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The Entwined Mysteries of Anesthesia and Consciousness

Is There a Common Underlying Mechanism?

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Introduction: Entwined Mysteries

THE mechanism by which general anesthetics prevent consciousness remains unknown largely because the mechanism by which brain physiology produces consciousness is unexplained. But the two mysteries seem to share a critical feature— both consciousness and actions of anesthetic gases are mediated through extremely weak London forces (a type of van der Waals force) acting in hydrophobic pockets within dendritic proteins arrayed in synchronized brain systems. Unraveling this common thread may reveal not only how anesthetics act, but also why we are conscious in the first place.

What is anesthesia? Anesthesia provides immobility, amnesia, and loss of conscious awareness, although the latter—loss of consciousness—is often omitted from operational definitions.[1] In recent years, putative sites of anesthetic action for immobility (spinal cord[2]), amnesia (dorsolateral prefrontal cortex,[3] amygdala[4]), and loss of consciousness (networks involving thalamocortical and intracortical— corticocortical—loops, prefrontal cortex, and other areas[5,6]) have been discriminated both anatomically and in terms of sensitivity to anesthetics. Immobility is least sensitive to anesthetics, followed by loss of consciousness and then amnesia, which is most anesthetic sensitive.[7] (Implicit memory may occur without consciousness or movement, but at light levels of anesthetic.[8]) Therefore, lack of movement— even though mediated by spinal cord rather than brain—in the absence of muscle relaxants is a good indicator of both loss of consciousness and amnesia. Autonomic responses are even less anesthetic sensitive than immobility[9] and, in the absence of autonomic-blocking drugs, are thus useful (although not perfectly reliable) early warning indicators of changes in anesthetic depth.

What is consciousness? Unlike other receptor-mediated pharmacologic targets, consciousness is ill-defined, cannot be measured, and generates heated debate about its very nature. Indeed, except for the "dark age" of behaviorism in psychology during most of the 20th century (in which consciousness was, almost literally, a dirty word), conscious awareness has been a prominent mystery in science and philosophy.[10] However, many articles promising to discuss consciousness avoid the issue, *e.g.*, using bait-and-switch techniques to describe memory, learning, sleep, or other related activities. Others deconstruct consciousness into a group of cognitive functions so that the essential feature— conscious awareness— gets lost in the shuffle.[11]

In this article, consciousness will be considered equivalent to even minimal awareness, the ineffable phenomenon of pure subjective experience— our "inner life." Thus, conscious awareness can exist irrespective of memory, cognition, or organizational sophistication (*e.g.*, reflective self-consciousness, higher-order thought, human—as opposed to animal— consciousness[12]). These more complex levels, although difficult to explain, are relatively straightforward compared with the issue of why or how even a slight glimmer of any form of conscious experience occurs at all.

Anesthesia offers a unique and profound opportunity to understand consciousness because it is relatively selective—many brain activities (*e.g.*, evoked potentials, slower electroencephalography, and autonomic drives) continue during anesthesia while conscious awareness disappears. Thus, details of anesthetic mechanism may illuminate how the brain specifically produces consciousness and *vice versa*. This article reviews what is known about mechanisms of consciousness and anesthesia, finding that the "fine grain" of neuronal activities supporting consciousness and the molecular actions of anesthetic gases are one and the same—van der Waals London forces acting in hydrophobic pockets of coherently synchronized dendritic brain proteins. London forces are not chemical bonds but weak quantum interactions (in this regard, anesthetic gases differ in their actions from all other pharmacologic agents). Thus, the relative selectivity of anesthetic gases implies that the quantum nature of London forces may play an essential role in brain function leading to consciousness.

Because consciousness is not directly measurable or observable, we begin with brain functional organization, systems, and activities known to correlate with consciousness.

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The Neural Correlate of Consciousness

Consciousness and Functional Brain Organization

The particular brain systems and their functional activities related to consciousness are known as the neural correlate of consciousness (NCC). Depending on the level of detailed description, the NCC can be identified without necessarily addressing how consciousness is produced within or by the NCC.

Functional frameworks for consciousness stem metaphorically from 17th century French philosopher Rene Descartes' "Theater of Consciousness" (hence "Cartesian theater"). Cognitive scientist Bernard Baars described this idea: ". . . consciousness acts as a 'bright spot' on the stage, directed there by the selective 'spotlight' of attention . . ."[13] Outside the spotlight are vast unconscious contents. But who or what is the audience, and who or what directs the spotlight? Despite these obvious problems, the theater metaphor has proven useful.

In the 1970s, artificial intelligence computer models of brain function used a virtual "blackboard" on which specialized processors and knowledge sources could post their hypotheses about particular stimuli and then "vote" on which one was best. In the early 1980s, brain theorists combined this notion with the Cartesian theater metaphor and anatomical evidence about consciousness, resulting in "global workspace" theory.[14] The stage, blackboard, or workspace is associated with widely distributed ("global") corticocortical neural networks and (in some versions) thalamocortical networks representing perceptual systems and memory. Particular content "on the stage" or workspace is spotlighted or chosen by attentional focusing *via* "bottom-up" thalamic and limbic inputs and "top-down" executive action from prefrontal cortex. Spotlighted networks become the NCC, which continually changes with dynamically shifting, temporary alliances/networks of neurons. Thus, global workspace models demonstrate a dynamical, functional architecture for the NCC.

On the other hand, consciousness may apparently occur in neural networks within localized, selected brain regions. Excessive activity in any feature-selective region may be sufficient on its own for that feature to enter consciousness. Thus, activity in cortical visual "color" area V4 alone can result in the visual experience of color.[15] Other brain regions have been suggested as NCC candidates, *e.g.*, the brainstem and limbic system in Antonio Damasio's and Jaak Panksepp's (separate) views of emotional "core consciousness."[16]

So theoretically, consciousness can occur in what may be termed a global workspace (*e.g.*, for general surroundings, planning and processing—corticocortical and thalamocortical networks) but can also arise in more localized and perhaps separate regions, *e.g.*, overwhelming colors in a sunset (area V4), profound emotional feelings (brainstem, limbic system). The best scientific evidence for the NCC comes from brain imaging and electrophysiologic monitoring with loss of consciousness due to induction of general anesthesia.

The NCC, Anesthesia, and γ Synchrony

Functional brain imaging techniques (positron emission tomography and functional magnetic resonance imaging) show that anesthetic induction/loss of consciousness correlates with reduced metabolic and blood flow activity in brainstem, thalamus, and various regions of cortex, including thalamocortical and corticocortical networks.[5] However, the metabolic and hemodynamic decreases are delayed secondary effects of loss of consciousness rather than its cause. Electrophysiology provides a better correlate.

