

Review

The neurophysics of consciousness

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Abstract

Consciousness combines information about attributes of the present multimodal sensory environment with relevant elements of the past. Information from each modality is continuously fractionated into distinct features, processed locally by different brain regions relatively specialized for extracting these disparate components and globally by interactions among these regions. Information is represented by levels of synchronization within neuronal populations and of coherence among multiple brain regions that deviate from random fluctuations. Significant deviations constitute local and global negative entropy, or information. Local field potentials reflect the degree of synchronization among the neurons of the local ensembles. Large-scale integration, or ‘binding’, is proposed to involve oscillations of local field potentials that play an important role in facilitating synchronization and coherence, assessed by neuronal coincidence detectors, and parsed into perceptual frames by cortico-thalamo-cortical loops. The most probable baseline levels of local synchrony, coherent interactions among brain regions, and frame durations have been quantitatively described in large studies of their age-appropriate normative distributions and are considered as an approximation to a conscious ‘ground state’. The level of consciousness during anesthesia can be accurately predicted by the magnitude and direction of reversible multivariate deviations from this ground state. An invariant set of changes takes place during anesthesia, independent of the particular anesthetic agent. Evidence from a variety of neuroscience areas supporting these propositions, together with the invariant reversible electrophysiological changes observed with loss and return of consciousness, are used to provide a foundation for this theory of consciousness. This paper illustrates the increasingly recognized need to consider global as well as local processes in the search for better explanations of how the brain accomplishes the transformation from synchronous and distributed neuronal discharges to seamless global subjective awareness. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Many serious researchers are currently proposing ways to approach the biological problem of how consciousness and subjective awareness are produced by the brain. It is beyond the purview of this article to provide a comprehensive review of the surge of publications on the problem of consciousness in the last decade, ranging from basic neuroscience through psychology to philosophy. Attention of many is shifting to focus on integrative processes of the system as well as properties of the components. The theoretical positions of a number of renowned neuroscientists and philosophers on the neural correlates of consciousness have been presented in several volumes

[72,133]. A comprehensive overview of this body of thought has recently appeared [216].

The theory presented herein has been much influenced by several studies and previous formulations supporting the idea that processes mediating cognition and volition should be considered as non-local cooperative integration across spatially distributed local processes. Prominent among such studies is the research of Doty on the bilateral effects of the two hemispheres on emotion and information processing, even in the absence of the forebrain commissures [36]. Freeman followed up his pioneering insights into mass action in the brain by evidence which he interprets to show that a world image emerges throughout the brain as order emerges from chaotic activity [54,55].

Nunez and his colleagues have studied the large scale dynamics of the EEG, precisely describing interference patterns of standing waves of post-synaptic potentials which may be superimposed on neurons embedded in these potential fields. Changes in long range coherence between remote cortical regions of certain frequencies during cognitive tasks give support to their concept of ‘globally dominated dynamics’ [142,143]. Llinas has described MEG studies showing extensive cross-cerebral coherence that led to the proposal that consciousness may arise from the resonant coactivation of sensory specific and non-sensory specific systems binding cerebral cortical sites to evoke a single cognitive experience [117,119].

Global theories by Penrose and Hameroff invoking quantum mechanical concepts [64,151] and by Tononi and Edelman introducing measurements of system entropy and complexity [201] have been proposed to account for the emergence of consciousness. The approach of global chaos theory and non-linear dynamics has received continuing attention from the extensive studies of Basar et al. [13,14]. Perhaps the most audacious and comprehensive approach to the explication of global integrative processes has been made by Pribram, who contends that the chaotic terminology is misleading and suggests that a holographic encoding of the nodes of interference patterns contains all of the information about the environment described by Gabor elementary functions, the ‘quanta of information’ [157]. He has explicated the relations between entropy, chaotic attractors and the organization of ensembles of Gabor quanta [158].

In an excellent overview of current theories of consciousness, Searle [173] has characterized neuroscientific approaches to the problem of consciousness as either building block models or unified field models. This paper is neither, since blocks of facts from different domains of neurophysiology are assembled and reconciled to construct a field theory of consciousness. This model can be summarized as follows.

Information about a complex stimulus is fractionated and dispersed to numerous neuronal ensembles specialized for detection of specific attributes of the multimodal sensory input. Significant input is identified by the production of non-random levels of synchronization within and coherence among such ensembles. Local coincidence detectors assess such fractionated activity by comparing exogenous sensory specific and substantially endogenous non-sensory specific influences on the neurons. Congruence in these comparators transforms these fragmented sensations to fragmented perceptions, and greatly enhances synchronized output from each ensemble. How local neural activity from multiple brain areas is integrated to produce a unified perceptual experience has been called ‘the binding problem’ [30,183]. Functional binding has been postulated to be based on correlated activity across distributed cortical (and subcortical) sites involved in sensory processing or motor output for various behaviors

[21,43]. We hypothesize that the cortico-thalamic outputs from the comparator ensembles are bound by their coherent convergence on thalamic sites.

Critical observations about dependence of information encoding upon synchrony within a region, dispersion of feature extractors across brain regions, coherence among regions and the relevance of statistical considerations to explain brain functions cannot be reconciled with hypotheses based upon discrete processes in dedicated cells. It is not plausible that a neuron can encompass the global information content of the multidimensional system to which it belongs.

Perceptual awareness involves the integration of distributed synchronous activity representing fragments of sensation into unified global perception. How this statistical information is transformed into a personal subjective experience is the problem of consciousness. This article proposes that consciousness may emerge from global negative entropy in dispersed, non-random, coherent neuronal ensembles, sustained by an electrical field resonating in a critical mass of brain regions. Non-random neural activities in multiple brain regions are continuously enhanced and made more coherent by local field potentials (LFPs), evaluated and assembled by large-scale integrative processes into a global whole, a seamless subjective experience. This does not imply that consciousness is monolithic. Nonetheless, inputs to this unified whole from some brain subsystems may be constant and relatively invariant, representing the stable contributions of maturation and past experience, as well as interoceptive monitoring of vegetative functions. Input from other more specialized subsystems may be absent or a defect might exist in a particular thalamo-cortical circuit, as in agnosias or hemi-spatial neglect.

2. Not all neural discharges constitute information for the brain

Neuronal firing may be spontaneous, arise from unrelated elements of transient background ‘noise’, or specialized to detect a specific attribute of a relevant figure. Conversely, a ‘feature detecting’ neuron may be refractory when that attribute appears. Informationally significant or ‘meaningful’ must somehow be discriminated from meaningless discharges. Single and multiple unit recordings in brain slices *in vitro* and in anesthetized as well as unanesthetized animals reveal synchronized discharges in diffusely distributed ensembles in different sensory modalities [19,169]. The problem is how multiple cortical areas of synchrony are welded into a holistic unity that constructs (the illusion of) continuous awareness of the outside world and of itself.

In studies of behaving unrestrained animals, cortical, thalamic, hippocampal, and brainstem regions showed

coherent but distinctive slow wave and unit activity when differential visual cue stimuli were correctly discriminated [80]. By ‘coherent’ is meant that recordings from chronically implanted, moving multiple microelectrode arrays revealed that components of average evoked potentials and peaks of multiple unit post stimulus histograms were time-locked with essentially zero phase lag between widely separated anatomical regions. Spatiotemporal patterns of covariance differed in correct and incorrect performance [76,79]. Recently, it has been shown that information is encoded by the spatial principal components of anatomically distributed synchronized activity [141].

Stimulation of non-specific as well as specific brain regions by electrical pulse patterns which contradicted concurrent auditory or visual conditioned stimuli achieved complete differential behavioral control, proportional to the amount of current delivered [95]. When behavior corresponded to the global sum of temporally interleaved fractions of pulse patterns delivered to two different brain regions, recordings from the intralaminar nuclei (but not from a number of other regions) revealed integration of the two patterns [85].

Thus, non-random activation synthetically imposed upon the neuronal populations in arbitrarily selected pairs of brain regions, or upon various single regions together with visual or auditory conditioned stimuli, was combined by the brain into information equivalent to a single cue to select adaptive behavior. Informational significance or cue value is represented by integration of temporal patterns of synchronized non-random local discharges that are coherent across multiple dispersed regions, rather than by the firing of dedicated cells.

3. Oscillations are crucial to synchronize informational neural activity

Cortical and thalamic regions display fast subthreshold oscillations of neuronal membranes [57]. Synchronization of these fast rhythms may be subserved by intralaminar neurons which fire rhythmic spike bursts in the gamma frequency range and have diffuse cortical projections [191,192]. Sensory stimulation has been shown to increase synchrony [28], which has been postulated to facilitate synaptic connectivity [17,145]. High frequency stimulation induces long-term potentiation, presumed to be related to memory formation [180].

Synchronized discharges of neurons in different brain regions may serve to bind spatially dispersed representations of a multimodal stimulus into an integrated percept [60,104]. Coherent gamma activity to auditory stimuli increases with selective attention [200]. Modulation and neuronal synchronization by gamma oscillation (30–80 Hz) has been suggested as a necessary condition for awareness of stimuli to occur [44,103,119] and facilitate synchronization during task performance [12].

Gamma oscillations may result from intrinsic neuronal properties and synaptic summation [17,25,152,190,195]. Cortical activation via mesencephalic reticular formation stimulation can increase gamma synchronization without altering overall stimulus responsive cortical firing rates [69]. Gamma waves in the cortex are influenced by the thalamus, mesencephalic reticular formation, and cholinergic modulation [23,124]. Human as well as animal studies employing iEEG or MEG have shown gamma to be higher in wakefulness and REM than slow wave sleep [62,117,126].

4. Relationship between oscillatory local field potentials (LFPs) and ‘binding’

Slow potentials (electroencephalographic or EEG waves) recorded from the scalp as well as local field potentials (LFPs) are integrated EPSPs and IPSPs of neuronal membranes. They reflect extracellular currents caused by synchronized neural activity within the local brain volume. If firing within a local neural ensemble were random, LFPs would be small or essentially absent. LFPs recorded from deafferented cortical slabs are essentially isopotential. Since they reflect the joint synaptic activity common to a significant proportion of the cells within local neural ensembles, fluctuations in LFPs are related to afferent synaptic inputs. The shapes of peri-stimulus time histograms of phase-locked neural discharges correspond closely to the waveshape of the local evoked potentials. Thus, LFPs are the envelope of the probability of non-random coherence in the neuronal ensembles near to the recording electrodes [53,76,80].

LFPs reflect the actions of brain regions one upon the other, transactions mediated by transcortical pathways as well as by inputs from thalamo-cortical and subcortical nuclei. The temporal evolution of spectral coherence between LFPs from diverse brain regions has been termed ‘cortical coordination dynamics’, to indicate that it reveals coordination of activity among different cortical sites [22]. Coherent spontaneous oscillations may play a decisive role in binding. Under certain circumstances, extrinsic LFPs oscillating in the gamma range appear to be superimposed as a modulation of the membrane potentials of the neurons in a brain region. Rhythmic modulations of coherence have been demonstrated in the cross-correlograms between the simultaneous activity of neurons in two recording sites, in such conditions as during performance of fixation tasks [104], binocular rivalrous stimulation [56] or between striate cortical sites on different hemispheres in anesthetized animals when visual stimuli were preceded by electrical stimulation of the midbrain reticular formation [138]. The modulation of such synchronized multiple unit activity has a period of ~20 ms, or in the so-called gamma frequency range around 50 Hz or even higher. Modulation by oscillatory field potentials may contribute to synchronization even when the interaction involves large conduction

delays [103]. Subthreshold oscillatory modulations of membrane potentials can establish synchronization in cortical slices among cells with considerable differences in response time, where the maximum delay interval depends on the oscillation frequency and can amount to nearly one cycle [209]. Gamma coherence sometimes occurs with phase lag in the millisecond range or close to zero and has been found over large cortical distances.

5. Relevance of oscillatory LFPs to perception

Electroencephalographic activity in the gamma range has been associated with attentional mechanisms for several decades [177,178]. Coherent activity in the gamma range (40–80 Hz) has been postulated to underlie conscious awareness by integrating neural activity across different cerebral areas, and thus bind the distributed processing of different features into a unified global percept [20,30,43,139,182,183]. A study in cats found widespread synchronization with zero time-lag when responding to a change in visual stimulus [169]. Phase-locked gamma oscillations have been hypothesized to be the neural correlates of conscious awareness [20,30]. Hypotheses about the relationship of gamma coherence to tasks requiring conscious perception remain controversial [132].

