Review Article

On the Role of the Microtubules in Cognitive Brain Functions

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Abstract

In this article we review the role microtubules (MTs) have been conjectured to play as a substrate for information processing and signaling mechanisms in the brain at a sub-cellular level. We discuss their structure, known biophysical functions and theoretical predictions related to signaling, conduction and transport, all of which may contribute to pre-conscious processing at a molecular level. Major criticisms of microtubule information processing based concepts of cognitive brain function are examined, and the progress in work addressing these issues is also discussed. It is concluded that the question of whether any of these processes operate at a quantum level is still open to debate and speculation.

Key Words: microtubules, information processing, cognitive function, consciousness, mind and brain theory

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I. Introduction

1.1 Overview

Consciousness is a major unsolved problem of modern science. In fact, some scientists are of the opinion that consciousness is an area of intellectual pursuit lying outside the domain of scientific investigation. There are a number of theories of consciousness in existence, some of which are based on classical physics while some others require the use of quantum concepts. Although quantum mechanics lies at the most fundamental level of the physical understanding of matter, it still remains to be seen if it can contribute significantly to our understanding of human cognition and consciousness. Undeniably, quantum

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theory has invoked new perspectives on consciousness since its inception. It is generally accepted that consciousness is correlated with the behavior of the material brain as its substrate. Since quantum theory is the basic theory of matter, it is legitimate to assume that it can help us to understand consciousness.

The general consensus is that the state of being conscious is a condition of being aware of one's surroundings and one's own existence (self-awareness). The currently accepted view is that the substrate of consciousness emerges as a property of an ever-increasing computational complexity among neurons hence this approach relies on emergence as a framework for understanding consciousness. Emergent phenomena are characterized by a higher level of complexity resulting from an aggregation of units whose individual properties differ from those of the aggregate. While an individual neuron may only participate in information transfer, their clusters may collectively process information and clusters of neuronal clusters may achieve a yet higher level of complex behavior giving rise to awareness eventually leading to self-awareness or consciousness. Most accepted views within neuroscience see the brain as a nested hierarchy of information processing subsystems. The firings of nerve cells and the transmissions between them via action potentials are at the bottom rung of the hierarchy—the fundamental units of information, analogous to bits in a computer. These classical, deterministic activities, while explaining most neuro-physiological phenomena cannot account for several key properties of conscious experience such as free will and the unitary sense of self. Hence it is reasonable to search for a way to connect with the quantum level within the neuron.

Neurons and synapses are the fundamental units of information processing hardware in the brain, similar to microprocessor silicon chips manipulating information bits in a computer. Although individual neurons are assumed to have only two different states, *on* when the neuron is firing and *off* when it is not, there is a critical level of complexity above which many neurons interact with each other to form a conscious experience. While this appears to be the currently accepted approach to explaining consciousness, it may not be adequate to properly explain the richness of the neuron's biophysical state space. Moreover, the fact that neuronal assemblies are mostly described in terms of classical behavior does not rule out the possibility that quantum effects play a role in sub-neuronal components such as proteins, DNA or neurotransmitters. The brain contains both electrical and chemical synapses. At electrical synapses, the current generated by the action potential at the pre-synaptic neuron flows

directly into the postsynaptic cell, which is physically connected to the pre-synaptic terminal by a gap junction. At chemical synapses, there is a cleft between the pre- and postsynaptic cell. In order to propagate a signal, a chemical transmitter (e.g., glutamate, acetylcholine) is released from the pre-synaptic terminal by exocytosis. The transmitter diffuses across the synaptic cleft and binds to receptors embedded in the postsynaptic membrane, resulting in the opening of an ion channel or in the initiation of a signal transduction cascade. Although these steps seem to operate according to classical physics, quantum processes may come into play, too. For example, they may be relevant for a quantitative understanding of exocytosis, which is tightly related to states of consciousness. Chemical synapses using NMDA receptors are critical to perception and consciousness because of the plasticity expressed by NMDA receptors. Anesthetic agents block NMDA receptors and consequently lead to a loss of consciousness.

Another reason to look beyond classical models is that currently accepted models of consciousness are unable to properly explain even the rather primitive consciousness in single-celled organisms. Single-celled organisms, such as the paramecium, have no neurons or synapses, but still exhibit proto-consciousness, an apparent awareness of and responsiveness to their environment. One can conclude from this that the rudiments of consciousness lie someplace other than the complex interactions between neurons and synapses, although the latter are certain to contribute to the richness of sensory experience and the resulting behavioral repertoire. The neuronal cytoskeleton is the most ubiquitous and most basic sub-cellular level site thus far proposed for quantum processes in consciousness. The cytoskeleton consists of three types of protein networks: microfilaments, intermediate filaments and microtubules (MTs). MTs are essential for axoplasmic transport, signaling and neuronal plasticity, among cellular processes within neurons. The cytoskeleton can be viewed as the control center of the cell. MTs provide an ideal bridge between classical and quantum processing; moreover, these structures literally fill the interiors of neurons.

Information processing at the level of MTs within each neuron would provide an enormous increase in the brain's computing power even at a classical level. The currently accepted scientific model suggests that consciousness arises as a result of computational complexity among the approximately 10^{11} neurons in the brain. There are on the order of 10^4 synapses per large neuron, which switch their states at a rate of some 10^3 switches per second, so that we arrive at a number of $\approx 10^{18}$ operations per second in the brain on average. While this is a truly

