SciMedCentral

Annals of Psychiatry and Mental Health

Review Article

Neural Fabrics of the Mind: Systems Neuroscience, Systems Psychology and Consciousness

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Submitted: 02 October 2015

Accepted: 03 November 2015

Published: 05 November 2015

Keywords

- Neural fabrics
- Systems science
- Mind
- Consciousness

Abstract

Mind operates on the fabrics of signaling of systems biology of astrocyte-neuron mosaic. Conversion of signal to information and its handling by operations of mind is not a solo affair. Operations of mind are interlinked with operations of self, 'life' and consciousness. Could all these be brought within the ambit of systems science? When the automated cell signaling system in systems biology fails to operate at the desirable level of perfection, how self is called upon for application of mind to take a conscious decision on the remedial measures is the issue at hand. What we see as mental disorders, have deep roots in cell signaling and in failure of handling of information by operations of mind, self and 'life'. The purpose of this review is to take lead from the renaissance in emerging knowledge in glia-neuron relationship for developing the molecular foundation of a systems neuroscience, which is inclusive of cognition and consciousness and excludes nothing from the behavior. A nested three-tier systems has been constructed where, in the first tier/nest there is systems biology of glia and neuron that form functional mosaic in the context of their origin, survival, migration, trophism, metabolic shuttles, ion homeostasis and circuit development. In the second tier/nest there is systems biophysics and informatics, which includes electrical signaling, communication and information partnership between astrocytes and neurons. The knowledge on operations within the third tier/nest is still at the formative stage. However, this leads us from the domain of information to those of mind, self, 'life' and consciousness. This specific way of looking at the systems brain in one hand brings useful insights in pathogenesis of many neurodegenerative and neuropsychiatric disorders and on the other hand could be utilitarian for its translational potential in systems engineering for developing a conscious ware from the present level of software.

ABBREVIATIONS

AC: Alternate Current; AIDS: Acquired Immuno Deficiency Syndrome; AD: Alzheimer's Disease; AGD: Agyrophilic Grain Disease; ATP: Adenosine Triphosphate; BBB: Blood Brain Barrier; BDNF: Brain Derived Neurotrophic Factor; CNS: Central Nervous System; CRH: Corticotrophin Releasing Hormone; DC; Direct Current; ECM: Extracellular Matrix; FKN: Fractalkine; GCI: Glial Cytoplasmic Inclusion; GDNF: Glial Cell line-Derived Neurotrophic Factor; GFAP: Glial Fibrillary Acidic Protein; GGF: Glial Growth Factor; HIV: Human Immunodeficiency Virus; IGF: Insulin-like Growth Factor; IIT; Integrated Information Theory; LSD: Lysergic Acid Diethyl amide; LTP: Long-term Synaptic Potentiation; MAPK: Mitogen-Activated Protein Kinase; MHC: Major Histocompatabilty Complex; MSA: Multiple Systemic Atrophy; Myelin NOGO: Myelin associated neurite outgrowth protein; NGF: Neural Growth Factor; NMDA: N-methyl-D-aspartate; NMDAR: N-methyl-D-aspartate receptor; NMR: Nuclear Magnetic Resonance; FNMR: Functional Nuclear Magnetic Resonance; nRT: Thalamic Reticular Nuclei; OPC: Oligodendroglia Progenitor Cells; PET: Positron Emission Tomography; RTN: Retro Trapezoid Nucleus; SCAP: SREBP cleavage-activating protein; SREBP: Sterol Regulatory Element-Binding Protein; VPA: Varicose Projection Astrocyte

INTRODUCTION

Neuroscience has shown two major advancements. First, there is far-reaching development in cell signaling system involving the metabolome-proteome-genome of neuron. Second, almost a renaissance in emerging knowledge in glia-neuron relationship has been observed in terms of cognition, memory, learning and behavior. As a result, there is an intense urge to bring all revealed data in neurological science under the ambit of systems neuroscience. In psychology and psychiatry, the blurred distinction between mind and consciousness has been becoming clear with an understanding that no information inside the brain is an island. Operations of mind with information are not seen isolated but interconnected with operations of self and life. Consciousness has been recognized as an undisputed and not-eliminable causal operator in cognition, emotion (feelings)

and will. The author works on the question, could the systems psychology be brought in line with systems bioinformatics and systems biology? This review forms opinion on this issue, makes an effort to bring systems biology of individual neurons and glia with systems neuroscience within the ambit of systems psychology and systems consciousness.

