Article

Neuropsychiatric Illness: A Case for Impaired Neuroplasticity and Possible Quantum Processing Derailment in Microtubules

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Abstract

There is a great deal of evidence that cytoskeletal proteins, in particular microtubules, are dysfunctional in mental illnesses such as schizophrenia and affective disorder. Since cytoskeletal proteins are major arbitrators of neuroplasticity, this evidence fits with recent theories suggesting that neuroplasticity is compromised in mental illness and that the efficacy of antidepressant and antipsychotic drugs may depend, at least in part, on their ability to enhance neuroplasticity. Quantum theories of mind, particularly those implementing information processing in microtubules, are useful on many levels. Quantum theories attempt to explain the more enigmatic features of mind, some of which are disrupted in mental illness. Quantum information processing theories also attempt to link molecular events at the atomic level to higher cognition. These approaches are highly ambitious, and multiple potential obstacles abound as a consequence of working in largely uncharted territory.

Key Words: neuropsychiatry, neuroplasticity, quantum processing, microtubules, psychopathology

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1. Introduction

Neuropsychiatric illnesses are major health problems associated with increased morbidity and decreased quality of life. These illnesses range from fairly uncommon to relatively common. In a given year, schizophrenia, bipolar disorder, major depression, and anxiety disorders affect 1.1%, 2.6%, 6.7%, and 18.1%, respectively, of the adult population (Kessler *et al.*, 2005). Across the board, these disorders affect mood and mind: emotions and thought processes being distorted to the extent that psychosocial, academic, and vocational functions are impaired. Various models of neuropsychiatric illness – based on neuropharmacology, neuroanatomy, or neurophysiology – provide clues as to which neurotransmitters may be deficient (or in excess), what parts of the brain may be

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dysfunctional, and what neural firing patterns correlate with various mental disorders. Still none of these approaches identify the root causes of neuropsychiatric illnesses or fully explain aspects of thought disorder or emotional dysregulation.

In this issue Globus (2010) argues that the unique states of consciousness associated with the schizophrenic patient, namely the splitting of agency with the retention of a unified consciousness, cannot be described adequately by nonlinear dynamic systems founded in classical neurophysics. Likewise, in a companion article Mender (2010) discuses the numerous incongruities of the bio-psychosocial paradigm of psychiatric illness, with its parallels to neural network theory and classical statistical mechanics. Both argue that new quantum paradigms of psychiatric illness could advance perspectives on brain, mind, and mental disorders. New theories implicating dysfunction in neural networks and neuroplasticity offer fresh perspectives that account better for certain findings than do theories of "chemical imbalances" among levels of neurotransmitters (Castrén, 2005). Even though pharmacological interventions are first-line treatments for depression, there is no evidence that putative chemical imbalances are reversed. The time course of therapeutic effects does not fit an imbalance being present. Antidepressant drugs, which are known to increase levels of neurotransmitters serotonin and norepinephrine, do not act to immediately improve the patient's mood. Instead, it takes 2 – 6 weeks for these drugs to elevate mood. Similar arguments can be made for schizophrenia not being caused by a chemical imbalance. The "dopamine hypothesis" was advanced in the 1960's and 1970's in the wake of the marked success of antipsychotic drugs blocking dopamine receptors. However, this hypothesis is not wholly supported by experimental evidence; instead there exist both equivocal and negative evidence for dopamine being overactive in schizophrenic brain (Moncrieff, 2009). Like antidepressants, antipsychotic drugs take 2 – 6 weeks to diminish psychotic symptoms. The lower end of this time interval (2 weeks) is the same time interval over which reorganization of the cytoskeleton in neurons occurs after learning, suggesting that neuropharmacological agents may exert their therapeutic effects via the cytoskeleton (Woolf, 2009).

At least two quantum theories of brain function depend heavily upon the neuronal cytoskeleton (Hameroff, 1998; Jibu and Yasue, 1995). Could the role of the cytoskeleton in psychiatric illness lend credence to Globus and Mender's arguments (Globus, 2010; Mender, 2010), and provide a physical substrate on which to base future discussion? The remainder of this paper explores these issues with the next logical question being: are there genetic markers related to the cytoskeleton associated with increased vulnerability to neural network dysfunction and mental illness? This discussion is followed by microtubule (MT) involvement in higher cognition, a brief mention of the effects of psychotherapeutic drugs on the cytoskeleton, animal models of psychiatric illness involving the cytoskeleton, cognitive impairments in mental illness and free will, followed by a discussion of quantum models of mind and speculations on thought disruption based on cytoskeletal quantum models of cognitive processing.

2. Genetic Bases for Psychiatric Disorders

Schizophrenia and bipolar disorder demonstrate a strong genetic component that is believed to interact with environmental factors resulting in concordance rates of ~40% among monozygotic twins (Cardno *et al.,* 1999). Although most investigators attribute phenotypic variance to environmental factors, an alternative hypothesis is that polygenic factors influence the outcome of a mental disorder diagnosis in a probabilistic rather than a deterministic manner (Procopio, 2005). Regardless of how much environment plays a role, most cases of mental illness are thought to be due to polygenetic effects consisting of multiple instances of single nucleotide polymorphism (SNP) or gene copy number variation, with specific genes being affected in at least some families or populations (Gill *et al.,* 2009). Variant genes associated with psychiatric diagnoses include those coding for

disrupted-in-schizophrenia-1 (DISC1), neuregulin-1, dysbindin, and neurexin-1. These aforementioned proteins regulate neuroplasticity via interactions with the cytoskeleton supporting the idea that neuroplasticity is impaired in mental illnesses, particularly schizophrenia and affective disorders.

A balanced translocation in the DISC1 gene was first established as a risk factor for schizophrenia, bipolar disorder, and recurrent major depression in a Scottish family exhibiting a large number of psychiatric diagnoses (Blackwood *et al.,* 2001; St. Clair *et al.,* 1990). Since that initial discovery it has been shown that DISC1 plays a role in more widespread cases of schizophrenia. More than 50 splice variants of DISC1 are formed, and in early development and in adults with schizophrenia there is an increased number of shorter variants of DISC1 (Nakata *et al.,* 2009). These truncated variants of DISC1 lack the C-terminus responsible for protein-protein interactions, resulting in abnormal cell signaling and disruption of cytoskeletal networks. Normally, unmodified DISC-1 protein plays a role in neural development and synaptic plasticity, in part, by regulating transport mediated by dynein along MTs and by modulating actin filament reorganization (Brandon *et al.,* 2009). Knockout mice having the gene for DISC1 deleted demonstrate decreased neural migration and dendrite branching, functions mediated by MTs and actin filaments (Austin *et al.,* 2004). Variants for DISC1 in schizophrenia are furthermore associated with altered expression of isotype-specific MT subunits: β III-tubulin and δ I-tubulin (Hennah and Porteus, 2009).

Meta-analyses for genome-wide scans found six neuregulin-1 SNPs associated with schizophrenia in Icelandic and Scottish populations, while only two neuregulin-1 SNPs associated with schizophrenia in an Asian population (Li *et al.,* 2006). The neuregulin-1 gene has also been found to contribute to a diagnosis of schizophrenia in a northern Swedish population (Alaerts *et al.,* 2009). Five SNPs were associated with schizophrenia, whereas another SNP conferred reduced risk for the disorder. Similar to that of DISC1, neuregulin-1 regulates neurodevelopmental functions including cell proliferation and migration, neurite outgrowth and synaptogenesis, as well as maturation and myelination (Jaaro-Peled *et al.,* 2009). Many of these functions are mediated through direct actions on the cytoskeleton.

An initial study demonstrating genetic variation in the dysbindin-1 gene assessed 270 Irish pedigrees (Straub et al, 2002). Not all European groups show an association, however; and familial loading, rather than ethnicity, may be the most critical factor (Van Den Bogaert *et al.,* 2003). In agreement with that conclusion, certain variants of the dysbindin-l gene confer increased risk for schizophrenia in European Americans, but not in African Americans or in Koreans (Zuo *et al.,* 2009; Joo *et al.,* 2006). Dysbindin-1 associates with postsynaptic densities and MTs, and is also found in axon terminals where it regulates the release of the neurotransmitter glutamate (Talbot *et al.,* 2006). Dysbindin-1, along with neuregulin-1, mediates neurodevelopment and neuroplasticity, which are perturbed in schizophrenia leading to cyto-architectural and molecular abnormalities (Arnold *et al.,* 2005).

