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REVIEW

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Synaptic microenvironment and altered state of consciousness in schizophrenia: a possible link between synapse geometry and orchestrated objective reduction theory

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Abstract

In recent decades, studies have provided convincing evidence indicating abnormalities in some aspects of consciousness in schizophrenia patients. One of the pioneering theory, orchestrated objective reduction (OR) on the mechanism of consciousness has been proposed by Hameroff and Penrose. According to OR, consciousness roots in microtubules (MTs) which act as quantum computation apparatus. OR theory attribute the consciousness generation to MTs, while the "inception" of the events begins at synaptic level where other players regulate the signal transduction and neurotransmitters bioavailability at synaptic microenvironment. Homeostasis and geometry of synaptic microenvironment are actively regulated by glial cell particularly astrocytes. Experimental and post mortem studies have documented evidence indicating the involvement of main participants of synapse such as astrocytes and extracellular matrix (ECM) in schizophrenia. This literature aims to review the role(s) of active participants of synaptic microenvironment and disturbed state of consciousness based on OR theory in schizophrenia.

Keywords Astrocytes, Schizophrenia, Consciousness, Objective reduction, Extracellular matrix

Introduction

Schizophrenia and consciousness

The term schizophrenia is rather a new terminology in comparison with other psychiatric disorders such as mania and melancholia. Its story began during the middle of nineteenth century, when psychiatrists faced with a debilitating disorder with unknown etiology affecting more young people [1]. Morel (French psychiatrist) applied the term démence précoce, Clouston referred "adolescent insanity" term to describe such cases, in Germany Kahlbaum coined the term catatonic syndrome and Hecker described "Hebephrenia" [2]. Emil Kraepelin (1856–1926) was first who proposed to integrate such diverse description under the term of "dementia praecox". As he stated "we meet everywhere the same fundamental disorders in the different forms of dementia praecox […] in very varied conjunctions, even though the clinical picture may appear at first sight ever so divergent" [3]. However, the term schizophrenia was coined by Eugen Bleuler (1857–1939). In his belief, schizophrenia was not a simple disease, but it should be considered as a complex disorder with various clinical manifestation [4]. Nowadays schizophrenia is known as a chronic debilitating psychiatric illness afflicting 1% of the population worldwide [5]. Schizophrenia is a multifaceted psychiatric disorder characterized clinically by positive, negative and cognitive symptoms. Positive symptoms include psychosis, hallucination and thought disorder, negative symptoms are the symptoms associated with lack of functions such

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as lack of motivation, social withdrawal and progressive cognitive deficits [6].

In recent decades, studies have provided compelling evidence that indicate abnormalities in some aspects of consciousness involving self-awareness and time perceptions in schizophrenia patients [7, 8]. From this perspective, schizophrenia can be conceived as a disorder involving fundamental perturbations in consciousness [9]. The results of studies also support the time perception and self-abnormalities in schizophrenia patients [10–12].

There are grounds for supporting that synaptic pathology is at the core of the pathophysiology of schizophrenia [13]. In recent decades, the concept of synapse has been fundamentally revolutionized and a new concept, tetrapartite synapse, has been noticed. This new notion is defined as a "theater scene" with more than two players. According to this new concept, the tetrapartite synapse has a plastic geometry with specific permeability which is controlled and monitored by astrocytes and ECM. In other word, the synaptic talk between pre- and postsynaptic neurons is being processed constantly by other players namely astrocytes and ECM. To put it another way, astrocytes and ECM could be considered as mason and material of the synaptic architecture (Fig. 1) [14]. When seen in this light, any changes in the geometry, components and morphology of the synaptic components would affect the performance of this micro-theater scene. Accumulating data suggest that at least two factors including astrogliopathy and extracellular matrix (ECM) deficit at the synaptic level may lead to aberrant developmental synaptic pruning of neuronal circuits. It has been suggested that maturation of ECM may also play a critical role in the termination of developmental synaptic pruning [15]. Therefore, ECM deficit can directly affect the synaptic pruning. It would seem that these mechanisms may contribute to the onset of schizophrenia by compromising the synaptic architecture that is necessary for