The objectives of this review are to (i) catalog available information, extract meaning and refine knowledge on the rock bottom infrastructure of mind, (ii) build up generalizable theme and concepts from the perspectives of systems neuroscience, with reference to neurodegenerative disorders and neuropsychiatric disorders and (iii) identify knowledge gaps and help idea/hypothesis generation that can guide construction of theoretical model or design experiment. The aim is to prepare the ground to develop a distinct three-tier framework for a holistic integrated systems science of the nervous system, which is inclusive of cognition and consciousness and excludes nothing from molecular signaling or behavior.

The Review has four parts.

Part I deals with glia-neuron systems biology, metabolic signaling and their breakdown in various neurodegenerative and neuropsychiatric disorders (Nest/Tier I).

Part II has two sections, A & B.

Section A deals with the systems communications in neuron-neuron-astrocyte-neuron circuits (Nest/Tier II). In section B, we describe the infrastructure scaffolding for mind-consciousness activities combining tiers/nests II and III. The section, in fact, prepares ground for nest III.

Part III is on the decision-making systems labyrinth of mind, self 'life' and consciousness (Nest/Tier III). This all is for a doable inter connected systems science of the brain and consciousness (Table 1).

Part IV of the Review deals with a possible paradigm shift, emergence of a new Paradigm and our heading for a revolution. It ends with concluding remarks and perspectives.

The special feature of the article is its discussion in full possible details the biochemical and molecular facets of the most of the relevant areas as known till date. This strengthens the foundation of molecular psychiatry considerably. By radically replacing the old monolithic concept of psyche with an integrated systems operation of information, mind, self, 'life' and consciousness interlinked with their rock bottom at molecular level, this review shows a new way for investigating mental health and illness.

PART - I

GLIA-NEURON MOSAIC: Neurocentric conditioning as prevalent in education system and teaching compels us to behave as neuro-chauvinist. By the word 'brain', we are immediately reminded of only neurons and remain completely oblivious to brain's other major constituent cells called glia. To many of us the science of the brain is synonymous to neuroscience. We use the terms like neuroanatomy, neurophysiology, neuropathology, neuropharmacology, neuropsychology, psychoneuroimmunology, neurobiology, quantum neurology and even neurophilosophy, neurosociology, neuroeconomics ignoring completely neuron's dynamic biological partners, the glial cells.

Glial cell within the brain are of three distinct types: two are microglia, astrocytes, oligodendrocytes and the third one is microglia. Oligodendrocytes make myelin within CNS; microglial cells belong to immune system and act as foot soldiers in the defense of the nervous system, while astrocytes bear multifaceted relationship with neurons. All would be discussed in detail in the perspectives of systems neuroscience with a view to, as said, "fostering synergy between cell biology and systems biology" [1].

Appropriate Metaphor of Glia-neuron relationship: The term glia is derived from a Greek word for glue, 'packing material', nonliving soft stuff that surrounds the neurons in the brain. Most of us, however, work with the metaphor that the glial cells play the supporting role [2] as the side-actor or play as 'woman' in the brain [3], may be as mother (lactate shuttle), sister (common progenitor) or wife (glial processes wrapping naked axon), all assigning a secondary status to them. However, as reviewed in this essay, glial cells and neuron maintain a dynamic biological partnership and both play an active role in information processing and even in decision-making locally, focally and globally. As we will see their relationship covers supportive, active and proactive role of each member with differential distribution of responsibilities. An alternate metaphor would be in a socio-political-governing context. From this review it would be obvious that the glia manages the ministry of home (astrocyte and oligodendroglia), finance (astroglia), defense (microglia) and 'cell resource' (astrocytes). Probably, only the ministry of external affair is dealt by the neurons and perhaps for this reason neurons are endowed with the ability to 'fire' (action potential) that glia cannot! However, foreign policy cannot be independent of home, resource, finance, and defense departments.