huge number, it may pale by comparison with the yield given by the brain if neuronal MTs were actively involved in computational processes. MTs are composed of tubulin dimers, which are globular protein subunits. Consider that at the cytoskeletal level there are roughly 10^7 MT tubulin molecules in each neuron which can switch their conformational states on the order of nanoseconds resulting in10^{16} operations per second per neuron or 10^{27} operations per second in an entire brain instead of 10^{18} operations per second estimated for neurons taken as the smallest computational units. Moreover, if each tubulin dimer does function as a qubit and not a classical bit processor, the computational power becomes almost unimaginably vast. It has been claimed that as few as 300 qubits have the same computational power as a hypothetical classical computer comprised of as many processing units as there are particles in the universe. Experimental evidence shows that MTs do propagate signals in cells. Moreover, interactions between MTs and membrane activities are clearly recognized. That computations are carried out by MT subunits may imply that one of the brain's fundamental units of information is tubulin's protein conformational state. Other processes involved in the functioning of the brain, such as ion channels opening and closing, enzymes catalyzing, motor proteins moving cargo inside cells, and the propagation of ionic waves along filaments, may be inextricably linked to tubulin's conformational changes. There is evidence that MTs are computationally relevant to neuro-cognition. For example, neurons in the visual cortex produce massive amounts of tubulin during the critical period. Tubulin is implicated in these developmental cognitive processes. On the other hand, Alzheimer's disease, which is accompanied by deficits in intellect, memory and consciousness, has been linked to MT degradation. Paired helical filaments are aberrant formations resulting from hyper-phosphorylated MT-associated protein tau. Axonal transport is compromised in Alzheimer's disease given that MTs are responsible for the transport of nutrients from the cell body to the axon terminal. MTs also provide a non-selective mechanism for general anesthesia. Anesthetics inhibit a number of neurotransmitter receptors, but differ from receptor inhibitors by having effects on the cytoskeleton, especially actin. The most likely mechanism for general anesthetics acting upon MTs is inhibition of electron movement within the hydrophobic pockets of tubulin dimers. These hydrophobic pockets occupy approximately $1/30^{th}$ – $1/250^{th}$ the total volume of the protein, which amounts to around 0.4 cubic nm. Moreover, their properties create a suitable environment to induce electron delocalization. The link between hydrophobic pockets,

consciousness and anesthesia can be explained in terms of electron motion. Electron mobility is essential to quantum superposition, but in the presence of anesthetic gas, the electron motion that is required for protein conformational stability and quantum superposition is inhibited. Considering consciousness to be a quantum-mechanical process, in the absence of electron movement, we would expect to also see a loss of consciousness. Conversely, instead of inhibiting electron movement, hallucinogenic drugs such as LSD appear to be potent electron donors. Thus, actions of both anesthetics and hallucinogens may involve alterations in electron states within hydrophobic pockets, which in turn may affect the state of human consciousness. However, it is still far from trivial to reconcile these qualitative statements with the perverse decoherence effects dominating quantum phenomena at physiological temperatures. In the sections below we discuss at a greater biophysical detail how MTs may be at the center of information/signal processing in the brain's neurons.

1.2 Historical Background

Almost since the inception of the quantum theory of matter in the early part of the last century it has been suggested that its unique properties play an important role in life processes. Perhaps the first attempt to describe the brain using the terminology of quantum physics was made by Ricciardi and Umezawa (Ricciardi, 1967). Based on experimental observations of brain activity they proposed that the brain could be conceived of as a spatially distributed system placed into particular quantum states by stimuli from the external environment. Thus, information can be thought of as being coded into the brain in the form of metastable excited states representative of short-term memory. This code would then be later on transferred to the ground state of the system by means of a condensation to the ground state in the manner of Bose-Einstein condensation accounting for learning and long-term memory. This model proposes that brain functions are manifestations of spontaneous symmetry breakings in the dynamics of the brain regulated by long-range correlations. The model put forth by Ricciardi and Umezawa relating macroscopic quantum states to brain function, memory specifically, was later extended proposing that the brain is a mixed physical system (Stuart, 1978). In this model the brain is considered to consist of two distinct interacting parts, the first part consisting of the classical electrochemical interactions of the neurons of the brain, and the second being the macroscopic quantum state responsible for the creation and maintenance of memory.

Inspired by the application of quantum theoretical methods to the

study of the brain and other biological structures, scientists began to study brain functioning from the microscopic level of quantum physics. Several groups focused specifically on protein polymers located within individual cells known as the cytoskeleton (Hameroff, 1982; Delgiudice, 1986). Anesthesiologist Stuart Hameroff investigated many of these relationships between molecular biology, computers and future ideas of nanotechnology in a book dealing with the co-evolution of consciousness and technology (Hameroff, 1987). Specifically it highlights the cytoskeletal structure of living cells to act as a cellular nervous system via computations in the cytoskeleton giving numerous arguments based on theory and experimental observation. Using physical models including models based on previous theoretical notions of holography, biological coherence and solitons acting in MTs (Hameroff, 1974) the computations of the cytoskeleton are shown to provide plausible explanations of the mechanisms observed in brain cells, and in turn their relation to the functioning of the brain including consciousness. In general, Hameroff indicated two main concepts that are essential to the understanding of cytoskeletal brain activity from the viewpoint of modern physics. The first is that MTs act as dielectric waveguides for electromagnetic energy, or photons, creating coherent excitations within MTs via Frohlich's theory of biological coherence. The second is that via interference of coherent electromagnetic waves, or photons, through the interaction of MTs, a network of MTs acts as a holographic information-processing device.

Mathematical physicist Roger Penrose examined the relationship between consciousness and modern physics in a tour de force exposition of Turing machines, Godel's theorem, chaos, classical and quantum mechanics, thermodynamics, relativity, cosmology, quantum gravity, quasi-crystals, and brain neurophysiology (Penrose, 1989). In this investigation Penrose introduced mathematics as a bridge from the artificial world of computers to the natural world of physics and argued via Godel's incompleteness theorem that human consciousness is non-algorithmic, and thus that physical theories of brain function are incomplete due to their dependence on computable algorithmic laws. He further hypothesized that quantum effects play a fundamental role in the understanding of human consciousness by enabling the brain to perform non-computable operations. In his explanation of the new physics required to explain the mind and consciousness he examined the division between classical and quantum physics, specifically the measurement problem, and related the collapse of the wave function to conscious events using the notion of Objective Reduction (Penrose,

1994). This led to the suggestion that MTs within neurons provide the brain with structures capable of orchestrating the collapse of the wave function via quantum computations. This union of Penrose and Hameroff's theories has become known as the Penrose-Hameroff Orchestrated Objective Reduction theory.