Electrophysiologic brain monitors used in anesthesiology (*e.g.*, BIS Monitor®, Aspect Medical Systems, Inc., Newton, MA; Patient State Analyzer, Physiometrix, Inc., N. Billerica, MA; Narcotrend, MonitorTechnik, Bad Bramstedt, Germany) provide reasonably accurate correlates of anesthetic depth and presence or absence of consciousness.[17] They rely on spectral analyses and measures of synchrony in the electroencephalogram, particularly γ synchrony: approximately 30–70 Hz or higher, in various brain regions. Similar devices measure entropy in the electroencephalogram, or auditory-evoked γ synchrony.[18,19]

A comprehensive electroencephalographic analysis of anesthetic-induced loss of consciousness was conducted by John and Prichep.[6] Using various anesthetic drugs and techniques, they found that loss of consciousness is a fairly abrupt transition (less than 20 ms) involving interruption of γ synchrony between frontal and posterior cortical regions. Similarly, Imas *et al.*[20] showed that volatile anesthetics disrupt frontal–posterior cortical γ synchrony.

Gamma electroencephalographic synchrony reflecting coherence among different brain regions is the best measurable correlate of consciousness, but is difficult to explain physiologically. Experiments show that γ synchrony is marked by "zero-phase-lag coherence,"[21,22] precisely synchronized voltage fluctuations occurring among varying regions of cortex and thalamus (and spinal cord[23]). Such precise coherence cannot be easily explained by neural networks involving thalamocortical pacing, recurrent feedback, reciprocal connections, propagating action potentials, and/or synaptic transmissions, which all convey significant delay or dephasing.[21,24] As will be discussed below, voltage potentials in cortical dendrites connected by electrotonic gap junctions apparently mediate γ synchrony, but even dendritic potentials introduce significant delay. Some collective field effect must be at play, and electromagnetic field–mediated synchrony is untenable.[25,26] Several experts conclude that a type of quantum field mediates γ synchrony and consciousness.[21,27]

Gamma synchrony is also implicated in "binding" of conscious content. Various aspects of sensory percepts and volitional actions are processed in different cortical regions within single sensory modalities (*e.g.*, visual shape, motion, color), among different sensory modalities (*e.g.*, sight, touch and sound), and at different times, separated from each other by 80 ms or so.[14] But our conscious percepts are somehow "bound" into unified objects and simultaneous events. At any one time, there is only one NCC, and γ-synchronized activities in different brain regions are thought to tie together components of consciousness into unified entities.

Anesthesiologist George Mashour[28] proposed that anesthesia prevents consciousness by unbinding neural activities, primarily by disrupting γ synchrony. This proposal equates binding, consciousness, and the transition from unconscious processes to consciousness through γ synchrony.

The transition from unconscious processes to consciousness is a key question. Most authorities agree that only a small fraction of the brain's 100 billion or so neurons manifests the NCC at any one time, although many more are active.[13] But the same neurons and networks are not always "conscious"—signals and information do not travel to a particular part of the brain where consciousness happens. In the theater metaphor, the spotlight is constantly shifting, with represented content of particular γ-synchronized neural groups becoming conscious sequentially, selected by attentional processes and emotional saliency. (But why γ-synchronized neural activity has the subjective character of experiential awareness remains unexplained.)

Therefore, consciousness seems to be a process, a sequence of transitions from unconscious activity to experienced content, *e.g.*, frames or scenes shifting up to approximately 40 times per second in γ synchrony.[29] But apparently not all brain activity can become conscious. For example, activity regulating autonomic functions almost never becomes conscious, and during anesthesia, nonconscious sensory evoked potentials and some electroencephalographic activity continue in the absence of consciousness. Because dreams (which can potentially become conscious, *i.e.*, when we awaken and remember them) probably do not occur during deep general anesthesia, it is possible that unconscious processes capable of becoming conscious are prevented by anesthetics. Therefore, anesthesia may simply inhibit the necessary antecedent to conscious awareness. But then the specific nature of the necessary antecedent—unconscious processes capable of becoming conscious—must be identified and distinguished from those nonconscious processes which lack the potential to become conscious and are resistant to anesthesia. One line of speculation holds that potentially conscious (unconscious, preconscious, dreaming) brain activities manifest as quantum information originating in intraprotein hydrophobic pockets in the NCC, also the precise site of anesthetic action.

Brain activities of all types are considered to use networks of neurons as functional units. Two types of neural networks operate in the brain, one of which accounts for γ synchrony.

Two Types of Neural Networks

Individual neurons are usually composed of multiple dendrites, one cell body (soma), and one axon (figs. 1A and B). The multiple dendrites receive and integrate many synaptic inputs from axons of other neurons in the form of chemical neurotransmitters, which bind on "postsynaptic" dendritic membrane receptors. Depending on the neurotransmitter, depolarizations (excitatory postsynaptic potentials [EPSPs]) and hyperpolarizations (inhibitory postsynaptic potentials [IPSPs]) are integrated, reach depolarization threshold, and trigger action potentials ("firings" or "spikes") through the neuron's single axon.

In 1949, Canadian neuroscientist Donald Hebb[30] suggested that repeated activity of a given synapse decreased its threshold for subsequent firings, that synaptic "plasticity"—dynamical changes in synaptic strength—sculpted and reinforced specific paths through a network of neurons that would then be easily triggered by a partial stimulus. Evidence verified Hebb's idea that neural activity in the form of EPSPs leading to axonal spikes can follow paths of least resistance through low-threshold synapses, like water flowing downhill (fig. 1C). Such neural "assemblies," as Hebb termed them, could be ignited by particular inputs and remain active for hundreds of milliseconds, after which another related assembly would ignite, then another, and so on in a phase sequence. A commonly held view is that, at any one time, a single particular "Hebbian" neural assembly corresponds with the NCC.

But axonal–dendritic Hebbian networks/assemblies are incompatible with γ synchrony electroencephalography, which is mediated by local field potentials or surface potentials generated by dendritic EPSP/IPSP activity (*i.e.*, dendrites may be synchronized, axonal spikes are not).[31] Although precise zero-phase-lag coherence remains unexplained, coordination of dendritic EPSPs/IPSPs leading to γ synchrony derives from a second type of neural network (fig. 1D)[32]: neurons connected by dendritic–dendritic gap junctions in conjunction with inhibitory synapses mediated by receptors for γ-aminobutyric acid (GABA).