Yet another gene that codes for a protein involved with neuroplasticity is linked to schizophrenia. Copy number variations for the neurexin-1 gene increase susceptibility to schizophrenia in a Japanese population (Ikeda *et al.,* 2009), and in seven European populations (Rujescu *et al.,* 2009). Neurexin works with neuregulin to regulate synaptic plasticity (Gottman, 2008).

Three recent reviews list approximately 34 genetic regions as possibly being involved in bipolar disorder (Hayden and Nurnberger, 2006; Cheng *et al.,* 2006; Segurado *et al.,* 2003). Comparing these with the Entrez Gene (NIH) entries for the human tubulin proteins reveals 18 matching tubulin isoforms. These proteins include β IIA-, β IIB-, and β IIC-tubulin, β III-tubulin, and β VI-tubulin, as well as proteins similar to α II-tubulin, β chain tubulin, vI-tubulin, β IV-tubulin, and β V-tubulin, pseudogenes for β IVQ-tubulin, β II-tubulin, and β V-tubulin, and β IV-tubulin polypeptide. There is a predominance of

genetic linkages with regions containing β – isoforms of tubulin. A polymorphism, deletion, or insertion occurring in any of these genetic regions may affect the expression of one, or more, of these β – tubulin isoforms, and subsequently alter the structure and function of the resulting MTs and thereby contribute to the expression of bipolar disorder.

A variety of experiments provide evidence showing that 30 – 40% of the variance contributing to anxiety disorders is also heritable (Norrholm *et al.,* 2009; Martin *et al.,* 2009). While multiple candidate genes exist for the various disorders, in the context of this paper a current discovery is worth noting.

The gene encoding the protein stathmin is highly expressed in the lateral nucleus of the amygdala as well as in the thalamic and cortical structures that relay information to the lateral nucleus about learned and innate fears (Shumyatsky *et al.,* 2002). Stathmin knockout mice exhibit deficits in spike-timing-dependent long-term potentiation as determined by whole-cell recordings from amygdala slices, decreased memory in amygdala-dependent fear conditioning, and they recognize less danger in innately aversive environments (Shumyatsky *et al.,* 2005). Investigations on the impact of stathmin gene variation on fear- and anxiety-controlling effector-systems of the amygdala found that the human gene coding for stathmin, coupled with gender, significantly impacts fear and anxiety responses as measured with the startle and cortisol stress response (Brocke *et al.,* 2009). Thus, the stathmin genotype has functional relevance for basic fear and anxiety responses in humans as well as rodents.

Stathmin is enriched in neuronal cells, and is an MT-destabilizer (Curmi *et al.,* 1999) acting by isolating free-tubulin dimers (Howell *et al.,* 1999) or by increasing MT catastrophe (Belmont *et al.,* 1996). Phosphorylation negatively regulates the MT destabilizing activity of stathmin, suggesting that stathmin may link extracellular signals to the rearrangement of the neuronal cytoskeleton (Grenningloh *et al.,* 2004). Down-regulation of stathmin during cerebellar development promotes dendritic arborization in mouse Purkinje cells, while over-expression limited dendritic growth (Ohkawa *et al.,* 2007). However, stathmin depletion with antisense oligonucleotides prevents nerve growth factor-stimulated neurite outgrowth in rat Purkinje cells (Di Paolo *et al.,* 1996). These data suggest that proper regulation of stathmin activity is a key factor for controlling the dendritic MT dynamics. Dysfunction of such activity is suggested to relate to the fear responses associated with anxiety disorders.

Despite the large and increasingly growing number of genes having potential linkages to multiple mental disorders, the result appears the same – an underlying deficit to neuroplasticity at various levels: the individual synapse, neuron structure (particularly dendrites), and overall pattern of connection between neurons. How deficits in neuroplasticity relate to cognitive deficits in mental disorders still needs to be clarified. Cytoskeletal protein involvement in higher cognition appears to provide clues.

3. Microtubule Involvement in Higher Cognitive Processes

Biological clues for mental disorders derive in large part from behavioral genetics, but genes code for proteins, many of which are macromolecules that cannot easily be modeled to account for the complexities of human cognition – normal or abnormal. One way to attempt this leap is to identify the macromolecules that mediate the most basic types of cognition. Cognition includes learning, memory, perception, and other simpler functions, which serve as fundamental building blocks for higher cognitive functions – including those disrupted in mental illness. In addition to the obvious role in neuroplasticity, direct evidence shows that cytoskeletal proteins, such as MTs and actin filaments, play pivotal roles in both simple and complex types of learning and memory. Neurons in Alzheimer's disease, a disorder with marked cognitive impairment, for example, have reduced MT density and length (Cash *et al.,* 2003). In one of the many animal studies exploring biological correlates of behavior, O'Connell and colleagues (1997) demonstrated a profound 3-fold increase in

MTs of hippocampal granule neurons following 6 hr of passive avoidance training. Changes with learning are also detected in microtubule-associated proteins (MAPs). MAP2 is a dendrite-specific MT linker protein that increases MT polymerization and stability, as well as serving as a site for phosphorylation enabling signal transduction. Using cDNA microarrays, MAP2 mRNA was shown to increase with filial imprinting in domestic chicks, a species-specific form of learning (Yamaguchi *et al.,* 2008). Also, TAU, another MAP that modulates the stability of axonal MTs, when over-expressed in *Drosophilia* mushroom body neurons has been shown to produce learning and memory deficits (Mershin *et al.,* 2004).

Dependence of learning and memory on MTs is also shown in studies using cytoskeletal toxins. Colchicine, which binds to tubulin and blocks MT function, interferes with performance on the Morris water maze, radial-arm maze, aversive conditioning, and operant conditioning (Mileusnic *et al.,* 2005; Nakayama *et al.,* 2002; Bensimon and Chermat, 1991; Di Patre *et al.,* 1990). Aluminum poisoning, which results in depletion of MTs in large pyramidal cells of hippocampus, also results in cognitive deterioration in aged rats (Walton, 2009).

A host of additional studies indicate that the MT matrix in dendrites is structurally reorganized with learning and memory. Using an associative learning paradigm combined with immunohistochemistry, fear conditioning to either tone or to the training context induced significant changes in MAP2 in circumscribed regions of the cerebral cortex or hippocampus, with alterations correlating with the type of training (Woolf *et al.,* 1994; 1999). Increases in MAP2 immunostaining were further correlated with proteolysis and increased breakdown products with a molecular weight of ~90 kD determined by Western immunoblots. When tone was paired with shock MAP2 breakdown was noted in the auditory cortex, where tonotopic information is stored. When the context of the training chamber was paired with shock, enhanced MAP2 breakdown was evident in pyramidal cells of the hippocampus, where contextual information is stored. Neurons in the auditory cortex and hippocampus affected by training corresponded with the 15% of neurons containing elevated levels of MAP2, many of which are large pyramidal neurons (Woolf, 1993). Learning-related changes in MAP2, muscarinic receptor, and protein kinase C were similarly noted following avoidance training (Van der Zee *et al.,* 1994). To further uncover the mechanisms by which MAP2 participates in the learning process, the N-terminus of MAP2 was truncated in transgenic mice; this led to contextual memory impairment and reduced ability to bind cAMP-dependent kinase leading to reduced phosphorylation of MAP2 (Khuchua *et al.,* 2003). What happens after MAP2 is broken down with memory formation is not entirely clear. It is most likely, however, that a new MT matrix is built. This suggestion of dendritic reorganization is consistent with increased expression of MAP2 in motor cortex found on days 1, 5, and 7 of training, with increases shifting to later times with increasing task difficulty (Derksen *et al.,* 2006). Mitsuyama and colleagues (2008) found evidence of new MT tracks linking the cell nucleus with the postsynaptic membrane with long-term potentiation, a learning-like phenomenon. Reorganization of MT matrices would be expected to alter information processing achieved by means of electrical signaling within networks of MTs (Priel *et al.,* 2006).