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 [34,199]. Observation of such phase-locked gamma coherence between brain regions in human intra-cranial EEG (iEEG) recordings has been used to support proposals that perception involves integration of many distinct, functionally specialized areas [198] and that the ‘self’ may be a transient dynamic product of a distributed array of many brain regions integrated by such [206].

Multimodal exogenous afferent input must be reconciled with endogenous recent as well as episodic memories, expectations based upon past experience, levels of motivation, and planned future actions, which must involve many anatomical structures. There may be a relationship between the scale of anatomical interaction required for functional integration and the synchronizing frequency. During visual processing, local synchronization in the visual cortex was shown to evolve in the gamma frequency range (25–50 Hz); during multimodal semantic processing, EEG coherence between neighboring temporal and parietal cortical regions evolved in the lower beta frequency range (12–18 Hz); and during tasks requiring retention in working memory and mental imagery, long range fronto-parietal interactions evolved in the alpha (8–12 Hz) and theta (4–8 Hz) frequency ranges [210]. Such interactions may reflect ‘top-down processing’ and may involve both feedback and feedforward integration among neural ensembles.

Other kinds of evidence indicate the consistent relevance

of events in the gamma range to perceptual processes and suggest that information processing may be limited to events at that rate.

5.1. 40-Hz auditory steady state response, or ASSR

The auditory steady state response (ASSR), first described by Galambos et al. [57], is largest for stimulus rates around 40/s and thus is often referred to as the 40-Hz ASSR. The logarithm of the ASSR amplitude is reliably correlated with the concentration of anesthetic [156]. The blockade of ASSR during anesthesia does not merely indicate a correlation between ASSR and anesthetic levels. Rather, it reflects a relationship between the loss of consciousness and ASSR disappearance, since administration of physostigmine restored consciousness with concomitant increases of ASSR [134]. The generation of endogenous gamma oscillations and the ASSR might involve similar cellular mechanisms. Relationships have been shown between preservation versus disappearance of the ASSR during anesthesia and the retention versus loss of implicit as well as explicit memories [125,155]. It has been proposed that 40-Hz oscillations may underlie short-term memory by binding together the fragmented attributes of a complex stimulus [115]. Review of this extensive literature is available in a recent monograph [116].

5.2. The auditory middle latency response, or MLR

The auditory middle latency response (MLR) has been found sensitive to anesthesia, showing attenuation proportional to concentration of anesthetic [109]. The MLR contains substantial power at or near 40 Hz and the effects of general anesthetics on the MLR are caused at least in part by reduction of this component [125,172].

5.3. The coherence index

A speculation by Galambos, that the stimulating frequency required to achieve the phase locking that yields the ASSR might change progressively with increasing anesthetic dose [92], has been confirmed by studies using wavelet analysis [196] and the ‘coherence index’ [9,137] showing ASSR power to be maximum at frequencies near 40 Hz, decreasing with increasing sedation.

5.4. Fusion of intermittent sensory stimuli

Flickering will be perceived as perfectly steady light as the frequency of alternation is increased between a dark phase and a light phase. The ‘critical fusion frequency’, or CFF, at which all subjective impression of flicker disappears is ~50–55 Hz. Similarly, the subjective auditory sensation changes from a tone to an intermittent sound at ~30–35 cycles per second [211]. The 40-Hz MEG oscillations time-linked to an auditory click can be altered by a second click, but only if the interval between two stimuli is

sufficient for them to be perceived as two separate stimuli (>14 ms) [90]. Numerous psychophysical investigations of temporal resolution have been reviewed by Landis [105]. Such phenomena lend support to the suggestion that oscillatory rhythms in the gamma frequency range may play a critical role in binding and perception.

5.5. Sleep

During slow wave sleep, the EEG reveals a diffuse pattern of high voltage slow waves. While in waking or REM sleep, firing of individual neurons is continuous or tonic, in slow wave or NREM sleep it follows an oscillatory pattern of high frequency bursts followed by silent pauses dispersed across the brain [194]. Neural activity in slow wave sleep is reduced in anterior neocortical regions (most of prefrontal cortex) and parietal association areas, in the anterior cingulate cortex and insula, and in the reticular activating system, thalamus and basal ganglia. It is not depressed in unimodal primary sensory areas [18,127].

In sleep, MEG recordings reveal 40-Hz oscillations which display high coherence across brain regions during waking or rapid eye movement (REM) periods, but low spatial coherence during slow wave sleep. Stimulus presentation during waking or REM sleep, but not during slow wave sleep, causes phase resetting of this activity [117]. A phase shift was reported from rostral to caudal regions of ~ 12.5 ms, or about one-half of the 40-Hz period.

6. A comparator constructs perceptions from sensations

Fading but persistent recollection of the recent past coexists in subjective continuity with the momentary present. A degree of constancy must persist across a sequence of perceptual frames, analogous to a 'sliding comparator'. Adaptive response to the environment requires that the sensory information in the immediate perceptual frame be evaluated in the context of the just previous perceptual frame, as well as working and episodic memories. Some earlier experimental results suggest how this might occur.

As sensory stimuli acquired cue value, EPs from trained animals displayed widespread emergence of a secondary component, present when appropriate conditioned responses were elicited but absent when performance failed. The early component was presumed to reflect projections from specific pathways activated by the sensory cues, while the later component was released from a non-sensory specific representational system, established during learning, reflecting memory, motivation and affect related to the stimuli [16,79].

Direct electrical stimulation, phase-locked to a peripheral conditioned stimulus to block the primary component of cortical sensory receiving areas, had little effect on be-

havioral accuracy in conditioned animals. Identical electrical disturbances, delayed to block the secondary non-sensory specific component, greatly impaired performance. Concordance of specific and non-specific influences, presumably converging on a comparator at the cortical level, was proposed to be essential to convert the 'sensation' of the stimulus into a 'perception' [79]. Other investigators have proposed similar hypotheses [185].

Previous views of specific and non-specific thalamo-cortical projections have been modified by recent neuro-anatomical studies using different protein tagged staining techniques [91]. Parvalbumin staining fibers from a 'core system' of cells in the sensory relay nuclei project topographically upon pyramidal cells in lower layers of the corresponding primary sensory cortex. Other calbindin staining fibers projecting from thalamic 'matrix' cells are not restricted by the borders of individual nuclei, but project diffusely to superficial layers of multiple cortical areas. Cortico-cortical as well as cortico-thalamic projections can thus distribute exogenous sensory information as well as endogenous state assessments throughout the thalamus and cortex. Enhanced by phase locked oscillatory modulation of membrane potentials and back-propagation, this system might play a critical role in establishing coherence, and facilitating coincidence detection and binding. This integrative mechanism may contribute to establishment of a resonating field encompassing coherent ensembles. The actual binding process has been envisaged by some as a global resonance state [199].

Using intracranial (iEEG) as well as scalp EEG recordings, synchronization of gamma activity has been studied during auditory, visual, and somatosensory stimulation and during cognitive or perceptual tasks. In each modality, a transient burst of phase-locked gamma (of varying frequencies) occurs, most prominently in the primary sensory cortex, ~ 100 ms after stimulus onset [34,198,199]. In this latency domain, gamma augmentation in auditory association cortex was significantly greater in phoneme- than in tone-discrimination tasks [32].

Transient gamma-band iEEG synchronization (maximum at 230 ms) between frontal and parietal cortical regions has been reported when stimuli were perceived as faces [206]. 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' [146,168]. Face-selective increases were found in gamma iEEG coherence between the fusiform gyrus (known to be critical in face processing) and temporal, parietal and frontal cortices at 160–230 ms post-stimulus onset [96]. Several other studies also support the idea that gamma activity in different regions is time-linked and topographically specific [21,33,184]. The long distance between the synchronized regions rules out volume conduction, which decays rapidly as a function of separation between electrodes. 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 [58,80]. The latency of the so-called cognitive potential, P3A, is 230 ms; P3A is prominently displayed in anterior regions of the human scalp after detection of an unexpected event.

In conscious neurosurgical patients, electrical stimuli delivered to the somatosensory cortex [110] or center median nucleus of the thalamus [68], phase-locked but delayed to coincide with the late component of the cortical EP, blocked perception of median nerve stimulation. Presence of early but not late components of multi-sensory evoked potentials has been used to provide a scale to estimate the severity of traumatic brain injury in comatose patients [61]. The return of the late evoked potential component is predictive of subsequent recovery of consciousness [7].

Recent studies have provided direct evidence of the existence of a coincidence detector capable of integrating inputs to cortical neurons from sensory specific and non-sensory specific pathways. When an axosomatic triggered action potential is followed shortly by a stimulus delivered to the apical dendrites of pyramidal neurons, a powerful apical action potential may evoke a burst of spikes generated at the axon [106,181]. Back-propagating action potentials play an important role in the generation of gamma oscillations. This regenerative activity is very dependent upon critical high frequencies of axonal action potentials [106].

High frequency stimulation is more effective in inducing long-term potentiation, presumed to be related to memory formation [180]. These influences have been demonstrated to facilitate synchronization during task performance [12]. Associative synaptic plasticity appears to be facilitated by active back-propagation of axosomatic action potentials to the dendritic arborization of neocortical neurons, thereby acting as a filter to modulate synaptic efficacy [186]. Such mechanisms can create as well as detect synchrony of spike timing across cortical laminae [11]. It has also been reported [135] that coherent gamma activity in human EEG occurs during associative learning. The facilitation of memory by attention may be due to the dual role that gamma coherence plays in perception and synaptic linkages.

Thus, ‘top-down’ axo-dendritic signals may modulate the saliency of a ‘bottom-up’ axosomatic signal, changing the neuronal output from a single spike into a burst. Simulations have been performed which demonstrate the possible contribution of such processes to synaptic plasticity and learning [102,175]. This neural enhancement process has thus far only been shown to operate at intervals on the order of tens of milliseconds separating the axosomatic and axodendritic inputs. This duration may be extended by depolarizing after-potentials arising from influences such as long duration back-propagating Na^+ spikes. Persistent shifts of membrane potentials on the order of a hundred milliseconds or more involving the NMDA receptor may serve as a local ‘binding’ mechanism facilitating the

synergic interaction of specific and non-specific inputs [203].

This body of data supports the hypothesis that a comparator or coincidence detector, between neuronal activity in sensory specific and non-specific systems reflected in late components, is essential for sensations to be perceived [79,185], and may be reflected by the induced long-distance synchronization of gamma oscillations [146,168,206]. Others have more recently proposed that temporal binding occurs as a result of coincident activation of specific thalamic input to lower layers and non-specific input to upper layers of the cortex. The specific thalamocortical system works in conjunction with the non-specific thalamus system, especially the intralaminar complex, to generate a recurrent gamma-band oscillation when coincidence is achieved [119,122]. This model has been expanded in a current paper [121], in which it is postulated that gamma-oscillations in neurons of the specific thalamic nuclei establish cortical resonance through direct activation of pyramidal cells in layer IV, returned to the thalamus via layer VI collaterals. The non-specific thalamic nuclei project to the uppermost layer of the cortex. Conjunction of these two influences generates coherent oscillations, entraining corticothalamic loops. Coincidence detection enhanced by temporal coherence binds the fragmented cortical information that pertains to the external world, represented by the specific afferents, together with interoceptive features provided via the non-specific system to generate a single cognitive experience.

7. Oscillatory brain activity may be genetically regulated

Since the EEG and LFPs reflect integrated excitatory and inhibitory post-synaptic neuronal potentials, regularities found in rhythmic macropotential activity reflect corresponding regularities of synchronized discharges within nearby neuronal populations. Normative baseline modes of EEG oscillation have been identified, which provide an accurate, quantitative description of local activity, interactions between brain regions, and regular global sampling of changes in state. These normative data change in a regular way with age and can be described as simple polynomial functions [82,87]. Such normative modes are herein used to define a reference state of the resting human brain.

The EEG power spectrum has conventionally been divided into several wide frequency bands, typically defined as: delta (0.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz) and beta (12.5–25 Hz), which we have extended [88] to include several gamma bands: gamma 1: 25–35 Hz; gamma 2: 35–50 Hz; and gamma 3: 50–100 Hz. Normative parameters, age-regressed and computed for each band at each location, include: absolute power (microvolts squared), relative power (% of total power), inter- and intra-hemispheric coherence and inter- and intra-

hemispheric symmetry/gradients (respectively, the synchronization of activity and the ratio of power between pairs of homologous electrodes or leads over the same hemisphere). A model of some salient features of this regulatory system is shown in Fig. 1.

