 with latency about 50 ms, reflecting initial registration of fragments of sensation. Corresponding synchronized volleys from the thalamo-cortical relay nuclei, and collateral pathways transmit the modified time series, $f(t)$, to the reticular formation in the brainstem where it is further modulated to reflect the arousal level.

$f(t+1)$. At time $t+1$, efferent volleys from sensory cortical regions instruct nucleus reticularis to modulate the thalamo-cortical relay neurons to focus attention by raising the threshold of those pathways that do not significantly contribute to the ascending volley of synchronous activity received at time t. These corticofugal volleys cause the ERP component N1 at about 130 ms. At the same time, the ARAS sends the time series $f(t+1)$ to the non-sensory-specific intralaminar and dorsomedial nuclei of the thalamus and to the raphe nucleus and structures of the limbic system.

$f(t+2)$. At time $t+2$, the intralaminar nuclei send the nonrandomly synchronized time series $f(t+2)$ modified by the ARAS to the apical synapses of cortical Layer 1, enhancing the excitability of pyramidal neurons in which coincidence detection occurs, thereby transforming fragments of sensation into islands of local negative entropy. This coincidence causes vigorous discharge causing the ERP component P2 at about 210 ms, accompanied by back-propagation of reverberatory cortico-thalamo-cortical gamma activity. The time series $f(t+2)$ is rapidly transmitted from posterior cortical regions and converges with $f(t+2)$ from the dorsomedial thalamic nucleus upon the prefrontal cortex, which in turn relays $f(t+2)$ to Layer 1 of the entorhinal cortex. Activity then propagates from area CA3 to CA1, hence to the amygdala, nucleus accumbens, septum, and hypothalamus. Memories originally encoded as time series of nonrandom synchrony and stored in the neural networks of this system are activated by associational processes modulated by emotions, providing the valence most relevant to the sensory pattern initially encoded by the exogenous system.

$f(t+3)$. At time $t+3$, the circuit of the time series $f(t+2)$ through the memory storage

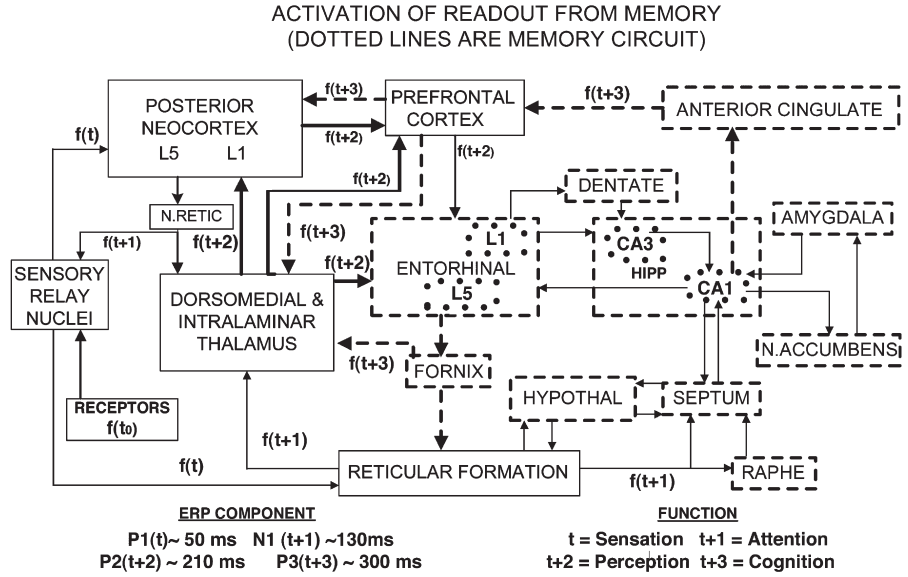

Fig. 2. Simplified scheme of the neurophysiological transactions resulting in the automatic readout of relevant memories from neuroanatomical structures of the endogenous memory storage and retrieval system, and their relation to major components of the event related potentials (see text for details).