MT matrices are linked to the actin filament networks that directly contact the neuronal membrane (Priel *et al.,* 2009). Actin filaments also fill what are called dendritic spines, with the growing plus-end tips of MTs invading these appendages (Jaworski *et al.,* 2009). Actin filaments are very plastic and appear to play a key role in learning and memory, especially in dendritic spines. Extinction to contextual fear involves rearrangements of actin filaments in spines (Fischer *et al.,* 2004). Actin, along with tubulin and F-actin capping protein increase their binding to other proteins during memory consolidation (Nelson *et al.,* 2004).

The study of cytoskeletal proteins in learning and memory in laboratory animals has yielded a great many results. Laboratory animals are also used to study neuropsychiatric illness and treatments.

4. Effects of Psychotherapeutic Drugs on the Cytoskeleton

Only recently have there been a handful of reports describing the effects of psychotherapeutic drugs on the MT matrix (Benitez-King *et al.,* 2004; 2007). Antipsychotic drugs, for example, appear to increase expression of MAPs (MacDonald *et al.,* 2005; Law *et al.,* 2004), but some may also produce temporary damage to MTs (Dean, 2006). Valproic acid and lithium are the most widely used mood stabilizers for treating bipolar disorder. Valproic acid glucuronide, the major metabolite of valproic acid, inhibits the polymerization of tubulin into MTs by reversibly and irreversibly bonding and subsequently forming adducts with both tubulin dimers and MAPs (Cannell *et al.,* 2002). Laeng *et al.,* (2004) showed both valproic acid and lithium have positive effects on neurogenesis and increase the number of β III-tubulin cells in rat cortical cultures. In this aforementioned study, β III-tubulin was used primarily as a marker for neurons.

5. Animal Models of Depression, Anxiety, and Schizophrenia Involving the Cytoskeleton

Animal models of human disease states make it possible to generate hypotheses about the causes of those disorders in ways that would be impossible in human subjects, and to test potentially effective drugs and treatments before enough is known about drug safety and efficacy. The validity of an animal model is variable, and the degree to which particular symptoms are produced is one way to assess relevance or validity. In accordance with the central theme in this paper, a number of animal models link mental illnesses with the cytoskeleton and neuroplasticity. Transgenic mice lacking a protein related to the cytoskeleton often exhibit behaviors that mimic some behavioral aspect of a particular mental illness or set of disorders. Another type of animal study implicating cytoskeletal proteins has presented conditions that induce animal behaviors typical of a mental illness and evaluated brain for perturbations of cytoskeletal proteins.

Stable tubule only peptide (STOP) binds to MTs and inhibits dissociation of subunits (Pabion and Margolis, 1984). The STOP null mouse (in which both alleles for the STOP protein are deleted) exhibits atypical behaviors and deficits in synaptic plasticity, making it a successful animal model of schizophrenia (Andrieux *et al.,* 2002). STOP null mice have additional cognitive deficits in recognition and long-term memory similar to those found in schizophrenia (Powell *et al.,* 2007). Moreover, antipsychotic drugs used to treat schizophrenia alleviate social and cognitive impairments in STOP null mice (Bégou *et al.,* 2008). MT-stabilizing drugs also ameliorate the behavioral symptoms in STOP null mice suggesting a possible use for drugs of this type (or less toxic variants) to treat schizophrenia or other mental illness (Andrieux *et al.,* 2006).

The discovery of genes conferring increased risk for schizophrenia and affective disorders (many of which have associations with the cytoskeleton and neuroplasticity as described earlier) motivated the engineering of specific transgenic mice. Dominant-negative DISC1 transgenic mice, which have the C-terminus of DISC1 truncated, show behavioral abnormalities such as hyperactivity and depression-like behavior making these mice potentially useful as an animal model of schizophrenia (Hikida *et al.,* 2007). Neuregulin-1 transgenic mice are impaired on contextual fear and social learning of potential relevance to deficits in schizophrenia (Ehrlichman *et al.,* 2009). Mice having the dysbindin-1 gene deleted are impaired on the spatial learning as shown by decreased performance on the Morris water maze task (Cox *et al.,* 2009). As has been done in STOP null mice, these transgenic strains can be used to test experimental drug regimens.

Environmental conditions that produce behaviors that are similar to those found in certain mental illnesses include social isolation, aversive stimuli, and stress. Social isolation of male rats results in recognition memory deficits, along with decreased levels of α-tubulin and MAP2 levels in the hippocampus as measured by Western blots (Bianchi *et al.,* 2006). Learned helplessness is a depressed-like behavioral state produced by inescapable shock that is associated with alterations in proteins linked

to neuroplasticity (e.g., MAP-2) and is blocked or reversed by antidepressant treatments (Iwata *et al.,* 2006). Repeated exposure to chronic unpredictable stress, a known trigger for depression, causes accelerated increases in acetylated tubulin (which is associated with stable MTs) and decreases in tyrosinated MTs and phosphorylated MAP2 (which are associated with labile MTs); moreover, these cytoskeletal changes can be reversed by the antidepressant fluoxetine (Yang *et al.,* 2009).

Other animal model studies go further, linking neuropharmacological deficits with cytoskeletal changes. STOP null mice, known for their disrupted cytoskeletons, demonstrate reduced glutamate release and enhanced dopamine making them potentially similar to untreated schizophrenics (Brenner *et al.,* 2007). Depletion of the neurotransmitter serotonin causes a marked deficit in MAP2 in dendrites, reminiscent of the deafferentation found in schizophrenic brain (Whitake-Azmitia *et al.,* 1995). Lesions of acetylcholine neurons in basal forebrain results in decreased dendritic complexity (regulated by cytoskeletal proteins) and impaired working memory and spatial navigation (Fréchette *et al.,* 2009). Since neuropharmaceutical agents that either stimulate or inhibit glutamate, dopamine, serotonin, norepinephrine, or acetylcholine have as a common effect an influence on the dynamics of the cytoskeleton, the effects of these agents on mental states is perhaps best appreciated in the context of neuroplasticity. Forms of neuroplasticity, such as synaptic redistribution and dendritic reorganization, are critical to higher cognition.

6. Cognitive Impairments in Mental Illness and Free Will

Individuals diagnosed with mental illness demonstrate a range of cognitive deficits. Often these deficits can be localized to particular brain regions using cognitive neuroscience methods such as functional magnetic resonance imaging (fMRI). As one might expect, cognitive deficits are most severe in the psychotic states of schizophrenia. Schizophrenic patients are particularly impaired in the social-cognitive "theory of mind" function, along with impairments to executive function and verbal memory – traditional measures of higher cognitive function (Woodward *et al.,* 2009). Impaired theory of mind function is found during acute phases of schizophrenia, as well as in schizophrenics in remission and in relatives of schizophrenics and those affected with bipolar disorder (Bora *et al.,* 2009). Some of the inexplicable aspects of this function make it a particularly relevant function to consider in the context of quantum mind models.

Theory of mind is the ability to discern one's own intentions, to carry out those intentions in the form of overt behavior, and to accurately assess the intentions of others as different from one's own (Brüne, 2005; Frith, 1992). That schizophrenics are impaired in their ability to distinguish their own versus other's intentions can be used to explain:

- delusions in which subjectivity is confused with objectivity,
- the perception of alien control where the patient's intentional thoughts are confused with thoughts originating from others, and
- thought disorder as a consequence of reduced social interaction and impaired perception of social cues.

While behavioral scientists do not know exactly how humans sense the intentions of others, there appear to be two complementary neural systems mediating voluntary action: one responsible for motor simulation and the other mentalizing intentions (de Lang *et al.,* 2008). The neural network for linking one's own intentions to overt behavior is located in the fronto-median cortex, and since activity within that network correlates with inhibiting intended actions, this area has been proposed as the free will center in the brain (Brass and Haggard, 2007). This idea runs counter to widespread, highly distributed neural activity contributing to higher cognitive function, which cannot be fully accounted for by activity in a limited number of neurons in a circumscribed region of cerebral cortex. Moreover, some scientists argue free will is purely illusory (Hallet, 2007; Wegner, 2004).