The Penrose-Hameroff Orchestrated Objective Reduction (OrchOR) theory of consciousness is perhaps the most well-known theory of quantum consciousness. Objective Reduction is a solution to the measurement problem in quantum theory, which considers the superposition of quantum states as a separation in underlying reality at its most basic level, the Planck scale. The solution involves a description of loop quantum gravity, which identifies superpositions as curvatures of opposite direction in space-time, and thus a separation in fundamental space-time geometry. These separations are considered unstable and reduce to a single space-time curvature once an objective threshold is reached (Hameroff, 1998a). The theory considers a conscious event as a quantum computation concluding via objective reduction. Quantum computation within the brain was considered to occur within neuronal MTs. The individual molecules of tubulin that comprise a MT were taken as biological qubits. Tubulin molecules are proposed to interact and compute with other tubulin molecules in MTs via entanglement. The biological conditions in the brain, including synaptic activity, are considered to influence the quantum computations thus orchestrating the collapse of the qubits and giving rise to a conscious event.

However, the Penrose-Hameroff theory of consciousness is not the only theory to relate brain function to MTs. Based on the pioneering work of Umezawa, Jibu and Yasue give a systematic account of advanced brain functions including consciousness and memory, based in the fundamental principles of quantum theory known as Quantum Brain Dynamics (QBD) (Jibu, 1995). In their theory, the QBD system, consisting of the rotational field of water in the brain interacting with the electromagnetic field, exchanges energy directly with what is termed as the external system. The external system surrounding the QBD system includes the microscopic protein filament networks of the cytoskeleton, including MTs, as well as the macroscopic systems of dendritic and neural networks. Hameroff in conjunction with Jibu, Yasue and others predict that MTs play the role of nonlinear coherent optical devices that take advantage of the specific quantum mechanical ordering of water molecules within the hollow core of the MT to produce signaling free of thermal noise and loss, a process which they term 'superradiance' (Jibu, 1994). The optical computing proposed to occur in networks

of MTs and other cytoskeletal structures as a basis for cognitive brain functions again implicates information processing within MTs as playing a key role.

1.3 The Structure of MTs, Tubulin and MAPs

As described above, MTs have been implicated to play an important role in the functioning of neurons and the brain, and are purported to give rise to cognitive brain functions such as memory (Woolf, 2006) and consciousness (Hameroff, 1998a), but what are they? Within all living cells there exists a filamentous protein network called the cytoskeleton. This cytoskeleton, aptly named for its role in supporting cell structure, is composed of actin filaments, intermediate filaments, and MTs. MTs are long hollow cylindrical structures with inner and outer diameters of approximately 15 and 25 nanometers (nm) respectively, and variable length that ranges on the order of a few hundred nanometers to millimeters.

MTs themselves are a protein polymer consisting of tubulin. The typical tubulin protein molecule is a hetero-dimer formed from a -tubulin and b -tubulin monomers. The tubulin dimer itself is composed of nearly 900 amino acids and roughly 14,000 atoms, possesses a molecular weight of nearly 110 kilodaltons (kD), and measures approximately 4 nm by 5 nm by 8 nm. The tubulin dimer is a polar molecule with its positive end near the b subunit. Both of the a -tubulin and b -tubulin monomers can bind a molecule of GTP. The molecule of GTP that binds to a -tubulin does not hydrolyze, while that bound to the b -tubulin will hydrolyze to GDP under certain conditions. When the b -tubulin bound GTP hydrolyzes, the hetero-dimer undergoes a conformational change resulting in a 27^{o} shift between the original center-to-center line joining the a and b tubulin monomers and the new configuration's center line, and a release of approximately 0.42 eV of energy per molecule. Henceforth, the term 'tubulin' will be used to refer to the tubulin hetero-dimer specifically, unless otherwise stated.

Tubulin dimers polymerize initially in the form of long protein chains called protofilaments (pfs) and laterally into sheets of parallel pfs that fold to form the cylindrical MT. The typical MT *in vivo* is formed of 13 pfs with very little exception, although *in vitro* MT structures with 7, 9, 12, or 15 pfs have been experimentally observed. When pfs arrange themselves side by side there is a slight shift between adjacent pfs such that following a row of adjacent tubulin dimers across pfs would result in spiraling up the MT in a left-handed spiral. From the monomer point of view, MTs consist of three left handed 3-start helices. The MT can also be viewed in terms of 5-start, 8-start and 13-start helices, but these are not discussed here. The shift in position of the helices as they wrap around to form a MT can give rise to two types of lattice structures. The so-called A-lattice structures consist of

helices with alternating monomer types (i.e., a , b , a , b , a etc.). This pattern continues for the entire length of the helix resulting in a MT with rotational symmetry and continuous wrapping, and a shift of 3.1nm between identical monomers on neighboring pfs. The so-called B-lattice structures consist of helices with identical monomer types that change after one complete turn (i.e.,13 monomers, 13 b monomers, 13 a monomers etc.). This pattern results in a shift of 0.9 nm between like monomers on adjacent pfs and a physical discontinuity running the length of the MT between pfs 1 and 13 known as a seam. Experimental evidence strongly suggests that most of the cytoplasmic MTs possess the B-lattice structure (Nogales, 1998).

The rate of MT polymerization significantly depends on the concentrations of tubulin, GTP and ionic specifications of the solution. Although tubulin dimers form a regular array, each MT is characterized by its polarity, i.e., its distal (plus) end grows faster than the proximal (minus) end. This functional polarity is related to electrostatic differences between the two ends of a MT. Only tubulin dimers to which GTP is bound are capable of binding to a MT. Upon binding, GTP rapidly hydrolyzes into GDP except perhaps for the top layer or two which is commonly referred to as the GTP-cap. It is this chemical energy supply, transfer and dissipation, which is at the center of the dynamic instability issue. It is also noteworthy that the geometry of growing MT's (mainly straight pfs) differs from that of shrinking ones (curved pfs). The above tends to imply that polymerization involves the formation of axial bonds while depolymerization consists in breaking the already weakened lateral bonds. It is, therefore, conceivable that mechanical stress, which maybe associated with the presence of unhydrolyzed GTP, in different places on the surface of a MT may explain the stochastic nature of the dynamic instability phenomenon that characterizes the intermittency of growth and shrinkage phases in the MT polymerization process.