Glia-Neuron Ratio: The glia-neuron number ratio is variable. According to the standard textbook on neuroscience [4] the glial cells are 2-10 times that of number of neurons in the vertebrate's brain. This 'ten times' has been perpetuated in the neurojournalism with grand comment such as, "meet the forgotten 90% of your brain" [5] since approximately 10% of cell populations inside the brain are neurons, 60% are astrocytes, 20% are oligodendrocytes and 10% are microglias. There are riders of course; the ratio varies from the brain to brain, in

Table 1: Hierarchically nested, three-tier Systems science for the brain.

Tier	Operations involved	Systems Science
Nest/Tier I	Metabolome–Proteome-Genome-Epigenome	Systems Biology of Glia-Neuron
Nest/Tier II	Information channeling, Signal transmission and transduction, Communication between cognitive networks	Systems Bioinformatics and Systems Biophysics
Nest/Tier III	Operations of Information Mind, Self, Life and Consciousness	Systems Psychology and Systems Consciousness

different geographical location of the brain and in different phases of life in the same brain. The primary source of this information of glia: neuron ratio as 10:1is not available in the searchable literature. The earliest literature available in search engine regarding glial role in the brain function is from Stephen Kuffler [6] and his group [7]. This widely held view has been challenged by the findings in the laboratory of Suzana Herculano-Houzel [8], the Brazilian neuroscientist, who over the period of 2005-2014has shown that the glia/neuron ratio in human brain is nearly 1:1. Astrocytes constitute about 20-40% of total cells of mammalian brain. Her methodology merits to be replicated in laboratory of other researchers.

Why there is so much variation in glia neuron ratio? Probably because we are dealing with a socio-politico-governing congregation of billions of cognitive living cells! In politics, one requires a number of supporters while the leader makes its own supporters and in business, one may requires partner. In Governance, there is a trade-off for this number. In the paradigm where glial cells are considered as 'supporters' of neuron, their numbers are proportionately high; neuron: glia ratio is 1:2-10. When the glial cells are considered business partner of neurons, the ratio could be nearly 1:1. In the Governance of the brain the glial cells work as cabinet colleagues of neurons and the ratio varies according to the size of the cabinet. Even when one considers glia as 'woman' of the neuron, the paradigm shifts from promiscuousness to monogamy. With the evolution of neuron, one or two astrocytes per such neuron probably would be sufficient to take care of the governance in the brain!

Origin and Survival of Glial cells and Neurons: Neurons, astrocytes and oligodendrocytes originate from common stem cell. Their differentiation is determined by microenvironment and the cell's functional propensity towards either neuronal or glial activity [9-11]. Asymmetrical cell division is seen during generation of neurons [12] while the presence of single transmembrane notch receptor can determine [13] whether the cell generated will have phenotypic specifications for glia. Experimentally, astrocytes have been seen to generate even in heterotopic grey matter in the brain of the microcephalic mice [14]. Generation of glia can also be studied in cerebral organoids model of human brain [15].

Can neuron survive and operate without any glial (especially astrocytic) assistance? Perhaps not inside the CNS! Neurons survive with minimal or no glial influence only inside a ganglion, which is a collection of nerve, cells outside the CNS and also in the 'mini brain' of gastrointestinal tract. This kind of survival is doubtful within the CNS. Could glial cells survive within the CNS without presence of any neuron? The situation of having a brain without neuron and only glia is merely hypothetical! Microcephaly offers a closest model to study this issue (see below).

Interlinked Development and Trophism: Neuron and glia are trophically interlinked. Neuron produces GGF and glia produces NGF. Oligodendroglia produces BDNF, GDNF and IGF1 while microglial cells produce BDNF. Glia directs migration of neurons, axonal growth, dendritic arborization and synaptogenesis. In certain situations, glial factors evidently stimulate neurogenesis.