Gap junctions, or electrical synapses, are direct open windows between adjacent cells formed by paired collars consisting of proteins called connexin (fig. 2).[33] Membrane depolarizations travel bidirectionally across gap junctions so that neuronal processes connected by gap junctions are electrically coupled and depolarize synchronously.[34] In adult mammalian brain, gap junc-

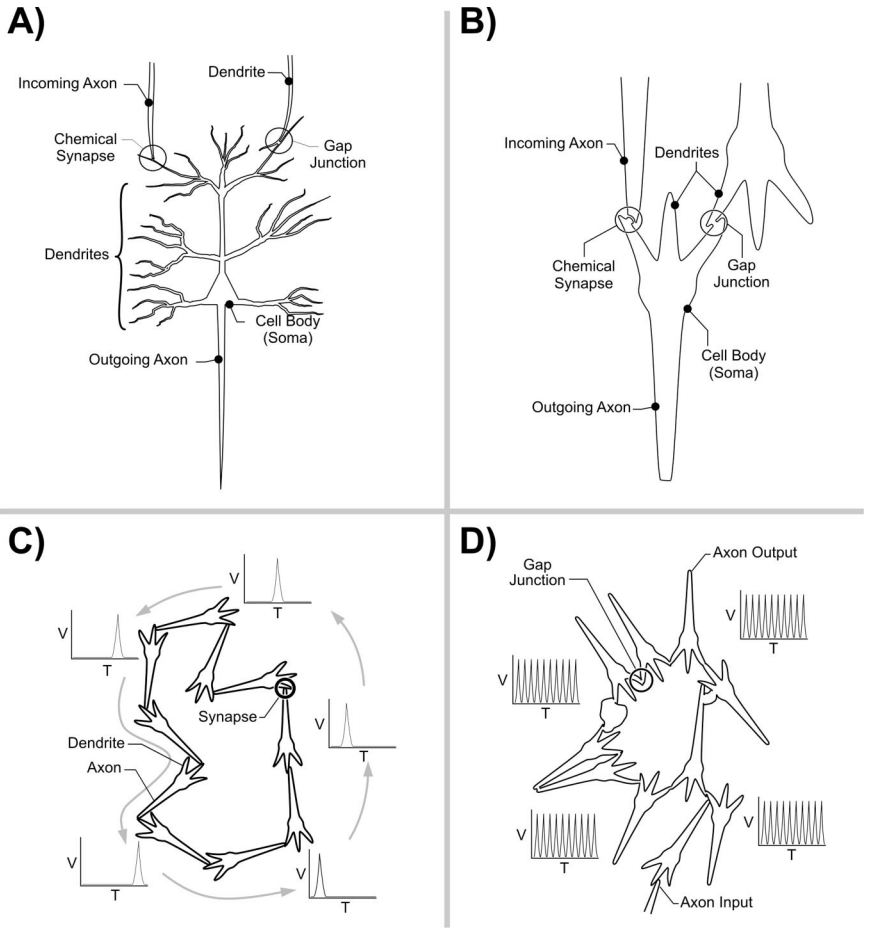

Fig. 1. Neuronal structure and two types of neural networks. (*A*) Cortical pyramidal cell architecture with multiple dendrites branching from a pyramid-shaped cell body (soma) from which descends a single, outgoing axon. Pyramidal cell dendrite (*upper left*) receives incoming axon signal at a chemical/neurotransmitter synapse. Another dendrite (*upper right*) links to another neuron's dendrite by a window-like (dendritic–dendritic) gap junction electrotonic synapse. (*B*) Schematic version of the same type of neuron with three dendrites and single axon, and connections as used in *A*. (*C*) Network of neurons connected serially by axonal–dendritic chemical/neurotransmitter synapses. Information/excitation flows unidirectionally (counterclockwise) from axon to dendrite through the network. Electrical recordings at various points in the network's spatial distribution show single voltage spike potentials propagating spatially through the network. (*D*) Network of neurons (and glia) linked by gap junctions, mostly dendritic–dendritic but also by glial cell gap junctions. Inputs to the network are from axonal–dendritic chemical synapses; outputs from the network are from axons of neuron components. Because gap junction–connected neuronal dendrites depolarize synchronously, electrical recordings at various points in the network's spatial distribution show synchronous voltage depolarizations, *e.g.*, at γ synchrony (coherent 40 Hz). Both membranes and cytoplasmic interiors are continuous throughout the network.

tions connect dendrites to other dendrites, as well as to axons and glia (and in some cases axons to axons).[33] Many cortical interneurons have dual synapses—their axons form inhibitory GABAergic synapses on a dendrite of another interneuron or pyramidal cell, while the same two cells share dendritic–dendritic gap junctions. Gap junctions open, close, and change location, controlled by the cytoskeleton within neuronal dendrites. Thus, dendritic–dendritic gap junction networks can adapt like Hebbian assemblies, extend widely through cortex, and account for γ synchrony.

The blood oxygen level–dependent signal used in functional magnetic resonance imaging—assumed to represent neural metabolic activity related to cognition and consciousness—corresponds more closely with dendritic potentials than with axonal spikes.[35] Evidence seems to confirm that γ synchronized dendritic networks represent the NCC.

Although axonal spikes are usually considered the primary currency of brain information, dendrites more actively process information and can, for example, change axonal spike threshold in a given neuron.[36] Some cortical neurons have no axons, and extensive dendritic activity may occur without causing spikes.[37] EPSPs below spike threshold (historically considered noise by many neuroscientists) oscillate coherently in the γ range across wide regions of brain.[38] Although it is widely assumed to be so, initiation of axonal spikes is not necessarily the *raison d'être* of dendrites. Neuroscientists Sir John Eccles,[39] Karl Pribram,[40] and others suggested that activities within dendritic–dendritic networks host consciousness.

Nor is dendritic processing limited to membrane potentials. Many postsynaptic receptors (including excitatory glutamate and inhibitory $GABA_B$ receptors) are metabotropic, sending signals internally into the dendritic cytoskeleton, activating enzymes, and causing conformational signaling and ionic fluxes along actin filaments and microtubules. Accordingly, brain function leading to consciousness might be ". . . more refined on a higher temporal and smaller spatial scale."[41]

The "Fine Grain" of the NCC: London Forces in Hydrophobic Pockets of Dendritic Proteins

The best electrophysiologic correlate of consciousness—γ synchrony—derives from coherent activities of dendritic postsynaptic receptors, with inhibitory $GABA_A$ receptors in dual synapse interneurons (*i.e.*, with gap junctions) playing key roles. Although the collective mechanism leading to zero-phase-lag coherence remains unknown, γ-synchronized activities of dendritic proteins regulating EPSPs/IPSPs are apparently essential molecu-

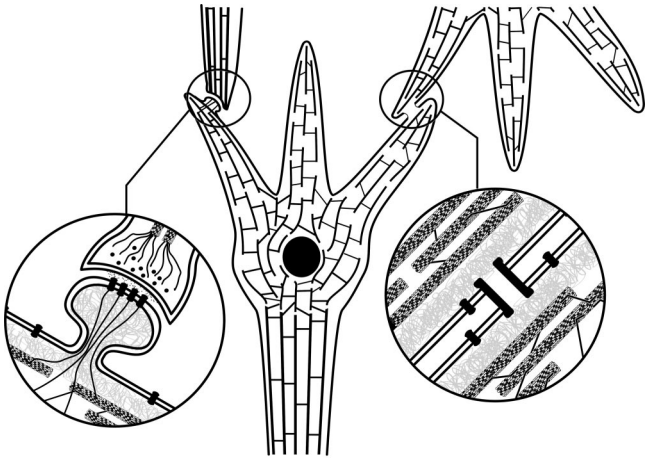

Fig. 2. Schematic neuron—enlargement of figure 1B. Dendrite (*upper left*) receives chemical/neurotransmitter synapse from incoming axon. Enlarged view (*circle*, *left*) shows postsynaptic receptors and cytoskeletal structures in dendritic spine. Actin filaments in spine link to microtubules in main dendrite. Dendrite (*upper right*) connected by gap junction to dendrite of another neuron. Enlarged view (*circle*, *right*) shows gap junction window-like opening formed by collar of connexin protein. Cytoskeletal microtubules interconnected by microtubule-associated proteins are also shown in both dendrites. Anesthetics act primarily on dendritic receptors, channels, and cytoskeletal structures.