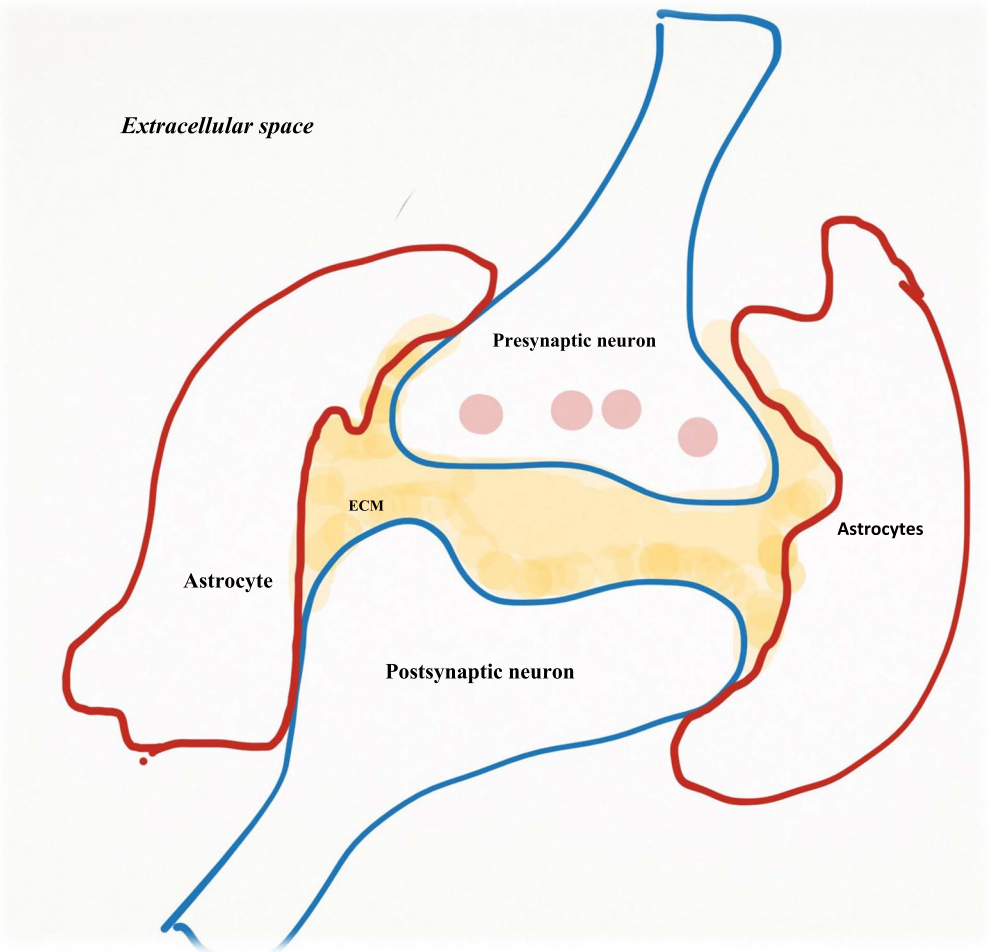

Fig. 1 Tetrapartite synapse and synaptic geometry. According to tetra or quadripartite synapse, bioavailability of neurotransmitter is controlled and regulated by astrocytes and ECM

reliable and predictable information processing [16]. The extracellular matrix (ECM) plays a critical role in brain development, maturation of neural circuits, and adult neuroplasticity. It has been suggested that processes affecting composition or turnover of ECM in the brain could be the principle factor behind the altered brain function in psychiatric disorders such as schizophrenia [17].

Now, a question may be raised that how can we translate tetrapartite synapse components to the consciousness and its altered state in pathologic circumstance?

For centuries the consciousness has been the matter of debate among philosophers and scientists. Although classic physics has revolutionized our understanding of the physical world, when it comes to explaining the intricacies of human consciousness, it falls short. The reductionist approach of classic physics, which look for to understand complex phenomena by breaking them down into smaller, more manageable components, seems inadequate in the face of consciousness. Unlike the physical properties of matter, consciousness cannot be measured, quantified, or dissected. It is an intangible entity that defies the confines of classical physics. Moreover, classic physics operates within a deterministic framework, assuming that the behavior of particles and objects can be predicted with certainty. However, consciousness introduces elements of unpredictability and free will, challenging this deterministic worldview. The complexities of human consciousness require a more holistic and multidisciplinary approach that encompasses not only the physical, but also the psychological, dimensions of human experience [18, 19]. Considering the limitations of the classic physics (vide supra), quantum physics which dealing with microscopic world of particles and their strange behaviors tried to enters the field by applying the principles of quantum mechanics to human consciousness [18, 20]. Orchestrated Objective Reduction (Orch-OR) theory, is a theory based on quantum physics which has been proposed by Hameroff and Penrose to explain the biologic mechanisms of consciousness. The Orch-OR theory provide a captivating perspective that bridge the gap between quantum physics and the mysteries of the human mind.

The Orch-OR theory attributes consciousness generation to quantum computations in microtubules inside neurons. The orchestrated oscillations entangle, compute, and terminate ('collapse of the wave function') result in sequences of Orch-OR moments with orchestrated conscious experience [21–23].

Considering the pivotal roles of astrocyte and ECM in synaptic processing, learning, behavioral functions and synaptic geometry in one hand and increasing experimental and postmortem evidence on the other hand strongly support the involvement, at least in part, of disturbance at the tetrapartite synaptic components in the pathogenesis of schizophrenia [24–35]. Although several lines of studies point toward the astrocytes and ECM involvement in pathogenesis of schizophrenia [36], but the possible role(s) of astrocytes and ECM in the perturbed state of consciousness in schizophrenia has been less discussed. In view of the fact that human consciousness explanation is based on the theoretical framework, bridging between the theory and research findings would shed new light on the nature of consciousness phenomenon and could lead to better understanding of the pathophysiology of the mental disorders.

Therefore, this article is aimed to review the role(s) of astrocytes and ECM in disturbed state of consciousness based on Orch-OR theory in schizophrenia.