We are aware of two situations where one finds true social and trophical mosaic between neurons and all three kinds of glia [16]. These situations are crucial for brain trophism and development, and are interlinked: myelination and iron homeostasis. Myelin not only insulates neural axons from each other but also segregates Na^+ ion channels at the node of Ranvier to make more energy-efficient salutatory conduction by axon possible. About 50 axons are myelinated by one oligodendrocytes. Myelination is a regulated process and is under neural control with major role of astrocytes and microglia as evident from various conditions when myelin formation is impaired or there is destruction of myelin [17]. Proliferation of OPC, which constitute about 5-8% of all CNS cells, their migration, differentiation and finally myelin synthesis are all molecularly linked with astrocytes and microglia. Iron is part of coenzymes engaged in myelin synthesis [18]. Oligodendroglia is richest cell in iron within the brain. The stainable iron in white matter is much more than in grey matter. In the crucial process of myelin synthesis, there are mechanisms of iron redistribution between all four cells and to see that iron is not in the free injurious form (iron homeostasis). Oligodendrocytes are the most vulnerable cell of CNS, because of its extremely high metabolic rate and a stupendous endoplasmic reticular activity for protein folding (it produces myelin membranes 100 times of its body weight!), rich iron content, reactive oxygen species and inadequate glutathione content. Astrocyte and microglia act protectively in all such difficult situations of oligodendrocytes. Besides other modes, cross talk between them via exosomes has also been suggested [19]. Another valuable ingredient for developing systems science of the brain is astrocyte-neuron phospholipid transfer. Astrocytes are considered as lipid-provider to the neuron. Neuron-phospholipid is crucial in organelle membrane, synaptic vesicles [20] and for the membranes wall of mechanoreceptor [21]. There is gradation or degree of saturation of phospholipids across different organelle membrane [22], most polyunsaturated phospholipids are in the synaptic vesicles while least unsaturated ones are on the cell membrane. A trade off is seen at the endoplasmic reticulum; a misbalance of saturation/unsaturation of phospholipids may contribute to endoplasmic stress in a highly synthetic neuron and so also in myelin producing oligodendrocytes. Phospholipids liquid crystalline matrix offers the support for non-enzymatic polymerization of mononucleotide. This compelling fact has suggested even prior existence of a lipid world preceding the RNA world in the issue of origin of life [23]. For utilization inside the brain, C22:6-n3 fatty acid synthesized from linolenic acid (an essential fatty acid) is transported across BBB by the transporter Mbsd2a [24]. Astrocyte guarding the BBB brings lipids to the neuron. Experimental model for this statement exist as SCAP mutant mouse in which SREBP cleavage-activating protein has been deleted by cre/lox technology. The mouse develops microcephaly, with a number of gemistocytic astrocytes (heavily loaded with dysfunctional mitochondria and without mitochondrial synapses) but without any alteration of their survival. Diet selectively rich in certain lipids can ameliorate neurological deficits caused by defective lipid metabolism in astrocytes [25]. Relating microcephaly with failure of lipid delivery to neuron is an astonishing journey from 'genome-to-phenome'!

Interlinked Evolution: Throughout evolution, neurons

and astrocytes are closely connected. While cognitive role of astrocyte can be traced back to C.elegans [26], its dual role in blood flow and synaptic control are seen in vertebrates [27]. The role of astrocyte in information processing within the brain became more evident in primates. Astrocyte-neuron ratio has been linked to the development of complexity of the brain. Banaclocha [28] has pointed out that one astrocyte serves twenty five neurons in leech, six neurons in C.elegans and three neurons in mouse/rat brain. While in mouse approximately 65% of brain cells are glia and in human brain they constitute 90% of cells, in elephant's brain they are 97% [2]. The estimate leaves room for speculation on their functional implications.

Besides protoplasmic astrocytes there are four more varieties of astrocytes three of which are most abundant in the cerebral cortex. There are inter-laminar astrocytes whose processes traverse through several layers of six-layered laminar cortex, polar astrocyte occupying the cortex at the grey-white junction, fibrous astrocytes in the white matter, and varicose projection astrocyte (VPA), which is supposed to be human characteristic. The domain occupied by one astrocyte is not as small as was thought earlier. One astrocyte can span the entire width of a hemisphere extending from periventricular to subpial region. In hippocampal region, astrocytes compartmentalize many sub-areas, each compartment being a domain of one astrocyte [29]. In cerebellum, the radial astrocyte related to Purkinje cell is also called Bregmann glia. The complexity of astrocyte population and their connectivity contributes to specifics and distinction of the human brain [30,31].

