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Understanding Schizophrenia as a Disorder of Consciousness: Biological Correlates and Translational Implications from Quantum Theory Perspectives

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From neurophenomenological perspectives, schizophrenia has been conceptualized as "a disorder with heterogeneous manifestations that can be integrally understood to involve fundamental perturbations in consciousness". While these theoretical constructs based on consciousness facilitate understanding the 'gestalt' of schizophrenia, systematic research to unravel translational implications of these models is warranted. To address this, one needs to begin with exploration of plausible biological underpinnings of "perturbed consciousness" in schizophrenia. In this context, an attractive proposition to understand the biology of consciousness is "the orchestrated object reduction (Orch-OR) theory" which invokes quantum processes in the microtubules of neurons. The Orch-OR model is particularly important for understanding schizophrenia especially due to the shared 'scaffold' of microtubules. The initial sections of this review focus on the compelling evidence to support the view that "schizophrenia is a disorder of consciousness" through critical summary of the studies that have demonstrated self-abnormalities, aberrant time perception as well as dysfunctional intentional binding in this disorder. Subsequently, these findings are linked with 'Orch-OR theory' through the research evidence for aberrant neural oscillations as well as microtubule abnormalities observed in schizophrenia. Further sections emphasize the applicability and translational implications of Orch-OR theory in the context of schizophrenia and elucidate the relevance of quantum biology to understand the origins of this puzzling disorder as "fundamental disturbances in consciousness".

KEY WORDS: Schizophrenia; Consciousness; Quantum theory; Microtubules.

INTRODUCTION

Schizophrenia as a Disorder of Consciousness

Schizophrenia is a complex and multifaceted neuropsychiatric disorder characterized by delusions, hallucinations, passivity phenomena, disordered thought process, disorganized behavior and progressive cognitive deficits.[1,2] From neurobiological perspectives, several overarching paradigms have been proposed to understand the pathogenesis of schizophrenia.[3-12] From neurophenomenological perspectives, schizophrenia has been conceptualized as "a disorder with heterogeneous manifestations that can be integrally understood to involve fundamental perturbations in consciousness".[2,13-16]

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While these theoretical constructs based on consciousness facilitate understanding the 'gestalt' of schizophrenia ,[17,18] systematic research to unravel translational implications of these models is warranted.[19] To address this requirement, one needs to begin with exploration of plausible biological underpinnings of "perturbed consciousness" in schizophrenia. In relation to this, it is noteworthy that a recent overview has aptly classified the types of contemporary approaches to understand consciousness as follows.[20] 1) Dualism/spiritualism: in this approach, "consciousness is considered as an entity distinct from physical actions and not controlled by laws of physics－a separate quality that has always been in the universe; in this view, consciousness lies outside science". 2) Scientific basis with materialistic perspective: in this view, "consciousness is conceptualized as a natural evolutionary consequence of biological adaptation of brains and nervous systems and it is not an intrinsic property of universe and thus consciousness does not have any distinctive role". 3) Scientific basis with consciousness as an essential ingredient of physical laws: this paradigm pro-

poses "consciousness as resultant of discrete physical events; such physical events have always existed in the universe in the form of non-cognitive, proto-conscious events and the physical laws that govern these events are yet to be fully understood".[20] An attractive proposition related to the third type of paradigms is "the orchestrated object reduction (Orch-OR) theory" which proposes the biology of consciousness to involve quantum processes in the microtubules of neurons.[20]

Quantum theory based conceptualizations of consciousness have invoked great interest in terms of their application to understand schizophrenia.[21,22] However, one is more likely to be intrigued by the proposal for application of a fundamental 'physical and mathematical' concept like 'quantum theory' to understand a complex 'biological' construct like schizophrenia. Nonetheless, impactful discoveries in the twentieth century have challenged the dogma that biological systems are too complex to be penetrable with mathematical methods; these discoveries have immensely facilitated productive cross-talk between biology and physics—the disciplines that rarely crossed paths earlier.[23] Contextually, it has been discovered that a variety of organisms might harness some of the unique features of quantum mechanics to gain biological advantage; for example, functional quantum biology like photosynthetic light harvesting, avian magnetoreception and similar others.[23] In turn, these discoveries have offered support to the proposition that "quantum-mechanical phenomena can play nontrivial roles in biology".[24] Along these lines, recent developments in quantum biology[25-27] have made initial small, albeit significant, strides towards solving one of the fundamental unsolved questions in science[28] "the biology of consciousness".