networks of the limbic system is completed. The readout of the activated memory is transmitted as the time series $f(t+3)$ via a hippocampus-entorhinal-fornix circuit to the reticular formation and thalamus, and via the anterior cingulate gyrus to the prefrontal cortex, where coincidence detectors compare the time series $f(t+3)$ with time series previously received from posterior sensory regions and the thalamus. If the cortical coincidence detection indicates a discrepancy between time series from these two sources, a discharge produces the ERP component P3 at about 300 ms. The timing of the sequential perceptual frames may be reset whenever a discrepancy is noted.

The process just described must be envisaged as a sliding window of successive microstates, continuously matching the representation of the present in posterior regions of the cortex with representation of the recent past in the prefrontal cortex, together with episodic memories retrieved from the limbic system. As subsets of neurons in the coincidence detector network of the prefrontal cortex match the two time series, sustained gamma reverberations link posterior and prefrontal cortex together with cingulate-limbic and thalamus a resonant field that establishes global negative entropy, i.e., the content of consciousness.

Relevance of local field potentials to extraction of information

The central issue is how coherent, informational neuronal activity in multiple cortical areas is welded into a seamless unity that becomes aware of itself. We postulate that the ground state of local synchronization within neuronal ensembles, spontaneous interactions among cells in different brain regions, and periodic integration intervals is regulated intracerebrally by the same genetically specified homeostatic system that regulates the EEG. While the power spectrum of an artifact-free sample of resting EEG from a given scalp electrode reaches a stable and reproducible composition (stationarity) in as little as 8 s in the alert resting person, the power spectrum of LFPs around an intracerebral electrode in the cat can be considered stationary on the scale of 1 s (Bernasconi and Konig, 2001). Numerous reports in the literature document the relationship between amplitude and polarity of LFP in a domain and the probability of neural discharge from local ensembles (Fox and O'Brien, 1965; John and Morgades, 1969b; Ramos et al., 1976). The evidence of homeostatic regulation of the EEG and the ambient extracellular electrical field clearly implies homeostatic regulation of the probability of synchronized neural activity in the regions of the brain. Single and multiple unit recordings in brain slices *in vitro* and in anesthetized and unanesthetized, unrestrained animals reveal coherent discharges in diffusely distributed ensembles (John et al., 1990; Roelfsema et al., 1997; Brecht et al., 1998). Some of this coherence must be anatomically "hard-wired," while some reflects transient functional interactions and coupling.

Fast spontaneous oscillations in intrathalamic and thalamo-cortical networks may play a decisive role in binding. Synchronization of fast rhythms may be subserved by intralaminar neurons that fire rhythmic spike bursts in the gamma frequency range and have diffuse cortical projections (Steriade et al., 1991, 1993). Sensory stimulation increases synchrony (Castelo-Branco and Neuenschwander, 1998), and synchronized discharges of neurons in different brain regions may bind spatially dispersed representations of a multimodal stimulus into an integrated percept (Llinas, 1988; Gray et al., 1989; Kreiter and Singer, 1996; Llinas and Ribary, 1998). Functionally coherent cell assemblies may represent the constellation of features defining a particular perceptual object, with transient synchrony dependent upon state variables related to the EEG. Such coherence has been proposed as crucial for awareness and conscious processing, including attentional focusing, perceptual integration, and establishment of working memory (Singer, 2001; Engel and Singer, 2001). The signal to noise ratio for several multimodal attributes of a complex attended stimulus may be enhanced by higher order convergence upon a particular neuronal neighborhood (Sheinberg and Logothetio, 1997). Gamma oscillations facilitate coherence of neural activity within and between regions, and have been suggested as a necessary condition for the occurrence awareness stimuli (Llinas and Ribary, 1998; Engel and Singer, 2000). LFP fluctuations predicted response latency to visual stimuli, with negative LFPs associated with earlier responses and positive LFPs with later responses (Fries et al., 2001).