An additional feature in human brain organization, which gives the human brain the faculty of language and social cognition [32], is its specific neuropil protein, the astrocyte-derived thrombospondin, which regulates dendritic arborization and synaptogenesis [33,34]. As compared to chimpanzee and macaque, the human cerebral cortex expresses six times more m-RNA for thrombospondin. Thrombospondins have also been reported to have role in functional recovery after cerebrovascular accident [35].

Metabolic Partnership: While the brain constitutes only 2% of body mass, it consumes 10% of cardiac output and utilizes 20% of the energy consumed by the whole organism [36]. In 1890, Roy and Sherrington proposed, "… the brains possess an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity" [37]. What is responsible for this coordination was not known at that time. This has become clearer now that astrocytes perform this function and also participates metabolically with neurons to manage its 'finance'. Astrocytic foot processes guard the blood-brain barrier and regulate the flow of oxygen, glucose and other nutrients such as lipids from the blood to the neurons [38-40] in one hand and prevent entry of many other chemicals available in the blood to interact with neurons. The former property has been used in designing the techniques like PET [41] and fNMR, ^{13}C NMR spectroscopy [42]. Astrocyte regulates neurovascular-metabolic coupling as well as synaptic transmission [43,44]. Following an excitation impulse when neurons release CO_2, K^+ and NH_3, the glial cells, in analogy of a housekeeper, clean the floor. Released K^+ is swiftly removed by astroglia in a regulated way (ion homeostasis) to modulate the duration and strength of firing by neuron. CO_2 is taken care of by both astrocytes and oligodendrocytes. NH_3 is mopped up by released/intra-glia glutamate (glutamate-glutamine shuttle) converting it into innocuous glutamine (neurotransmitter clearance). This mechanism restricts glutamate accumulation and thereby prevents tonic activation of receptors and excitotoxicity. About 90% of cortical synapses use glutamate as neurotransmitter [45]. Glutamate has been demonstrated to induce Ca^{++}- wave in astrocyte culture [46]. In addition to this glutamate-glutamine shuttle, there exist malate-aspartate shuttle and 'lactate-shuttle' [47] between astrocyte and neurons. Metabolically active astroglia produces more than sufficient lactate, which diffuses out and nurses the neurons. This reminds us of the similar situation like lactate being used by myocyte in Cori's cycle, as well as by the testis. Further, astrocytes are cells, which generate so much ATP within, that the excess ATP and its metabolite adenosine (a purine) are released ('gliotransmitter') in intercellular space. ATP works as extracellular signaling molecule between neuron and glia [48]. Adenosine works through purinergic receptors on neurons (therefore altering neuronal function), on oligodendroglia (therefore influencing myelin formation), and on microglia (therefore altering immune function). ATPs feed neurons and other glia and even work on the blood vessel wall (vasoconstriction). Beside adenosine, ATP and glutamate [29], the other important gliotransmitters are prostaglandins and D-serine (the target of which is NMDA receptors) [49,50]. NMDA is involved in synaptic transmission, excitotoxicity and synaptic plasticity. From the facts cited above it becomes clear that "Astrocytes put down the broom and pick up the Baton" [51]. Jeffrey, S. Diamond [52] commented on this insight in the same issue of the journal *Cell*. ATP has been recognized as a ubiquitous gliotransmitter integrating neuron-glial networks [53]. Astrocyte is the only cell in the body so far recognized which in healthy condition releases its "cash' energy, ATP, in substantial amount for the utility of other cells such as neurons.