In relation to this, the Orch-OR model for consciousness has been commented as a 'credible and testable' proposal to understand how mental activity enters the physical world.[29] While the earlier reviews on quantum paradigms of schizophrenia have summarized the relevant literature predominantly from 'quantum biology' perspectives, the present review attempts to a) expand the utility of quantum consciousness to understand schizophrenia from the neurophenomenological viewpoint as well as its relationship with quantum biology, and b) more importantly, illustrate the potential translational implications of this approach.

Accordingly, the initial sections of this review focus on the compelling evidence to support the view that "schizophrenia is a disorder of consciousness" through critical summary of studies that have demonstrated self-abnormalities, aberrant time perception as well as intentional binding in this disorder. Subsequently, these findings are linked with 'Orch-OR theory' through the research evidence for aberrant neural oscillations as well as microtubule abnormalities observed in schizophrenia. Further sections emphasize the applicability and translational implications of Orch-OR theory in the context of schizophrenia and elucidate the relevance of quantum biology to understand the origins of this puzzling disorder as "fundamental disturbances in consciousness".

MAIN SUBJECTS

Schizophrenia and Consciousness: Self Abnormalities

Consciousness is the state of being aware of one's own surroundings and one's own existence or self-awareness.[30] "Self" is a necessary condition for the constitution of experience and consciousness".[31] Disordered self has been proposed as amongst the critical fundamental aberrations in schizophrenia.[14] From phenomenological perspectives, notion of the self means that "we live our conscious life in the first person perspective, as a self-present, single, temporally persistent, embodied, and bounded (demarcated) entity, who is the subject of his experiences".[13] Profound alteration or shattering of these basic structural aspects of self-hood forms the core of schizophrenia.[13]

Propositions implicating self-disturbances in schizophrenia have been in vogue since the times of Kraepelin and Bleuler. It is noteworthy that Emil Kraepelin (1896) postulated "loss of unity" of consciousness (i.e., "orchestra without a conductor") as a core component of schizophrenia; along these lines, Eugen Bleuler (1911) also observed that "the most manifold alterations in the patient's ego that included splitting of self and loss of the feeling of activity or the ability to direct thoughts" as an important characteristic of schizophrenia.[14]

Disparate lines of evidence support schizophrenia patients to show abnormalities in critical facets of consciousness involving self-awareness and time perception. Within the "self-abnormalities" paradigm, schizophrenia has been proposed as an "ipseity disturbance"; ipseity refers to the experiential sense of being a vital and self-coinciding subject of experience or first person perspective of the world.[14] This is also referred to as "minimal self"—the immediate conscious experience of oneself.[15] Fundamental disturbances in 'ipseity' (the ongoing sense of "being there" accompanying all conscious experience) has been proposed as the overarching aberration that can explain the contrasting manifestations (positive, negative and dis-

organization symptoms) of schizophrenia.[14,15)]

Studies implicated on phenomenological research methods support the notion that disturbance of the basic sense of self may be a core phenotypic marker of schizophrenia spectrum disorders.[32)] This encompasses disruption of the sense of ownership of experience and agency of action with associated bewildering dimensions of anomalous subjective experiences. In a meta-analysis evaluating the studies that have altogether examined 690 patients with schizophrenia patients and 979 healthy controls,[33)] patients showed deficits in the sense of the minimal self, driven by abnormal sense of body ownership and sense of agency. The authors have suggested that the disturbed sense of agency in schizophrenia as observed in this meta-analysis suggests an exaggerated self-consciousness.[33)] This has been aptly commented that the "self-disorder model offers an integrative and dynamic view of schizophrenia congruent with recent trends in cognitive neuroscience and consistent with the heterogeneous, varying, and holistic nature of this enigmatic illness".[34)]

One of the mechanistic basis for 'self-disorder' has been shown to be related to the confusion in the experience of temporal causal relations between the self and the external world which, in turn, might result in self-disturbances in schizophrenia.[2)] In tune with this, neurophenomenal formulation of schizophrenia emphasizes upon the temporal discontinuity between the contents of the consciousness to underlie schizophrenia pathogenesis.[2)] This points towards aberrations in another critical component of consciousness in schizophrenia, namely, the temporality or the subjective experience of time.