The behavior of MTs within cells is modulated by several proteins known as the MT associated proteins (MAPs). MAPs, which are tissue- and cell type-specific, bind, manipulate and interact with the MTs of the cell and can be broadly categorized into two main groups. The first group is identified as motor MAPs, of which kinesin (KN) and dynein are the two most well known, and are responsible for generating sliding between MTs and driving the transport of vesicles and organelles throughout the cell. Non-motor MAPs, or assembly MAPs, comprise the second group and are responsible for regulating the polymer state of MTs and controlling MT organization within the cell.

Within the majority of cells MTs originate from organelles called MT-organizing centers (MTOCs). MTOCs, which are specialized structures consisting of an array of MTs, anchor newly forming

MTs, through the use of ring complexes composed of g -tubulin, allowing MT assembly to initiate. The two most common organizing centers are basal bodies and centrosomes. Basal bodies are responsible for anchoring the axonemal MTs of cilia and flagella, whereas centrosomes anchor cytoplasmic MTs. Centrosomes are usually positioned near the cell nucleus, thus the MTs of most common cells radiate out from the centrosome forming an aster around the cell's nucleus.

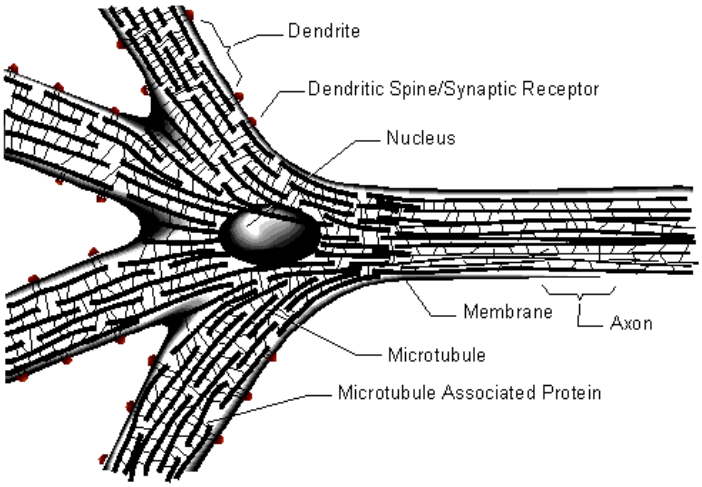

Figure 1. Schematic representation of a neuron showing the arrangement of MTs and MT associated proteins.

Neurons, unlike the common cell, possess a highly organized arrangement of MTs. This is due to a high number of specialized non-motor MAPs within nerve cells. Four of the five main assembly MAPs identified and studied at this point in time (MAP1A, MAP1B, MAP2, MAP4 and Tau) are localized within the axons and dendrites of neurons, MAP4 being the only protein found in other eukaryotic cell types. The specialized assembly MAPs in neurons link neuronal MTs into organized networks. Unlike the radial aster that forms in other eukaryotic cells, MTs within axons and dendrites form parallel bundles. Within the axons of neurons MTs align with uniform polarity resulting in the plus end of all axonal MTs being directed distally, while it has been found that MTs in dendrites align themselves equally with both plus and minus ends directed distally. It has been suggested that the different MT organizations within axons and dendrites may play a role in neuronal signaling.

1.4 MT Functioning

Now that we have a general idea of the structural definition of a MT it becomes a pertinent question to ask what the role is of a MT in the living cell. From the viewpoint of cellular biology MTs perform a wide variety of tasks. In the general cell MTs are involved in maintaining structural shape, assisting in the intracellular transport of organelles and vesicles, providing cell locomotion through cilia or flagella, separating chromosomes during cell division, and signal transduction within the cell (Gundersen, 1999). More recently, MTs have been discovered to play a role in the communication between

the cell exterior and the cell nucleus although the exact mechanisms of this process are not yet fully understood (Glanz, 1997; Manitois, 1997).

Within the neuron it has been a common assumption that the primary task of the MT, and the cytoskeleton in general, is to provide structural rigidity within the cell. Neuronal MTs provide structural support to the neuron and can be found in the soma, axons and dendrites. In the neuron this architectural role of the MT takes on the added importance of being involved in the growth and guidance of axons and dendrites, thus implying that MTs play a role in forming synapses and in the process of rearranging synapses known as synaptic plasticity (Priel, 2006).

However, the role of cellular scaffold is not the only function of the MT. As in the general cell MTs in neurons are involved in the intracellular transport of organelles and vesicles through the use of motor proteins that attach to the surface of MTs. In this case MTs act as guides or tracks to which motor MAPs, such as KN and dynein, attach. KN transports cargo towards the plus end of the MT (Muresan, 2000) while dynein transports neurofilaments, another component of the cytoskeleton, towards the minus end of MTs (Shah, 2000). In turn, the motor proteins bind to organelles or membrane bound vesicles, containing receptors, signal-transduction molecules or neurotransmitters, cytoskeletal proteins such as tubulin, and mRNA among other material. It should be noted that the exact molecular mechanisms by which the motor proteins attach and move along the MT track is not known at this time but is currently being investigated.

An indication that links exist between MT activity and cognitive function is supported by accumulated evidence showing that MTs are involved in cognition. Early evidence implicates tubulin in the development of cognitive processes by showing that during the period when the formation of synapses and visual learning occur at their highest rates the visual cortex of the brain produces massive amounts of tubulin (Cronly-Dillon, 1979). More recently the link between MTs and cognition has been illustrated by studies involving patients with Alzheimer's disease. Alzheimer's disease is a neurodegenerative disease characterized by the deterioration of a patient's intellect, memory and consciousness. Impairment of neuronal MTs resulting from hyper-phosphorylation of the MAP tau in Alzheimer's patients has been shown to result in memory loss, therefore suggesting a connection between MTs and memory (Vogel, 1998). Examinations of the brains of deceased Alzheimer's patients has revealed an increased amount of neurofibrillary tangles, which are bundles of twisted MTs that are no longer held apart by their MAPs, and this has been correlated with

duration and severity of the disease (Arriagada, 1992). As well, it has been shown that Alzheimer's compromises axonal transport indicating a link to MTs since MTs are responsible for the transport of material from the soma to the axon terminal (Sisodia, 2002).