Martin Heisenberg (2009) argues that free will must be a part of animal behavior, citing work from his laboratory demonstrating that fruit flies are capable of actively initiating completely novel behaviors to solve problems. Inspired by the classic principles discovered by his father Werner Heisenberg, he argues that behavior (and life in general) involves the interplay between deterministic and random events, much in the same way that quantum physics counterbalances the strictly deterministic nature of classical physics at intermediate scales. He posits that neuronal function lies in that intermediate scale, an opinion that is not universally shared.

In addition to an impaired sense of intention, schizophrenics exhibit thought disorders and hallucinations. Cognitive neuroscientists have discovered that networks of neurons active during visual hallucinations include the visual, superior parietal cortex, and dorsolateral prefrontal cortex, whereas auditory hallucinations involve the auditory, superior temporal, and prefrontal cortex (Bennett, 2008). A possible cause of hallucinations is deafferentation of selected parts of these networks, the exact nature of the hallucination being related to the brain area affected. Deafferentation can result as a function of reduced neuroplasticity making this hypothesis compatible with the general working hypothesis argued in this paper that mental disorders result from impaired neuroplasticity. Hallucinations are distortions in transitive consciousness prevalent during acute psychosis, constituting abnormal mental states that can arguably be analyzed from the standpoint of quantum mind theories.

7. Quantum Models of Mind

Neurobiological models of consciousness and cognition succeed at localizing mental functions and pinpointing areas of neural dysfunction in mental disorders. Nonetheless, neurobiology alone does not appear equipped to explain higher order human consciousness. The particular element lacking is an explanation for subjective experience, sense of self, qualia, volition, and spontaneity. Actions that derive from sensory stimuli are by nature mechanical, thereby lacking the necessary animus or life force that we know is a critical ingredient to human psychological experience. To fill this apparent void, a number of multidisciplinary scientists - ranging from neurobiologists to physicists to mathematicians – have forcefully argued for quantum models of mind that attempt to account for many of the enigmatic features of the mind, such as free will, self-understanding, and qualia. British neurobiologist Christopher Smith (2009) recently reviewed the four most prominent quantum theories of mind originated by: John Eccles and Frederich Beck, Henry Stapp, Stuart Hameroff and Roger Penrose, and David Bohm. These theories are quite distinct, with each incorporating different elements of quantum physics.

Beck and Eccles (1992; Beck, 2008) hypothesize that the Heisenberg uncertainty principle comes into play during the regulation of vesicular release of neurotransmitters. They further suggest that the introduction of quantum indeterminacy into neurotransmitter release mechanisms would allow for human free will of action. Their notion is that an atomic process, such as an electron tunneling through an energy barrier, triggers exocytosis. The sheer size of the vesicle and the large number of neurotransmitter molecules contained in it make it next to impossible to lend itself to quantum tunneling processes. Although the Beck-Eccles model abounds with novel ideas, the crux of the theory is incompatible with the molecular biology of vesicular neurotransmitter release as known today (Smith, 2009).

Stapp (2005) models consciousness as a quantum Zeno effect, a curious effect that occurs following multiple observations. An adherent to the Copenhagen interpretation, Stapp views consciousness as an observer-based collapse of the wave function and the emergence of the discrete. Regarding specific neurobiology, Stapp's model places quantum effects at the Ca^{2+} ion channel, the mechanism that governs neurotransmitter release. The main criticism of this idea is that ions flow in single file across Ca^{2+} channels and large numbers of proteins are involved in regulating that flow,

which would be expected to cancel out any subtle quantum effects (Smith, 2009).

The quantum mind model developed by Hameroff and Penrose is a synthesis of the notion Penrose (2004) put forth on objective reduction with ideas Hameroff (1987) put forth regarding MTs being subcellular automata in cells. Objective reduction, while controversial in physics, attempts to get around the problem of needing an observer to have collapse of the wave function according to the Copenhagen interpretation of quantum events. The solution invokes loop quantum gravity, which, controversial in its own right, identifies superposition states as curvatures in space-time, which reduce to a single space-time curvature at an objective threshold (Hameroff, 1998). A plausible motive force for objective collapse in the brain needs to be identified, and it is conceivable that MTs or the subunit tubulins that compose them have something to offer to this concept. Tubulins, acting as qubits that communicate with one another via quantum entanglement induced by physical interactions, perform quantum computations that would be influenced by synaptic activity, and other neuronal conditions, to orchestrate the collapse that gives rise to cognitive events. The notion that MTs are capable of performing computations that are sensitive to quantum effects is quite intriguing and will be elaborated upon in more detail later in this paper.

Bohm's quantum mind model (1990) is a significant departure from the others and does not have a neurobiological correlate. Nonetheless, Bohm's ideas about implicate order may offer explanations as to how events at widely discrepant time scales may be interdependent.

A fifth (but historically first) quantum model of the mind is also notable. Thermofield Brain Dynamics (TBD), originally postulated by Ricciardi and Umezawa (Ricciardi *et al.,* 1967), and advanced by Jibu and Yasue (Jibu *et al.,* 1995), and further developed by Vitiello (Vitiello, 1995; 2003), describes the brain in terms of a coherent water dipole field created by dipolar solitons interacting with the neuronal cytoskeleton. Lost symmetry in the dipole field vacuum state, from stimuli induced symmetry breaking, is preserved by low energy boson condensates that may be re-excited by similar stimuli, thus recalling memories. The brain tunes itself by influencing the vacuum state through the generation of background signals, while energy exchange with the environment allows dual ground state modes (one for the system, and the other for the environment). These three wave functions (environment, memory, and self-tuning) interfere in the vacuum state with resulting matches between wave functions giving rise to conscious events.

8. Speculations on Thought Disruption Based on Quantum Models of Cognitive Processing

As has been discussed earlier in this paper, neurobiological evidence exists for MTs and actin filament participating in neuroplasticity relevant to cognitive functions. Moreover, there is an apparent derailment of cognition and of dynamic cytoskeletal function in mental illness. Those facts alone, however, do not lead to an understanding of how cytoskeletal proteins contribute to or mediate higher cognitive functions. This is especially true for those inexplicable functions such as self-awareness and volition. A radically new view of MT and actin filament networks inside neurons can potentially account for these higher functions.

Based on their ability to propagate signals through the neuron, MTs and actin filaments can be viewed as computationally relevant nanowire networks that operate within neurons (Woolf *et al.,* 2010). Rather than inputs to neurons being limited to causing discrete responses, this viewpoint offers the possibility of local and global neuroplasticity, based on the cytoskeleton computing and storing templates that translate patterns of inputs across widespread synapses into the "behavioral" output of the neuron. This behavioral output of the neuron is not limited to axonal firing and dendritic integration of electrochemically mediated inputs. Instead, it includes connecting the cell nucleus with the postsynaptic density, initiating transport of receptor molecules, membrane proteins,

organelles, and mRNA, regulating neurite motility, restructuring of spines and complex dendrite architecture, the lateral movement of receptor and membrane proteins of neurons, governing the availability of ion channels in the membrane, and more. Potential computational modes for MTs and actin filaments are beginning to be understood, with at least two quantum models for MT information processing having been proposed.