Schizophrenia and Consciousness: Time Perception Abnormalities

One of the fundamental components of human consciousness is the subjective experience of time[16)] "we exist within a transparent web of time"[35)]; temporal continuity is a critical requirement for even the simplest of conscious experience like perception.[35)] In turn, this renders consciousness to be fundamentally dynamic with temporality being its intrinsic characteristic.[16)] Indeed, time perception abnormalities in schizophrenia are demonstrated through several lines of research studies—thus, adding further support for the concept that schizophrenia is disorder of consciousness.[36,37)]

Time perception model proposes an internal pacemaker that contributes to the subjective perception of time[38)]; the quantity of temporal units is accumulated over a specified interval and this results in experienced representation of duration. If the pacemaker is accelerated, it will lead to an overestimation of duration; on the contrary, a slow internal pacemaker will result in underestimation.[38)]

Erroneous estimation of time, especially in the context of relating the actions with their sensory consequences, can result in aberrant agency attribution.[39)] Thus, an abnormally excessive production of mental associations between unrelated events might occur in secondary to time perception deficits; indeed, this has been shown to be associated with Schneiderian first rank symptoms of schizophrenia.[39)] Time perception abnormalities have been shown to correlate with more severe positive as well as negative symptom dimensions in schizophrenia.[40)]

Importantly, time perception might be influenced by dopaminergic as well as glutamatergic pathways[41,42)]; these are indeed among the most critical neurochemical aberrations in schizophrenia.[43)] A specific experimental paradigm that links the time perception with sense of agency, namely, 'intentional binding' that reveals instances of subjective compression of time in such a way there is a perception that actions and their effects are bound together across time[44,45)]; this paradigm has been extensively examined in schizophrenia (as summarized in the next section) offering further support to the link between sense of agency and time perception[45)]; thus, adding further support for the postulate that 'schizophrenia is a disorder of consciousness'.

Time Perception and Sense of Agency: Intentional Binding Abnormalities in Schizophrenia

"Intentional binding refers to the observation that an action and an ensuing sensory effect are perceptually attracted toward one another in time (bound), as compared to when either event occurring in isolation".[44,46)] It has been shown that conscious representations of sensorimotor events surrounding voluntary action are bound by a specific cognitive function of the central nervous system;[44)] this function is characterized by temporal contiguity and temporal predictability—two critical general principles of association. Perceptual shifts that occur in these contexts have been construed to be secondary to a conscious aspect of a general linkage through time between representations of actions and effects. Hence, this function has been referred to as 'intentional binding'.[44)]

Since the association between one's own action and an external effect is considered as the key mechanism underlying the sense of agency, intentional binding can provide an implicit measure of the sense of agency.[44,47)] Intriguingly,

using the intentional binding paradigm, action-effect associations has been shown to produce systematic distortions of time perception linked to voluntary action. For instance, it was shown that a subject perceives one's own action (e.g., a key press) as occurring later when this action is followed by an external effect (e.g., a tone), compared to action not followed by such effect.[44] Thus, actions that produce an outcome (a tone) are perceived as occurring later than actions that do not produce an outcome. Conversely, an outcome (a tone) that is produced by an action is perceived as occurring earlier than an outcome that simply occurs at random in the absence of an action. Thus, voluntary actions and outcomes are experienced as bound together in time. Contrastingly, involuntary movements were shown to exhibit the reverse pattern, i.e., repulsion rather than binding. Hence, this 'intentional binding' effect has been considered to offer a precise, implicit measure of sense of agency.[48]

In the first study to examine the status of 'intentional binding in schizophrenia patients, it was observed that patients bind together their own action and a consequent auditory signal to a greater extent than controls.[47] A subsequent study demonstrated that this hyperbinding effect is found for somatic sensory events such as passive movements as well as auditory events. In addition, comparable magnitude of hyperbinding in patients was observed various different kinds of event pairings, including sequences of somatic sensations, the patient's own agency, and a social condition in which the patient's somatic sensations were triggered by the experimenter's action.[49] Hyperbinding in schizophrenia was replicated in another recent study as well.[50]

It is plausible that this excessive contraction of subjective time in schizophrenia patients might be a general feature of their perception.[49] Hence, in schizophrenia patients, the general proclivity to underestimate the temporal interval between events could reflect their tendency to overestimate the association between events. Based on these observations, it has been hypothesized that hyperbinding between a movement and a previous causal action could result in misidentification of the agency of the movement; this, in turn, could produce the "alienation phenomena" that are experienced in delusions of influence.[49]