What might be the role of these ubiquitous potential oscillations? The neuronal population in any brain region displays a range of excitability at any moment, depending upon the recency and number of synaptic inputs that have affected their membrane potentials. A small fraction of cells are depolarized almost to the threshold for firing spontaneously and a small proportion are refractory after recent firing. The central limit theorem leads us to expect an overall gaussian distribution of excitability in the population of neurons as a whole. We hypothesize that a weak rhythmic modulation of membrane potentials, insufficient in itself to produce axonal discharges and perhaps arising from and distributed synchronously by the diffuse projection nuclei of the thalamus, is superimposed upon the neurons throughout the brain. As the oscillatory influences impinge, neurons should discharge whose state of membrane depolarization, and the modulatory depolarization exceeds the local firing threshold. At the other end of the excitability distribution, those neurons in a relatively refractory state while their normal resting membrane potential is being restored after a recent discharge should be further inhibited by the subsequent hyperpolarizing phase of the oscillations. The mean excitability of the ensemble should fluctuate at the frequency of the modulatory rhythm to an extent proportional to the depth of modulation. On the basis of a review of evidence relevant to the possibility of non-synaptic modulation of neuronal membranes by extracellular fields, Jefferys (1995) concluded that "In general, electrical field effects can mediate neuronal synchronization on a millisecond time scale." Weaver et al. (1998) computed the theoretical threshold for such effects as requiring a gradient of the order of 100 μV/mm. We have observed gradients of 100–200 μV/mm in intracerebral recordings from human patients.

The effect of this hypothetical rhythmic fluctuation of excitability should be to enhance the synchronization of neural firing within any local brain region. To the extent that if the same modulatory influence is imposed across the cortex, it should increase the level of coherence of non-random output across distant brain regions. If cell assemblies of feature detectors are dispersed throughout the cortex such that some subset of them encoded specific attributes of the afferent stimulus complex as "fragments of sensation," and if the hypothesized comparator network had achieved coincidence between exogenous and endogenous inputs to certain patches of cells thereby to identify "fragments of perception" and selectively increase their excitability, then the consequence of this rhythmic modulatory influence would be to facilitate a coherent corticofugal discharge converging upon the thalamus from many dispersed cortical detectors. These coherent cortico-thalamic volleys are proposed as the integrative process, which enables the brain to bind the spatially dispersed multimodal attributes into an integrated percept.

Abundant evidence has been presented, which establishes that there are distinctive power spectra for any cortical region, with a wide range of frequencies. These cortical rhythms reflect thalamo-cortical and cortico-cortical interactions, which may exert complex modulating influences upon local ensembles. It has been proposed that lower the frequency, the more remote the brain region from which the influence arises (von Stein and Sarnththeim, 2000; Bressler and Kelso, 2001). The observation that about 65% of the EEG is coherent across the cortex (John, 1990) suggests that the hypothesized binding process is actually mediated by a resonance or common mode interference pattern shared among a number of systems generating these rhythms. This proposal is reminiscent of the scansion mechanism suggested half a century ago (Pitts and McCulloch, 1947). It must also be considered that although the LFPs converge rapidly to a predictable power spectrum, on the short term these potentials can be considered as a random ambient noise. Recent studies have shown that the effect of ambient noise on a weakly interconnected network of weakly responsive elements is to synchronize them by stochastic resonance, a process that functions best at high frequencies (Allingham et al., 2004; Torok and Kish, 2004).