Main subjects

Astrocytes: more than inert supporting elements

Astrocytes morphology

Central nervous system is composed of two major cell types including neurons and glial. Astrocytes are the most abundant glial cells in the central nervous system and traditionally were considered as passive supportive cells in the CNS, while recent years' studies have provided convincing evidence challenging this old notion. Based on the glial fibrillary acidic protein (GFAP) expression four classes of astrocytes have been characterized in human brain as following [37]: interlaminar astroglia with tangential and long vertical processes are located in the superficial layers of the cortex (layer I and II). The functional importance of this type of astrocyte has not been fully understood, but it is speculated their abnormalities to be involved in pathologic paradigm such as Alzheimer's disease [38]. Protoplasmic astroglia resides in layers II to VI of cerebral cortex. Protoplasmic astrocytes end feet contact blood vessels and cover the synapses. Therefore, they might be involved actively in modulating information processing and inter-neuronal communication [35–38]. Varicose projection astroglia are third type of astrocytes located in layers V–VI. Their long varicose processes end on the walls of vessels. The exact role(s) of this class of astroglia has not been revealed, but given to their long processes it has been suggested that varicose projection astroglia to be involved in long-distance communication across cortical layers and higher cognitive functions. The fourth class of astroglia, fibrous astroglia, are restricted to the white matter. Fibrous astroglia make contact with vessels and provide support for axonal fibers in the white matter. It seems in contrary to other astroglia, fibrous astrocytes play a crucial role in metabolic demands of neurons [38]. Functionally, astroglia involve

in wide spectrum of activities to ensure homeostasis for neurons.

Diverse functions of astroglia: from neuronal homoeostasis to extracellular matrix synthesis

Since Cajal our understanding and insight to the glial cells, particularly astrocytes, have been fully revolutionized. There are compelling documents that astrocytes are responsible for wide variety of complex functions in the CNS. Astroglia are known to contribute actively in synaptogenesis and synaptic maturation, controlling synapses through the secretion of multiple factors, formation and regulation of brain–blood and brain–cerebrospinal fluid barriers, regulation neurotransmitter turnover (glutamate, γ-aminobutyric acid (GABA), glycine and adenosine), supplying neurons with glutamine, brain thermoregulation, water transport and antioxidant activity [35–37]. Additionally, it has been demonstrated that astroglia are also active participant of extracellular matrix (ECM) synthesize.

Moreover, studies have shown that astrocytes are required for synaptogenesis, the structural maintenance and proper functioning of synapses. In particular, astrocytes appear to play a pivotal role in the organization of the brain's extracellular matrix (ECM)—most prominently the so-called perineuronal nets (PNNs), complex macromolecular assemblies of ECM components [38].

ECM in the CNS is a highly organized complex structure around the neurons and play imminent roles in cell migration, neurite outgrowth and synaptogenesis, synaptic plasticity and stability and cognitive flexibility [39]. Approximately 10–20% of the brain volume is occupied by the extracellular matrix (ECM). ECM participate actively in neuro-glial communication as well as synaptic plasticity [40, 41]. Brain ECM components include hyaluronic acid (hyaluronan, HA), thrombospondin, and proteoglycans, such as neurocan, aggrecan, phosphacan, versican, brevican, tenascin, fibronectin, elastin, and entactin [42, 43]. The ECM components function as ligands for cellular adhesion receptors, through which they transmit signals to the inside of cell [44]. Three ECM compartments can be distinguished: the basement membrane, the interstitial matrix, and perineuronal nets (PNNs) [45]. Chondroitin sulfate proteoglycans (CSPGs) is one of the main components of the ECM. CSPGs are mainly synthesized by astrocytes and organized into perisynaptic aggregates known as perineuronal nets (PNNs). It has been suggested that PNNs modulate synaptic signaling and plasticity during postnatal development and adulthood. Notably, recent studies have documented marked CSPG abnormalities in several brain regions of people with schizophrenia [46].

PNNs tightly surround synaptic contacts on distinct populations of neurons. PNNs represent key players in the regulation of synaptic connectivity and plasticity. Postmortem and human genetic studies show genetic vulnerabilities for genes encoding several key ECM molecules. Consistent with human studies, animal models have provided compelling evidence that abnormalities affecting the ECM may contribute to the pathophysiology of schizophrenia. Pantazopoulos et al. (2016) reviewed extensively the ECM/PNNs abnormalities in schizophrenia. Briefly, they discussed several key ECM molecules including chondroitin sulfate proteoglycans, reelin, semaphorin 3A and PNNs. They showed abnormalities in all these molecules, particularly decrease in distribution and expression of PNNs in schizophrenia [47, 48]. Loss of the PNNs might lead to more vulnerability of neurons to glutamate excitotoxicity [49].

Human consciousness entity and quantum interpretation of consciousness

Ongoing endeavor to unravel the human consciousness

Consciousness can be defined as inner, qualitative, subjective states, and processes of sentience or awareness [50]. The generation of consciousness depends on the integration of the various sensory modalities from different brain areas including the paraventricular nucleus [50], claustrum [51], posterior brain regions and hindbrain [52]. It was widely accepted that most neuronal communication and information transmission initially occurred among synapses and subsequent transferring the information to various parts of the interior cell [53]. While tremendous progress has been achieved to unravel the detailed mechanisms, basic facts—how and where does the consciousness emerge—have not been fully understood. There are several theories that attempt to explain the nature of consciousness. One such theory is the Integrated Information Theory (IIT), which posits that consciousness arises from the integration of information within a complex system. This theory suggests that the more complex a system is, the more conscious it is likely to be [54].