7.1. The LFP homeostatic system

The observed predictability of the EEG power spectrum arises from regulation by anatomically complex homeostatic systems in the brain. Brainstem, limbic, thalamic and cortical processes involving large neuronal populations mediate this regulation, utilizing all the major neurotransmitters [26,27,118,123,129,193].

Pacemaker neurons distributed throughout the thalamus normally oscillate synchronously in the alpha (7.5–12.5 Hz) frequency range. Efferent globally distributed thalamo-cortex projections produce the rhythmic electrical activity known as the alpha rhythm, which dominates the EEG of an alert healthy person at rest. Nucleus reticularis can hyperpolarize the cell membranes of thalamic neurons by gamma-aminobutyric acid (GABA) release, slowing the

dominant alpha rhythm into the lower theta range (3.5–7.5 Hz), and diminishing sensory throughput to the cortex. Theta activity can also be generated in the limbic system, possibly by theta pacemaker cells in the septal nuclei which can be inhibited by entorhinal and hippocampal influences. Slow delta activity (1.5–3.5 Hz) is believed to originate in oscillator neurons in deep cortical layers and in the thalamus, normally inhibited by input from the ascending reticular activating system in the midbrain. Delta activity may reflect hyperpolarization of cortical neurons resulting in dedifferentiation of neural activity. Activity in the beta band (12.5–20 Hz) is believed to reflect cortico-cortical and thalamo-cortical transactions related to specific information processing. Activity in the gamma bands (25–50 Hz) may reflect cortico-thalamo-cortical reverberatory circuits, as well as back-propagation of axonal discharges to the dendrites of cortical pyramidal cells, which may play an important role in perception as proposed in this paper.

Relevance to consciousness of the complex interactions hypothesized in Fig. 1 may be clarified by an example. Assume that a subject is somnolent, with diminished activity in the ascending reticular activating system, an

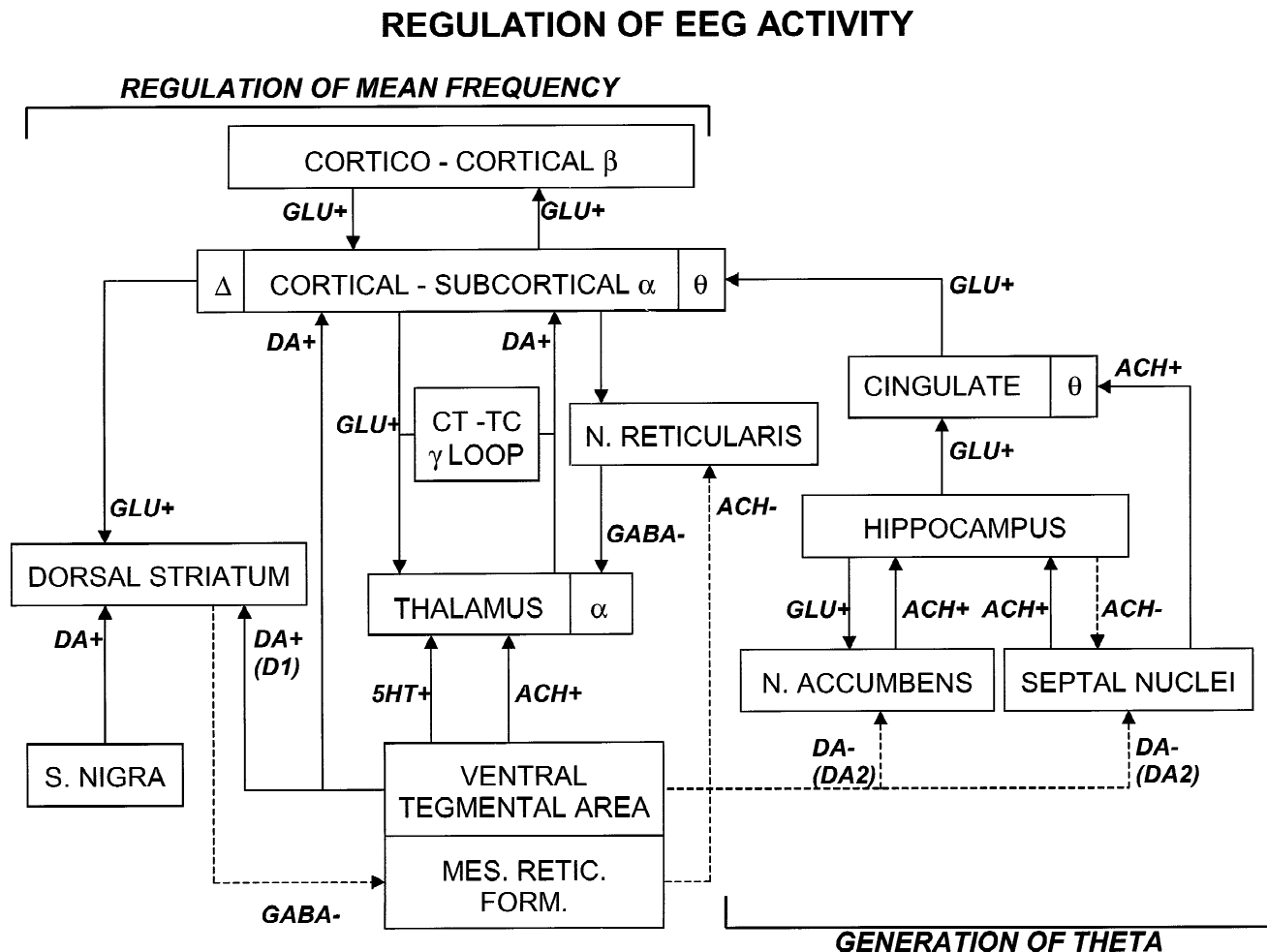


Fig. 1. A schematic representation of the homeostatic system which regulates the parameters defining the ground state of brain electrical activity.

EEG dominated by slow delta and theta waves reflecting inhibition of the thalamus by nucleus reticularis and consequent diminution of sensory input to the cortex. Activation of the mesencephalic reticular formation (MRF) and thalamic relay nuclei by a sudden increase of stimuli in the environment results in inhibition of nucleus reticularis via collaterals by cholinergic and serotonergic mediation, thereby releasing the thalamic cells from inhibition by n. reticularis. The dominant activity of the EEG power spectrum becomes more rapid, with return of alpha activity. Increased flow of information through the thalamus to the cortex is facilitated, resulting in cortico-cortical interactions reflected by increased beta activity. Coincidence detection by pyramidal cells comparing this exogenous input with readout of endogenous activity activates cortical-thalamic loops generating gamma activity and mediating perception of the sensory information.

Collaterals go to n. reticularis from corticothalamic axons. The cortex can activate n. reticularis by these axons indirectly en passage or directly by glutamatergic pathways, to suppress the arrival of information to the cortical level. Indirectly, as an alternative result of cortical influences, dopaminergic striatal projections can inhibit the MRF. Such inhibition of the MRF enables inhibition of thalamic neurons by n. reticularis, blocking transmission from the thalamus to the cortex. The dominant activity of the power spectrum slows toward or into the theta range. The cortex can thus modulate its own information input. The potential role of this mechanism in awareness and the focusing of attention should be apparent.

7.2. Normative data have been established for LFP power spectra

The power spectrum can reasonably be expected to be stable and characteristic for healthy, resting human beings due to this homeostatic regulation. In fact, the power spectrum of spontaneous LFP oscillations changes predictably, as a function of age and internationally standardized electrode positions, in healthy normally functioning individuals in a resting but alert state. This power spectrum is highly specific, independent of ethnic or cultural variables [70], and very stable across intervals of hours, days, or even years [101]. Distributions of ‘baseline’ power spectra and covariance matrices (See ‘regional interactions’), have been mathematically described from age 6 to 95 in large normative quantitative electroencephalographic (QEEG) studies [74,77,78,82]. Recently, very narrow band (VNB) norms have been constructed at 0.39-Hz intervals across the range 0.39–50 Hz, which reveal the same stability as the wide band norms [16,197,204]. These normative LFP equations define the range of spontaneous deviations from truly random neural behavior due to interactions among the elements of the ensembles.

Striking regularities have been found in these hundreds of QEEG parameters, which may reflect genetic charac-

teristics common to all healthy human beings. The specificity and independence from ethnic factors of QEEG measures have been established in cross-cultural studies from Barbados, China, Cuba, Germany, Holland, Hungary, Japan, Korea, Mexico, Netherlands, Sweden, US and Venezuela [2,8,35,38,59,65,93,128,144,166,205,207,214].

The composition of the power spectrum has been shown to reflect a variety of cognitive processes [77]. The model shown in Fig. 1 suggests that deficiencies or excesses of any neurotransmitter should produce marked departures from the normative power spectrum. Such neurotransmitter perturbations make decisive contributions to much psychiatric pathophysiology. Distinctive, differential power QEEG abnormalities have been well documented in a wide variety of developmental, neurological or psychiatric disorders [70].

7.3. Regulation of transcortical modes of oscillation

The symmetry, power gradients, coherence and cross-spectra quantifying electrical interactions among brain regions are similarly mathematically predictable. Normative values (Mahalanobis distances) have been established for covariance matrices between sets of QEEG variables as well as among sets of brain regions. These descriptors of relationships among LFPs display stability and replicability across the life span [77,101]. High levels of common mode resonance of the whole power spectrum exist across the cortex with very high global correlations over long-range cortical-cortical distances [86], which necessarily implies existence of modes with high covariances among regions at some frequencies.

7.3.1. Spatial principal components: parallel functional subsystems

In this [40] and other [39,188] laboratories, spatial principal component analysis (SPCA) of the multi-channel EEGs from large groups of normally functioning individuals has been used to analyze the spatial and spatio-temporal covariance matrix among leads across the power spectrum. These covariances are presumed to reflect functional neuroanatomical subsystems whose coherent activities coexist in the signal space during the same time periods. This yields the most parsimonious explanation for simultaneous, parallel spatiotemporal patterns of activity and their phase relationships.

The complex electrical activity of the brain reflects the contribution of a limited number of simultaneously active functional neuroanatomical subsystems, each with its characteristic mode of oscillation. With 19 channels and four wide frequency intervals, as few as five SPCs account for ~90% of the variance of the EEG signal space of 76 measures [40]. As few as 30 SPCs can account for 92% of the full space of 1.5 million cross-spectral measures resulting when very narrow band spectra are analyzed [71].

What is important is not so much the ‘true’ number of

such subsystems (which depends on the arbitrary selection of the number of channels and the resolution of the power spectra being analyzed), but that such studies have repeatedly revealed the same factor loadings, that is, the same topography and weighting of interactions between specific brain regions. An SPC loading quantifies a mode of oscillation describing the dynamic relationship among a set of brain regions. Normative data only provide estimates of the expected form and intensity of certain ongoing neural interactions, and do not give access to the particular content of cognitive processes. Since norms have been constructed for these descriptors of ongoing transactions between brain regions organized into functional subsystems, we postulate that such interactive modes are also genetically specified.

7.4. Instantaneous LFP microstates resemble SPC modes of oscillation

Examination of the momentary voltage fields on the scalp reveals a kaleidoscope with positive hills and negative valleys on a landscape, or ‘microstate’, which changes continuously [107]. Computerized classification of microstates observed in EEGs of 400 normal subjects, aged 6–80 years, yielded the same small number of basic topographic patterns in every individual, with approximately equal prevalence. The topographies of these instantaneous brain voltage fields closely resemble the computed modes of factor loadings obtained in SPC studies. This correspondence suggests that the SPC loadings are not a computational artifact, but may reflect biologically meaningful processes.

The mean microstate duration slowly decreases during childhood, stabilizing for healthy young adults at $\sim 82 \pm 4$ ms [98]. Although the field strength waxes and wanes, the stable landscapes persist with this duration. A possible role in binding has been suggested for the similarly persisting changes in membrane potentials caused by activation of the NMDA receptor [52]. Temporal extension of neural activity has been considered critical for binding. Durations of long lasting EPSP-IPSP sequences, omnipresent in mammalian forebrain neurons, commonly range from 80 to 200 ms [162].

The transition probabilities from microstate to microstate are apparently altered during cognitive tasks [149]. Different microstates seem to correlate with distinctive modes of ideation [108]. The stability of the microstate topographies and their mean duration across much of the human life span again supports the suggestion of genetic regulation.