Microglia: Foot soldier for integrated systems science of defense: Robertson (1900) and Nissl (1898) first reported about microglia and it was Pio del Rio-Hortega (1919), 'the father of microglia', who demonstrated microglia by silver stain inside the brain. There is a general consensus that the cells from myeloid monocyte lineage invade the brain parenchyma during embryonic hemopoiesis from yolk sac and become the resident microglia of CNS. Fetal hemopoiesis from liver or bone marrow hemopoiesis later did not contribute to microglial population because of development of BBB by that time. A recent review [54] highlights several characteristics of microglia. They are 'captive', extremely long-lived, self-replicating and responsible for maintaining their own territory having connections more with neurons, astrocytes and oligodendroglia rather than other microglia. They have signal connections with gut microbiota (embryonic connection with gut!), which might make 'thinking from the gut' [55] easier. The term, "psychobiotics" has been coined to describe an emerging class of probiotics of relevance to psychiatry [56]. Since embryonic life and in adulthood, the microglial cells are involved in synaptic pruning, modeling and re-modeling the synaptic architecture and seem essential for development and maintenance of the neural fabrics of mind. Microglias modulate dopaminergic neurons in

the forebrain wiring [57] and selective depletion of microglia in the formative stage can lead to neuropsychiatric problems. Microglia is rarely resting, and even in non-migratory phase senses the environment through its sensors, ramified processes, and maintains homeostasis by clearing debris. When activated, usually immunologically, it transforms into amoeboid microglia, which is more phagocytic and can wander a little in specified direction.

Fractalkine (FKN), a chemokine is expressed on neuronal cell. Its receptor, CX_3CR1, is expressed in microglia. Neuron-microglia crosstalk through FKN-CX_3CR1 pair has been implicated in health and disease [58]. In health, this interaction starts from invasion of nervous system, architectural modulation of synapses and regulation of synaptic density and therefore in the process of memory storage and learning. This interaction is active in disease condition such as multiple sclerosis and Alzheimer's disease. Expression of FKN in astrocytes opens up crosstalk between astrocyte, microglia and neuron.

Microglias secrete neurotrophic factors (BDNF) affecting neural growth, functions and regeneration (as shown in Facial nerve axotomy model [59]). Also, being responsible for iron storage and turnover of iron inside the brain (iron homeostasis), they might play a crucial role in generating iron-containing granules (Nissle granule) in the neurons. Microglia is the only cell of CNS, which has all the enzymes for quinolic acid synthesis [60]. Quinolic acid is NMDA receptor agonist (in contrast to kynuric acid which is antagonist) in the synapses. It has a protective role against oxidative stress.

During infection of CNS, the microglia defends the system like any other macrophage of the body by secretion of pro-inflammatory cytokines, metallo-proteases, some factors of complement system and reactive oxygen species intermediates and reactive nitrogen species intermediates. Astrocyte-derived GDNF plays as a potent inhibitor [61] of microglial activation. When there is no such inhibition there may be collateral damage to other glias and neurons during such battle. The property like neuron-phagia and glia-phagia is observed by activated amoeboid microglia.

When metalloproteases released from microglia break down the integrity of BBB and allows the inflow of other systemic immune cells like T- and B-lymphocytes, the battle cry within the brain is converted into war! The co-operation between local and the systemic immune orchestra in defense system begins, the details of which is yet to be explored for obtaining a clearer picture on how from the level of foot soldiers microglia matures in management of defense. Microglias are themselves infected by the HIV-I virus (through receptors CCR3, CCR5, CXCR4) and are incapacitated to execute their defensive function. Rock et al has published an extensive review relating different CNS infection and microglial functions [62].

Failed systems explains Disease: Myelin is more than insulation [63].We all know of demyelinating and dysmyelinating disorders, primary or secondary, either because of oligodendroglial destruction or their malfunction, or because of expression of myelin inhibitory molecules. This kind of primary glial disorder damages the functioning neurons and cripples the patient as seen in multiple sclerosis. Oligodendrocytes have been recently implicated in schizophrenia [64] where prefrontal cortex suffers from reduced myelin content resulting from some defects in the regulation of genes directly involved in myelin formation. In Alexander's disease, which is also a demyelinating disorder, surprisingly there is involvement of astroglia. The gene encoding GFAP (a molecular marker of astrocyte) in astrocyte is mutated and the altered product attacks the myelin integrity [65].