Zero-phase synchronization

It is possible (Engel and Singer, 2000) that zero phase lag plays a critical role in binding dispersed fragments of sensation into a coherent whole (König et al., 1995; Engel et al., 1997). Phase-locking of 40 Hz oscillations, with zero delay between the prefrontal and parietal human cortex, has been observed in scalp recordings during focused attention and conscious perception of recognized auditory or visual events. Using intracranial as well as scalp recordings in humans, the amplitude, long distance, and local synchronization of gamma activity have been studied during auditory, visual, and somatosensory stimulation and during cognitive or perceptual tasks (Desmedt and Tomberg, 1994; Tallon-Baudry et al., 1997; Tallon-Baudry, 2000; Varela, 2000). In each modality, a transient burst of phase-locked gamma (of varying frequencies) occurs, most prominently in the primary sensory cortex, about 100 ms after stimulus onset. About 230 ms after stimulus onset, there is a pattern of gamma oscillations synchronized between frontal and parietal cortical regions. The latency of 230 ms corresponds approximately to the latency of the so-called cognitive potential, P3A, prominently displayed in anterior regions of the human scalp. This gamma activity is induced by but not synchronized with stimulus onset, occurs only in trials when a figure or a word is perceived, and has been proposed as "the correlate of perception itself" (Pantev, 1995; Rodriguez et al., 1999). Such phase-locked synchrony between distant brain regions has been adduced as support for proposals that perception involves integration of many distinct, functionally specialized areas (Tallon-Baudry, 2000), and that the "self" may be a transient dynamic signature of a distributed array of many brain regions integrated by such coherence (Varela, 2000). This induced long-distance synchrony seems to be the equivalent in humans of the late component in animal EPs, described above, when stimuli acquire meaning (Galambos and Sheatz, 1962; John, 1972). The long distance between regions synchronized with zero-lag rules out volume conduction, which decays rapidly with distance between electrodes. It is possible that the apparent zero-lag arises from a common source of thalamo-cortical reverberations, but the alternative that it is evidence for a resonating field must also be considered.

Critical neuroanatomy of consciousness

Various strategies have been used to find anatomical structures or brain processes critical for consciousness, including lesioning, imaging, and pharmacological techniques. Recent proposals have included an extended reticulo-thalamo-cortical distributed network, the intralaminar nuclei of the thalamus, nucleus reticularis, anterior cingulate cortex, or hippocampus. Prolonged activity in some set of unique "awareness cells" sparsely distributed over many regions, or a pattern of activity among regions rather than within a particular brain region, have been proposed as the neural correlate of consciousness (Koch, 1998). A "Dynamic Core Hypothesis" has been proposed, constituting a set of spatially distributed and meta-stable thalamo-cortical elements, sustaining interactions that maintain unity in spite of constantly changing composition (Tononi and Edelman, 2000).

One approach to identify such a system is to determine whether a particular set of brain regions changes its state with the loss of consciousness due to the action of anesthetics. Using ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), cerebral metabolism was studied during propofol anesthesia (Alkire et al., 1998). At loss of consciousness, mean cerebral metabolic rate was globally reduced throughout the brain by 38%, relatively more in cortex than subcortex. Similar global quantitative results were found with isoflurane. In sedation, very similar but lesser global reduction was observed. It was initially concluded that loss of consciousness was not caused by changes within a specific circuit, but rather by a uniform reduction below a critical level in a distributed neural system. In a more recent study using $H_2^{15}O$-PET to measure dose-related changes in regional cerebral blood flow (rCBF) during sedation with midazolam, a similar global reduction of about 12% was found (Veselis et al., 2000). In addition, however, a discrete set of brain regions displayed a significantly more extreme reduction in cerebral blood flow. These regions included multiple areas in the prefrontal cortex, the superior frontal gyrus, anterior cingulate gyrus, parietal association areas, insula, and the thalamus (see Fiset, this volume; Alkire, this volume; for an extensive review of functional imaging in general anesthesia).