7.5. Perceptual time is regulated, parsed into discontinuous intervals

Although subjective time is experienced as continuous, brain time is discontinuous, parsed by some neurophysiological process into epochs of ~ 80 ms which define

a ‘traveling moment of perception’ [5]. Sequential stimuli that occur within this brief time interval will be perceived as simultaneous, while events separated by a longer time are perceived as sequential [42]. Other evidence has led to similar proposals that consciousness is discontinuous and is parsed into sequential episodes by synchronous thalamo-cortical activity [119]. Multimodal asynchronous sensory information may thereby be integrated into a global instant of conscious experience [215]. The correspondence between the experimentally obtained durations of each subjective episode and the mean duration of microstates suggest that a microstate may correspond to a ‘perceptual frame’. The phenomenon of ‘backward masking’ or metacontrast, consisting of the ability of a later sensory input to block perception of an event earlier in time [6], suggests that perhaps two separate events within a single frame are required for conscious perception. These two events might represent independent inputs to a comparator.

The exact time at which conscious perception occurs following sensory input is unclear. Certainly, it is delayed beyond 50–100 ms since stimuli are particularly susceptible to masking by a competing stimulus during this period [6,111,130]. Psychophysical evidence shows that the perceptual frame closes at ~ 80 –100 ms after occurrence of a specific event. Although it is clear that time for the brain is discontinuous, the frame duration may differ in the various sensory modalities. A mechanism may be required to synchronize sensory elements sampled at different rates in disparate modalities [215]. Based on train duration studies, Libet has suggested that perception may occur as late as 300–500 ms post stimulus. Extending train duration of repetitive direct cortical stimuli up to but not beyond 300–500 ms lowered perceptual threshold [113]. These train duration effects have been reproduced for stimuli applied to the cerebral cortex via intracerebral electrodes [114,165]. Similar duration effects have been shown using repetitive transcranial magnetic or direct electrical stimulation of the cortex and sensory deficit or neglect in healthy volunteers [131,164].

7.6. The ‘hyperneuron’

In order to achieve the stable persistence of LFP topography revealed by microstate analysis, while displaying such duration effects and susceptibility to disruption by masking stimuli, some reentrant or reverberatory brain process must sustain cortical transactions as a steady state, independent of the activity of individual neurons. Occurrence of a discrete stimulus complex with multiple attributes might generate excitation in the receptor arrays of a processor system comprised of many synchronized multiplexed parallel channels. The subset of cells most reactive at any instant of time in each array encodes the momentary multimodal attributes of the stimulus complex and constitutes a ‘channel’. Activation of a channel causes a volley of synchronized, possibly syncopated non-random neural discharges. This afferent activity propagates to distributed

ensembles of feature detector neurons, causing some ensembles to deviate significantly from the usual random background resting activity. This perturbation may reverberate via re-entrant circuits for ~100 ms, at which time the initial perceptual frame closes. Standing waves reflecting this reverberation might account for the observed stability of microstates.

Many different subsets of neurons in the multimodal receptor arrays will successively encode the same set of attributes, but with inter-channel temporal offsets of ~20 ms. If the stimulus complex is unchanged, the afferent volley arriving via other channels of the parallel processor may resonate with the still-persisting reverberation reflecting the previous volley, enhancing the signal to noise ratio of the non-random pattern. Stimuli can be reliably detected which occur much more closely together than the duration of a single perceptual frame. If some elements of the stimulus complex were to change rapidly, then the above enhancement of reverberation cannot take place. An interference pattern might ensue. This mechanism might serve as a filter to detect subtle shifts of attributes in the complex stimulus, perhaps by abrupt blockade of reverberation by a competing significant non-randomness. The consequent change in reverberating cortico-thalamic elements could focus attention on those attributes which had changed. Such mechanisms require elaborate feed-forward as well as feedback circuits in the brain.

Such a process, called the ‘hyperneuron’, has been postulated and described in some detail [75,81,176]. This persistent electrical field, produced by reverberating loops, may correspond to a neural correlate of the ‘dynamic core’ postulated by Tononi and Edelman [201,202]. According to this concept, there must exist a set of spatially distributed and meta-stable thalamo-cortical elements that sustains continuity of awareness in spite of constantly changing composition of the neurons within that set.

7.7. Basis vectors, ‘ground state’ and ‘excited state’

The normative data described above were collected in the eyes-closed resting state. We propose that when all measures fall within the normative distribution, the information content in this state be considered as zero. This does not imply absence of mental activity or no ongoing processing of information. Clearly, there is abundant thought content as individuals ruminate with their eyes closed. However, the high test-retest replicability of QEEG analyses over long as well as short intervals [101] indicates that such activity fluctuates sufficiently during a sufficiently long (~2 min of artifact-free EEG), unconstrained period of observation so that the perturbations randomize out to the average baseline values. These norms describe the ‘form’ and not the ‘content’ of brain activity and encompass the range of these normal fluctuations.

These norms define a set of ‘orthogonal basis vectors’ which span the brain signal space. The ‘ground state’ (G) of the brain is defined as a confidence region or hyper-

sphere of uncertain radius, centered around the origin of the basis vectors. Distances in the direction of each of the basis vectors are all scaled in the common units of *probability*, proportional to the standard deviations of age-appropriate normative parameters.

The ‘excited state’ of an individual brain is defined as the set of all statistically significant momentary deviations from the ground state (Z-scores). The probabilities of the instantaneous values of all neuronal regions encompassed by all SPC loadings define a spatio-temporal probability distribution, or ‘ Ψ ’. This state is presumed to be refreshed at the closing of each perceptual frame.

8. Deviations from ground state appear with alterations of consciousness

8.1. Cognitive activity

Profiles of significant deviations from normative resting modes of oscillation have consistently been demonstrated during cognitive activity, with accentuation or attenuation of the LFPs in and covariance among different brain regions [50,51,66,67,83,84]. Changes in microstate abundance have been observed during cognitive tasks [108,149]. Such deviations reveal reallocation of resources in an idiosyncratic manner by individuals engaged in a variety of cognitive tasks.

8.2. Psychiatric disorders

Distinctive profiles of departures from the ground state have been consistently found in over 250 EEG or QEEG studies of groups of patients with brain dysfunctions such as attention deficit disorder, dementia, head injury, mood disorders, obsessive-compulsive disorder, schizophrenia, substance addictions and many other behavioral and cognitive disorders [70]. Accurate, replicable statistical classification of patients into different diagnostic categories has been accomplished, based upon QEEG deviation profiles [70,101,160]. Distinctive profiles of SPC factor scores have also been reported for groups of patients with particular psychopathology [39]. Deviations distinctive for some dysfunctions have been found to be opposite from those induced in normals by drugs which are clinically effective for that dysfunction [170]. In animals, factor scores change in a distinctive manner with administration of members of different classes of centrally active drugs [89].

8.3. Depth of anesthesia

Recent clinically approved QEEG instruments reliably monitor the depth of anesthesia, independent of the particular anesthetic agents, in the individual patient during surgery (see Section 10 below). Such instruments provide

an index of the level of consciousness by state defined above.

These observations validate the relevance of the proposed definition of the ground state to consciousness and subjective experience. The ground state reflects the functional organization and defines the range of variations in activity of the normal human brain at rest. Phasic modulations of the ground state reflect cognitive activity, responses to stimulation, interpersonal interactions, emotional reactions, alterations of the level of arousal, or other transient influences upon states of the individual. Tonic departures from these modes indicate sustained changes in the level of consciousness due to anesthetics, effects of substances, developmental or psychiatric disorders. When the ground state is restored, consciousness returns or psychiatric disorders often normalize. It is hypothesized that metabolic processes during sleep restore the system to the ground state from the cumulative displacements persisting from the recent static perturbations, replenish storage depots of metabolites essential for proper homeostatic regulation, and install adaptive changes in the value system which reflect the information accumulated during the waking period.

9. PET studies of regional effects of anesthetics

Various strategies have been used to seek the ‘neural correlate of consciousness’ (NCC), including lesioning, imaging and pharmacological techniques. It has been proposed that there is not conscious awareness of activity in the primary sensory area [31] and that prolonged activity in some sparse but widely distributed set of unique ‘awareness cells’, or a pattern of regional interactions comprises the NCC [97]. The thalamus in interaction with the neocortex has been postulated to play a major role in conscious perception [10,15,140]. Activation of the mid-brain reticular formation and of thalamic intralaminar nuclei has been reported in a PET study of focused attention in humans [94].

One approach to the NCC search is to seek a set of brain regions which invariably change state with the loss of consciousness (LOC) due to anesthetics. ^{18}F FDG-PET glucose metabolism was studied during propofol anesthesia. In sedation, a small global reduction was observed. At LOC, 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. It was concluded that LOC was not caused by changes within a specific circuit, but rather by a uniform reduction below a critical level in a distributed neural system [3]. In a study using H_2^{15}O PET during sedation with midazolam, a smaller but similar global reduction in rCBF was found, but a discrete set of brain regions displayed significantly greater reduction [208]. These regions included multiple areas in the prefrontal cortex, the superior frontal gyrus, the anterior cingulate

gyrus, parietal association areas, the insula, and the thalamus.

Further FDG studies showed both global reduction and specific regional changes of brain glucose metabolism during both isoflurane and halothane anesthesia. Local maximal effects common to both agents (significant at the $P < 0.001$ – 0.007 level) were found in the thalamus, mid-brain reticular formation, basal forebrain, occipital cortex (Brodmann’s area 18), medial frontal cortex (area 47), the fusiform gyrus of the temporal lobe (area 36), anterior and ventrolateral thalamic nuclei, the midbrain reticular formation, and the cerebellum [4]. These authors suggested that different anesthetics might act through one or all of several modes: hyperpolarization of membrane potentials, loss of arousing inputs to corticothalamic-thalamocortical-reticulothalamic loops as in natural sleep, and enhancement of inhibitory circuitry due to GABAergic neurotransmission.

10. Deviation from ground state quantifies level of consciousness

Routine surgical anesthesia offers a naturalistic environment where loss and return of consciousness can be studied in a systematic manner. EEG power spectra and bispectra variables have been repeatedly shown to be related to anesthetic end points [163,174]. We collected continuous 19 channel EEG recordings throughout 176 surgical procedures, during anesthesia using a wide variety of agents administered according to standard clinical practice. Trajectories of hundreds of quantitative EEG (QEEG) measures were constructed and subjected to multivariate statistical analysis. Reversible changes in brain electrical activity were sought which would be (i) invariantly associated with loss (LOC) and return (ROC) of consciousness but (ii) independent of the particular anesthetic agents used for induction and maintenance. A set of variables was found which satisfied these criteria, using MANOVA to evaluate data from five stages: stage 1, the premedicated baseline just outside the operating room, corresponding to the ground state; stage 2, on the operating table while counting, showing signs of sedation as anesthesia was induced with several different agents; stage 3, loss of consciousness (LOC); stage 4, during prolonged surgical anesthesia, maintained by a different set of agents; stage 5, return of consciousness (ROC).

Two kinds of reversible changes in brain activity were found that were independent of the eight different agents used for induction and maintenance of anesthesia during the 176 procedures. Further details of the results of these studies have been reported elsewhere [37,88,159]. The reliability of these observations has since been confirmed in a large number of surgical procedures. The consistency and reliability of these changes can be inferred from the fact that a multivariate algorithm quantifying these observations has been installed in a QEEG monitor of the

depth of anesthesia (PSA 4000, Physiometrix, N. Billerica, MA), approved by the U.S. Food and Drug Administration for routine clinical use.

10.1. Disruption of LFP coherence

During LOC induced with any agent, significant decreases of coherence took place abruptly in every frequency band. Rostral brain regions became functionally disconnected from posterior regions and the two hemispheres became uncoupled. During emergence from anesthesia and ROC, this uncoupling was reversed first in the gamma band. These unique changes in coherence of the gamma 2 band (35–50 Hz), averaged across 176 cases and many different agents, are illustrated in Fig. 2 (see legend for details). Those changes that reverse more slowly reflect effects upon brain biochemistry not critical for emergence of consciousness and may be related to the observation of post-operative alterations in consciousness.

10.2. 3D source localization of invariant LFP changes with loss of consciousness

At LOC, EEG power on each hemisphere displayed shifts to power spectra dominated by low frequencies. The

‘burst suppression pattern’, considered by some to reflect a ‘thalamocortical switch’, did not appear until depths of anesthesia far below the level at which LOC occurred. Power became strongly anteriorized, clearly evident in topographic QEEG maps [88].

A variable resolution electromagnetic tomographic analysis (VARETA) method was used for 3D neuroanatomical localization of the sources of the frequency (3.5 Hz) that displayed the most significant invariant as well as reversible QEEG change in power with LOC and ROC. VARETA solutions are depicted as statistical probability images, color coded for significance of deviation from the normative data for each voxel at the corresponding frequency, superimposed upon slices from a probabilistic MRI atlas [45]. A complete mathematical description of VARETA has been published elsewhere [16]. (An overview of the computational details can be found in Appendix A).