Within the paradigm of intentional binding, the association between 'action' and 'effect' has been understood to be generated either "predictively" (i.e., an action is predicted to result in a given effect) or "retrospectively" (i.e., one infers retrospectively that one's action caused the effect). Indeed, intentional binding has been demonstrated to involve both predictive and retrospective components.[51] In a study that characterized the "predictive" and "retrospective" generation of intentional binding,[51] when participants frequently (about 75% probability) experienced key presses followed by tones, they perceived the time of action as shifted towards the anticipated tone, even on rare trials where no such tone occurred; this indicated that the subjects predicted the tone during the key press. Intriguingly, a shift in action awareness also occurred when a tone was not highly predictable (about 50% probability), but did actually occur; this has been inferred that in the absence of prediction, the actual occurrence of the tone retrospectively changed the experience of action.[51]

Using this probability paradigm to differentially assess the "predictive" and "retrospective" generation of intentional binding, it was observed that in schizophrenia patients the "predictive" contribution to intentional binding was absent.[50] In contrast, this study reported that the inferential contribution (i.e., "retrospective" component) was stronger in these patients. However, the magnitude of the predictive deficit in patients correlated with the severity of certain positive symptoms. Moreover, schizophrenia patients were found to generate imprecise predictions rather than no predictions.[50] Prediction errors involving agency attribution in schizophrenia has replicated in another study that utilized a different agency paradigm.[52] Imprecise sensorimotor prediction might have led to the stronger retrospective contribution to intentional binding in patients. Since the internal sensorimotor predictions more likely to be unreliable, the patients' experience of agency may be strongly influenced by the more reliable external cues to agency. This is consistent with Frith's model of delusions, the so-called 'comparator model'.[53]

Evaluation of intention binding in patients that were in the prodromal stage of psychosis revealed excessive 'predictive' contribution[48] which is in contrast with the patients that exhibited excessive 'retrospective' contribution.[50] Together these disparate findings suggested hyper-prediction in the psychotic prodrome and hypo-prediction in established schizophrenia.[48] These contrasting findings are in tune with the postulated roles of glutamatergic and dopaminergic pathways in contemporary models of delusions.[43] For instance, in prodromal states, increased error signalling mediated by glutamatergic mechanisms might strengthen the association between action and outcome resulting in stronger 'predictive' contribution to intentional binding; in the later stages of 'established' schizophrenia, hyperdopaminergic state could add noise to the signal resulting 'corrupted' error

signalling with a resultant strong and indiscriminate action-outcome leading to 'erroneous' predictions.[45] Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist anaesthetic agent which produces a 'schizophrenia-like state' at sub-anaesthetic doses, has been found to induce hyperbinding in healthy subjects.[54] Examination of Parkinson's disease patients who were treated with dopaminergic agents revealed that intention binding was significantly stronger than healthy controls as well as during the patient's own performance during off-drug state.[55] Together, these observations support the influence of glutamatergic and dopaminergic mechanisms underlying intention binding.

In summary, several lines of compelling evidence support definitive aberrations in critical components of consciousness involving self-awareness as well as time perception in schizophrenia. Contemporary theoretical models of time perception implicate critical role for neural oscillations in the neurobiology of temporality.[56] In the striatal beat frequency model of interval timing,[57] striatal spinal neurons play a critical role by monitoring the activation patterns of neural oscillations in the cortex. The underlying neuroanatomical circuit involves cortico-thalamo-striato-cortical loop with neurochemical influence by glutamate, dopamine and γ -aminobutyric acid (GABA); cerebellum also contributes to this loop.[57] Contextually, it is interesting to note that cortico-cerebello-thalamo-cortical circuit has been implicated to explain the pathogenesis of schizophrenia through the construct of "cognitive dysmetria"[58]; moreover, striato-cerebellar abnormalities have also been demonstrated in schizophrenia patients.[59] The overlapping neural basis for time estimation as well as schizophrenia pathogenesis further supports the role for aberrant time perception[36] with resultant consciousness perturbations in this disorder.