Another alternative theory is the Global Workspace Theory (GWT), which proposes that consciousness results from the brain's ability to integrate and broadcast information to a global workspace. This theory suggests that consciousness is not a property of individual brain regions, but instead arises from the interactions between these regions [55]. There is also the Higher Order Theory (HOT), which argues that consciousness arises from the brain's ability to recognize and reflect upon its own mental states. This theory suggests that consciousness is not simply a matter of sensory input and output, but is instead a reflective process that allows us to be aware of

our thoughts, emotions, and perceptions [56]. Another theory of consciousness, orchestrated objective reduction theory (ORT), suggests that consciousness is a product of quantum mechanics, and that it emerges from the collapse of the quantum wave function [57].

Objective reduction (OR) theory is a relatively recent and fascinating theory in the field of quantum physics and philosophy that attempts to explain the phenomenon of human consciousness. Orch-OR theory is not complete and has its own limitations such as the difficulty in testing and verifying the theory, relying heavily on the concept of quantum mechanics and subjectivism nature of consciousness. Admittedly, each theory or hypothesis has its own limitations and so-called ALL theory would be far fetching at present, but Orch-OR theory may be the most easily falsifiable theory of consciousness [57]. The ORT attributes consciousness to quantum computation in microtubules (MTs) inside the brain. The function of the MTs is thought to be necessary for cognition. Several line of studies have shown dysfunctions in the MTs system have a direct role in neurodegeneration [58]. Interestingly, Emerson et al. (2013) showed that anesthetics may interact selectively with quantum computation in microtubules and thereby expunge consciousness [59].

Orch-OR theory and microtubules

Orchestrate-Objective Reduction (Orch-OR) theory suggests consciousness to consist of distinct moments, an action rooted in quantum aspects of the fine structure of space–time geometry, this being coupled to brain neuronal processes via microtubules (MTs) [53]. According to this theory, MTs composed of protein polymers (alpha and beta tubulins), playing a central role in consciousness (Fig. 2) [60]. Proper microtubule function is regulated by microtubule-associated proteins (MAPs), actin, and intermediate filaments. MTs are interconnected by MAPs; thus, their physiological activities are modulated by MAPs in different phosphorylation states [61]. Tau protein is one of the MAPs that is thought to be involved in neurodegenerative disorders like Alzheimer [18]. It has been argued that MTs possess structural and functional characteristics that are consistent with quantum coherent excitations in the aromatic groups of their tryptophan residues [62]. Accordingly, it has been proposed there is a quantum biology in neurons underlies the emergence of the consciousness. Ergo, MTs have been considered as the quantum apparatus of consciousness generation [63]. Binding the neurotransmitters like glutamate to the receptor on the post-synaptic membrane leads to

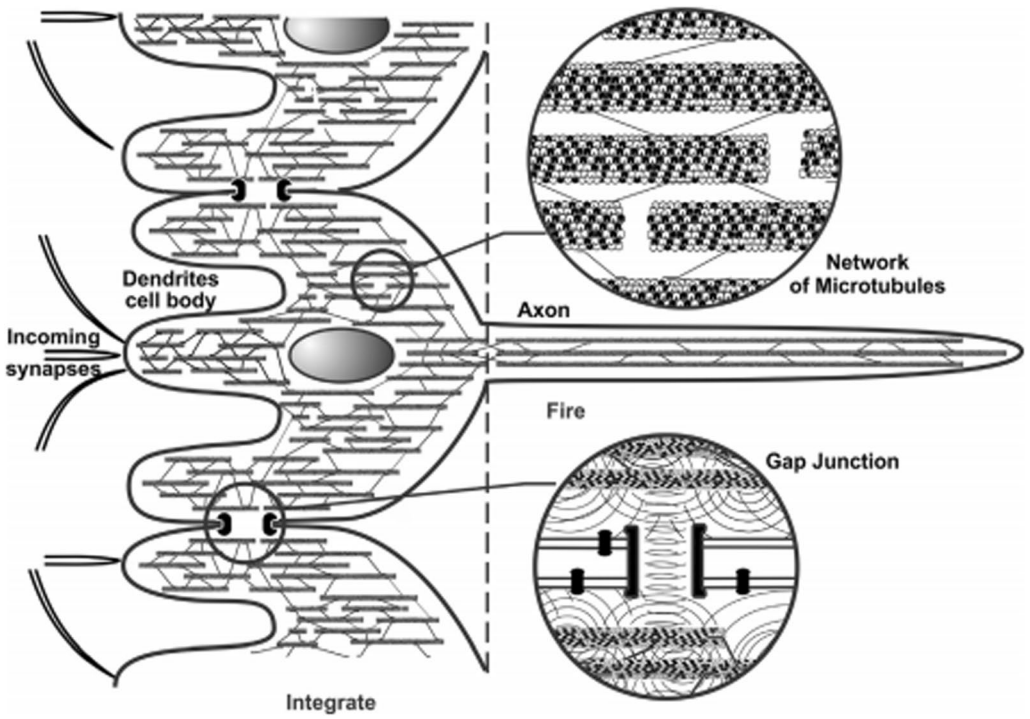

Fig. 2 Orch-OR and microtubules. Each neuron receives and integrates synaptic inputs as membrane potentials. Subsequently, actin filaments connect to cytoskeletal microtubules in main dendrite. Dendritic microtubules (right) are arranged in local networks, interconnected by microtubule-associated proteins (MAPs). Adjacent dendrites are connected by gap junction electrical synapses in "dendritic web", showing internal cytoskeletal microtubules connected by microtubule-associated proteins (Hameroff S, Penrose R. Consciousness in the universe: a review of the 'Orch OR' theory. Phys Life Rev. 2014 Mar;11(1):39–78)