In the Penrose-Hameroff model, tubulin dimers made up of α-tubulin and β-tubulin act as qubits, existing in superposition until a collapse selects one of two conformations (Hameroff, 1998). The biological feasibility of the model has been questioned because the rapid thermal decoherence of entangled states would appear to be incompatible with millisecond time scales relevant to neurophysiology (Tegmark, 2000). Coherence times can be extended by counterion shielding, actin shielding, intrinsic error correction, among other properties; nonetheless, decoherence remains an issue (Hagan *et al.,* 2002). However, recent experiment has shown room temperature quantum effects in photosynthesis (Lee *et al.,* 2007; Engel *et al.,* 2007) and conjugated polymer chains (Collini *et al.,* 2009). Nonthermal radiation at 8.085 MHz has been observed from MTs, and while not necessarily an indication of a quantum condensate or coherence, it remains a possiblility (Pokorný *et al.,* 2001). Reimers *et al.,* (2009) and McKemmish *et al.,* (2009) state that this radiation could only be the result of a weak condensate that could not result in the coherent motion necessary for the Penrose-Hameroff model, however their results are based on a linear chain of coupled oscillators rather than the cylindrical geometry of MTs leaving the question still open. An alternative possibility is that this radiation results from coherent water within the MT lumen as suggested by the TDB model. Another issue at hand is the range of motion in tubulin dimers when they are polymerized into stable MTs, bringing into question whether intact MTs allow two potential conformations of tubulin dimers. McKemmish et. al. (2009) clearly demonstrate that repeated exchanges between the GTP and GTP-bound forms of tubulin within MTs are not supported by current experimental evidence; however while the conformational states are generally identified as tubulin-GTP and tubulin-GDP the Penrose-Hameroff model does not specify the precise nature of the conformational states envisaged, so alternatives remain a possibility. Notably, there is evidence for conformational changes (i.e., tilting to one or the other side) for β-tubulins in intact MTs depending on whether they are bound to motors such as kinesin or to MAPs such as tau (Santarella *et al.,* 2004; Hirose *et al.,* 1999), however the consistency of the timescales between such interactions and the Penrose-Hameroff requirements remains in question. Clearly, these issues are not completely resolved as Reimers, McKemmish and colleagues suggest.

In an alternative model, Craddock and Tuszynski (2009) describe classical and quantum information processing in MTs based on a double-well potential in the interior of the tubulin dimer. This double-well potential enables a mobile electron to pass over an energy barrier, transitioning from a ground state to an excited state, whereupon these states interact with the MT lattice vibrations. Isolation from thermal energy present at physiological temperatures would be necessary for any such delicate states to have an impact on neurophysiology or neuroplasticity.

Cellular automata models indicate that classical and quantum information processing in MTs is in principle possible at room temperature, given there exists a synchronizing clocking mechanism in the picosecond range (Craddock, Beauchemin, and Tuszynski, 2009). A global clocking mechanism might derive from coherent molecular vibrations, electric fields that span across membranes, or other yet to be described phenomena. Craddock and colleagues describe four potential types of behavior exhibited by MT automata consisting of tubulin arrays where progression over 300 steps leads to: a homogeneous state (type I), a simple stable or periodic structure (type II), an unpredictable pattern (type III), or complex, sometimes long-lived localized structures (type IV). Type IV behavior, which is associated with information processing

systems, is possible in MTs at physiological temperatures if the tubulin dielectric constant is above 7.8 and the potential barrier height exceeds 116 meV. The dielectric constant of tubulin has been calculated at 8.41 (Mershin *et al.,* 2004), consistent with this model.

MT dysfunction occurring in mental illness might be expected to cause abnormal mixtures of types I – IV behaviors. For example, one might imagine that depression results from too little type IV behavior, whereas anxiety, mania and thought disorder might result from too much type IV behavior. The strength of a model that deals with information processing modes in MTs is that it enables a direct relationship to be made between fundamental protein function at the atomic level and complex cognitive functioning. A remaining hurdle for this particular cellular automata model is that the synchronous updating was calculated to occur on a picosecond time scale, which lies below the millisecond time scale relevant to neurophysiology by a factor of ~10^9. MT dynamics do produce an endogenous clocking mechanism in the form of periodic phases of polymerization and depolymerization, but the time scale for these oscillations is in order of minutes (Mandelkow *et al.,* 1988). There are multiple oscillators, clocking mechanisms, and generators of synchrony in brain, however, and the way they interact may have implications for MT information processing.

Neural rhythms, with time scales ranging from milliseconds to seconds, synchronize the forebrain and are mediated by neurotransmitter systems such as acetylcholine, norepinephrine, and serotonin (McCormick, 1989; Steriade, 2004; Cape and Jones, 1998). These neurotransmitter systems further fluctuate according to endogenous, 24-hr circadian rhythms that further fluctuate according to the season of the year (Kafka *et al.,* 1983). There is enormous range: millisecond time scales differ from circadian time scales by an order of magnitude of ~10^8, and if one extends that to a 4-month season, an order of magnitude of ~10^{10}. Given that neural events at the millisecond time scale can affect neural states at the circadian and seasonal level, it is possible that quantum states at the picosecond scale could affect neural activity at the millisecond scale and above, at least in principle. It is also conceivable that these multiple oscillators operating at widely discrepant time scales in brain are connected on some basic level, not entirely dissimilar from Bohm's notions of an implicate order.

It is not necessarily a requirement for MT information processing to avoid decoherence up to millisecond time scales to have effects on neural events. What would be essential is that multiple oscillators be interdependent and sensitive to redundant patterns. Such interdependence might enable events operating at the shortest time scales and tapping into quantum mechanisms to affect larger scale events. It is easy to see how patterns of neural activity in a given individual occurring during any given day could affect their sleep that night and their mood the following day (and in the case of affective disorders mood changes that persist for months, even years). It is not the single firing of a single neuron, but rather patterns in neural firing that affect future sleep and mood. In the case of quantum events scaling up, billions of quantum computations in MTs would be responsible for moving millions of proteins over nanometer distances, with the most salient among the collective effects affecting neural activity on millisecond time scales.

Dysfunction among the multiple oscillators that govern cognitive function may be a fundamental feature of mental disorders. Disturbances in synchronous neural activity from 2 Hz to >40 Hz (which binds information into cognitive percepts) are found in schizophrenia (Singer, 2009). The affective disorders are associated with disrupted circadian rhythms (Mendlewicz, 2009; Schulz and Steimer, 2009). Rapid cycling affective disorder produces dramatic mood shifts with regular periodicities ranging from 29 – 185 days (Mizukawa *et al.,* 1992). Seasonal affective disorder specifically occurs in winter months, thereby having an annual cycle (Rastad *et al.,* 2008). Without modern treatments, bipolar disorder episodes of mania or depression recur in multiyear cycles ranging from several months to nearly a decade (Oepen *et al.,* 2004). Perhaps the most convincing evidence for disturbed rhythms in mental

illness is that drugs commonly used to treat mental illness act on neural rhythms. Cortical oscillations are produced or modulated by neurotransmitters – serotonin, norepinephrine, acetylcholine, or dopamine – systems that are targets for neuropharmacological agents effective at treating symptoms of mental illness.

Given that mental illnesses are associated with dysfunctional MTs, abnormal oscillations between polymerization-depolymerization cycles might additionally come into play. It is further conceivable that classical and quantum information processing in brain MTs could be impaired in mental illness, to the extent that such information processing modes are validated by experimental support.

9. Conclusion

As mentioned by Mender (2010), the two most notable quantum-neurodynamic perpectives on brain function are the TBD model (Ricciardi *et. al.,* 1967; Jibu and Yasue 1995; Vitiello 1995), and the Penrose-Hameroff Orchestrated Objective Reduction (Orch OR) model (Hameroff, 1998). Both the TBD model, expounded by Globus (2010), and the Orch OR model rely on the cytoskeletal matrix in the neuron, particularly the MT network. In the TBD framework Globus attributes the split agency of schizophrenia to a disintegration of the brain self-tuning process. He then furthers the paradigm by suggesting that all psychiatric disorders are the result of mal-attunements in the self-tuning process. It has been shown here that psychiatric illnesses, including schizophrenia, bipolar disorder, and anxiety disorders, share dysfunction in the cytoskeleton lending credence to his arguments. While the exact physical mechanisms of quantum brain function remain in debate it is clear that if quantum effects do play a role in cognitive processing then the cytoskeleton, due to is mesoscopic scale and involvement in learning, memory, and mental disease, serves as a prime candidate for the physical substrate on which to base further discussion of the quantum mind and psychiatric illness.

References

Alaerts M, Ceulemans S, Forero D. *et al.,* Support for NRG1 as a susceptibility factor for schizophrenia in a northern Swedish isolated population. Arch Gen Psychiatry 2009; 66 (8):828-37.