Time Perception, Consciousness and Schizophrenia: The Role of Aberrant Neural Oscillations and Link with Quantum Consciousness

As per the striatal beat frequency model,[56,57] the levels of tonic dopamine-glutamate activity in the neural circuits between ventral tegmental area and cortical regions determine the clock speed through modulation of cortical oscillations. Input from cortical neurons with different frequency of activity patterns converge onto striatal spiny neurons. These cortical neural oscillations are synchronized with concurrent resetting of the status level of the spiny neurons by the respective phasic dopaminergic input from the ventral tegmental area and substantia nigra pars compacta at the beginning of an interval. At the target duration, the delivery of reinforcement results in a pulse of dopamine which strengthens the striatal synapses that are activated as a result of the beat frequency pattern of the cortical neurons (i.e., cortical neural oscillations) at that specific point in time. With additional mechanisms involving long-term potentiation and long-term depression, the synaptic weights are strengthened and weakened respectively to create a memory record of target duration. Subsequently, when the same signal duration is timed again, neostriatal GABAergic spiny neurons compare the current pattern of activation with the earlier one stored in memory to ascertain whether the target duration has been reached. When there is match between the clock and memory patterns match (as ascertained by coincidence detection), the spiny neurons fire to indicate that the interval has elapsed.[56,57]

Cortical neural oscillations have been established to mediate the basic processes for the establishment of specific temporal relationships between neuronal responses that are in turn significant for memory, perception and consciousness.[60] Contextually, it is important to note that neural oscillation aberrations are amongst the critical pathogenetic factors in schizophrenia. Several lines of evidence support abnormal oscillations and synchrony to underlie cognitive dysfunctions and some of the symptoms of schizophrenia.[60,61]

Among several types of neural oscillations, gamma band activity has been shown to influence time perception.[62,63] Disrupted neural synchrony involving gamma oscillations has been demonstrated in schizophrenia patients in several studies.[64,65] Gamma synchrony is proposed as the best measurable correlate of consciousness from the perspectives of a popular quantum paradigm for consciousness — namely, Orch-OR theory.[20]

The Orch-OR model offers a biological platform for understanding consciousness[20]; critically, with regards to the brain microstructure — the Orch-OR theory implicates microtubules. This is interesting especially since several lines of compelling evidence suggest microtubule basis for schizophrenia (as summarized in the later sections); hence, among the several competing models of consciousness — the Orch-OR model is discussed further because of its potential link with schizophrenia especially due to the shared 'scaffold' of microtubules as summarized in the next sections.

Quantum Consciousness: Importance of Microtubules

Orch-OR theory proposes consciousness to consist of

discrete moments, each an 'orchestrated' quantum-computational process terminated by object reduction, an action rooted in quantum aspects of the fine structure of space-time geometry, this being coupled to brain neuronal processes via microtubules.[20] The Orch-OR theory predicts a wireless communication of axons through resonant vibrations around a domain of hundred micrometres. The orchestration of resonant vibrations can potentially occur globally between all neurons in the brain. This cascade of communication can be triggered throughout the brain by conical radiation/absorption within the vicinity of the neurons involving the dual polar ends.[20,27]

Inspired by the striking evidence for quantum effects in biology,[23,24] it has been argued that microtubules, which play critical roles in all eukaryotic cells, possess structural and functional characteristics that are consistent with quantum coherent excitations in the aromatic groups of their tryptophan residues[66]; the consequence of these observations have been put forth with a proposition that "quantum biology in neuronal processes underlie the emergence of consciousness and these processes are sub-served by microtubules".[66] From information processing perspectives, microtubules in brain has been proposed to serve as a communication channel that facilitates information transfer and storage; these sub-neuronal processes occurring at the level of microtubules might underlie the generation of consciousness.[67]

Tau, a neuronal microtubule-associated protein, is implicated in microtubules stabilization, axonal establishment and elongation during neuronal morphogenesis.[68] Recently, it has been demonstrated in a mice-model based study that the lack of normal phosphorylated tau during early stages of development might influence the maturation of parvalbumin interneurons affecting the spatiotemporal structure of long-range gamma synchronization.[69] Indeed, gamma abnormalities in schizophrenia occur due to deficient parvalbumin positive interneurons.[70] Importantly, hippocampal parvalbumin plays a fundamental role in schizophrenia pathogenesis.[71] Moreover, a host of gene as well as environmental factors that accentuate the risk for schizophrenia operate through resultant aberrations in parvalbumin positive interneurons.[72]