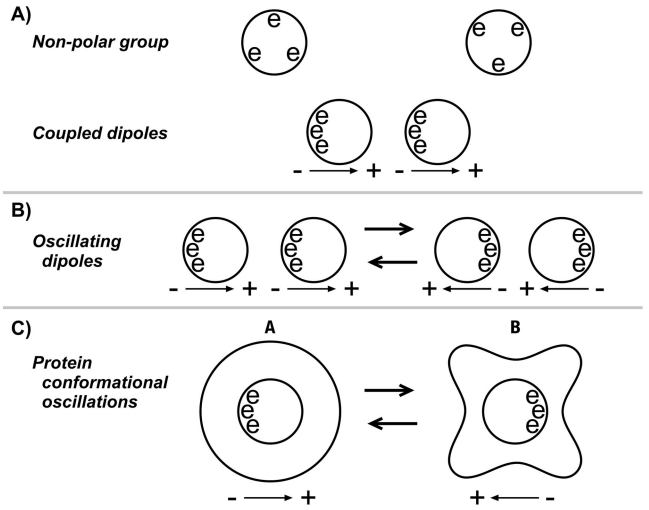

Fig. 3. Van der Waals London forces. (*A*) Electron clouds in two nonpolar groups (*e.g.*, aromatic rings, methyl groups, anesthetic gases) induce instantaneous mutual dipoles which then attract each other, forming a coupled dipole pair. (*B*) The instantaneous electron cloud dipoles (London forces) oscillate. (*C*) Schematic protein oscillates between two conformational states A and B, governed by London force dipoles in nonpolar, hydrophobic pockets. For simplicity, only one nonpolar group is shown in the hydrophobic pocket.

lar-level correlates of consciousness: Coherent dynamics of dendritic proteins accounts for γ synchrony. (Anesthetic gases also act on γ-synchronized activities of dendritic proteins.)

Proteins perform their functions by changing shape, or conformation, switching between energy minima. For example, ion channels open and close, receptors and enzymes grab ligands and substrates, *etc.* Many such changes, or prevention of change, occur in response to binding of a ligand at a site on the protein structurally removed (by up to 3 to 4 nm) from the conformational effect. To account for such indirect actions, Monot, Wyman, and Changeux proposed "allosteric" mechanisms in the early 1960s, superseding steric hindrance models, which required more direct contact between ligand and affected sites and activity.[42] In the absence of ligand, proteins undergo spontaneous dynamical transitions between two or more distinct conformations. According to allosteric theory, binding of a ligand in one particular conformational state stabilizes/activates that state and inhibits the dynamical switching, thereby preventing, depopulating, or deactivating alternative states. Allosteric theory also predicted (correctly) that many proteins such as receptors/ion channels are oligomeric complexes comprised of multiple subunits with rotational symmetry whose function depends on cooperative transitions among the subunits. Thus, ligand binding in one region of one subunit could affect the function of the entire complex.

However, allosteric theory does not account for spontaneous conformational dynamics in the absence of ligand. Most functional protein transitions occur in the range from 10^{-6} to 10^{-11} s,[43] but their regulation remains unclear. Proteins have large energies with thousands of kilojoules per mole available from amino acid side group interactions, but proteins are only marginally stable against denaturation by approximately 40 kJ/mol. Consequently, protein conformation is a "delicate balance among powerful countervailing forces."[44] As higher energy, longer time scale chemical and ionic bonds cancel out, weak but fast forces (*e.g.*, van der Waals forces) acting collectively can tip the delicate balance.[44]

Van der Waals forces are dipole couplings among nearby atoms or molecules, and there are three types. The first occurs between permanent dipoles in polar molecules, like two tiny bar magnets attracting each other's opposite poles. The second type of van der Waals force is between a permanent dipole and a neutral atom or molecule with a nonpolar (but polarizable) electron cloud. The permanent dipole induces a temporary dipole in ("polarizes") the nonpolar electron cloud; the permanent and temporary dipoles then attract each other. The third type of van der Waals force is the London force, which occurs between two neutral, nonpolar atoms or molecules (figs. 3A and B). Adjacent nonpolar electron clouds polarize each other, inducing mutually fluctuating temporary ("instantaneous") dipoles, which then attract each other like oscillating bar magnets.[44] London force attractions depend critically on precise distance between electron clouds, and are extremely weak. (If the electron clouds get too close, strong repulsive forces take over.) However, groups of

individually weak London forces acting collectively/coherently are sufficiently strong to regulate protein conformation. Confluences of London forces which occur within some proteins in nonpolar regions called hydrophobic pockets can exert such collective effects (fig. 3C).

Individual proteins are linear chains of amino acids which fold into three-dimensional conformations, driven by merging of uncharged nonpolar amino acid groups repelled by solvent water (hydrophobic effect). Once in proximity, these nonpolar groups (*e.g.*, aromatic rings of phenylalanine, tryptophan, and tyrosine as well as side groups of leucine, isoleucine, and valine) attract each other by van der Waals forces, avoiding water and burying themselves within protein interiors, forming hydrophobic pockets.[44] In many proteins, two or more aromatic rings form groups or stacks within pockets, which stabilize and regulate protein structure.[45] Hydrophobic pockets can be on the order of approximately 0.3 nm^3, roughly one hundredth the volume of single proteins.[46]

Within hydrophobic pockets, weak London forces—instantaneous electron movements/dipoles—are able to tip the balance in protein conformational dynamics by acting collectively and coherently.[44] Thousands of London force interactions exist among the many atoms and atomic groups in the amino acids that comprise a protein, but only in proteins having significant hydrophobic pockets are London forces confluent and apparently able to act cooperatively to collectively control other London forces throughout the protein.