Andrieux A, Salin PA, Vernet M. *et al.,* The suppression of brain cold-stable microtubules in mice induces synaptic defects associated with neuroleptic-sensitive behavioral disorders. Genes Dev 2002; 16(18):2350-64.

Andrieux A, Salin P, Schweitzer A., *et al.,* Microtubule stabilizer ameliorates synaptic function and behavior in a mouse model for schizophrenia. Biol Psychiatry 2006 1; 60(11):1224-30.

Arnold SE, Talbot K, Hahn CG. Neurodevelopment, neuroplasticity, and new genes for schizophrenia. Prog Brain Res 2005;147:319-45.

Austin CP, Ky B, Ma L, Morris JA, Shughrue PJ. Expression of Disrupted-In-Schizophrenia-1, a schizophrenia-associated gene, is prominent in the mouse hippocampus throughout brain development. Neuroscience 2004; 124(1):3-10.

Beck F and Eccles JC. Quantum aspects of consciousness and the role of consciousness. Proceedings of the National Academy of Science of the United States of America 1992; 89: 11357–11361.

Beck F. Synaptic Quantum Tunnelling in Brain Activity. NeuroQuantology; 2008; 6(2): 140-151.

Bégou M, Volle J, Bertrand JB., *et al.,* The stop null mice model for schizophrenia displays [corrected] cognitive and social deficits partly alleviated by neuroleptics. Neuroscience 2008;11;157(1):29-39.

Belmont L, Mitchison T. Identification of a protein that interacts with tubulin dimers and increases the catastrophe rate of microtubules. Cell 1996:84(4):623– 31.

Benitez-King G, Ramirez-Rodriguez G, Ortiz L, Meza I. The neuronal cytoskeleton as a potential therapeutical target in neurodegenerative diseases and schizophrenia. Curr Drug Targets CNS Neurol Disord 2004 Dec;3(6):515-33.

Benitez-King G, Ramirez-Rodriguez G, Ortiz L. Altered Microtubule Associated Proteins in Schizophrenia. NeuroQuantology 2007; 5(1): 58-61.

Bennett A O MR. Consciousness and hallucinations in schizophrenia: the role of synapse regression. Aust N Z J Psychiatry 2008;42(11):915-31.

Bensimon G, Chermat R. Microtubule disruption and cognitive defects: effect of colchicine on learning behavior in rats. Pharmacol Biochem Behav 1991;38(1):141-5.

Bianchi M, Fone KF, Azmi N, Heidbreder CA, Hagan JJ, Marsden CA. Isolation rearing induces recognition memory deficits accompanied by cytoskeletal alterations in rat hippocampus. Eur J Neurosci 2006;24(10):2894-902.

Blackwood DH, Fordyce A, Walker MT, St Clair DM, Porteous DJ, Muir WJ. Schizophrenia and

affective disorders--cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes: clinical and P300 findings in a family. Am J Hum Genet 2001;69(2):428-33.

Bohm D. A new theory of the relationship of mind to matter, Philosophical Psychology 1990; 3:271–286.

Bora E, Yücel M, Pantelis C. Theory of mind impairment: a distinct trait-marker for schizophrenia spectrum disorders and bipolar disorder? Acta Psychiatr Scand 2009; 120 (4):253-64.

Brandon NJ, Millar JK, Korth C, Sive H, Singh KK, Sawa A. Understanding the role of DISC1 in psychiatric disease and during normal development. J Neurosci 2009; 14; 29 (41):12768-75.

Brass M, Haggard P. To do or not to do: the neural signature of self-control. J Neurosci 2007; 27(34):9141-5.

Brenner E, Sonnewald U, Schweitzer A, Andrieux A, Nehlig A. Hypoglutamatergic activity in the STOP knockout mouse: a potential model for chronic untreated schizophrenia. J Neurosci Res 2007;85(15):3487-93.

Brüne M. "Theory of mind" in schizophrenia: a review of the literature. Schizophr Bull 2005; 31(1):21-42.

Cannell GR, Bailey MJ, Dickinson RG. Inhibition of tubulin assembly and covalent binding to microtubular protein by valproic acid glucuronide in vitro. Life Sci 2002; 71(22):2633-43.

Cape EG, Jones BE. Differential modulation of high-frequency gamma-electroencephalogram activity and sleep-wake state by noradrenaline and serotonin microinjections into the region of cholinergic basalis neurons. J Neurosci 1998; 18(7):2653-66.

Cardno AG, Marshall EJ, Coid B., *et al.,* Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. Arch Gen Psychiatry 1999; 56(2):162-8.

Cash AD, Aliev G, Siedlak SL., *et al.,* Microtubule reduction in Alzheimer's disease and aging is independent of tau filament formation. Am J Pathol 2003; 162(5):1623-7.

Castrén E. Is mood chemistry? Nat Rev Neurosci 2005; 6(3):241-6.

Cheng R, Juo SH, Loth JE., et al. Genome-wide linkage scan in a large bipolar disorder sample from the National Institute of Mental Health genetics initiative suggests putative loci for bipolar disorder, psychosis, suicide, and panic disorder. Mol Psychiatry 2006; 11:252–260.

Cox MM, Tucker AM, Tang J, Talbot K, Richer DC, Yeh L, Arnold SE. Neurobehavioral abnormalities in the dysbindin-1 mutant, sandy, on a C57BL/6J genetic background. Genes Brain Behav 2009; 8(4):390-7.

Craddock TJA, Tuszynski JA. A critical assessment of the information processing capabilities of neuronal microtubules using coherent excitations. J Biol Phys 2010; 36(1): 53-70.

Craddock TJA, Beauchemin C, Tuszynski JA. Information processing mechanisms in microtubules at physiological temperature: Model predictions for experimental tests. Biosystems 2009; 97(1):28-34.

Curmi P, Gavet O, Charbaut E., *et al.,* Stathmin and its phosphoprotein family: general properties, biochemical and functional interaction with tubulin. Cell Struct. Funct 1999: 24(5): 345–57.

de Lange FP, Spronk M, Willems RM, Toni I, Bekkering H. Complementary systems for understanding action intentions. Curr Biol 2008; 18(6):454-7.

Dean CE. Antipsychotic-associated neuronal changes in the brain: Toxic, therapeutic, or irrelevant to the long-term outcome of schizophrenia? Prog Neuropsychopharmacol Biol Psychiatry 2006; 30(2):174-189.

Derksen MJ, Ward NL, Hartle KD, Ivanco TL. MAP2 and synaptophysin protein expression following motor learning suggests dynamic regulation and distinct alterations coinciding with synaptogenesis. Neurobiol Learn Mem 2007; 87(3):404-15.

Di Paolo, G, Pellier V, Catsicas M, Antonsson B, Catsicas S and Grenningloh G. The phosphoprotein stathmin is essential for nerve growth factor-stimulated differentiation. J Cell Biol 1996; 133(6):1383-90.

Di Patre PL, Oh JD, Simmons JM, Butcher LL. Intrafimbrial colchicine produces transient impairment of radial-arm maze performance correlated with morphologic abnormalities of septohippocampal neurons expressing cholinergic markers and nerve growth factor receptor. Brain Res 1990; 523(2):316-20.

Ehrlichman RS, Luminais SN, White SL., *et al.,* Neuregulin 1 transgenic mice display reduced mismatch negativity, contextual fear conditioning and social interactions. Brain Res 2009; 1294:116-27.

Fischer A, Sananbenesi F, Schrick C, Spiess J, Radulovic J. Distinct roles of hippocampal de novo protein synthesis and actin rearrangement in extinction of contextual fear. J Neurosci 2004; 24(8):1962-6.

Fréchette M, Rennie K, Pappas BA. Developmental forebrain cholinergic lesion and environmental enrichment: behaviour, CA1 cytoarchitecture and neurogenesis. Brain Res 2009; 1252:172-82.

Frith CD. The Cognitive Neuropsychology of Schizophrenia. Hove, UK: Lawrence Erlbaum Associates, 1992.