Also, the proper functioning of gap-junction channels might be compromised by the absence of tau in hippocampal networks.[69] From the quantum perspectives on the origins of consciousness, these observations become significant in the context of critical influence of both gamma synchrony as well as gap-junctions in the proposed neural basis of consciousness as per Orch-OR theory.[20]

Microtubule Abnormalities in Schizophrenia

Microtubules form integral part of neuronal cytoskeleton; organization, assembly and dynamics of the microtubules critically influence the neuronal polarity, plasticity and synapses.[73] Microtubules are non-covalent cytoskeletal polymers found in all eukaryotic cells that participate in mitosis, cell motility, intracellular transport, secretion, the maintenance of cell shape and cell polarization. These are polarized structures that are composed of α- and β-tubulin heterodimer subunits assembled into linear protofilaments. A single microtubule is comprised of 10-15 protofilaments (usually 13 in mammalian cells) that associate laterally to form a 24 nm wide hollow cylinder.[73]

One of the earliest evidence for microtubule pathology in schizophrenia was supported by a seminal post-mortem study of hippocampus depicting prominent and specific alterations in the distribution of two microtubule-associated protein (MAP) 2 and MAP5 that were anatomically selective for the subiculum and entorhinal cortex. These lesions were inferred to result in distortion of the polarized geometry of neurons which in turn could have played a role in the emergence of aberrant behavior in schizophrenia.[74] Over the past years, several lines of evidence argue for a compelling role for abnormalities of cytoskeletal architecture involving microtubule in schizophrenia pathogenesis.[75]

The neurodevelopmental origins of schizophrenia have been linked with microtubule dysfunction that can result in defective neuronal migration as well as aberrations in outgrowths of axons and dendrites during brain development.[76] The resultant gray matter deficit in schizophrenia has been shown to be secondary to neuropil abnormalities.[77] Furthermore, this neuropil defect has been traced to reduced density of dendritic spines in schizophrenia[78] and microtubules play a significant role in influencing the morphology of dendritic spines.[73] Interestingly, dendritic spine aberrations have been linked to NMDA receptor hypofunction—a critical pathogenetic mechanism in schizophrenia; contextually, it is important to note that NMDA activation is critical for increasing the number of microtubules in dendritic spines.[79]

Certain genes that are critically implicated in schizophrenia (*DISC1*, glycogen synthase kinase 3-beta [*GSK3*β], *PCM1*, fasciculation and elongation protein zeta-1 [*FEZ1*]) have critical role associated with microtubules.[80] In a genome-wide analysis of 5,100 common missense single nucleotide polymorphisms (SNPs) genotyped in

476 schizophrenia patients and 447 control subjects,[80] significant overrepresentation of the DISC1 interacting proteins was identified supporting the role of this gene set in schizophrenia risk. Strikingly, the seven leading-edge genes (*MACF1*, *UTRN*, *DST*, *DISC1*, *KIF3A*, *SYNE1*, and *AKAP9*) that were responsible for the overrepresentation are critically involved in neuronal cytoskeleton organization and intracellular transport through the microtubule cytoskeleton, suggesting that these processes may be impaired in schizophrenia.[80] Apart from DISC1, other effectors that modulate the dynamics and stability of microtubules like stable tubule only polypeptide (STOP; also known as microtubule associated protein 6 [MAP6]) and dysbindin-1 are important for optimal neuronal morphogenesis and connectivity during neurodevelopment as well as plasticity of synapses in adulthood.[81] Hyperphosphorylation of tau, a protein that regulates microtubule assembly and stability, has been implicated in pathogenesis of schizophrenia.[82]

Dysfunction of neuronal microtubule, as inferred through the experimental studies on STOP knockout mice, can result in behavioral changes that resemble schizophrenia accompanied by reduced synaptic vesicle and synaptic plasticity impairments.[83,84] Indeed, several critical cognitive impairments that are consistently observed in patients with schizophrenia[85] — namely, diminished social cognition, executive dysfunction, aberrations in memory/attention — have been linked with variations in microtubule dynamics and stability.[81,86]

Antipsychotic medications, the mainstay treatment for schizophrenia, have been found to impact upon microtubules in several studies.[75] Medications like chlorpromazine can inhibit tubulin polymerization, thus affecting the cytoarchitecture of microtubules.[87] Interestingly, the effects of antipsychotic medications on microtubule might be dose dependent with lower concentrations facilitating re-establishment of cytoskeletal organization & increased neurite formation resulting in enhancing synaptic connectivity[75]; on the contrary, higher concentrations might lead to collapse of cytoskeleton.[75] Antipsychotics might induce synaptic plasticity through cytoskeletal rearrangements.[75,88]