In regards to a direct experimental link between consciousness and MTs investigations into the working of anesthetic molecules provide the best evidence. It has been suggested that MTs can provide a nonselective mechanism for general anesthetics. Purely biophysical studies on the mechanisms of anesthesia have shown unequivocally that the long-debated action of anesthetics is not on the lipid membrane proteins but on the dynamic conformational functions of proteins (such as ion channel operation, receptor activation and cytoskeletal function). It is known that anesthetics inhibit a variety of neurotransmitter receptors; however they differ from other receptor inhibitors by exhibiting effects on the cytoskeleton (Bjornstrom, 2003). It has been proposed that anesthetics inhibit the movement of electrons within hydrophobic pockets located within tubulin (Hameroff, 1998b). This is directly relevant to our suggestion regarding the role of the tubulin conformational changes as follows: binding of an anesthetic molecule to the hydrophobic pocket of the tubulin dimer may have the effect of preventing changing the electron orbitals (i.e. the tubulin's ability to flip its electronic state) thus shutting the whole system down. Electron mobility within the tubulin hydrophobic pockets determines the proteins overall conformational state, and this state has been implicated as key to a MTs ability to process information, as will be discussed in the next section. This loss of processing capability is thus likened to a loss of consciousness. Following along the same lines of reasoning, hallucinogenic drugs, such as LSD, appear to donate electrons to the system thus augmenting consciousness (Snyder, 1965).

2. MTs and Information Processing

2.1 How do MTs Process Information?

In models of microtubular information processing, the basic computational unit is the tubulin dimer. Each dimer is taken to exist in a given informational state determined by the states of its surrounding neighbors and environmental influences. Thus, information takes the form of specific patterns of dimer states along the MT length. Processing of information involves the changing of the dimer states in time as determined by dimer-dimer interactions as well as environmental interactions including the effects of MAPs bound to the MT, thermal effects, and the effects of the surrounding cytoplasmic medium.

Depending on the model design the informational state of the tubulin dimers can have either discrete degrees of freedom, such as charge distribution, and

continuous degrees of freedom, such as dipole orientation. Models that focus on discrete degrees of freedom consist of an array of coupled binary switches. Models focusing on continuous degrees of freedom consist of arrays of coupled oscillators. In principle, a classical model of microtubule based computation can be quantized, by replacing the binary switch between information states with states capable of existing in superposition, harmonic oscillators with quantum harmonic oscillators, and coupled states with entangled states.

Entanglement is a property of superpositions involving more than one system. Just as two classical bits can be in any of four states (00, 01, 10, 11), the general quantum state of two qubits is a superposition of the form $c_{00}|00>+c_{01}|01>+c_{10}|10>+c_{11}|11>$; and the quantum state of N qubits can be represented by a complex-valued vector with 2^N components. This is the basis of the exponential superiority of quantum computation: instead of N Boolean registers, one has 2^N complex variables, even though there are only N physical switches. But to be computationally useful, the joint quantum state must be 'non-separable'. A separable state can be expressed as an abstract product of individual states:

$$|00\rangle = |0\rangle_{A^*}|0\rangle_B \text{ and}$$

$$|00\rangle + |01\rangle = |0\rangle_{A^*}\left(|0\rangle + |1\rangle\right)_B .$$

But the 'Bell state' $|00\rangle + |11\rangle$ cannot be factorized in this way, and is therefore non-separable. The entanglement of a state is a measure of its non-separability, and arguably represents the fundamental resource used in quantum computation.

State reduction is the process whereby quantum systems assume definite values. Its physical nature is still something of a mystery, but heuristically one assumes that it occurs whenever a property is actually measured. If the bit value of a qubit in the state $c_0|0> + c_1|1>$ is measured, it will be found to be 0 with probability $|c_0|^2$ or 1 with probability $|c_1|^2$. This is the reason for the constraints on the complex coefficients of a superposition: the probabilities must add to one. The reduction process will therefore occur whenever one actually reads out a result from a quantum computer.

2.2 Models of MT Information Processing

The method of cellular automata is an example of a discrete model and has been used to a great extent to show the potential for information processing in MTs. Cellular automata with rules based on various biological interactions are good models of biological pattern formation offering examples of universal computation and self-organization in self-organizing systems. The interactions of the individual unit cells with one another can lead to complex behavior capable of computation. Cellular

automata models of MTs based on tubulin dipole oscillations represented as a discrete charge within the tubulin dimer have demonstrated self-organizing patterns suggesting the potential for MTs to process information (Smith, 1984; Rasmussen, 1990; Campbell, 2002). It has been shown that MT cellular automata networks may signal, adapt, recognize, and subserve neural-level learning and such models have also been used to simulate associative learning in MT networks as well as the dynamics of MT assembly and disassembly (Rasmussen, 1990). These results suggest that such activities in MTs may have importance in biological regulatory functions as well as cognition. While the cellular automata rules and patterns discovered by these investigations were somewhat arbitrary, they demonstrated that cellular automata-like information processing within MT lattices is feasible.