Grenningloh G, Soehrman S, Bondallaz P, Ruchti E, Cadas H. Role of the microtubule destabilizing proteins SCG10 and stathmin in neuronal growth. J Neurobiol 2004; 58(1):60-9.

Gill M, Donohoe G, Corvin A. What have the genomics ever done for the psychoses? Psychol Med 2009; 12:1-12.

Globus G. Toward a quantum psychiatry: hallucination, thought insertion and DSM. NeuroQuantology 2010; 8(1): 1-13.

Gottmann K. Transsynaptic modulation of the synaptic vesicle cycle by cell-adhesion molecules. J Neurosci Res 2008; 86(2):223-32.

Hagan S, Hameroff SR, Tuszyński JA. Quantum computation in brain microtubules: decoherence and biological feasibility. Phys Rev E Stat Nonlin Soft Matter Phys 2002; 65(6 Pt 1):061901.

Hallett M. Volitional control of movement: the physiology of free will. Clin Neurophysiol. 2007; 118(6):1179-92.

Hameroff SR. Ultimate computing: Biomolecular consciousness and nanotechnology. Amsterdam: North Holland, 1987.

Hameroff S. Quantum computation in brain microtubules? The Penrose–Hameroff 'Orch OR' model of consciousness. Phil Trans R Soc Lond A 1998; 356: 1869–1896.

Hayden EP, Nurnberger JI Jr. Molecular genetics of bipolar disorder. Genes Brain Behav 2006; 5(1):85-95.

Heisenberg M. Is free will an illusion? Nature 2009; 459(7244):164-5.

Hennah W, Porteous D. The DISC1 pathway modulates expression of neurodevelopmental, synaptogenic and sensory perception genes. PLoS One 2009; 4(3):e4906.

Hikida T, Jaaro-Peled H, Seshadri S., *et al.,* Dominant-negative DISC1 transgenic mice display schizophrenia-associated phenotypes detected by measures translatable to humans. Proc Natl Acad Sci USA 2007; 104(36):14501-6.

Hirose K, Löwe J, Alonso M, Cross RA, Amos LA. 3D electron microscopy of the interaction of kinesin with tubulin. Cell Struct Funct 1999; 24(5):277-84.

Howell B, Larsson N, Gullberg M and Cassimeris L. Dissociation of tubulin-sequestering and microtubules catastrophe-promoting activities of Oncoprotein 18/stathmin. Mol Biol Cell 1999; 10(1): 105-18.

Ikeda M, Aleksic B, Kirov G., *et al.,* Copy number variation in schizophrenia in the Japanese population. Biol Psychiatry 2010; 67(3):283-6.

Iwata M, Shirayama Y, Ishida H, Kawahara R. Hippocampal synapsin I, growth-associated protein-43, and microtubule-associated protein-2 immunoreactivity in learned helplessness rats and antidepressant-treated rats. Neuroscience 2006; 141(3):1301-13.

Jaaro-Peled H, Hayashi-Takagi A, Seshadri S, Kamiya A, Brandon NJ, Sawa A. Neurodevelopmental mechanisms of schizophrenia: understanding disturbed postnatal brain maturation through neuregulin-1-ErbB4 and DISC1. Trends Neurosci 2009; 32(9):485-95.

Jaworski J, Kapitein LC, Gouveia SM,, *et al.,* Dynamic microtubules regulate dendritic spine morphology and synaptic plasticity. Neuron 2009; 61(1):85-100.

Jibu, M., Yasue, K. Advances in Consciousness Research Vol. 3, Quantum brain dynamics and consciousness: An introduction. John Benjamins Publishing Company, Philadelphia, 1995.

Joo EJ, Lee KY, Jeong SH, Ahn YM, Koo YJ, Kim YS. The dysbindin gene (DTNBP1) and schizophrenia: no support for an association in the Korean population. Neurosci Lett 2006; 407(2):101-6.

Kafka MS, Wirz-Justice A, Naber D, Moore RY, Benedito MA. Circadian rhythms in rat brain neurotransmitter receptors. Fed Proc 1983; 42(11):2796-801.

Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). Archives of General Psychiatry 2005; 62(6):617-27.

Khuchua Z, Wozniak DF, Bardgett ME., *et al.,* Deletion of the N-terminus of murine map2 by gene targeting disrupts hippocampal ca1 neuron architecture and alters contextual memory. Neuroscience 2003; 119(1);101-111.

Laeng P, Pitts RL, Lemire AL., *et al.,* The mood stabilizer valproic acid stimulates GABA neurogenesis from rat forebrain stem cells. J Neurochem 2004; 91(1):238-51.

Law AJ, Hutchinson LJ, Burnet PW, Harrison PJ. Antipsychotics increase microtubule-associated protein 2 mRNA but not spinophilin mRNA in rat hippocampus and cortex. J Neurosci Res 2004; 76(3):376-82.

Li D, Collier DA, He L. Meta-analysis shows strong positive association of the neuregulin 1 (NRG1) gene with schizophrenia. Hum Mol Genet 2006; 15(12):1995-2002.

MacDonald ML, Eaton ME, Dudman JT, Konradi C. Antipsychotic drugs elevate mRNA levels of presynaptic proteins in the frontal cortex of the rat. Biol Psychiatry 2005; 57(9):1041-51.

Mandelkow EM, Lange G, Jagla A, Spann U, Mandelkow E. Dynamics of the microtubule oscillator: role of nucleotides and tubulin-MAP interactions. EMBO J 1988; 7(2):357-65.

Martin E, Ressler K, Binder E, Nemeroff C. The neurobiology of anxiety disorders: brain imaging, genetics, and psychoneuroendocrinology. Psychiatr Clin N Am 2009; 32(3):549-75.

McCormick DA. Cholinergic and noradrenergic modulation of thalamocortical processing. Trends Neurosci 1989; 12(6):215-21.

McKemmish LK, Reimers JR, McKenzie RH, Mark AE, Hush NS. Penrose-Hameroff orchestrated objective-reduction proposal for human consciousness is not biologically feasible. Phys Rev E Stat Nonlin Soft Matter Phys 2009; 80(2 Pt 1):021912.

Mender D. Post-classical phase transitions and emergence in psychiatry: beyond George Engel's model of psychopathology. NeuroQuantology 2010; 8(1): 29-36.

Mendlewicz J. Disruption of the circadian timing systems: molecular mechanisms in mood disorders. CNS Drugs 2009; 23 Suppl 2:15-26.

Mershin A, Kolomenski AA, Schuessler HA, Nanopoulos DV. Tubulin dipole moment, dielectric constant and quantum behavior: computer simulations, experimental results and suggestions. Biosystems 2004; 77(1-3):73-85.

Mershin, A., Pavlopoulos, E., Fitch, O., Braden, B.C., Nanopoulos, D.V., Skoulakis, E.M.C. Learning and memory deficits upon TAU accumulation in Drosophilia mushroom body neurons, Learning & Memory 2004:11:277-87.

Mileusnic R, Lancashire CL, Rose SP. Recalling an aversive experience by day-old chicks is not dependent on somatic protein synthesis. Learn Mem 2005; 12(6):615-9.

Mitsuyama F, Niimi G, Kato K., *et al.,* Redistribution of microtubules in dendrites of hippocampal CA1 neurons after tetanic stimulation during long-term potentiation. Ital J Anat Embryol. 2008; 113(1):17-27.

Mizukawa R, Iitsuka M, Hazama H, Ueda K, Tsushima J, Sugihara T, Kaneda W. Periodicity of episode occurrences in rapid cycling affective disorders. Biol Psychiatry 1992; 32(8):652-67.

Moncrieff J. A critique of the dopamine hypothesis of schizophrenia and psychosis. Harv Rev Psychiatry 2009; 17(3):214-25.

Nakata K, Lipska BK, Hyde TM., *et al.,* DISC1 splice variants are upregulated in schizophrenia and associated with risk polymorphisms. Proc Natl Acad Sci USA 2009; 106(37):15873-8.

Nakayama T, Sawada T. Involvement of microtubule integrity in memory impairment caused by colchicine. Pharmacol Biochem Behav 2002; 71(1-2):119-38.