Routine surgical anesthesia offers a naturalistic environment where loss and return of consciousness can be studied in a systematic manner. In many such studies of anesthetic effects, quantitative features have been extracted from EEG power spectra (QEEG) and bispectra. Such variables have been repeatedly shown to be related to clinical signs or anesthetic endpoints (Sebel et al., 1997; Rampil, 1998; Veselis et al., 2000). Changes in the level of consciousness cause distinctive shifts from the EEG ground state. Using quantitative analysis of continuous EEG recordings collected during several hundred surgical procedures, we sought invariant reversible changes in brain electrical activity with loss and return of consciousness. Details of these studies are given elsewhere (Prichep et al., 2000; John et al., 2001). Two kinds of changes in brain activity were found, independent of anesthetic agents used: (1) At loss of consciousness, in all EEG frequency bands dramatic changes took place in coherence within and between the cerebral hemispheres. Rostral brain regions abruptly became functionally disconnected from posterior regions and the two hemispheres were functionally uncoupled (i.e., incoherent). Only in the beta and gamma bands is coherence restored upon return of consciousness. (2) At loss of consciousness, EEG power on each hemisphere became dominated by low frequencies and strongly anteriorized. Normal posterior power dominance was restored at return of consciousness. These changes were used to construct a multivariate algorithm to provide a quantitative index of the level of consciousness. This algorithm has been implemented in a clinical monitor of the depth of anesthesia (PSA 4000, Physiometrix, Inc., N. Billerica, MA). Three-dimensional source localization revealed that regions of the mesial orbital and dorsolateral prefrontal and frontal cortex, paracentral gyrus, anterior cingulate gyrus, amygdala, and basal ganglia invariably displayed profound reversible inhibition with loss and return of consciousness, independent of the anesthetic agents (Prichep et al., 2000; John et al., 2001). An overview of recent electrophysiological and brain imaging studies has provided the basis for a recently published comprehensive theory of anesthesia (John and Prichep, 2005).

An integrative theory of consciousness

This theory is largely based upon experimental evidence from many levels of neuroscientific inquiry, some cited but much not explicitly mentioned. However, I must concede that much of this formulation represents my speculations of "how things must be," in order for the brain to generate the sense of self that we all share and the abnormal behaviors we observe in clinical surroundings. Assertions that are considered as basic propositions of this theory are summarized below.

Apperception defines content of consciousness

A major hypothesis underlying this theory is that the content of consciousness is dominated by apperception. By apperception, we mean integration of momentary perception of the external and internal environment with the working and episodic memories activated by associative reactions to that perception. I contend that the conscious organism, and particularly the human being, is continuously interpreting awareness of the present in the context of both the recent and the remote past, to attribute "meaning" to the present events. A further major hypothesis of this theory is that information in the brain is not encoded by the firing of dedicated neurons in particular brain regions that represents specific stimulus attributes or features, but rather by distinctive temporal patterns of synchronized firing dispersed among many brain regions. Individual neurons can participate in numerous such temporal patterns.

Information is nonrandomness

Information establishes local negative entropy consisting of spatially distributed time series of synchronized activity in multimodal, sensory-specific systems (the "exogenous system"). Energy reaching the receptor surfaces of multiple sensory systems activates a barrage of neural activity that propagates through successive levels of afferent pathways to widely dispersed ensembles of cells responsive to particular aspects of the complex, multimodal environmental stimuli. In each brain region, this barrage impinges on populations of neurons with a range of excitability, with membrane potentials varying from hyperpolarization, refractory just after discharge, to relatively depolarization, just on the verge of discharge. Circulation of the input throughout local networks causes some responsive subsets of neurons distributed in these many brain regions to respond with a distinctive temporal pattern, producing a time series of synchronized neural discharges. Intrinsic excitability cycles modulate the reactivity of cell ensembles at frequencies in the range of gamma oscillations (35–50 Hz), selecting particular subsets of neurons in the receiving system that can discharge synchronously with this distinctive temporal pattern. This distributed, improbable synchrony constitutes fragments of sensation, which represent islands of local negative entropy, relative to a regulated ground state. These exogenous inputs are encoded as time series of synchronized firing in parallel, multiplexed channels within each sensory pathway, offset by 25 ms and sampled every 80 ms. The cyclic modulation of excitability produces multiplexed, parallel channels encoding the same information. However, this information is phase-shifted so that the temporal patterns of synchronized activity encoding information in the multiplexed channels are asynchronous, offset by some temporal delay on the order of 20 ms. Within each such channel, the length of the representational time series appears to be 80–100 ms.