increases the intracellular calcium ion concentration. Subsequently conformational changes, phosphorylation and dephosphorylation occur in microtubules and MAPs due to changes in calcium concentration [64–68]. It has been suggested that MAPs are bridged by actin to the cytoplasmic membrane. The cascades of receptor–ligand–second messenger lead to MAPs phosphorylation and sol to gel phase transition of cytoplasm thereby decoupling MTs from outside of neuron. Such transition between sol (classical) and gel (quantum) states occur every 25 ms (40 Hz) [69]. These changes could "orchestrate" tubulin states and leads to microtubule simulation. Tubulin quantum coherent superposition and computations are increasingly combined to augment their superposed mass energy. Once the energy meets the critical threshold of quantum gravity, self-collapse occurs. That is, at this moment, the consciousness event occurs [70]. Quantum vibration travels through the neurons via gap junction or electrical synapses. Gap junctions are membrane protein complexes in adjacent neurons (or glia) which fuse the two cells and synchronize their membrane polarization states, e.g., in gamma synchrony EEG [71]. According to the OR, ligand/receptor, MAPs, actin and MTs are known as the main players of the consciousness phenomenon that begins at chemical synapse and propagate through electrical synapse. While OR theory seeks the consciousness generation in MTs, the other signal transmission players at the synaptic level have been less noticed. The next paragraph we will discuss the role of other synapse participants such as astrocyte and ECM.

What had been missed in orchestrate OR?

From neurobiological perspective consciousness, sense of awareness and being conscious, is resulted from the function of the neural networks at the synaptic level [72]. The quantum based OR theory attribute the consciousness generation to MTs, while the "inception" of the events begins at synaptic level where other players regulate the signal transduction and neurotransmitters bioavailability at synaptic microenvironment. Classically chemical synapse has been defined as dipartite synapse as composed of two main elements, i.e., the presynaptic and postsynaptic elements. This concept has been evolved during the last decades to include third and fourth elements. Thus, tetrapartite synapse has been proposed to signify the importance of astrocytes and PNNs [46]. Structurally synaptic environment is enveloped by astrocytic process. Additionally, astrocytes express virtually all neurotransmitter and neuromodulator receptors associated with higher-level consciousness and subjective emotional responses [73]. For instance, astrocytes express high – affinity glutamate transporters that allow them to monitor glutamate bioavailability [74]. There is convincing evidence that astrocytes are not silent elements because astrocytic calcium excitability occurs as rapidly as that of neurons that is compatible with the fast synaptic modulation [75]. Together these findings compellingly point to speculation that astrocytes are instrumental in consciousness and memory [43, 76–83]; besides, astrocytes actively participate in shaping the geometry of synapsed by synthesis of ECM [84]. Chondroitin sulfate proteoglycans (CSPGs) are the key organizer of ECM. These macromolecules consist of core proteins linked to varying numbers of chondroitin sulfate glycosaminoglycan chains. There is growing body of evidence that point to their complex and vital role in synaptic plasticity [48, 85]. PNNs are part of ECM with distinct molecular composition aggregate around the neurons. The molecular composition of PNNs consists of CSPGs, hyaluronan and glycoproteins. PNNs represent key players in the neuronal protection [86], modulation of glutamate transmission and regulation of synaptic connectivity and plasticity. Numerous lines of studies have documented results indicating the abnormalities in the main components of synapse including astrocytes, ECM and PNNs in schizophrenia [87, 88]. These findings reflect the abnormality in architecture of tetrapartite synapse microenvironment and ECS.

Geometry of synapse and signal transduction

According to the OR theory consciousness generation is triggered by binding ligand to receptor, leading to MAPs phosphorylation, decoupling MTs from outside of neuron and finally quantum computation [69]. For the purpose of our discussion, these cascades of events could be segregated into outside and inside of neuron. Inside or neuronal elements include receptor, MTs, MAP and actin filaments. The vibrational state of MTs and ultimate quantum computation depend on neurotransmitter bioavailability which itself in part could be determined as a function of several factors including astrocytes activity, ECM, and PNNs. Specifically, geometry of synapse or extracellular space (ECS) contributes to clustering of neurotransmitters in functional synaptic microenvironment [89–91]. Diffusion of neurotransmitters through the ECS is hindered by ECS geometry and contents [92]. Recent findings have shown that astrocytes morphology and PNNs altered in ketamine-induced schizophrenia [93]. Ketamine, a noncompetitive NMDA receptor antagonist, is used in experimental model of schizophrenia [94]. Studies have shown neurodegenerative effects of ketamine on vital elements of synapse [95, 96]. Hayashi et al. reported that repeated ketamine exposure correlates with increased neuronal degeneration in the developing rat brain [97]. Also in another study, Jin et al. showed that ketamine induces tau hyper phosphorylation