The invariant reversible changes in brain state typically seen in the five stages defined above are illustrated in Fig. 3. Five rows of paired VARETA images are shown, superimposed upon two levels vertically separated by 7 mm, of transaxial slices from a probabilistic MRI atlas [16,45]. Each image is based upon mean voxel values of absolute power in a 0.39-Hz spectral window centered at 3.5 Hz averaged across 15 patients under the corre-

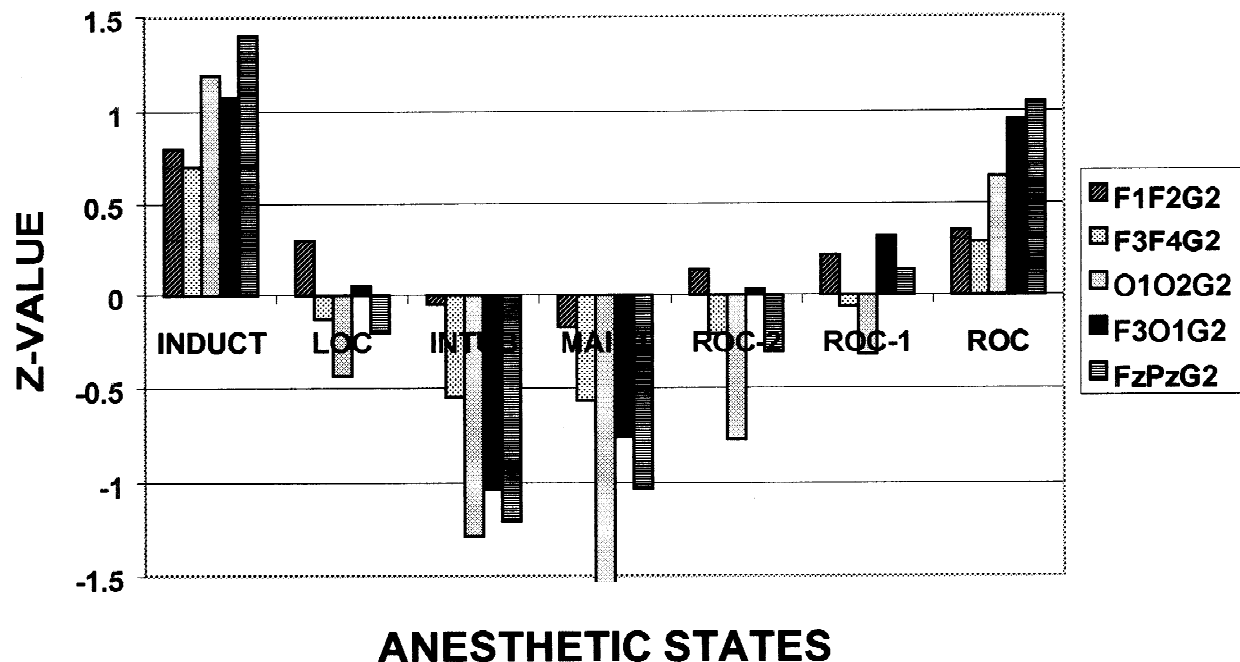


Fig. 2. Mean Z-scores of intra- and inter-hemispheric coherence in the gamma band (35–50 Hz), averaged across 176 surgical procedures, quantifying coherence changes at different stages of anesthesia. These stages include: INDUCT (patient counting during administration of various induction agents, see text), LOC (just after cessation of counting and abolition of lash reflex), INTUB (at intubation), MAINT (during surgical maintenance with a variety of other anesthetic agents), ROC-2 (during emergence, 10 min before eyes opened), ROC-1 (5 min before eyes opened) and ROC (return of consciousness defined by opening of eyes in response to a verbal command). These Z-scores were computed relative to mean values and standard deviations of the distributions of these measures across 176 patients in the pre-induction database. Note that since the statistical significance of averaged Z-scores is proportional to the square root of the sample size, to estimate the confidence level the value on the Y-axis should be multiplied by 13. Relative to the mean values before onset of induction, intra- as well as inter-hemispheric coherence of gamma increases upon sedation during induction. At loss of consciousness (LOC), prefrontal cortical regions briefly remain coupled but interhemispheric coupling between frontal and occipital regions, as well as frontal-occipital coupling, diminishes. As anesthesia deepens, this uncoupling intensifies. During emergence from anesthesia there is a gradual increase of coherence which, upon return of consciousness (ROC) and responsivity to verbal commands, abruptly returns to the values seen before LOC.

sponding conditions. At this frequency, the heterogeneity of variance across states was greatest but variance across agents within any state was minimal, based upon analysis of all findings in the full sample of 176 cases ('gases': desflurane, $n=24$, isoflurane, $n=30$, or sevoflurane, $n=14$; nitrous oxide/narcotic, $n=49$; and intravenous propofol, $n=59$).

These statistical probability images illustrate the invariance of changes in absolute power within (row 1) premedicated baselines; (row 2) during induction of anesthesia while counting; (row 3) just after loss of consciousness (LOC) with various agents (pairs of slices, from left to right: propofol, thiopental, etomidate); (row 4) similarity of changes upon LOC to stable states during surgical maintenance with a different set of agents (pairs of slices, from left to right: propofol, gases (desflurane, isoflurane, sevoflurane), nitrous oxide/narcotic; (row 5) reversal of these induced QEEG changes with return of consciousness at ROC (eyes opened).

Every voxel is color-coded to correspond to the mean Z-score, across the 15 patients, of the deviation from the normative resting distributions of that voxel and frequency. Hues of red to yellow indicate positive deviations and blue through turquoise negative deviations around the mean pre-induction baseline values across 176 cases. The palette on the color bar corresponds to the voxel Z-scores. Note that in order to assess the statistical significance of data from any voxel, the voxel Z-score must be multiplied by the square root of 15, or 3.8 (for more details, see Ref. [88]).

The increment of theta when baseline is compared to counting during induction reflects the global effects of sedation. Note that when row 2 (induction-counting) is compared to row 3 (LOC), the anatomical regions which display the further increment of theta activity indicated by the yellowish colors are essentially the same as seen in row 4 (surgical plane). Finally, these theta increments disappear abruptly in row 5 (eyes open, ROC).

Regions of the mesial orbital and dorsolateral pre-frontal and frontal cortex, paracentral gyrus, anterior cingulate gyrus, amygdala and basal ganglia displayed profound (yellow hues) reversible inhibition with loss and return of consciousness, independent of the anesthetic agents. While not visualized in these slices, the dorsolateral prefrontal cortex and the paracentral cortex showed corresponding reliable changes of state. A more complete serial scan of transaxial slices is available in the references cited above. These brain regions correspond well to those identified in $H_2^{15}O$ and ^{18}F -DG PET studies of anesthesia [208], and those implicated in studies of 'absence' seizures [150].

11. Field theoretical proposals

Other contemporary theorists have recognized the need to focus upon the system rather than its individual ele-

ments. An electrical field must be generated by synchronized oscillations and the resulting inhomogeneity of ionic charge distribution within the space of the brain. Llinas and his colleagues [120] suggest that consciousness is inherent in a synchronized state of the brain, modulated by sensory inputs. Libet [112] proposed that subjective experience may arise from a field emerging from neural synchrony and coherence, not reducible to any known physical process. Squires [187] suggested that consciousness may be a primitive ingredient of the world, i.e. not reducible to other properties in physics, and includes the qualia of experience. Others [201,202] have proposed that consciousness arises within a dynamic core, a persisting reverberation of interactions in an ensemble of neurons which maintains unity even if its composition is constantly changing.

12. Quantum theoretical proposals

Quantum mechanical solutions have been suggested as a way to reconcile discrete neuronal processes and seamless subjective experience. A quantum mechanical state collapse or a state selection mechanism may help to bridge this 'explanatory gap'. Brain substrates might sustain a variety of quantum fields. Discrete moments of experience may resemble quantum state reductions. Reduction is only possible if two well-defined quantum states are present and collapse into one of the components. In such formulations, two distributions of ionic plasmas or charged particles (specific and non-specific) are envisaged within the brain. Each is the source of a distributed voltage field, which generates a quantum wave function. When these two superposed wave functions achieve a sufficient degree of coherence to exceed some threshold, the quantum fields collapse. Consciousness is postulated to emerge from the collapse of these two wave functions, generating a perceptual frame [29,41,151,179,189].

Several theoretical proposals have focused upon possible mediation of quantum mechanical processes by microtubules. The microtubular structure within neurons constitutes channels where mitochondria pump ions. Bundles of pyramidal cells bound together by cooperative processes produce spatio-temporal patterns coupled by long-range coherence in microtubular connections, which may establish consciousness, or 'awareness' [41]. Jibu and colleagues [73] presented a theoretical prediction that microtubules could act as non-linear coherent optical devices, based upon dynamic interactions produced by boson condensations between the dipole fields of water molecules confined within their hollow core. Super-radiant optical computing in cytoskeletal microtubule networks was suggested as a basis for biomolecular cognition and a substrate for consciousness. The conformational states of microtubule subunits (tubulins) are coupled to internal quantum events and interact cooperatively with other tubulins. If such interaction took place throughout significant brain

QEEG VARETA Images at 3.5 Hz

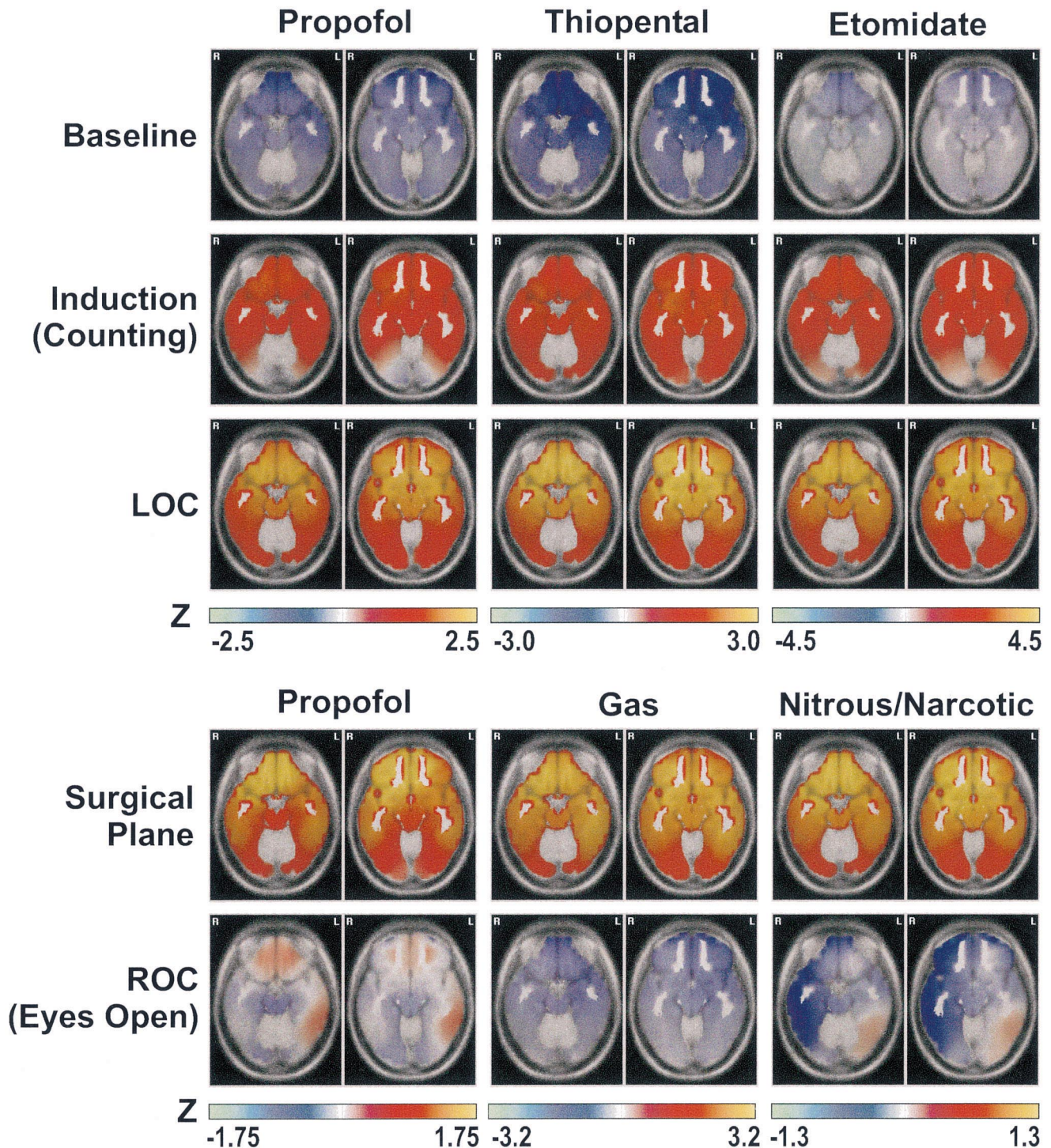


Fig. 3. Five rows of paired VARETA images are shown, superimposed upon two levels vertically separated by 7 mm, of transaxial slices from a probabilistic MRI atlas [16,45]. Each image is based upon mean voxel values of absolute power in a 0.39-Hz spectral window centered at 3.5 Hz., averaged across 15 patients under the corresponding conditions. 3.5 Hz was the frequency at which the variance across states was greatest, typical of findings found to be independent of anesthetic agent in the full sample of 176 cases which were studied. These images illustrate statistical probability VARETA images in five states: (row 1) premedicated baselines; (row 2) during induction of anesthesia while counting; (row 3) just after loss of consciousness (LOC); (row 4) typical stable state during surgical maintenance, and (row 5) reversal with return of consciousness as eyes opened (ROC). Note the similarity of changes although different agents were used during induction and during surgical maintenance. Every voxel is color-coded to correspond to the Z-score of the deviation from the normative resting distributions of that voxel at that frequency. Hues of red to yellow indicate positive deviations and blue through turquoise negative deviations relative to the mean pre-induction baseline values across 176 cases. The palette on the color bar corresponds to the voxel Z-scores. Statistical significance of changes in any voxel can be estimated by multiplying the voxel Z-score by the square root of the sample size, or 3.8. (For more details, see Ref. [88]).