In a recent study that examined gene expression using a mouse brain model,[89] clozapine was shown to significantly increase the expression of microtubule-associated protein kinase (MAPK) signalling as well as regulated the transcripts of microtubule functions that included PCM1, microtubule-associated protein 7 (MAP7), microtubule associated protein RP/EB member 2 (MAP2) and microtubule associated protein RP/EB, member 3 (MAP3); in contrast, haloperidol did not alter these parameters. These observations support the possibility that the differential effect of clozapine on microtubule might underlie the superior therapeutic efficacy of clozapine.[89]

Contextually, it is interesting to note that neurotrophic factors like brain-derived neurotrophic factor (BDNF) play a significant role in microtubule integrity.[90] Deficient BDNF is an established pathogenetic factor in schizophrenia[91-93]; importantly, BDNF links the hippocampus deficits in schizophrenia[94,95] with microtubule abnormalities.[96,97] Indeed, the microtubule mice model of schizophrenia (STOP-null mice) demonstrates striking aberrations involving hippocampus.[83,98] Finally, BDNF also links microtubules with cell signalling pathways (Akt/GSK) as well as cell cycle involvement in schizophrenia pathogenesis[89,99]; in addition, microtubule is intricately connected with these biological pathways as well[99] as well as with the immune pathogenetic perspectives[100] in schizophrenia.[101] In summary, microtubule mediated mechanisms provide an overarching link that cut across several disparate but critical pathobiological mechanisms of schizophrenia.

Translational Implications of Quantum Consciousness and Schizophrenia: Theoretical Perspectives

Transliminality based research studies is a potential paradigm that might facilitate the much-needed link between 'consciousness', brain biology and clinical/behavioral phenotypes. Transliminality refers to individual differences in the threshold at which unconscious processes or external stimuli enter into consciousness.[102] Certain characteristics like magical ideation, paranormal beliefs, creativity and heightened mystic experiences are possessed by subjects that score high in transliminality.[103] In a electroencephalography research that examined the electrophysiological correlates of transliminality using the revised transliminality scale,[104] individuals high in transliminality exhibited greater gamma power over the frontal-midline region[105]; these observations were interpreted to be consistent with the previous findings related to reductions in left temporal/parietal activity, as well as the desynchronization of right temporal activity in schizotypy and related schizophrenia spectrum disorders.[105] The brain biology of transliminality has been linked with cerebral asymmetry based theories[106,107] on the origins of schizophrenia as well — with right hemisphere hyperactivation (plausibly due to failure of left hemisphere dominance) being one of the postulated pathogenetic

bases.[105] Interestingly, increased right hemisphere activation with involvement of parahippocampal gyrus has been associated with certain paranormal phenomena.[108,109]

While these "left-hemisphere dominance failure" findings have been conceptualized as "abnormal" in their tendency to increase of a person's proclivity towards psychosis, evolutionary theories on psychosis propose an alternative possibility that some of these traits might be of critical utility in survival advantages.[101,110,111] It has been proposed that this dominance failure (and consequent right hemisphere over activation) facilitates the emergence of paranormal and delusion-like ideas by way of right hemispheric associative processing characteristics,[112] that is, coarse rather than focused semantic activation. In this context, transliminality based research paradigms offer a unique platform to explore the interactions between the biology of consciousness and the clinical/cognitive/experiential components as well as evolutionary neuroscience constructs through several brain imaging research tools. Certain preliminary attempts at applying certain quantum principle based approaches have offered initial leads for feasibility of diagnostic approaches using quantum resonance principles.[113] These studies need further clarity in terms of the conceptual basis on quantum theories; nonetheless, such research attempts illustrate the potential for research in this area with translational implications.