at serine 404, which is known as a hallmark of Alzheimer [98]. It is well established that one of the fundamental functions of astrocytes is to uptake synaptic-released glutamate, which maintains neuronal functions and prevents glutamate excitotoxicity. Ketamine is known as a competitive NMADA receptor antagonist, but its use is associated with increased glutamate in presynaptic zone, escalating accumulation of presynaptic glutamate. The main route of glutamate uptake is achieved through two types of glutamate transporters, Na + -independent and Na + -dependent transporters. Interestingly some isoform of Na + -dependent transporters is mainly expressed by astrocytes. Ergo astrocytes have the ability to maintain glutamate homeostasis, support normal neuronal function, and protect against glutamate excitotoxicity [99–103]. Morphological changes of astrocytes and biochemically altered PNNs in schizophrenia [11, 104, 105] likely result into alterations in extracellular space (ECS) and disturbed level of neurotransmitter [92]. This may raise a question that how altered synaptic geometry affect quantum computation by MTs. In the following, we are discussing a specific neuronal membrane structure, glycocalyx, which acts as a fine-scale transducer.

Glycocalyx quantum vibration: quantum transducer

Glycocalyx is the cell's interface with ECS. Sialic acid is a unique constituent of the glycocalyx. Sialic acid is an integral structural and functional component of the nervous system. Structurally sialic acids comprise a family of 43 naturally occurring derivatives of the nine-carbon sugar neuraminic acid (5-amino-3,5-dideoxy-D-glycero-D-galactononulsonic acid). One branch of the sialic acid family is N-acetylated to form N-acetylneuraminic acids (Neu5Ac, NANA, Sia), which are the most widespread form of sialic acid and almost the only form found in humans [106]. Neuronal cell membrane has the highest concentration of sialic acid compared to other cell membrane throughout the body [107]. Sialic acids play an important role in molecular interactions of glycans in mammals. Interruption of sialic acid biosynthesis results in variety of diseases in humans. It has been demonstrated that Polysialic acid is involved in a wide range of activity including neuronal cells migration, myelination, synapse formation, functional plasticity of the nervous system, learning and memory. Interestingly, dysregulation of polySia has been reported in psychiatric disorders such as schizophrenia [108, 109]. Frontal affinity chromatography (FAG) analyses showed polysialic acid could bind directly to neurotransmitters and some ions with high affinity [110]. It is noteworthy to mention that neurotransmitter binding to polysialic acid has been observed in physiological conditions (Fig. 3) [111]. Semi-empirical method bases study has also shown that acid sialic is of quantum vibration state and under different level of neurotransmitter may affects the MTs and actin molecule. Therefore, it would be arguable to assume that polysialic acid regulates sol to gel phase change of neuronal cytoplasm during quantum computation (Fig. 4) [112].

Transition from sol to gel leads to isolating MTs and subsequently initiate phases of quantum coherent superposition in microtubules, and then the Orch OR mechanism, resulting in phenomenal consciousness. Similar transition of cytoplasm has been proposed to explain the mechanism of dark neuron formation. An enigmatic structure with metastable form envelop the MTs. This structure stores noncovalent energy that can be released after exposure to various noxae such as increased level of glutamate, and so a chain of chemical reactions like polymerization would begin and spread (domino likes effect) gel–gel hypothesis [113]. Under the normal healthy condition, bioavailability of neurotransmitter, e.g., glutamate at synaptic space is restricted and regulated by the components of the tetrapartite synapse including astrocytes processes, ECM and PNNs. Pathologic reactions of synaptic elements, e.g., astrocytes hypertrophy result in alteration in synaptic geometry and disturbance in the amount of neurotransmitter at synaptic microenvironment [92]. Increased synaptic level of excitatory neurotransmitter, e.g., glutamate interferes with the vibrational state of polySia and thereby disturbs sol–gel phase transition [114]. Phase transition is essential for decoherence of MTs [115]. Similar mechanism has been proposed to explain dark neuron formation during ketamine exposure. Ketamine exposure leads to excitotoxicity and neurodegeneration [116]. One of the most striking feature of dark neurons is structural abnormality in cytoskeleton and tauopathy [117]. Tau belongs to MAPs and its phosphorylation–dephosphorylation is essential for coherence–decoherence states of quantum computation by MTs [23, 118]. In healthy condition, the privacy of synapse is ensured by cooperation of all synaptic components. It seems morphological rebuilding of astrocytes along with quantitative and qualitative alteration of ECM components influence the ECS parameters, which in turn affect profoundly the geometry of the synaptic microenvironment [94]. Computational model study demonstrated that geometry of synapse could affect the receptor dynamic and synaptic strength [119]. Passing on now to altered state of consciousness in schizophrenia. Brain development during adolescence is a dynamic period, marked by profound functional and anatomical changes at the synaptic level [32, 120]. It would be reasonable to assume altered synaptic geometry in schizophrenia leads to: (1) increased level of glutamate