volumes, it might provide the global binding essential to consciousness [64]. Most recently, this group has proposed that visual consciousness occurs as a series of several-hundred-millisecond epochs, each comprised of 25-ms ‘crescendo sequences’ of quantum computations. These crescendo epochs correspond to perceptual frames [213].

A detailed model for quantum mechanical brain processes has recently been proposed by Pribram [158]. This model proposes that activity in the teledendron branches of an axon can be described by a Schrodinger-like wave equation. As propagating activity reaches the synaptic cleft it is ‘read’, and the wave equation collapses into a singularity. Pribram attributes this formulation to prior ideas that two quantum fields interacting with each other in an extended region of brain tissue in which a macroscopic ordered domain structure exists might mediate the storage and retrieval of memories. The macro-chemical synaptic process is the observing instrument that leads to the wave function reduction. This theory is similar to the self-orchestrated reduction of the wave function suggested by Hameroff and Penrose [64]; however, the process does not take place in the main trunk of the axons but rather in the branching teledendrons. While this is reminiscent of the earlier suggestion by Eccles that synaptic chemistry may play a role in a quantum-like neural process, it is compatible with the criticism of that proposal that synaptic chemistry must remain classical and not quantum-like, as pointed out by Wilson [212].

13. A neurophysical theory of consciousness

Much of the present formulation benefits from the insightful recognition by Tononi and Edelman [201] of the need to evaluate the simultaneous deviation from statistical independence among all elements of a system. Their concept of ‘complexity’ is particularly relevant, i.e. the sum of mutual information across all bipartitions of a system corresponds to its complexity. Mutual information refers to the statistical independence between any region in the system and the rest of the system. High values of complexity correspond to optimal differentiation and functional specialization within the brain. Edelman and Tononi concluded that conscious experience involves high complexity, with differentiated activation or deactivation of widely dispersed brain areas.

‘Level of complexity’ corresponds to the dimensionality of the signal space, which can be defined as the number of spatial principal components (SPCAs) needed to account for some specified high level of communality. During the alert state or REM sleep, complexity is high. A relatively large number of SPCs is required to span the signal space. Compared to the alert conscious state, the sleeping or anesthetized brain has low complexity. In cognitive deterioration of aging and in anesthesia, the dimensionality

of the signal space decreases and complexity diminishes [88]. Coherence changes in deep sleep have been found to be similar to those in anesthesia [1,117]. It seems probable that sensory specific and non-sensory specific inputs to the cortical pyramidal comparators do not achieve coincidence in these states [121].

Edelman and Tononi were cognizant of the difficulty of specifying an appropriate baseline from which to quantify such fluctuations. One possibility is to define the baseline or ground state as that found in the absence of consciousness, as in anesthesia or deep sleep. The difficulty with selection of ‘nothingness’ as the reference is that no relatively invariant descriptors of this state are known that are ethnically- and culturally-fair and have high test-retest reliability. For this reason, we prefer to define the ground state based upon the globally replicated norms of the eyes-closed resting EEG power spectrum and the number of SPCs or microstate categories required to account for a specified percentage of the system variance. Although it is apparent that cognitive processes, ‘day dreams’, frame creation and dynamics are continuously ongoing, the fluctuations of state that accompany such activity in the eyes-closed alert individual are so transient that, if averaged across a short period, they are subsumed within the variance of the normative distributions.

A brief synopsis of the theory, an endeavor to synthesize this body of experimental evidence, is as follows. Thresholds defining ‘non-random levels’ are provided by genetically specified systems that achieve homeostatic regulation of electrical transactions within and between brain regions. These thresholds constitute set points of the brain’s ‘ground state’. When there are no significant deviations from these set points, the brain is considered to contain zero information. Thus, the ground state is considered to define maximum entropy. Synchrony within and coherences among excited brain regions which deviate from this ground state are accordingly considered as negative entropy, and activate coincidence detector neurons throughout the cortical mantle. Cortico-thalamic volleys from the dispersed coincidence detectors converge to bind the fragmented information into a coherent process within the thalamus. Re-entrant pathways produce thalamo-cortical reverberations integrating the coherent thalamic ensembles with the cortical regions where these coherent volleys were initiated. Sustained reverberations lead to resonance in the re-entrant loops. Consciousness emerges as a physical property of this critical mass of resonating energy.

Mathematical formulations of the assumptions and ideas in the following sections of this paper can be found correspondingly numbered as items B.1–B.13 in Appendix B.

Note that for simplicity, the formalisms in Appendix B define brain states in an essentially linear fashion, as multivariate deviations which constitute negative entropy relative to the maximum defined by the normative set

points of the ground state. Global Negative Entropy might be better described as an inverted U-function. Phasic perturbations such as multimodal sensory input, task performance or other cognitive processes must decrease entropy. However, there are extremely significant deviations from the ground state, as in a variety of developmental, neurological and psychiatric dysfunctions, epileptic seizures, sleep, anesthesia and coma, which also reduce entropy. The central regions of a phase space which defines the ground state of maximum entropy is thus bounded on one side by ‘refractory states’ characterized by negative entropy and decreased complexity or dimensionality, and on the other side by decreased entropy but increased dimensionality. Differences between the refractory and reactive states would be reflected by differences in inter-regional coherence and in the abundance of coincidence between activity of pyramidal cell synapses in upper (non-sensory specific) and lower (sensory specific) layers of the cortex. For succinctness, this discussion will focus on reactive state changes related to consciousness and information processing.

13.1. ‘Ground state’

A genetically determined complex homeostatic system regulates three aspects of brain electrical activity: (i) local power spectra in each brain region, (ii) the covariance of power among regions across frequencies (coupling of functional subsystems mediating informational transactions) and (iii) parsing these spatiotemporal patterns into discrete epochs of time. These can be statistically predicted using normative mean values and standard deviations, which define the ground state, G (B.1). The power of the EEG is its variance, σ^2 (B.2). Therefore, the local LFP power corresponds to the variance of the local neural synchronization and the power of interactions among regions corresponds to their covariance.

13.1.1. Population normative reference

The probability that a present brain state deviates significantly from the ground state can be estimated by computing the statistical significance of the distance of the present state from an n -dimensional ‘hypersphere’, centered at the origin of the signal space as defined by the mean values and with radii defined by the standard deviations of normative parameters (B.3). The Mahalanobis distance across the multivariate descriptors provides such an estimate [78] (B.4).

13.1.2. Self norm reference

If probabilities of deviations were assessed relative to a ‘self norm’, a more physiological detection process can be envisaged in the brain. If $\sigma^2(G) = G$ is power in the ground state and $\sigma^2(E) = E$ is power in some excited state, then the ratio of power in the excited to that in the ground state can be considered as an F -ratio, i.e. $F = E/G$. Such a

ratio scales LFP proportionally, relative to the homeostatically regulated normative fluctuations of power around the ground state. Phasically adaptive, short-term reference values might be developed by the brain from the just previous perceptual frame or dynamically adjusted by current levels of arousal or of interoceptive and exteroceptive activity. A change of state from an adaptive reference might serve to detect changes in some component of the complex stimulus environment.

13.1.3. Entropy of the ground state

When distance of the present state from the ground state is not significant, the probability is approximately equal to 1.0 and the information is zero. In the ground state, the entropy of each region equals its maximum value, which is zero (B.5). The global entropy of the ground state is the sum of these maxima (B.6).

13.2. Information input causes an excited state

Informational ‘signals’ consist of significantly non-random synchronization within multiple dispersed brain regions and of altered coherent interactions between those regions. Power changes in any brain region or neural transaction greater than the threshold relative to the ground state may be thereby identified as information, an excited state (B.7).

13.3. Local negative entropy

When a change takes place in the complex of exteroceptive or interoceptive inputs, afferent effects propagate throughout the system. Synchronized non-random discharges occur within responsive brain regions. These significant deviations from the ground state are information (that which is improbable), and therefore entropy decreases in each of these neural assemblies. The difference in entropy between the excited state and the ground state defines the ‘local negative entropy’, $LNeg$ (B.8).

13.4. Global negative entropy

The entropy of the whole brain can be expressed as the sum of the entropies of all regions and interactions. When all local ensembles are in the ground state with a known spatial distribution of power, the global brain entropy is zero. Occurrence in any regions of significant differences in entropy between two successive perceptual frames results in an excited brain state with a distribution of power that could not be predicted. Comparators of sensory specific and non-sensory specific input to some regions achieve high levels of coincidence. Supra-threshold corticofugal discharges from such regions converge on sub-cortical structures and the resulting state of the system constitutes ‘global negative entropy’, $GNeg$ (B.9).

13.5. Information content of the brain

GNeg can be conceptualized as an intermittent avalanche of fluctuating coherent discharges converging upon some consciousness system, the hypothetical neural correlate of consciousness, NCC. This avalanche is the momentary information content of the brain. The definition of informational activity is thus essentially statistical in nature, derived from improbable local synchrony that is coherent across spatially distributed neuronal masses. GNeg is a spatio-temporal probability density function, Ψ_E .

Consciousness must encompass the information content of the brain. Were the brain itself sensitive to the momentary probability density function, this might correspond to ‘dynamic self-awareness’. Some brain process must detect dispersed improbable local states and recombine them into an integrated global perception. No cell in an ensemble can assess the non-random behavior of that ensemble nor mediate the required integration of globally distributed coherent activity represented by GNeg.

14. Fractionation of GNEG into sensory specific and non-sensory specific subsystems

The spatially distributed, temporally fluctuating probability density function that is GNeg, Ψ_E , can be quantitatively decomposed into multiple simultaneous spatially and temporally co-existing modes of oscillation, sharing the total population of cells in the cortex. These modes correspond to a set of spatiotemporal principal components (SPCs) that span the signal space, plus some residual variance.

Any individual neuron in a region may be recruited into alternative modes of interaction with many other local or distant assemblies. Resources can thus be allocated to augment or diminish the signal to noise ratio of the corresponding elements of information, while a reserve population is maintained to meet possible additional demand. The ‘loading’ of each SPC is a matrix that defines a particular pattern of spatiotemporal covariance in that global mode within a functional neuroanatomical subsystem of elements. Each subsystem consists of significantly synchronized neuronal ensembles or cell assemblies dispersed within all brain regions and their coherence with each other. The momentary engagement of any of these elements in a particular mode of interaction is quantifiable by its ‘factor score’, for which there are normative values. The factor score of an element within such functional subsystems may fluctuate to reflect some particular attribute of an excited state. Significant deviation of any element from such normative values constitutes local negative entropy. Their sum across an SPC quantifies the global negative entropy in that mode (B.10).