Due to the Mossbauer effect, London force electronic motions couple to protein nuclear motions (and thus conformation) *via* a recoil phenomenon.[47] Because of the extremely small mass of electrons relative to that of nuclear protons and neutrons, the conformational movement due to recoil is slight: A 1-nm shift of a single electron moves a carbon atom by only 10^{-8} nm, the diameter of its nucleus. However, the electrical charge on each electron is equivalent in magnitude to that on each nuclear proton. Collectively acting London dipole forces are thus able to influence nuclear motion and protein conformation by charge movements and, to a lesser extent, recoil.[48]

In the 1960s and 1970s, biophysicist Herbert Fröhlich proposed that fluctuating electron dipoles—London forces—in "nonpolar regions" of proteins in sets geometrically constrained in a voltage gradient (*e.g.*, membrane or cytoskeletal proteins) would synchronously couple.[49] Pumped by available metabolic energy, Fröhlich suggested such proteins would oscillate collectively, forming a laser-like quantum coherent state (essentially a pumped Bose-Einstein condensate). Some evidence supports biologic "Fröhlich coherence,"[50] which has also been implicated in binding and consciousness.[51]

Therefore, endogenous London forces are critically important in protein folding and—in proteins with significant hydrophobic pockets—conformational dynamics and (possibly) collective quantum coherence among spatially distributed proteins. As we shall see in the next section, brain proteins governed by hydrophobic pocket London forces—*e.g.*, γ synchronized dendritic proteins—are precisely the site/means by which anesthetic gases act with relative selectivity to prevent consciousness. Hydrophobic pocket London forces in these proteins are the likely neuromolecular correlate—the "fine grain"—of consciousness.

Where and How Do Anesthetics Act within the NCC?

The Meyer-Overton Correlation, London Forces, and Hydrophobic Pockets

What is meant by anesthetics? Modern anesthesia is often a potpourri, with various intravenous and inhalational agents causing or contributing to loss of consciousness, muscle relaxation, analgesia, amnesia, and anxiolysis. However, drugs such as etomidate, propofol, ketamine, and barbiturates by themselves cause loss of consciousness, apparently through actions primarily on $GABA_A$ (as well as glycine, glutamate, and *N*-methyl-D-aspartate) receptors.[52] Also, electrical currents passed through the brain from scalp electrodes can provide reversible loss of consciousness: "electroanesthesia."[53] We will consider such cases, but first focus on inhalational anesthetic gases.

At the turn of the 20th century, Meyer[54] and Overton[55] showed that anesthetic potency of a wide variety of gas molecules correlated with their solubility in a nonpolar, lipid-like medium that resembled olive oil (nonpolar, oily, lipophilic media exclude water and are also known as hydrophobic). This correlation was later refined by quantifying solubility, and anesthetic potency (as measured by immobility) was found to correlate with solubility in a particular range which implied some degree of polarity in an otherwise nonpolar environment.[56] Taheri *et al.*[57] compared solubility of anesthetic gases in various nonpolar solvents with potency in causing immobility in rats, dogs, and humans and also found a slight degree of polarity in an otherwise nonpolar site of anesthetic action. Sandorfy[58] emphasized the role of weakly polar hydrogen bonds in mediating anesthetic effects in nonpolar but polarizable media, and Trudell *et al.*[59] showed that induction of a dipole in an anesthetic molecule by an electrical charge at or near a nonpolar, hydrophobic site enhanced binding. Accordingly, sites of anesthetic action are often referred to as amphiphilic,[60] *i.e.*, both polar and nonpolar. But as immobility—the usual measure of anesthetic effect—is mediated in the spinal cord, precise solubility of sites mediating loss of consciousness in the brain is unknown, and could, for example, correlate with ideal nonpolarity.

In addition to polarity, differences in effects among

anesthetics and deviations from Meyer-Overton correlation occur due to variations in "stiffness," size (*e.g.*, the cutoff effect—molecules above a critical size lack anesthetic effect despite Meyer-Overton correlation), and stereoselectivity of anesthetic molecules and binding sites.[61,62] Nevertheless, the common denominator and overriding determinant of anesthetic effect remains Meyer-Overton solubility due to the largely nonpolar nature of anesthetic gases. Nonpolar solubility of anesthetic gases is accounted for by hydrophobic interactions and van der Waals London forces.[63,64] Within neurons in the NCC, precisely where do anesthetics bind and act by hydrophobic interactions and van der Waals London forces?

Before Meyer-Overton in the mid-19th century, Claude Bernard exposed amoeba to the anesthetic gas chloroform and found that protoplasmic streaming, the organized movement of cytoplasm within the cell interior, was halted. Based on this and other findings, Bernard proposed that anesthesia resulted from reversible "coagulation" of cellular proteins.[65] It is now known that protoplasmic streaming depends on polymerization cycles of the cytoskeletal protein actin and that anesthetic gases depolymerize actin in dendritic spines in neurons.[66]

But after Meyer-Overton and the recognition that neuronal membranes were composed largely of lipids, it was assumed that anesthetics bind and act in lipid regions of membranes. With the discovery that membrane proteins perform essential functions related to membrane excitability, attention eventually turned to anesthetic effects on proteins. In the 1980s, Franks and Lieb[67] resolved the apparently conflicting issues of lipophilicity/hydrophobicity, cutoff effect, and protein binding by demonstrating a Meyer-Overton correlation for anesthetic action in lipid-like hydrophobic pockets of membrane-free proteins (inhibition of light emission from firefly luciferase). Although anesthetics do reside in membrane lipid regions at clinical concentrations, and some proposals for lipid sites of anesthetic action are still supported,[68] the preponderance of evidence points to hydrophobic pockets within various brain proteins as primary targets of anesthetic effects.[69]

Dendritic Protein Hydrophobic Pockets: Sites of Anesthetic Action

In which hydrophobic pockets (*i.e.*, which proteins) do anesthetics bind and act? Anesthetic action is relatively selective—many nonconscious brain activities continue during anesthesia—and relatively few proteins have hydrophobic pockets large enough for anesthetics (approximately 15% of neural proteins[69]). Therefore, hydrophobic pockets in which anesthetics act may be expected to correspond—at least to some extent—with the "fine grain" of the NCC, *i.e.*, within dendritic proteins mediating γ synchrony.

Indeed, studies of synaptic transmission have shown that anesthetics act predominantly postsynaptically in dendrites (and inhibit γ synchrony), with minimal effects on axonal action potentials and neurotransmitter vesicle release.[70] Although some presynaptic effects continue to be demonstrated,[71] dendritic membrane proteins are the presumed primary targets of anesthetic gases (consistent with dendritic networks as the NCC). The usual suspects are postsynaptic ligand-gated ion channels, particularly inhibitory $GABA_A$, $GABA_B$, and glycine receptors and excitatory receptors for nicotinic acetylcholine, serotonin, and glutamate, as well as voltage-sensitive ion channels.[69,72,73]

Anesthetics also act within dendritic interiors, *via* both metabotropic receptors (including glutamate and $GABA_B$ receptors) and directly on cytoplasmic proteins. Cytoplasmic protein kinase C, adenylate cyclase, second messenger G proteins, postsynaptic density proteins, actin (*e.g.*, in dendritic spines), and tubulin in microtubules within cell interiors are all known to bind volatile anesthetics at or near clinically relevant concentrations.[69,72,74] (As an aside, clinical exposure to relatively high/prolonged anesthetic concentrations and low temperature may cause depolymerization of neuronal cytoskeletal proteins and mediate postoperative cognitive dysfunction.[75]) Some anesthetics also inhibit activity of gap junction (connexin) proteins.[76]