Perception is discontinuous, parsed into momentary episodes or "perceptual frames"

This discontinuity has been demonstrated in every sensory modality using a variety of experimental psychophysical procedures. These include the so-called "backward masking" and "perceptual frame" phenomena. The experimentally determined duration of such episodes appears to be of the order of 80 ms, during which a representational time series unfolds. This "experiential chunk" may correspond to the episodic synchronization that has been shown by Freeman (2004) to occur among remote cortical regions every 80 ms, and to the "microstates" of stable field topography shown to have a mean duration of 80 ± 2 ms across the age range from 6 to 90 years; as described by Koenig and colleagues (2002).

"Hyperneuron" de-multiplexes afferent input

Circulating updated, multiplexed channels maintain the stable representation of environment as a spatiotemporal steady state in an anatomically dispersed hyperneuron. No single neuron or dedicated set of neurons can maintain the distinctive pattern of times series of synchronization across successive perceptual frames to mediate the apparent continuity of subjective experience or "awareness." Rather, the multiplexed parallel channels converge successively upon the sensory receiving ensembles. Interactions caused by the circulation of temporal patterns of asynchronous activity in neural networks within spatially extensive, dispersed populations of neurons establish a spatiotemporal interference pattern in each region that remains stable for extended periods of time, like a standing wave of covariance. This sustained spatiotemporal distribution of nonrandom synchronization, independent of the firing of any particular neurons, constitutes a "hyperneuron." A hyperneuron is a sustained, improbable spatiotemporal pattern of negative entropy.

"Endogenous system"

Episodic memories are stored in non-sensory-specific brain regions that encode distinctive time series of incoming activity and constitute an "Endogenous system." Collaterals from the multiplexed afferent sensory pathways enter the pontine and mesencephalic reticular formation, and the encoded representational time series of synchronized activation from the brainstem and polysensory cortical areas are distributed via the parahippocampal and entorhinal cortex into the limbic system. When such nonrandom activation by successive inputs persists for a sustained but brief period, associational or "contiguity" mechanisms link together a network of neurons distributed throughout regions including portions of the neocortex together with the amygdala, nucleus accumbens, hippocampus, hypothalamus, and septum, establishing a representational assembly that is sensitive or "tuned" to that distinctive spatiotemporal pattern of input. This tuning in the endogenous system is consolidated over a brief period into a molecular structure, perhaps protein specified via RNA within the neurons in the network, so that it will be preserved by synthetic mechanisms that renew that capability by replication that preserves the tuning even after the initial structure is replaced.

Readout of relevant memory – "context"

At any later time, if a sufficient portion of the activity of sensory exteroceptors and/or interoceptors in the exogenous system becomes nonrandomly synchronized, the tuned representational network in the endogenous system with most similar temporal pattern becomes activated and discharges a synchronized time series from the participating limbic regions, providing a context of emotional tone and motivational valence to the retrieved episodic memory. The readout from this system is a time series of synchronized discharges, reflected by oscillations in the gamma frequency range that become phase locked to waves recurring about every 200 ms, or in the theta frequency range, with essentially zero phase lag among cortical regions. Owing to the multiplexed nature of sustained exogenous inputs and the duration of the stored representational time series, patterns of retrieved outputs from this endogenous system persist for a sustained period, producing an interference pattern similar to that of the hyperneuron.

Coincidence detection by pyramidal neurons

When input from the exogenous system of a nonrandomly synchronous temporal pattern to the basal dendrites of the cortical sheet of pyramidal neurons coincides with a nonrandomly synchronous input from the endogenous system to the apical dendrites with the same temporal pattern, the excitability of a spatially dispersed network of pyramidal neurons is significantly enhanced. This process converts fragments of sensation into fragments of perception, increasing the level of local negative entropy.