The ferroelectric model of the MT is an example of a continuous model (Brown, 1997). Due to the dipolar nature of the MT subunit tubulin and the regular arrangement of tubulin molecules within the MT structure, MTs may be viewed as an electret, which is an assembly of ordered dipoles. As such they are predicted to possess dielectric properties. Based on this evidence it was predicted that MTs are ferroelectric in nature. Originally, due to the structural symmetry of MTs the dynamics of the system were initially described in terms of the non-linear dynamics of dimer dipoles in a single pf based on tubulin conformational changes due to GTP hydrolysis (Sataric, 1993). Further examination modeled the MT as a lattice array of coupled local dipole states interacting with their immediate neighbors thus representing the system as an anisotropic two-dimensional Ising model on a triangular lattice (Tuszynski, 1995). These models indicated that the dipoles of the MT were likely to exist in two ordered phases, a ferroelectric phase and a length dependent intermediate weakly ferroelectric phase, which varied between one another through variation of temperature and an external electric field. The ferroelectric phase, in which the dipoles were parallel aligned, showed long-range order and alignment among the dipoles with the capability to transmit kink-like excitations indicating optimal conditions for MT signaling and assembly/disassembly. The intermediate phase, in which the dipoles exhibited a conflict in resolving the dipole couplings, showed properties suitable for information processing and computation. Investigations based on this ferroelectric model have revealed that the information storage capacity of MTs increases as the MT moves from a ferroelectric phase to a paraelectric phase (Trpisova, 1996), the presence of large transient electric fields, such as nerve impulses, make MTs more likely to exist in a ferroelectric phase indicating conditions for signaling rather

than information processing (Brown, 1999; Trpisova, 1996), and that MAPs affect the signaling and information processing of MTs (Trpisova, 1996)

One of the strongest criticisms of these MT models is that for such systems to work it must be shown that the electromagnetic interactions among the tubulin dimers are capable of overcoming decoherence resulting from the noise associated with the thermal environment (Tegmark, 2000). While the timescales for thermal decoherence of quantum states in MTs have been debated (Hagan, 2002; Rosa, 2004) the capability for quantum information processing within MTs still needs verification. Recently MTs have been modeled as quantum Hopfield networks to investigate this topic (Behrman, 2006). A Hopfield network consists of individual processing units, usually neurons, existing in one of two states. The units of a Hopfield system are fully connected to all other units in the system via multiplicative weights that add up to determine whether the individual unit changes state or not. The quantum Hopfield network model of a MT investigates the suggestion of quantum computation in MT protein assemblies numerically with qubits representing tubulin molecules interacting via Coulomb forces at finite temperature. It was found that quantum information processing in MTs is feasible although at temperatures of approximately 6K. However in this model environmental factors such as energy losses and dissipation are neglected, and several of the parameters used in simulation are not based on experiment suggesting that modifications of the model could affect the scale at which the phenomena occur. More recently a quantum cellular automata MT model that is governed by the electrostatic interactions of electrons located in double quantum well structures within tubulin has shown the emergence of self-organizing patterns at physiological temperature indicating a potential for information processing in this temperature regime (Craddock, 2007).

It has been observed that MTs give rise to intense second-harmonic generation, a frequency doubling, upon exposure to a sapphire laser in the 880nm range. MTs were one of the few biological materials having electric dipoles that constructively interfered with the diploes of neighboring MTs (Dombeck, 2003). This occurred for parallel MTs in axons, however it did not occur for anti-parallel MTs in dendrites. Since second harmonic generation is a nonlinear quantum optics phenomenon this evidence maybe construed as an indication of quantum coherence among neighboring MTs. However, despite these predictions concrete experimental verification of quantum effects within MTs is still lacking.

Another criticism of these models is the lack of experimental evidence indicating the conduction properties of

MTs. As such there has been a large number of experimental investigations aimed at discovering the conductivity of MTs in the last decade. The results of these experiments are discussed in the following section.

3. Advancements in the Understanding of MTs

3.1 MT Conductivity

Making conductance measurements on biopolymers is difficult due to the structural variety of polymers, the liquid state of samples and the dependence of biological systems on environmental factors such as pH, temperature and ion concentration. However recent advances in nano-scale technology are improving experimental conditions allowing for serious investigations to take place. Thus, despite the inherent difficulties in measuring conductivity in MTs many experimental tests have been performed to investigate the matter. Measurements of the resistance values of MTs have been investigated both intrinsically and in relation to MTs as ionic conduction cables.

Direct measurements of MT conductivity require making electrical contact with molecules on the nanometer scale. Electrical contacts have been made with MTs following dry etching of a substrate containing gold microelectrodes (Fritsche, 1998). Resistance measurements made on single MTs via these electrical contacts yielded values of 50 MΩ for MTs 12 µm in length. This indicates an approximate resistance value of 4 MΩ/µm. This value is only slightly larger than the theoretically predicted values in the range of 100's of kΩ predicted by tight binding Hubbard model of the MT (Tuszynski, 2007). Other direct conductivity measurements made on MTs in micro-channels require the integration of microelectronics, electrical measurements, and biotechnology. Measurements made on MTs grown in a buffer solution with high ionic strength were deposited on P-L-l coated oxidized silicon chips containing gold electrodes have revealed an approximate value of 40 MΩ/mm for MTs in dry state and an upper limit of 90 $\Omega^{-1}m^{-1}$ for MT conductivity (Umnov, 2007).

The dielectric nature of MTs, which is essential to information processing in MTs, has also been investigated. Due to the presence of an intrinsic dipole in MTs radio frequency (RF) reflectance spectroscopy has also been used as an investigative method to probe MT conductivity (Goddard, 2006). RF reflectance spectroscopy measures the electrical response of a sample in response to sinusoidally alternating currents as a function of frequency. Electrically investigating MTs allows the detection of polymerized state, tracks any related conductivity changes, and monitors the binding of MAPs. Radio frequency reflectance spectroscopy of 5 ml solutions of free tubulin (5 mg/ml),

bare MTs, MTs with MAP's (0.3 mg/ml), and the containing buffer solution yielded DC resistance values of 0.424 kΩ, 0.883 k Ω, 0.836 k Ω, and 0.999 k Ω, respectively. Assuming all tubulin is polymerized in the MT cases, and that the MTs are in a uniform distribution of parallel and series networks these values can be translated into a resistance of 8 MΩ for a MT 10 mm in length.