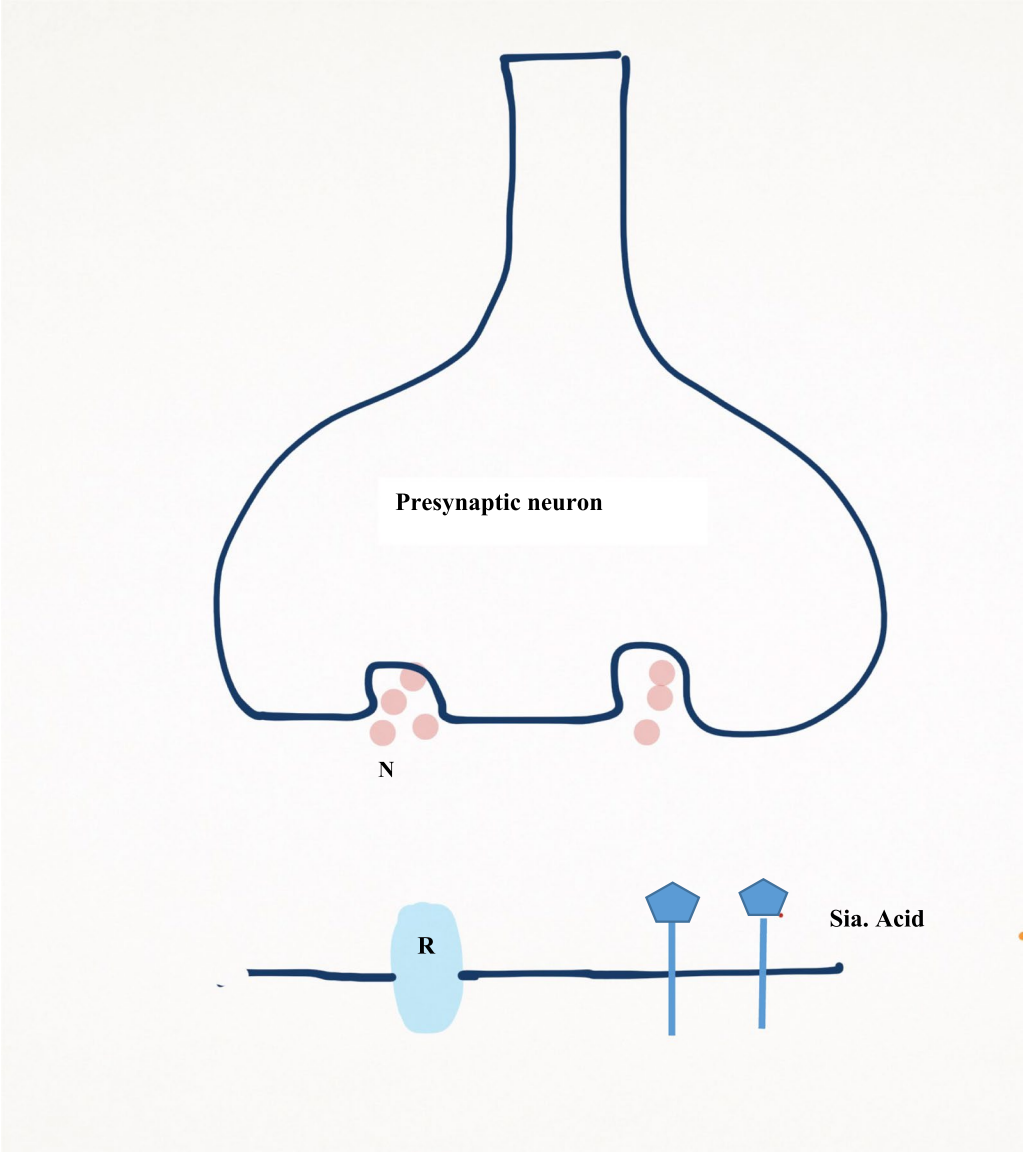

Fig. 3 The released neurotransmitter binds to receptor (R) and polysialic acid. Sialic acid is of quantum vibration state and under different level of neurotransmitter may affect the MTs and actin molecule

and subsequently brings about decreased NMDA receptors as a protective mechanism to avoid excitotoxicity [121]; (2) accumulated level of glutamate increases oxidative stress which leads to morphological changes (gliosis) of astrocytes [122] and resultant secondary altered geometry of synapse and finally; (3)increase in polySia exposure time and amount to glutamate at synaptic microenvironment. At normal physiologic condition, binding glutamate to sialic acid presumably leads to trigger spatio-temporal decoherence of vibrational state of polySia(s) at post-synaptic membrane and decoupling actin from glycocalyx which result into gel–gel phase change as discussed on DN formation [113]. Any disturbance in synaptic microenvironment such as increased level of glutamate or morphological and biochemically alterations of tetrapartite synapse components may affect the defined physiologic range of polySia vibrational state at post-synaptic membrane, hindering actin coupling–decoupling, thus impeding orchestrated OR.