Anesthetic effects on dendritic ligand-gated ion channels/receptors have been most extensively studied, largely because their responses may be quantified by ionic flux and membrane potentials. Inhibitory receptors for $GABA_A$ and glycine are apparently more sensitive to anesthetic effects than are most other target proteins,[77] but a review of such effects yields confusing results. Some anesthetics potentiate $GABA_A$ inhibition at concentrations below 1 mM but inhibit $GABA_A$ effects at higher concentrations.[74] Therefore, deep anesthesia should cause excitatory activity if $GABA_A$ receptors (and their membrane effects) are the exclusive or primary sites of anesthetic action. Some anesthetics have little or no effects on $GABA_A$ receptors,[78] but inhibit excitatory *N*-methyl-D-aspartate receptors for glutamate.[79] Overall, some anesthetics (logically) potentiate inhibitory channels or inhibit excitatory channels, but other anesthetics may have exact opposite effects in different systems, *e.g.*, to block inhibitory and potentiate excitatory receptors/channels.[80] Clinically, both excitatory and inhibitory effects may be seen, *e.g.*, in light anesthesia (*e.g.*, stage 2 excitation), and in seizure-like electrical activity in some brain regions, *e.g.*, with anesthetic doses of enflurane. The only common denominator among anesthetic actions is loss of consciousness in intact animals or humans.

Also confusing are the facts that some gases follow the Meyer-Overton correlation and bind in hydrophobic pockets but do not cause immobility (or, presumably,

loss of consciousness) and are called nonimmobilizers or nonanesthetics.[81] Other Meyer-Overton gases are predominantly excitatory and cause convulsions.[82]

So a variety of Meyer-Overton gases bind in hydrophobic pockets of a variety of neural dendritic proteins giving a variety of measurable effects. A unitary mechanism of anesthetic action seems out of reach. How do we make sense of this confusing picture?

It is usually considered that each anesthetic acts slightly differently, affecting a varying profile of receptors/channels to achieve a common end result. This is undoubtedly true to some extent, at least for immobility, accounting for slight variations in effects among different anesthetics due to polarity, stiffness, stereoselectivity, *etc.* But the notion of disparate effects is predicated on the lack of any unitary concept of consciousness.

For example, if a collective, cooperative field effect among many dendritic proteins in widely distributed regions of brain is necessary for γ synchrony and consciousness, anesthetic perturbation of the mechanism underlying the field effect in a subset of those proteins would be sufficient to ablate it. High-dose anesthetic blockade of $GABA_A$ receptors (for example) could disturb brain-wide collective fields regardless of local dendritic ion flux and membrane excitation.

A collective field basis for consciousness can also explain how etomidate, propofol, ketamine, and barbiturates can induce anesthesia by acting selectively on any key member of the collective action, *e.g.*, membrane-bound receptors for $GABA_A$ or glutamate. (The polar induction drugs have nonpolar ring structures that may act in hydrophobic pockets of their designated receptors.) For understanding consciousness, the task is to identify the nature of the "fine grain" of the collective field phenomenon, *e.g.*, by examining the precise mechanism of anesthetic action in hydrophobic pockets.

Anesthetic Action: "Just Being There" or "Doing Something"?

At clinically relevant concentrations, anesthetic gas molecules occupy hydrophobic pockets by forming London force interactions with nonpolar amino acid groups (and to some extent—at least at sites mediating immobility—polar interactions as well), thereby altering protein conformational dynamics and neuronal functions. But exactly how does anesthetic occupancy of hydrophobic pockets alter protein conformational dynamics? And why do anesthetics and other Meyer-Overton gases (nonimmobilizers/nonanesthetics, convulsants) have contrasting effects?

One possibility is that the mere presence of Meyer-Overton gas molecules in hydrophobic pockets ("just being there") is sufficient to impair protein conformational dynamics and function, at least in some (anesthetic) cases.

There are three types of "just being there" explanations. The simplest is steric hindrance: Anesthetic occupancy of a hydrophobic pocket retards protein flexibility, like placing a rubber ball in a door hinge. But the extremely small size of relevant hydrophobic pockets (approximately one hundredth of protein volume) and high energy of proteins makes this possibility seem unlikely.

A second type derives from the classic work by Franks and Lieb[67,73] on firefly luciferase which showed competitive binding between anesthetic gases and luciferin, a substrate required for luciferase luminescence. Franks and Lieb[83] extrapolated to suggest that anesthetics competed with endogenous ligands for hydrophobic binding sites in relevant proteins. Therefore, "just being there" would be sufficient to block endogenous ligand binding and ligand-induced effects. However, not all anesthetic target proteins have endogenous hydrophobic ligands.

A third type of "just being there" was proposed by Eckenhoff,[75] who applied allosteric mechanisms to anesthetic effects, suggesting that the mere presence of anesthetics in hydrophobic pockets (or cavities in Eckenhoff's description) had distal effects throughout the protein by stabilizing one particular conformation. In this approach, normally functioning proteins occupy an ensemble of conformations, only some of which contain hydrophobic pockets or cavities sufficiently large to bind anesthetics (fig. 4A). These particular states with large pockets, according to Eckenhoff, are inactive and stabilized by anesthetic occupancy, thus depopulating active states (fig. 4B). In this view, anesthetics and other Meyer-Overton gases may cause proteins to be (1) stabilized in an inactive state, (2) stabilized in an active state (*e.g.*, inhibitory channels, excitatory channels in convulsant/excitatory situations), or (3) not stabilized (nonanesthetic/nonimmobilizer). However anesthetics bind in preexisting pockets/cavities (at least in some proteins),[84] anesthetic-induced structural changes are negligible,[85] and stabilization of an ion channel active conformation (either inhibitory or excitatory) should soon attenuate the ionic gradient and fatigue the membrane. Therefore, it seems anesthetics prevent conformational dynamics, rather than causing or stabilizing a particular conformation. "Just being there" may be insufficient.