The dielectric properties of MTs have been investigated via an electro-orientation method with an alternating electric field under a dark field microscope (Minoura, 2006). The alternating electric field, with strength varying between 0.5-1.9 10^5 V/m and an oscillating frequency between 10 kHz–2 MHz, caused MTs to orient parrallel to the field. Analysis based on a dielectric ellipsoid model found MTs to be highly conductive with conductivity values in the range of 1.5±0.5 mS/m, fifteen times greater than the buffer solution. This conductivity was attributed to counter ion polarization where counter-ions bound to highly negatively charged MTs move along the long axis. As well impedance spectroscopy has also been used to examine the electrical properties of tubulin dimers in suspension (Sanabria, 2006). A sinusoidal electric field was varied over the frequency range of 1 Hz to 1MHz was used to find the complex ratio of the voltage and current amplitudes, including phase information. From this information large dielectric responses were observed to occur at low frequencies. It was also found that individual tubulin dimers possess a charge number of 306 e in saline solution which if maintained in polymerization would yield a MT linear charge density of 3.8 e/Angstrom. At the level of megahertz the conductivity of the sample was shown to increase with concentrations below 1mg/ml, and decrease above this level suggesting that such measurements may be used to monitor MT polymerization.

These results are seemingly vague leaving precise experimental determination of the values of MT conductivity in question. While much of this experimental evidence concerning the conductivities of MTs is still quite scattered and inconclusive, it does provide a broad basis for theoretical models. The conduction properties of MTs seem to indicate the capability for electrical signal transduction and information processing, but the question remains of how do the delicate, weak, very small scale quantum processes of electron movements within MTs influence brain cell firing and communication? The following sections looks at theoretical ideas advanced to explain how MTs can be implicated in brain functioning.

3.2 Signal Processing and Transduction via the C-termini Tails of Tubulin

Alterations of the structural MT associated protein MAP2 has been shown to alter contextual memory (Khuchua,

2003) and the expression of the motor MAP KN has been shown to affect learning (Wong, 2002). As well, the transport of mRNA's along dendritic MTs to the specialized cytoskeleton located at neuronal synapses, known as the postsynaptic density, has been suggested to play a role in learning and long-term potentiation (Kiebler, 2000). Priel et. al. examined the role of the tubulin C-termini tails in the MT's ability to transduce and process signals (Priel, 2006). The biophysical properties of the C-termini have been shown to affect the attachment of MAPs including KN and MAP2 (Sackett, 1995).

To investigate the role of C-termini in the functioning of dendrites, Priel et.al., develop a computational model based on the biochemical data of tubulin, their C-termini tails, and MAP2. Using molecular dynamics simulations the conformational states of the C-termini protruding from the MTs outer surface were calculated. The 3D structure of the tubulin dimer was determined by Nogales et. al., (Nogales, 1998) but several amino acids including some at the C-terminus of the protein were unresolved resulting in their omission from the Protein Data Bank. Structure files were created that include the C-termini of tubulin. Each tubulin dimer possesses two C-termini tails that can exist in several conformational states. According to the model the negatively charged C-termini interact electrostatically with the dimer surface, neighboring C-termini, and adjacent MAPs. The minimization of the overall interaction energy of the C-termini is believed to govern the system as it evolves in time. The surface of the tubulin dimer is highly negatively charged, with regions of positive charge attracting the C-termini tails causing them to end into a "downward" state. The "up" state, in which the C-terminus extends perpendicularly out from the dimer, was found to have the lowest energy. For situations in which the energy of the C-termini was less than 50 meV plus the lowest energy state, the C-termini tail was allowed to move freely due to thermal fluctuations. This corresponds to a cone with an angle of 40^o from the dimer surface. A local minimum corresponding to the "downward" state was found at 100 meV above the lowest energy state, and a saddle-point was found 160 meV above the lowest energy. It was deduced from these findings that two major metastable states exist with an energy difference between the two on the order of a few k_bT (Priel, 2006).

To facilitate the calculation a bead-spring model was developed in which the C-termini tails are taken as strings of beads with flexible connections. The electric field exerted by the dimer, the external field from the environment and interactions within individual C-terminus were taken into account. Simulations of the bead-spring model indicated the ability of ionic waves to

create waves of C-termini state changes from upright to downward orientations. Calculations performed on the model to find the minimum energy positions of the individual beads, corresponding to the C-termini amino acids, in two equal forms revealed a 15% probability for the tail to existing a full or partial attachment "downward" position. This indicates that the system favors the "up" state unless driven towards the "downward" state by outside influences.

The interaction between MAP2 and its ionic environment was modeled using counter-ions in order to investigate the ability of MAP2 to function as a wave-guide to transfer. The binding region is located at the C-terminus and the bond between MAP2 and a MT appears to be electrostatic in nature. It has been shown that MAP2 binds to MTs in a concentration-dependent manner (Pedrotti, 1994). However, since the 3D structure of MAP2 is unknown at this point in time, as it has not been crystallized, therefore it is not known whether or not MAP2 actually makes physical contact with MTs, but at the very least MAP2 enters into the immediate vicinity of the MT. As a simplification of the model Priel et. al. assumed MAP2 to be a straight chain along which the attraction sites for the counter-ions were equally spaced and arranged, and that the counter-ions move only in a plane perpendicular to the MAP2 cylinder. It was found that perturbations applied to the counter-ions at one end of the MAP2 chain initiated a wave traveling along the MAP2 moving the counter-ions out of equilibrium. The profile of the ion displacements revealed a "kink"-like perturbation along the MAP2 chain with a phase velocity on the order of 2 nm/ps.

The results of molecular dynamic modeling of MTs raise the possibility that MTs are capable of transmitting electrostatic disturbances. The propagation of ionic waves along MAP2 can be seen to influence the conformational states of surrounding C-termini that in turn affect other C-termini along the MT. Thus electrostatic disturbances can be understood to propagate along MTs in the form of collective disturbances among neighboring C-termini, or between neighboring MTs via MAP2 connections. The relation of these ideas to the cognitive functions of the brain is discussed in the next section.

3.3 Relation of MT Electrical Activity to Cognitive Brain Functions

The transport of proteins and receptors along neuronal MTs is likely to have an electromagnetic basis indicating that this function is possibly dependent on MT information processing. As discussed above KN mediated transport of mRNA has been implicated in memory and learning. KN mediated transport along MTs is affected by both the protein conformation of tubulin and the nature of

the C-termini (Priel, 2006, Sackett, 1995). The conformational state of tubulin, which is key to the notion of information processing within MTs and therefore the notion of quantum consciousness, is not only critical to effective transport, but appears to be altered in turn by motor proteins and MAPs. The binding of KN and the MAP tau have been observed to significantly alter the direction of the protruding protofilament ridges along MTs, which in turn influences their further binding abilities (Santarella, 2004). In fact it has been suggested that tubulin dimers along MTs alter their conformational state ahead of KN motor movement (Krebs, 2003). The conformational state of tubulin within a MT determines the dipole moment of the dimer and thus the electromagnetic field of the MT (Hagan, 2002).