For each mode of oscillation, SPC_i , one probability matrix, Ψ_i (ss), describes the non-random covariance of power caused by the axosomatic afferent input to the

stellate and pyramidal cell bodies in layers IV and V of each region in the cortex. The resulting field represents the encoding of exogenous sensory specific information about a set of attributes that are present in the complex external and internal environment and momentarily co-vary in the corresponding mode. A second matrix, Ψ_i (ns), represents the non-random covariance of power contributed to the same mode of oscillation by inputs to the apical dendrites of those same populations of pyramidal cells, in upper layers of each region. The resulting field represents the encoded readout of endogenous non-sensory specific information, arising from neural ensembles activated by collateral inputs from momentary contextual cues, accessing relevant working and episodic memories, affective valence and motivational influences of that context, interoceptive reports and kinesthetic tone (B.11).

Specific and non-specific inputs are postulated to each neural ensemble in every spatial mode of oscillation and represent two distinct sources of contributions to GNeg. These coherent patterns of discharges in multiple modes of oscillation coexist in parallel within the same neural space. At every moment, they contribute to the joint establishment of two momentary global spatial probability functions, Ψ_1 (ss) and Ψ_2 (ns), which coexist across the entire cortex (B.12).

15. Construction of ‘perception’ from sensation

Ψ_1 and Ψ_2 define two non-random charge distributions that are anatomically separated into two levels of the cortex, a superficial upper region (layer 1) and a deep lower region (layers 4 and 5). Ψ_1 identifies all multimodal features of the complex environment, dispersed to specialized ‘feature extractor’ ensembles in many different brain regions. Ψ_2 arises concurrently from the activation of past experiences and states, especially those which were relevant to or induced by the just-previous perceptual frame. Perception and adaptive subjective awareness of the environment requires a comparator between these two representations (B.13).

Recapitulating previously cited evidence: a neuronal mechanism couples inputs to these different cortical layers so that properly asynchronous somato-dendritic interactions greatly enhance axonal output from cortical neurons to other cortical regions and the thalamus [106,181]. Reverberatory activity in cortico-thalamo-cortical loops is especially reflected by oscillatory waves in the gamma band. Associative synaptic plasticity is facilitated by active back-propagation of axosomatic action potentials to the dendritic arborization of neocortical neurons, thereby acting as a filter to modulate synaptic efficacy [186]. Such mechanisms can create as well as detect synchrony of spike timing across cortical laminae [11]. Oscillatory LFPs in the beta, alpha and theta/delta frequencies are correlated with depolarization of neural membrane potentials and

may facilitate synchrony between distant regions of cortex [210].

It is postulated that non-random but asynchronous modes of coherent activity in spatially separated ensembles, identified by similar coincidence detectors distributed throughout the brain (B.12), are synchronized by inclusion within the same perceptual frame. Coherent corticofugal discharges from these coincidence detectors, parsed by the framing process into microstates, converge upon the thalamus and other subcortical structures. This convergence binds these elements into a unified percept and results in reverberation with the assemblies that initiated those discharges. Sustained reverberations build into a resonating electromagnetic field which is the ‘embodiment of the mind’ [153,154]. Consciousness is a physical property emerging from a critical mass of global negative entropy in the region of space within the brain.

16. A schematic model of the theory

This theory envisages five critical stages, schematized in elements 1 to 16 of Fig. 4. These stages are explained below and summarized in the figure legend.

16.1. Perceptual frame opens (elements 1–5)

At the onset of a ‘perceptual frame’, (1) multimodal complex environmental stimuli (A_i , V_i , S_i) impinge upon sensory receptors; (2) in the thalamus, these afferent inputs are directed to relay nuclei specific for each modality; (3) multiplexed thalamo-cortical volleys, parsed into ‘perceptual frames’, arrive at the cortex quickly over paucisynaptic pathways. The information about each complex is dispersed among the axosomatic synapses of specialized feature extracting cell assemblies, which decompose the stimulus into attributes which are ‘fragments of sensation’; (4) discharge in local ensembles becomes non-random, producing local negative entropy (LNEG-A1, LNEG-V1, etc.); (5) each perceptual frame lasts ~70–100 ms (1/alpha frequency) and successive frames are each offset by 20–25 ms (1/gamma frequency); this multiplexed activity will produce a steady state which will persist independent of the discharge of particular neurons, much like a ‘sample and hold’ process, which may be a local circuit reverberation or dynamic inhibition. The axosomatic field Ψ_1 (‘sensation’) becomes established throughout the cortex largely via these volleys of sensory specific thalamo-cortical projections. This spatially distributed activity encompasses all of the ‘fragments of sensation’, and corresponds to ‘local negative entropy of sensory attributes’ (LNeg(S)).

16.2. Relevant context is represented (elements 6–7)

In parallel with the afferent frames that enter the thalamus, (6) collaterals activate regions of the brainstem

reticular activating system, cerebellum, limbic system and other non-specific brain regions already primed by inputs in the immediate past; (7) consequent modes of oscillation, induced by but not time-locked to any of the multimodal stimuli contained in each perceptual frame, are endogenously generated. These ‘readouts’ of recent working memory, episodic memories, and the states of autonomic, emotional, motivational, and motor systems, are then projected to the thalamic diffuse projection nuclei. There they are combined into a hedonic ‘value’ state (meaning?) and projected via non-sensory specific thalamocortical pathways to axodendritic synapses of pyramidal cells, in layer 1 of the cortex. This projection generates Ψ_2 , necessary to provide a relevant context for evaluation of the complex afferent stimuli and selection of adaptive reactions to the incoming sensations. This readout arrives at axodendritic synapses with some delay, due to multisynaptic pathways relative to the latency of the paucisynaptic pathways activating the axosomatic elements of Ψ_1 .

16.3. Sensory fragments are converted to fragments of perception (elements 8–9)

As successive frames concatenate, (8) those elements of internal state most relevant to the present environment deliver an increasingly strong ‘value’ signal into the comparator system that is constituted by the pyramidal cell network distributed throughout the cortex; (9) in those pyramidal cells whose coherent axosomatic post-synaptic potentials deviated from randomness, producing uni-modal ‘fragments of sensation’ subsumed by the field Ψ_1 (LNEG-A1 or LNEG-V1), and upon which concordant axo-dendritic post-synaptic inputs impinged due to elements of the value signal Ψ_2 , shifts of membrane potentials exceed a critical threshold. Neurons in these ensembles consequently develop a significantly enhanced rate of cortico-thalamic discharge. They are thereby selected automatically and their activity is converted from unimodal fragments of sensation to become multi-modal ‘fragments of perception’, LNEG-P(A1,V1).

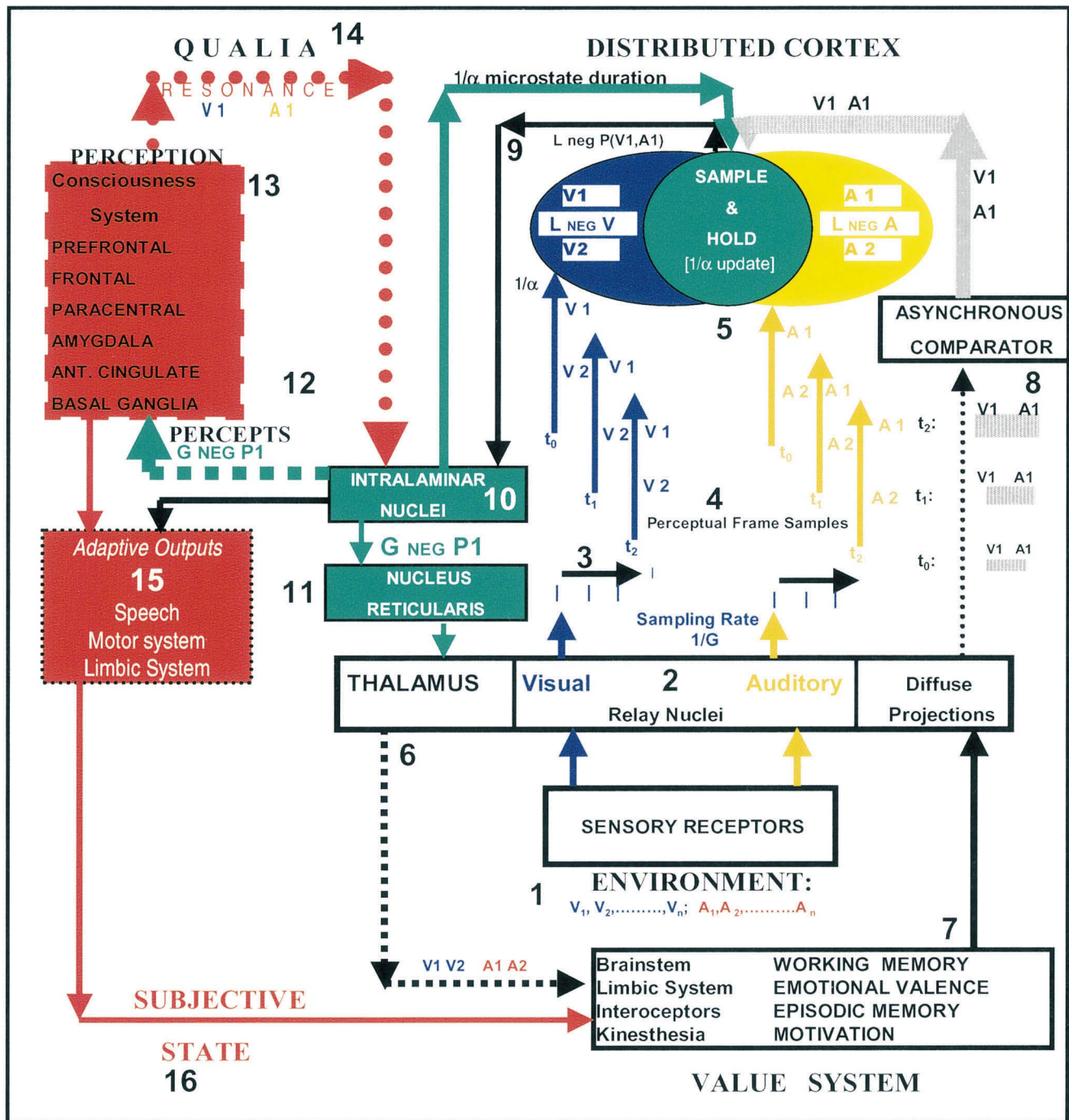
16.4. Perceptual elements are bound together (elements 10–11)

A cooperative process is required for the multidimensional binding which provides the fine texture of consciousness and the global nature of a momentary cognitive instant of experience. No cell nor ensemble can subserve the large scale integration required for cognitive interpretation of the totality of significant departures from randomness which constitutes the GNEGP, the integration of LNEGP activity synchronized across spatially distributed neuronal masses. The actual binding process has been envisaged as a global resonance state [199], resulting from the coincidence detection of concurrent specific and non-specific neuronal processes. (10) We propose that rhythmic

oscillatory potentials, closely phase-locked across the cortex, superimpose a fluctuating synchronizing or ‘scanning’ voltage which modulates the membrane potentials of cortical populations. Such influences may pertain to the entire EEG power spectrum or may be restricted to some special frequencies such as the gamma band or to all frequency bands. This formulation is reminiscent of the concept of scanning by a subcortically timed modulation, proposed a half century ago by Pitts and McCulloch [153]. Rhythmic fluctuation of cortical membrane potentials

intensifies a multi-modal cortico-thalamic volley of the distributed LNEG fragments of perception that is synchronously projected from many cortical areas upon appropriate thalamic regions. These fragments of percepts converge as a coherent cortico-thalamic volley upon the intralaminar nuclei, where they are ‘bound’ into the multimodal, global negative entropy of perception, GNEG-P1. GNEG-P1 is the information content of momentary self-awareness.

(11) Corollary discharges instruct nucleus reticularis to



inhibit those thalamic neurons whose activity just previously projected to the cortex did not contribute to the concordance, thereby optimizing the ensuing signal to noise ratio. This process binds the multi-modal attributes of a stimulus complex, assembled from departures from random firing in dispersed, specialized, feature extracting cell assemblies, into an integrated global pattern of covariance, which defines the information content of momentary self awareness, GNEGP1.

16.5. Consciousness emerges from resonating organized energy (elements 12–13)

A reverberatory thalamo-cortico-thalamo interaction arises between the thalamic nodes representing GNEGP and those brain regions wherein LNEGP arose, which endows GNEGP1 with specific sensory and emotional dimensions, the ‘qualia’ of the subjective experience.