Conclusion

Homeostasis of synaptic microenvironment, private-closed-type synapse depends on synaptic geometry. Astrocytes influence the geometry of synapse and by

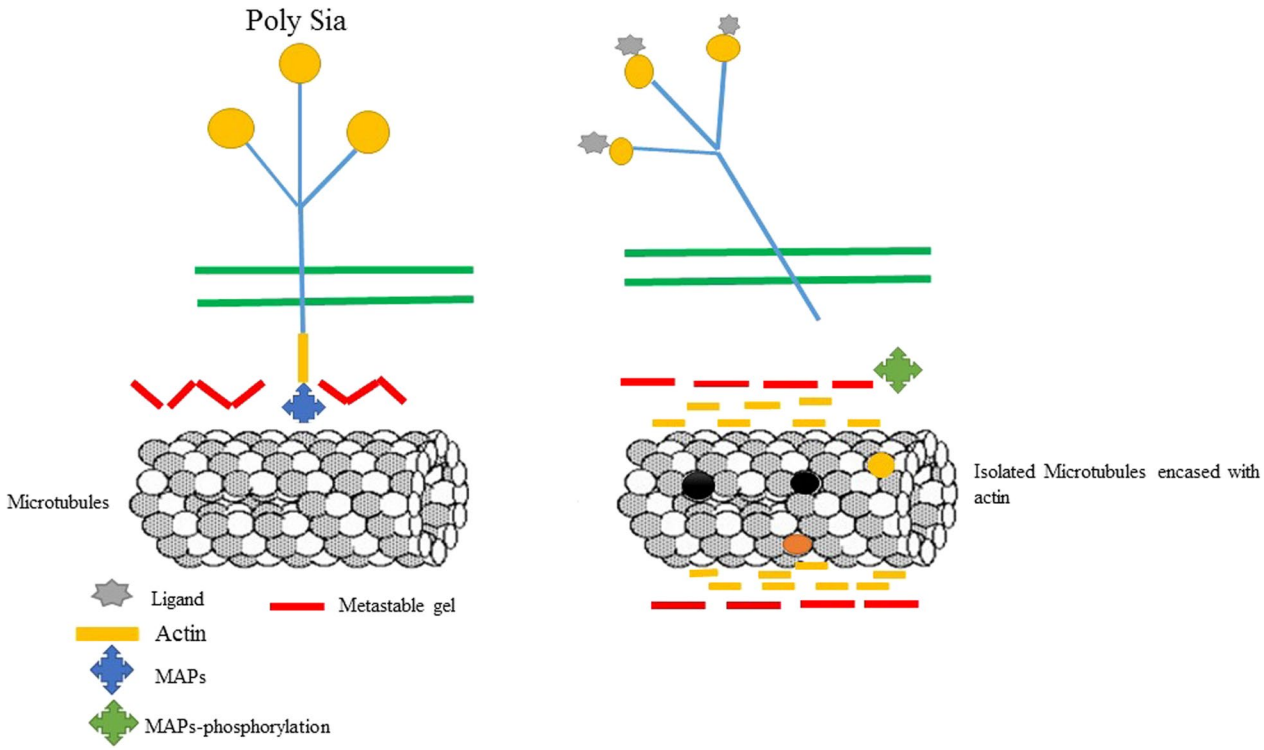

Fig. 4 Microtubules isolation and quantum computation. At healthy condition binding the ligand (glutamate) to polySia leads to spatio-temporal decoherence state of polySia(s) at post-synaptic membrane which result into trigger release of noncovalent energy by gel like structure and decoupling of Actin and MAP. These events lead to MTs isolation from outside of neuron and spin currents interact and compute along spiral lattice pathways. Geometric alteration of synapse may affect the defined physiologic range of polySia vibrational state at post-synaptic membrane, hindering actin coupling–decoupling, thus impeding orchestrated OR

this mean affect the level of neurotransmitter in synaptic microenvironment. Quantitative and qualitative alterations of synapse geometry and its active participants result in disturbance of neurotransmitter bioavailability which in turn leads to changes in the vibrational state of acid sialic. These events lead to interference with the function of intracellular elements involved in consciousness generation. Precisely any changes in the bioavailability of neurotransmitters such as glutamate would affect gel–gel phase transition and subsequently the isolation of MTs. It seems that polySia vibrational state could be considered as a potential therapeutic target in the treatment of schizophrenia. Finally, a semi-empirical model is highly recommended to examine the detailed mechanism and contributing factors of synaptic geometry in consciousness generation.

Abbreviations

CNS	Central nervous system
CSPG	Chondroitin sulfate proteoglycans
DN	Dark neuron
ECM	Extracellular matrix
ECS	Extracellular space
FAG	Frontal affinity chromatography
GFAP	Glial fibrillary acidic protein
GABA	Gamma-aminobutyric acid
HA	Hyaluronic acid
MTs	Microtubules
MAPs	Microtubules associated proteins
NMDA	N-Methyl-D-aspartate
NANA	N-Acetylneuraminic acids
OR	Orchestrated objective reduction
PNNs	Perineuronal nets
Sia	Sialic acid

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I give my consent for the publication of identifiable details, which can include photograph(s) and/or videos and/or case history and/or details within the text ("Material") to be published in the *Egyptian Journal of Neurology, Psychiatry and Neurosurgery.*

Competing interests
The author declares that there are no competing interests.

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