Priel et. al. building on the ideas discussed in the previous section suggest a direct regulation of ion channels, and thus the electrical response of neurons, by cytoskeletal structures (Priel, 2006). It is envisioned that arrays of dendritic MTs, equally arranged in parallel and anti-parallel fashion, receive signals from neuronal synapses either via actin filaments connected to the array via MAP2, or via direct connection of the array to the post synaptic density located at the synapse. While the investigations into the electrical activity of actin filaments have yielded results indicating a potential for ionic wave propagation, the discussion of the electrical properties of actin are beyond this scope of this article and therefore will not be discussed. Once the input signal is received the MT network evolves the signal by dynamically altering its C-termini conformations. The output of the signal moving through the MT network may then propagate along the via actin filaments to distant ion channels eliciting the channel to open or close. This process thus affects the electrical response of the neuron by regulating the temporal gating state of the voltage-sensitive channels. For this reason the process controls the membrane conductive properties as well as the axon hillock behavior by changing the rate, distribution and topology of open/close channels. The overall functions of the dendrite and neuron can thus be directed in this manner.

Recall that the binding of KN and MAP2 are affected by the conformational state of tubulin's C-termini as discussed in the previous section. Thus, the incoming signal from a neuronal synapse not only alters the C-termini conformational states along the MT, but also alters the binding of KN and MAP2. Through alterations of KN and MAP2 binding the tubulin conformational state is affected, thus the electromagnetic fields created by MTs could be altered by synaptic inputs.

MAP2 bridges keep the MT networks within the dendritic core aligned in parallel and anti-parallel arrangement by aligning portions of polarized MTs. The

anti-parallel alignment of MTs, which specifically occurs in dendrites, can be understood to severely attenuate any electromagnetic field generated by MTs. It is expected that KN-mediated transport is enhanced during heightened synaptic activity. Due to KN's effect on tubulin's conformational state it is expected that during this period MT bound MAP2 would be perturbed and may even detach from the MT temporarily. If it is assumed that some MAP2 remain connected to the MT, thus keeping the MT network intact, any net unidirectional transport along the array should enhance the strangth of its associated electromagnetic field resulting in the spread of that field to adjacent MTs. If a sufficient number of MTs engage in this activity it can be imagined that entire dendrites might be expected to interact. Due to lengthwise electric dipoles of tubulin dimers, information in the form of traveling waves propagated along MTs can, in principle, be transmitted between synapses with high fidelity (Tuszynski, 1998). Due to the parallel/anti-parallel arrangement of MTs in cortical dendrites and the ability of electromagnetic fields to pass from one dendrite to adjacent dendrites, information could, in principle, pass between neurons when such electromagnetic fields were sufficiently amplified as a result of changes in the binding of MAPs or KN.

The idea that there is one common type of energy responsible for perceptual and cognitive processes appears likely (Cronly-Dillon, 1999). This may be a particular electromagnetic state of a network of MTs that corresponds to a unique cognitive event. This has been referred to as an electromagnetic fingerprint (Priel, 2006). Due to the high degree of interaction described above activation of one electromagnetic fingerprint could, in turn, activate another electromagnetic fingerprint, independent of sensory input giving rise to the so-called stream of consciousness. Moreover, the subjective feels of this widespread pattern of electromagnetic energy can be specified according to those key physical properties of MTs that influence the transport of proteins to synapses.

4. Summary and Outlook

In this article we have discussed the arguments implicating microtubule information processing as a key process in cognitive brain functions, the structure and biophysical functions of MTs, specifically those functions related to signaling, conduction and cellular transport, and possible mechanisms for MTs to influence brain cell firing. Three major criticisms of this work are identified. The first major criticism indicates that decoherence arising from the thermal environment within the brain can destroy any quantum effects within MTs. While theoretical predictions indicate that this may not be so, direct experimental evidence of quantum effects within MTs is required. Experimental tests to investigate quantum effects in MTs have been

outlined (Mershin, 2006), however concrete results are still needed. The lack of definitive parameters of the conductive properties of MTs, and its effect on the predictions of theoretical models is the second criticism. However, as reported above significant headway has been made in the investigation of MT conductivity. This evidence indicates that MTs are likely conductive in nature, however precise values for inclusion within theoretical models are still lacking. The third major criticism questions how the functioning of MTs within neurons affects neuronal firing patterns, and thus the overall functioning of the brain. Based on the discussion of the experimental evidence linking MAP2, and KN to learning and memory, as well as the theoretical predictions of the computational ability of the dendritic cytoskeleton a specific functional role for MTs in neurons is proposed that differs from their well-characterized structural significance. The role of MTs within the neurons is outlined as follows:

1. Synaptic transmission signals arrive at the postsynaptic density causing ionic waves to move along associated actin filaments.
2. These waves propagate along MAP2 via the movement of counter-ions from the actin filaments to MTs.
3. These waves in turn affect the conformation states of the C-termini on the MT.
4. The change in C-termini states affects the KN based movement along MTs as well as the MAP2 connections along the MT affecting memory and learning.
5. The change in MAP2 connections then alters the electronic information processing within MTs that may give rise to a conscious event.
6. These changes in MAP2 connection also affect connections with other MTs.
7. The wave may then propagate along the new connections to other actin filaments that in turn affect ion channels and neuron signaling.

The above scheme may elucidate the way in which external stimuli affect our learning and memory as well as our conscious perception (i.e. by eliciting changes in MAP2 patterns affecting information processing). However, the key question now becomes how does the electronic information processing in MTs associated with consciousness affect the external system thus accounting for concepts such as conscious free will, the so-called mind-body problem?

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