Translational Implications of Quantum Consciousness and Schizophrenia: Clinical Perspectives

Neurophenomenologically, consciousness based approaches have been emphasized as critical to understand the fundamental features of schizophrenia.[13] In addition to providing 'inclusive' phenomenological understanding of this disorder,[13] such approaches, especially implicated upon quantum perspectives, have offered initial leads (albeit needing more clarity on theoretical basis) towards formulation of potential 'diagnostic tests'.[113]

Specifically, with the Orch-OR theory implicating microtubule basis for quantum consciousness,[20] there are several promising leads towards significant translational implications for treatment of schizophrenia. Microtubule mediated mechanisms play a role in the therapeutic effects of antipsychotics[75] as well as electroconvulsive therapy.[114] Informed by the cytoskeletal basis for schizophrenia, the effect of microtubule stabilizer was evaluated using the STOP-null mice (STOP protein) model for schizophrenia.[83] STOP-null mice display synaptic defects in glutamatergic neurons of hippocampus, limbic hyperdopaminergia, and severe behavioral disturbances (like fragmentation of spontaneous activity, hyperlocomotor activity, anxiety-related disorders, signs of severe social withdrawal, dramatic perturbations of maternal behavior, and a dysfunction of sensory-gating mechanisms) that are also seen in schizophrenia patients.[84,98] Importantly, dopaminergic abnormalities due to hippocampal dysregulation is critically implicated in the pathogenesis of schizophrenia.[115] In STOP-null mice, treatment with epothilone D, a microtubule stabilizer, resulting in increased synaptic vesicle pools, ameliorated both short- and long-term forms of synaptic plasticity in glutamatergic neurons; moreover, it had a striking beneficial effect on the behavioral abnormalities.[83] These observations suggested that microtubule stabilizer might offer a promising avenue for treatment of schizophrenia.[83] Davunetide, an eight amino acid peptide with action on microtubule leading to neuroprotective effects, has shown promising results in preliminary studies.[116] Interestingly, davunetide was shown to cause modest functional improvement in schizophrenia patients[117]; also, it led to modest increases in N-acetylaspartate/Creatine and Choline/Creatine in dorsolateral prefrontal cortex of schizophrenia patients.[118]

Recent discovery of microtubule's resonant oscillation (conductive resonances in single microtubules that are observed when there is an applied alternating current at specific frequencies[25]) has offered further support the Orch-OR theory of 'microtubule basis' for quantum consciousness.[20,27] As a direct translational implication of these observations, transcranial ultrasound—a safe, non-invasive technology for modulating brain activities (hypothesized to be mediated by action on microtubules) with relevance to cognition, consciousness and mental states/disorders, has been postulated as a potential therapeutic option in psychiatric disorders for further research studies.[119] Given the compelling evidence for perturbed consciousness in schizophrenia, such novel therapeutic options are worth systematic research studies for treatment of schizophrenia. Very recently, studies have shown promising evidence that transcranial focussed ultrasound can indeed be used to modulate cortical function.[120,121]

SUMMARY AND CRITIQUE

Understanding Schizophrenia as a Disorder of Quantum Consciousness

In summary, several lines of compelling evidence from studies examining self abnormalities, time perception, intention binding support perturbations of consciousness to underlie schizophrenia pathogenesis. Dysfunctional neu-

ral oscillations link these abnormalities with biological theories of consciousness. One specific theoretical paradigm (Orch-OR) was focused in this review especially due to the postulated microtubule basis for the quantum theory based origins of consciousness. While this does not negate the significance of other models of consciousness abnormalities in schizophrenia namely－the "corollary discharge of attention movement (CODAM)" neural network model of consciousness,[15] it is plausible that these models might be related at some level. Another critical dimension that needs systematic research is the interface between eastern philosophical approaches and the contemporary biological propositions for consciousness[29] and its relevance in understanding schizophrenia.

The microtubule basis for consciousness falls in line with several fundamental, preclinical as well as clinical research studies in schizophrenia that implicate aberrant microtubules as a critical pathogenetic mechanism. Moreover, this line of conceptualization has potential translational implications at theoretical as well as clinical perspectives in schizophrenia. Together, all these argue for the postulate that "Schizophrenia is a disorder of consciousness possibly due to microtubule dysfunction".

These translational leads are promising; nonetheless, one has to acknowledge that the available evidence is still preliminary and requires further systematic evaluation and replications to ultimately influence the clinical practice. In addition, cutting edge research studies need to establish unequivocal evidence for the microtubule basis for consciousness as well as its link with the clinical as well as neurobiological aberrations in schizophrenia. Given the ubiquitous involvement of microtubule in the genesis of various neuropsychiatric as well as other medical diseases, it is critical issue to identify the pathogenetic factors in this "consciousness paradigm" that might differentially influence the risk for schizophrenia and thereby elucidate specificity in the biomarkers for this debilitating disorder.

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