(12) Simultaneously, the global perception, GNEGP1, is projected to a consciousness system, CS. The CS is defined as that set of brain regions which changes its state reversibly with loss of consciousness, independent of the anesthetic agents. The CS is activated into a highly coherent state by neuronal projections from the nodes of covariance in the thalamus; (13) coherent activation within this set of structures transposes GNEGP into a concentrated electromagnetic field. Establishment of a sufficiently non-random spatio-temporal charge aggregate within a critical neural mass is postulated to produce consciousness, an emergent property of sufficiently organized energy in matter.

In this model, axosomatic and axodendritic synaptic inputs cause discrete neuronal discharges that can be

considered as ‘digital’ events, establishing non-random departures from system setpoints, and leading to coherent cortico-thalamic volleys. Coherent reverberating activation within the CS transposes these digital processes into a concentrated ‘analog’ electrical field in a restricted space. In electronic terms, the brain is a hybrid system.

16.6. The content of consciousness and the self (elements 14–16)

(14) By resonance between the CS and the intralaminar nuclei, and thence to the steady microstate sustained by the cortical reverberation, the percept ‘P1’ is endowed with the qualia A1 and V1, updated with each arriving perceptual frame; (15) subjective awareness of the percept P1 and its constituent attributes emerges as an intrinsic property of the coupling of the analog CS with the digital microstate. It is postulated that much of the early life of human beings is devoted to learning how to reconcile these two classes of brain activity; (16) the resonant activity impinging upon the adaptive output systems provides feedback to update the value system. Interactions of the intralaminar nucleus and other thalamic nuclei with CS structures modulate efferent systems to produce adaptive outputs such as speech, movement and emotional expression.

17. Testing the theory

The question of how such a theory can be tested must immediately arise. Since novel mechanisms have been

Fig. 4. The items below correspond to each numbered element of this figure. PERCEPTUAL FRAME OPENS: (1) Multimodal complex environmental stimuli (A_1, V_1, S_1) impinge upon sensory receptors; (2) in the thalamus, these afferent inputs are directed to relay nuclei specific for each modality; (3) multiplexed thalamo-cortical volleys, parsed into ‘perceptual frames’, disperse each complex among specialized feature extracting cell assemblies which decompose the stimulus into fragmented elements; (4) each perceptual frame lasts ~70–100 ms (1/alpha frequency) and successive frames are each offset by 20–25 ms (1/gamma frequency); (5) as each volley impinges upon the appropriate feature extracting population, local discharges become non-random, producing local negative entropy (LNEG-A1, LNEG-V1, etc.). This activity will be potentiated by a ‘sample and hold’ process which may be a local circuit reverberation or dynamic inhibition. RELEVANT CONTEXT IS REPRESENTED: (6) As the afferent frames enter the thalamus, collaterals activate regions of the ascending reticular activating system, limbic system and other non-specific brain regions already primed by inputs in the immediate past; (7) neural activity representing working memory, episodic memories, and the autonomic, emotional, motivational, and motor systems are projected to the thalamic diffuse projection nuclei, and combined into a hedonic state ‘Value’ (meaning?) to provide a relevant context for evaluation of the stimulus. SENSORY ELEMENTS ARE CONVERTED TO PERCEPTUAL: (8) As successive frames concatenate, those elements of subjective state most relevant to the present environment deliver an increasingly strong ‘value’ (meaning?) signal into an asynchronous comparator, induced by but not time-locked to any of the multimodal stimuli contained in each perceptual frame; (9) those elements of LNEGA or LNEGV which are matched to elements of the value signal (meaning?) in the comparator and thereby ‘identified’ are now projected from each region as a cortico-thalamic volley of fragments of perception, LNEG-P ($A1, V1$). PERCEPTUAL ELEMENTS ARE BOUND TOGETHER: (10) These fragments of percepts converge upon the intralaminar nuclei where they are ‘bound’ into the multimodal, global GNEG-P1; (11) intralaminar influences upon n. reticularis cause modulation of excitability of thalamic neurons, identifying the focus of attention to enhance the signal to noise ratio of the features A1 and V1. CONSCIOUSNESS EMERGES FROM RESONATING ORGANIZED ENERGY: (12) Simultaneously, the global perception, GNEG-P1, is projected to the consciousness system, CS; (13) subjective awareness of the percept ‘I’ emerges as a property of an electrical field resonating throughout CS. THE CONTENT OF CONSCIOUSNESS AND THE SELF: (14) by resonance between the CS and the intralaminar nuclei, and thence to the steady microstate sustained by the cortical reverberation, the percept ‘I’ is endowed with the qualia A1 and V1, updated with each arriving perceptual frame; (15) resonant interactions of the intralaminar nucleus with CS structures modulate efferent systems to produce adaptive outputs such as speech, movement and emotional expression; (16) the resonant activity impinging upon the adaptive output systems defines the momentary subjective state of the ‘self’ and provides feedback to update the value system.

proposed on several different levels, it is necessary to envisage several levels at which these hypotheses might be tested.

17.1. Coincidence detector experiments

(i) In differentially conditioned animals with intracortical electrodes and subdural cannulae over primary sensory cortical regions in the modality of the conditioned stimuli (auditory and visual CS), study the effect on accuracy of behavioral discriminations and cortico-thalamic afferent discharges of pyramidal neurons in response to a CS, with and without subdural micro-infusion of KCL to cause spreading depression. Spreading depression on the cortical surface has been shown to markedly decrease the firing of thalamic neurons [24]. This suggests that inhibition of axodendritic synapses might have blocked coincidence detection and cortico-thalamic discharge from being evoked by conditioned cues. It would be informative to titrate the KCl concentration against gamma abundance. If conditioned response blockade or loss of consciousness ensued when gamma disappeared, this would support some of these theoretical proposals. A similar experiment could be performed using infusion of CaCl to inhibit only apical dendrites in the cortex.

(ii) In human subjects during neurosurgery, stereotactically guided micro-injections of KCl, CaCl, barbiturates or anesthetics, analogous to the Wada test but made directly into brain parenchyma, could also be extremely informative.

(iii) In animals with electrodes implanted into sensory specific relay nuclei (SS) such as the lateral or medial geniculate bodies, non-sensory specific nuclei (NS) such as medialis dorsalis, and the visual and auditory cortex, study the efferent volleys from the sensory cortices to (1) the thalamus, and (2) the dorsolateral prefrontal cortex as a function of delays between electrical pulses delivered to the relay nuclei (SS) and subsequent pulses delivered to the intralaminar nucleus, medialis dorsalis or other NS nuclei.

17.2. Field perturbation experiment

Tests can be devised to probe the postulated dependence of consciousness upon an electrical field including the dorsolateral and mesial orbital prefrontal cortex, anterior cingulate cortex, amygdala and basal ganglia, comprising a hypothetical consciousness system (CS). In trained animals or in humans (when intracerebral electrodes have been implanted in patients for diagnostic evaluations), the effects can be studied of either (i) tonic disturbance of the electrical field by imposing DC voltages between electrodes in pairs, in several or all of these neuroanatomical regions, or (ii) phasic perturbations of the electrical field by superimposing low frequency electrical voltages upon

all members of this set of leads relative to a reference electrode or simultaneously between pairs of leads with opposite polarity in a montage which will span the postulated system, viz. 1(+) versus 2(-), 2(-) versus 3(+), 3(+) versus 4(-), etc.

17.3. Magnetic resonance studies

Other tests may be devised by readers interested in challenging these proposals and might include studies of changes in nuclear magnetic resonance spectroscopy (NMRS) or functional magnetic resonance (fMRI) studies of these regions during cognitive activity or action of anesthetics. Such tests might also include searching for evidence of intramolecular multiple quantum coherence, using variations of MRI techniques [167].

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Appendix A

VARETA is based upon computation of the full cross-spectral matrix and is a member of the class of minimum norm algorithms used to obtain solutions to the inverse problem in electroencephalography [148]. Such solutions provide an estimate of the locations inside the brain of source current densities which serve as generators of the electrical power measured on the scalp. VARETA requires no assumptions about the number or locations of the sources within the brain, overcoming the non-uniqueness obstacle to localization by assuming a spatially smooth distribution of current density and that activity in these smooth sources must be synchronized. In this regard, VARETA differs from dipole fitting algorithms such as BESA [171] or MUSIC [99,100,136].

This method is a discrete spline distributed inverse solution, which coregisters the scalp electrode positions with a probabilistic MRI atlas [45]. Neuroanatomical masks constrain the permitted source solutions to only lie within gray matter voxels. VARETA superimposes computed sources of deviations of QEEG measures from the ground state upon slices from this atlas. By color-coding each voxel to quantify the change in state, this method provides a ‘virtual MRI’ statistical probability image. Numerous validations of the localization attributed as the most probable position of the generators of abnormal activity within the brain, even in subcortical regions, have been provided by multimodal imaging studies of space occupying lesions [46–49,161].

Appendix B

1. The ground state of the brain is defined by a matrix of the most probable values of a set of parameters. A genetically specified neuroanatomical/neurochemical brain homeostatic system regulates these parameters, including the variance of the EEG or LFPs of a representative set of brain regions, the complex covariance which describes the strength of interactions among all regions, and the parsing rate at which the information content of the momentary set of values is integrated. The normative mean values locate the origins of a multi-dimensional signal space.

2. Variance of the voltage $V = \sigma^2 = \Sigma V^2/N - [\Sigma V/N]^2$. $[\Sigma V/N]^2 = 0$, since the mean voltage of the EEG is zero. Since $\Sigma V^2/N = \text{mean power}$, the variance of voltage is simply the mean power. Thus, the variance of regional neural synchronization is the local EEG power and the power of interactions among regions corresponds to their covariance.

3. Any present state can be defined as a spatio-temporal probability function, or ‘ Ψ ’. Ψ can be estimated by measuring the multivariate probability of deviations from the mean value of distributions of system parameters in the ground state. The probability of such deviations can be assessed by Z-scores relative to population normative data or by F-values of power in excited versus reference states, $F = (\sigma^2(\text{excited})/\sigma^2(\text{ground}))$.

4. Each dimension of the brain signal space is scaled in standard deviations of the random fluctuations around the mean value of a normative distribution derived from a reference sample. The position of any state point in this multi-dimensional space can therefore be interpreted as the probability that a corresponding set of coordinate values might be observed. Such multivariate probability can be estimated by computation of the Mahalanobis distance across the set of measures.

5. The entropy of any region x_i at any time t_k is defined as

$$H(x) = [\Psi_k] = \Psi_k \log \Psi_k.$$

6. In the ground state, the entropy of the brain is

maximum for each region x_i and interactions among all regions (x_{ij}), that is, the activity in every region and interaction does not significantly deviate from the mean value of the homeostatically regulated norms. Global brain entropy, $H(X)$, is simply the sum of the entropies of each region and their interactive relationships

$$H(X) = \sum_i [\Psi_G(x_i, x_{ij})] = \sum_i [1.0 \times \log 1.0] = 0.$$

7. Information in any brain region or interaction is defined as significantly improbable deviations from the random or most probable value, an excited state with negative entropy.

8. When activity deviates significantly from the regulated normative ground state, such a perturbation cannot be predicted. Information is present in the system. If regions or interactions have been perturbed from the ground state G to the excited state E, such a state can be represented by the spatio-temporal probability distribution $\Psi_E(x_i)$. In the excited state E, the local negative entropy, or LNeg is given by

$$LNeg = H[\Psi_E] - H[\Psi_G].$$

9. The global negative entropy (GNeg) integrates the overall loss of entropy at any time t_E , due to the change from the ground state to an excited state, of all regions x_i and their interactions, x_{ij}

$$GNeg = H(X) = \sum_i [H[\Psi_E] - H[\Psi_G]]$$

10. This spatially distributed probability density function, GNeg, can be decomposed into N simultaneous spatially and temporally co-existing modes, as follows:

$$GNeg = \sum [\Psi_1 SPC_1 + \Psi_2 SPC_2 + \dots + \Psi_n SPC_n]$$

11. The ‘loading’ of each SPC_i can be represented as a Ψ_i matrix with $[n \times f]^2$ elements. This Ψ_i matrix specifies the local negative entropy of all neuronal populations and their interactions with all other regions in the corresponding global mode of oscillation.

12. The Ψ_i matrix contains two superimposed components Ψ_i (SS) and Ψ_i (NS). Ψ_i (SS) is the probability density of the field arising from axosomatic inputs to pyramidal cells via sensory specific inputs from the thalamus. Ψ_i (NS) is the probability density of the field arising from axodendritic inputs from the diffuse projection nuclei and the ‘value’ system.

13. The union, Ψ_i (SS) \cup Ψ_i (NS), constructs perception from sensation and defines the content of consciousness, which arises as a property of resonance among all regions in which such coincidences are significant.

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