Apparently, anesthetics actively "do something" in hydrophobic pockets. By forming exogenous London force interactions with nonpolar groups (*e.g.*, aromatic rings) in hydrophobic pockets, anesthetics may actively impair endogenous London forces necessary for protein conformational dynamics and consciousness (figs. 4C and D).[86] London forces are instantaneous movements of electrons, and aromatic rings have highly mobile (delocalizable) electrons shared among numerous atoms, *e.g.*, extremely large electron clouds (particularly with groups or stacks of aromatic rings). This electron mobility (and excitability) in aromatic rings accounts for fluorescence, known to be inhibited by anesthetic binding.[87] If elec-

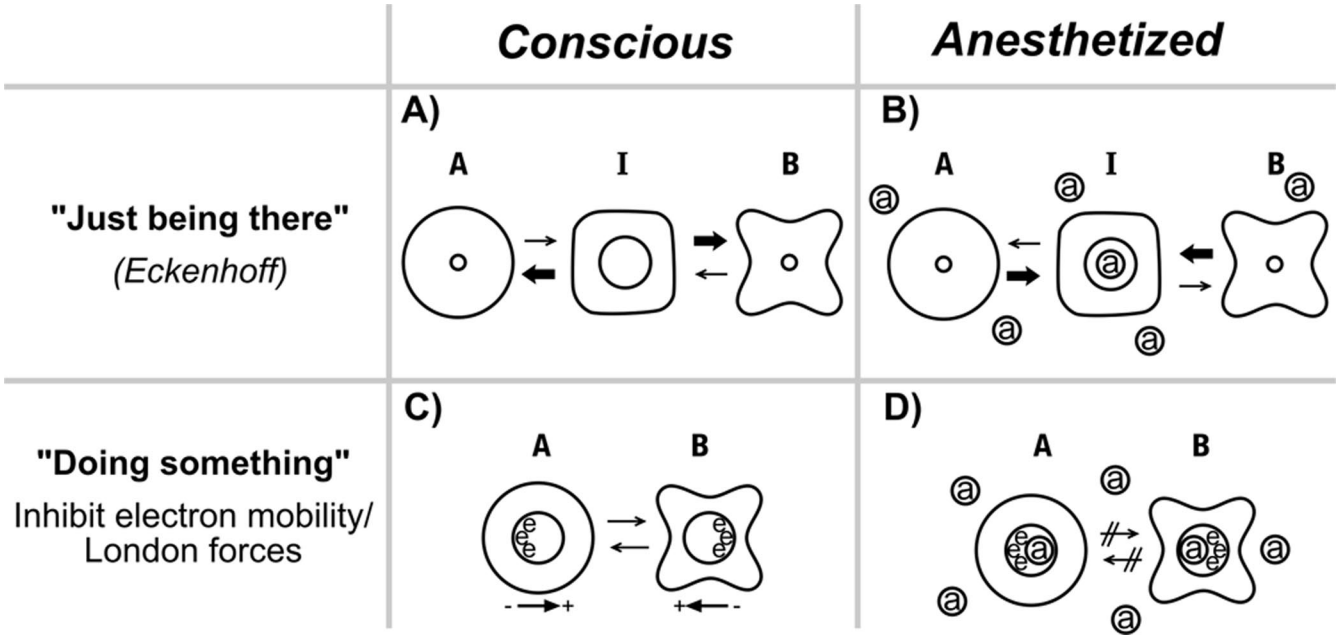

Fig. 4. Two approaches to anesthetic action in hydrophobic pockets. (*A*) Conscious condition in "just being there" Eckenhoff model: Anesthetic-sensitive protein dynamically switches between conformational states A and B *via* intermediate state I, which is relatively unstable. State I contains a large hydrophobic pocket (or cavity) not present in states A or B. (*B*) Anesthetized condition in Eckenhoff approach: Anesthetic gas molecule occupies the hydrophobic pocket/cavity in state I, which becomes stabilized, depopulating states A and B and limiting dynamical conformational transitions. (*C*) Conscious condition in "doing something" approach: Anesthetic-sensitive protein switches between conformational states A and B governed by endogenous London force dipole oscillation in hydrophobic pocket (fig. 3C). (*D*) Anesthetized condition in "doing something" approach: Anesthetics form exogenous London forces in hydrophobic pockets, preventing normally occurring endogenous London force dipole oscillations and protein conformational dynamics.

tron mobility (endogenous London forces) in confined hydrophobic pockets is inhibited by anesthetics, electron mobility in any region/situation should be so inhibited. Electron mobility can be measured directly *via* corona discharge.

A corona discharge ("St. Elmo's fire") is a plasma of mobile electrons and ions, "soft sparking" formed in a fluid or gas between two electrodes. Engineers have used the gas sulfur hexafluoride (a weak anesthetic that follows the Meyer-Overton correlation) to eliminate coronas in closed spaces in various electrical devices. In the 1980s, effects of anesthetics (and other gases) on electron mobility were studied in a corona discharge chamber in which electrons were liberated and their mobility/flow was quantified.[88,89] In the experiments, gas flowed through the corona discharge chamber. Starting with 100% oxygen, adding helium or nitrogen to the oxygen flowing through the chamber caused either an increase (helium) or no change (nitrogen) in corona discharge. Adding nitrous oxide reduced the corona discharge, with complete elimination at approximately 50% nitrous oxide. Addition of the potent anesthetic gases halothane, enflurane, and isoflurane markedly inhibited corona discharge, with complete elimination at approximately 6% anesthetic agent in oxygen. Thus, a crude Meyer-Overton correlation was obtained: Anesthetic gases inhibit electron mobility, roughly in proportion to clinical potency.

So anesthetic gases inhibit mobility of unconstrained electrons and presumably inhibit electron mobility/London forces in hydrophobic pockets. Is this the mechanism of anesthetic action?

If so, what about Meyer-Overton gases which are either excitatory or nonimmobilizers/nonanesthetics? Presumably, the precise fit/stiffness/polarity (deviation from nonpolarity) among Meyer-Overton gases in differing hydrophobic pockets serves to alter results. For example, excitation by Meyer-Overton gases apparently relates to more polar effects between site and gas molecule (*e.g.*, electrostatic/polar interactions mediate excitatory but not inhibitory anesthetic effects on serotonin 5-HT_{3A} receptors[90]). An appropriately aligned permanent dipole could reduce the van der Waals radii between anesthetic and protein nonpolar groups (pushing them together), leading to repulsive van der Waals forces which enhance electron mobility and increase excitatory conformational activity.

A similar explanation could account for pressure reversal of anesthesia. London force attractions vary with the 6th power of the van der Waals radius—"the closer the better" until reaching a limit when neighboring electron clouds approximate each other.[91] When electron clouds are pushed further together (*e.g.*, by increased pressure: PV = nRT) and overlap, strong repulsive forces which vary with the 12th power of the radius result.[91] Within hydrophobic pockets, such repulsive forces

could enhance electron mobility and increase protein conformational activity, causing excitatory dynamics.

Therefore, depending on the precise fit/stiffness/polarity, Meyer-Overton gas occupancy and London force interactions in hydrophobic pockets (1) inhibit electron mobility (anesthetic), (2) potentiate electron mobility (convulsant/excitatory situations) because of reduced van der Waals radii and repulsion, or (3) have no significant effect on electron mobility (nonanesthetic/nonimmobilizer).

The electron mobility proposal can also account for electroanesthesia.[53] Alternating or pulsed (*e.g.*, at electroencephalographic frequency) electrical currents passed through the brain from scalp electrodes (*e.g.*, frontal–occipital) can provide reversible loss of consciousness, sparing (in a relative sense) nonconscious brain activities. London force electron mobility in nonpolar hydrophobic pockets is likely to be more sensitive to disruption by such applied fields and currents than is transmembrane electrophysiology.