Nelson TJ, Backlund PS Jr, Alkon DL. Hippocampal protein-protein interactions in spatial memory. Hippocampus. 2004; 14(1):46-57.

Norrholm S, Ressler K. Genetics of anxiety and trauma-related disorders. Neurosci 2009; 164(1): 272–87.

O'Connell C, O'Malley A, Regan CM. Transient, learning-induced ultrastructural change in spatially-clustered dentate granule cells of the adult rat hippocampus. Neuroscience 1997; 76(1):55-62.

Oepen G, Baldessarini RJ, Salvatore P, Slater E. On the periodicity of manic-depressive insanity, by Eliot Slater (1938): translated excerpts and commentary. J Affect Disord 2004; 78(1):1-9.

Ohkawa N, Fujitani K, Tokunaga E, Furuya S, Inokuchi K. The microtubule destabilizer stathmin mediates the development of dendritic arbors in neuronal cells. J Cell Sci 2007; 120(8):1447-56.

Pabion M, Job D, Margolis RL. Sliding of STOP proteins on microtubules. Biochemistry 1984; 23(26):6642-8.

Penrose, R. Shadows of the mind. Oxford: Oxford University Press, 1994.

Priel A, Ramos AJ, Tuszynski JA, Cantiello HF. A biopolymer transistor: electrical amplification by microtubules. Biophys J 2006; 90(12):4639-43.

Priel A, Tuszynski JA, Woolf NJ. Neural cytoskeleton capabilities for learning and memory. J Biol Phys 2010; 36(1): 3-21.

Pokorný J, Hašek J, Jelínek F, Šaroch J and Palán B, Electromagnetic activity of yeast cells in the M phase, Electro- Magnetobiol 2001; 20(3):371-396.

Powell KJ, Hori SE, Leslie R, Andrieux A, Schellinck H, Thorne M, Robertson GS. Cognitive impairments in the STOP null mouse model of schizophrenia. Behav Neurosci 2007; 121(5):826-35.

Procopio M. Does god play dice with schizophrenia? A probabilistic model for the understanding of causation in mental illness. Med Hypotheses 2005; 64(4):872-7.

Rastad C, Ulfberg J, Lindberg P. Light room therapy effective in mild forms of seasonal affective disorder--a randomised controlled study. J Affect Disord 2008; 108(3):291-6.

Reimers JR, McKemmish LK, McKenzie RH, Mark AE and Hush NS. Weak, strong, and coherent regimes of Fröhlich condensation and their applications to terahertz medicine and quantum consciousness, PNAS 2009; 106(11): 4219–4224.

Ricciardi L and Umezawa H. Brain and Physics of Many-Body Problems, Kybernetik, 1967: 4(2):44-8.

Rujescu D, Ingason A, Cichon S., et al. Disruption of the neurexin 1 gene is associated with schizophrenia. Hum Mol Genet 2009; 18(5):988-96.

Santarella, R.A., Skiniotis, G., Goldie, K. N., Tittmann, P., Gross, H., Mandelkow, E. M., Mandelkow, E., & Hoenger, A. Surface-decoration of microtubules by human tau. Journal of Molecular Biology, 2004 Jun;339(3):539-553.

Schulz P, Steimer T. Neurobiology of circadian systems. CNS Drugs 2009; 23(Suppl 2):3-13.

Segurado R, Detera-Wadleigh SD, Levinson DF, et al. Genome scan meta-analysis of schizophrenia and bipolar disorder, part III: Bipolar disorder. Am J Hum Genet 2003; 73(1):49-62.

Shumyatsky G, Tsvetkov E, Malleret G., et al. Identification of a signaling network in lateral nucleus of amygdala important for inhibiting memory specifically related to learned fear. Cell 2002: 111(6):905–18.

Singer W. Distributed processing and temporal codes in neuronal networks. Cogn Neurodyn 2009; 3(3):189-96.

Smith CU. The 'hard problem' and the quantum physicists. Part 2: Modern times. Brain Cogn 2009; 71(2):54-63.

St Clair D, Blackwood D, Muir W, Carothers A, Walker M, Spowart G, Gosden C, Evans HJ. Association within a family of a balanced autosomal translocation with major mental illness. Lancet 1990; 336(8706):13-6.

Stapp H P. Quantum interactive dualism. Journal of Consciousness Studies 2005; 12(11):43–58.

Straub RE, Jiang Y, MacLean CJ., *et al.,* Genetic variation in the 6p22.3 gene DTNBP1, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. Am J Hum Genet 2002; 71(2):337-48.

Steriade M. Acetylcholine systems and rhythmic activities during the waking--sleep cycle. Prog Brain Res 2004; 145:179-96.

Talbot K, Cho DS, Ong WY., *et al.,* Dysbindin-1 is a synaptic and microtubular protein that binds brain snapin. Hum Mol Genet 2006; 15(20):3041-54.

Tegmark M. Importance of quantum decoherence in brain processes. Phys Rev E 2000; 61(4 Pt B):4194-206.

Van Den Bogaert A, Schumacher J, Schulze TG., *et al.,* The DTNBP1 (dysbindin) gene contributes to schizophrenia, depending on family history of the disease. Am J Hum Genet 2003; 73(6):1438-43.

Van der Zee EA, Douma BR, Bohus B, Luiten PG. Passive avoidance training induces enhanced levels of immunoreactivity for muscarinic acetylcholine receptor and coexpressed PKC gamma and MAP-2 in rat cortical neurons. Cereb Cortex 1994; 4(4):376-90.

Vitiello G. Dissipation and memory capacity in the quantum brain model. Int J of Modern Physics B 1995; 9:973-989.

Vitiello G. Quantum Dissipation and Information: A route to consciousness modeling. NeuroQuantology 2003; 2(1): 266-279.

Walton JR. Brain lesions comprised of aluminum-rich cells that lack microtubules may be associated

with the cognitive deficit of Alzheimer's disease. Neurotoxicology 2009 Jul 8.

Wegner DM. Précis of the illusion of conscious will. Behav Brain Sci 2004; 27(5):649-59; discussion 659-92.

Whitaker-Azmitia PM, Borella A, Raio N. Serotonin depletion in the adult rat causes loss of the dendritic marker MAP-2. A new animal model of schizophrenia? Neuropsychopharmacology 1995; 12(3):269-72.

Woolf NJ. Cholinoceptive cells in rat cerebral cortex: somatodendritic immunoreactivity for muscarinic receptor and cytoskeletal proteins. J Chem Neuroanat 1993; 6(6):375-90.

Woodward TS, Mizrahi R, Menon M, Christensen BK. Correspondences between theory of mind, jumping to conclusions, neuropsychological measures and the symptoms of schizophrenia. Psychiatry Res 2009; 170: 119–123.

Woolf NJ, Young SL, Johnson GV, Fanselow MS. Pavlovian conditioning alters cortical microtubule-associated protein-2. Neuroreport 1994; 5(9):1045-8.

Woolf NJ, Zinnerman MD, Johnson GV. Hippocampal microtubule-associated protein-2 alterations with contextual memory. Brain Res 1999; 821(1):241-9.

Woolf NJ. Bionic microtubules: potential applications to multiple neurological and neuropsychiatric diseases. J Nanoneurosci 2009; 1:85-94.

Woolf, NJ, Priel A, and Tuszynski JA. Nanoneuroscience: Structural and Functional Roles of the Cytoskeleton in Health and Disease, Springer, Berlin, 2010.

Yamaguchi S, Fujii-Taira I, Murakami A., *et al.,* Up-regulation of microtubule-associated protein2 accompanying the filial imprinting of domestic chicks (Gallus gallus domesticus). Brain Res Bull 2008; 76(3):282-8.

Yang C, Wang G, Wang H, Liu Z, Wang X. Cytoskeletal alterations in rat hippocampus following chronic unpredictable mild stress and re-exposure to acute and chronic unpredictable mild stress. Behav Brain Res 2009; 205(2):518-24.

Zuo L, Luo X, Kranzler HR, Lu L., *et al.,* Association study of DTNBP1 with schizophrenia in a US sample. Psychiatr Genet 2009; 19(6):292-304.