"Ground state" of the brain is defined and regulated by a homeostatic system

A genetically determined homeostatic system regulates normal brain electrical activity, controlling interactions among brain regions as well as excitability within local regions. Due to this regulation, the mixture of frequencies in rhythmic oscillations in each brain region, the spatiotemporal principal components of the cross-spectra (which quantify the relationships among all brain regions across frequencies), and the parsing of these spatiotemporal patterns into discrete epochs of time can all be precisely defined, describing the basic processes maintaining the system in stable resting equilibrium. These homeostatically regulated baselines of inter- and intra-regional oscillatory brain electrical activity define the normative, hence most probable, spatiotemporal distribution of variances and covariances in brain electrical activity, the "ground state" of maximum entropy, that contains zero information.

Brain state vector

If the electrical activity of the brain is conceptualized as a "signal space," the complete set of normative QEEG data define the ground state as a "hypersphere," a region around the origin of an N-dimensional signal space that encompasses the variance of the normative descriptors of brain electrical activity. The measurements from any individual, after appropriate rescaling, can be described as a multidimensional Z-vector or "brain state vector" in that signal space; each dimension is scaled in standard deviations (SD) of the distribution of the corresponding variable. The brain state vector of a resting, healthy individual will lie within the hypersphere of radius $Z < 3.2$ SD along all dimensions around the origin of the multidimensional signal space. The brain state vector of any individual in any state can be depicted as a point somewhere in the signal space thus defined. The content of consciousness in the resting state (eyes closed) is fleeting ideas and thoughts causing transient fluctuations of the brain state vector that remain within the normative hypersphere.

Local field potentials acting on pyramidal neurons can produce coherent reverberations

In the short term, LFPs can be considered as random noise that has been shown to synchronize activity among weakly interconnected networks of weakly responsive elements. This effect of LFPs makes coherent the cortico-thalamic discharge of the distributed pyramidal neurons whose excitability has been enhanced by coincidence between exogenous and endogenous inputs. The synchronous discharge from these spatially distributed islands of local negative entropy results in a coherent reverberation of cortico-thalamo-cortical gamma activity. Findings of zero or near-zero phase lag between prefrontal and parietal cortex may be the snapshots of momentary cross-sectional glimpses of these synchronized time series.

Global negative entropy is the content of consciousness

Sustained reverberations of multiple cortico-thalamo-cortical circuits become coherent and phase-locking between them, perhaps facilitated by transmission across gap junctions, leads to resonance in the coherent network. This phenomenon can be considered as a "phase transition," reflecting an integrative process whereby dispersed fragments of perception are bound into a unified global percept, which is global negative entropy. The resonant network includes the prefrontal, parietal, and cingulate cortex as well as regions of the basal ganglia, limbic system, thalamus, and brain stem identified in the discussion of Fig. 2. These brain regions correspond well to those shown to be uncoupled in conditions associated with an absence of consciousness in studies of anesthesia (Alkire et al., 1998; Fiset et al., 1999; Veselis et al., 2000), (Fiset, this volume; Alkire, this volume) deep sleep (Portas et al., 2000) and coma (Laureys et al., 2000, 2002) as well as "absence" seizures (Pavone and Niedermeyer, 2000; Blumenfeld, this volume). This resonant field corresponds in many respects to the parietal-prefrontal system that some have proposed may be the residence of the "observing self" (Baars et al., 2003; Baars, this volume). I believe this theory supports and extends that suggestion. The global negative entropy of the brain encompasses all of the momentary information content of the entire system, as an "information field" that subsumes the parallel processing circuits that are simultaneously activated at a nonrandom level in the brain, and comprises the content of consciousness. For the purpose of this theoretical formulation, the global negative entropy of a resting healthy individual whose brain electrical activity is at the precise origin of the ground state is proposed to be at a maximum. In this hypothetical state, the brain contains no information so that consciousness is void of content. One might speculate that this state corresponds to what Buddhists term ''Nirvana.''

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