The electron mobility proposal for anesthetic mechanism (anesthetics "do something" in hydrophobic pockets) has advantages over "just being there" in hydrophobic pockets: (1) pressure reversal and excitatory anesthetic effects can be accounted for by repulsion due to reduction in van der Waals radii, (2) experimental data support anesthetic effects on electron mobility, and (3) regulation of intrinsic protein conformational transitions (by electron mobility/endogenous London forces) is explained. Finally, (4) an essential role for electron mobility/endogenous London forces in anesthetic mechanism provides a potential "fine grain" for collective field effects underlying zero-phase-lag γ synchrony, binding, and consciousness.

Quantum Fields, Brain, and Consciousness

Mid-20th-century concepts of brain function were field theories. Karl Lashley wrote, "Here is the dilemma. Nerve impulses are transmitted from cell to cell through definite intercellular communication. Yet all behavior seems to be determined by masses of excitation.[92]

Field theories gave way to computer analogies, but zero-phase-lag γ synchrony has rekindled collective field approaches to binding and consciousness. Some theories suggest complex, brain-wide electromagnetic fields generated by neural electrophysiology manifest binding and consciousness.[93] But neuronal-based electromagnetic fields are shunted by glia and too weak to account for long-range coherence.[26,27]

An important clue may be that anesthetic gases are the only pharmacologic agents that act without forming covalent or ionic bonds with their targets (as far as their nonpolar effects are concerned). Relatively selective in affecting consciousness while sparing other brain activities, anesthetic gases act *via* London forces which are quantum interactions.

Quantum implies the smallest units of matter and energy, but at the quantum level (*e.g.*, atomic and subatomic scales), the laws of physics differ strangely from our everyday "classical" world. Quantum particles (1) can interconnect nonlocally and correlate instantaneously over distance (quantum entanglement, long-range dipole correlations), (2) can unify into single entities (quantum coherence, condensation), and also (3) can behave as waves and exist in two or more states or locations simultaneously (quantum superposition). When superpositioned particles are measured or observed, they immediately reduce to single, definite states or locations, known as quantum state reduction or "collapse of the wave function." Superposition and quantum state reduction are used in quantum computers in which information (*e.g.*, bits of 1 or 0) may be temporarily represented as quantum information (*e.g.*, quantum bits, or qubits, of both 1 and 0), which reduces to classical information as output.[94]

It is generally assumed that quantum effects are confined to atomic scales, but the boundary between quantum and classical domains is ill-defined, and quantum effects can occur at macroscopic sizes. For example, coherent collective modes due to long-range dipole correlations are macroscopic features of quantum origin which account for lasers and simple magnets. This same type of quantum correlation has been implicated in the unity, binding, and collective nature of brain functions since the 1960s, with a recent resurgence aimed at zero-phase-lag γ synchrony (fig. 5).[27] Similarly, psychiatrist Ian Marshall[51] suggested in 1989 that unity/binding of consciousness is due to quantum coherence among brain protein receptors, pumped by the biophysical laser-like mechanism suggested by Fröhlich. In these accounts, quantum London forces in hydrophobic protein pockets are the fundamental dipoles—the "fine grains"—that mediate collective unity.

Another enigmatic feature—the transition between unconscious processes and consciousness—is also approached through quantum explanations. Physicists Sir Roger Penrose[94] and Henry Stapp[95] (separately) suggested that unconscious-to-conscious transitions involve quantum state reduction/wave function collapse in the brain, *i.e.*, that unconscious/preconscious processes occur as quantum superposition/quantum information. Subsequently, Penrose and Hameroff[96] proposed that unconscious processing involves quantum computation in dendritic microtubules and receptors in brain neurons. The unconscious quantum information/qubits interact by coherent entanglement/long-range correlations (among neuronal proteins through gap junctions) and reach threshold for quantum state reduction (conscious moments) roughly 40 times per second, *i.e.*, at γ synchrony. In a comparable quantum field approach, consciously perceived classical information precipitates from unconscious quantum information "like raindrops from water vapor."[27] In both accounts, quantum infor-

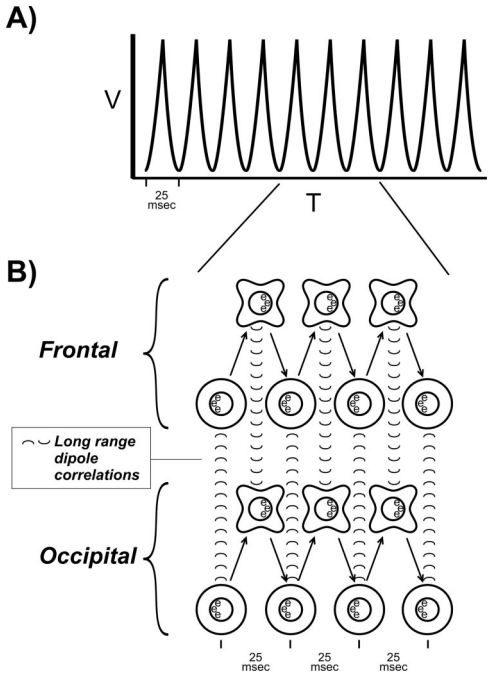

Fig. 5. Gamma synchrony and long-range dipole correlations. (*A*) Voltage/time plot of γ synchrony over 250 ms (fig. 1D). (*B*) Three "40-Hz" γ cycles (75 ms) of dendritic protein oscillations (figs. 3C and 4C) in which spatially separated proteins (*e.g.*, frontal and occipital brain regions) are coupled *via* long-range London force quantum dipole correlations, accounting for zero-phase-lag γ synchrony. Such long-range dipole correlations may occur through gap junction–connected dendrites.

mation/qubits may manifest from quantum London forces in γ-synchronized dendritic protein hydrophobic pockets.

These proposals are obviously speculative and face questions such as decoherence—how can presumably delicate quantum states operate macroscopically at warm brain temperatures?[97] However, theory and experiments suggest biology may use metabolic energy to pump quantum states, and mechanisms have evolved to avoid decoherence.[98,99]† Although considered unlikely by many authorities, quantum proposals for consciousness have sound theoretical bases and explanatory power for phenomena which confound conventional explanations: zero-phase-lag γ synchrony, binding, the transition from unconscious processes to consciousness and the profound but selective effects of anesthetic gases.

Conclusions

Loss of consciousness should be considered the essential component of general anesthesia, ensuring amnesia (though not necessarily immobility). Understanding the mechanism of action of anesthetic gases may answer scientific and philosophical questions regarding consciousness, and *vice versa*.

Consciousness correlates with γ-synchronized conformational activities of neuronal dendritic proteins in cortex and other brain regions. Within each protein, conformational states are regulated by endogenous London forces in hydrophobic pockets. Zero-phase lag γ synchrony suggests that consciousness may involve collective fields mediated by long-range dipole correlations among these endogenous London forces (fig. 5).

By forming exogenous London forces, anesthetic gases prevent consciousness by impairing endogenous London forces in hydrophobic pockets of dendritic brain proteins (figs. 4C, D).

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