Further, some of the dominantly inherited diseases of the nervous system which were hither-to known as primary neurodegenerative disorders like Parkinson's disease, Huntington's Chorea, Spinocerebellar ataxia, Amyotrophic lateral sclerosis etc. could have their origin in glial cells [29,66-68]. The mutant protein involved in this disease may act as detrimental substance to both neurons and glia resulting in severe strain leading to failure of glia-neuron partnership. Neurons and glias are equal victims of the toxic substance and oxidative stress, which accentuates visible neuronal damage in AD. Neurofibrillary tangle, the plaque, which is considered as histopatholgoical hallmark of AD has also been demonstrated inside astrocytes! The cytoskeleton crumbles into plaque in both neurons and astrocytes, perhaps from a common cause and thereby resulting in breakdown of neuron-glia partnership. Long back in 1992, Buee et al [69] have reported possible role of neuropil thrombospondins in formation of both senile and Alzheimer's plaque. Tau-protein has been demonstrated in neurons, astrocytes and oligodendrocytes in culture. This taupathy, involving both astrocytes and oligodendrocytes, is characteristic of Agyrophilic grain disease (AGD) and Pick's disease [70]. In mouse model, reactive microglial cells have been shown to drive tau pathology and contribute to the spreading of pathological tau within the brain [71]. Histopathologic hallmark of multiple system atrophy (MSA) is reported to be a round or crescent shaped glial cytoplasmic inclusion (GCI) [72]. Substantia nigra par compact of the brain has the lowest density of astrocyte and highest density of microglia. In pathogenesis of Parkinson's disease, astrocytes behave as 'good' protective glia to nigral neuons. Microglia, on the other hand, acts as a 'bad' destructive glia and the role of oligodendroglia remains puzzling like that of a 'mysterious' glia, altering resistance to degeneration of poorly myelinated fibers in nigro-strial pathway [73,74]. Further, astrocytes are said to be the first cells of CNS where Prion-protein replicates and produces neurotoxic PrP106-126, which damages the neurons [75]. Activation of P2X4 inotropic ATP receptor and p38, MAPK in the microglia around dorsal horn of spinal cord has been reported to be the cause of chronic pain following nerve injury [76].

"All vertebrates started out with a glial blood-brain barrier" [27]. Astrocytic foot processes are integral component of BBB. That this BBB is compromised during stress in immobilized rats was first shown by Sharma et al [77] in 1981. In 1996, Friedman et al [78] reported that pyridostigmine penetrates through BBB, enhances neural excitation and induces transcriptional response. Corticotrophin releasing hormone (CRH), which is abundant in stress, is directly implicated in breakdown of BBB and antalarmin (CRH receptor antagonist) can prevent such breakdown [79]. The condition of stress affects all kinds of cells and the neurons and glias are no exception. Taking all such views into account a hypothesis has been put forward by Shalev et al

[80] and strengthened by subsequent publications [81,82] that the breach of *BBB* is the gateway to psychiatric disorders like disturbed cognition, fluctuation of mood and abnormal behavior. The role of astrocyte is most crucial in this scenario. A reactive astrocyte, a sick astrocyte, a transformed astrocyte is not able to maintain the integrity of BBB when the substance which are normally prohibited to penetrate the brain gets a free rush to the neural tissue. S100B protein is upregulated by astrocyte in stress and its presence in serum is a marker for compromised BBB. In an immunomorphometric study S100B protein has been demonstrated to be elevated inside astrocyte in cases of paranoid schizophrenia as compared to residual schizophrenia [83]. Elevated level of S100B in blood is also found when an unconscious patient regains consciousness during recovery from cardiac arrest [84], a condition of extreme stress.

The role of astrocyte dysfunction in induction of addiction has been brought to the notice of the researchers recently. That deficient gliotransmission can influence cocaine-related behavior in mice has been reported in psychopharmacology [85]. Impaired glutamate homeostasis has been noted in astrocytic dysfunction, which has some kind of causal relationship with development of subsequent addiction [86]. Glia and neurons have been 'blemished' as partner [87] in drug addiction. Addiction to drugs or similar substance has been explained by modified synaptic potentiation and plasticity where there is definitive role of microglia and astroglia.

PART - II, Section A

INFORMATION CHANNELING: SYSTEMS BIOPHYSICS AND INFORMATICS OF GLIA-NEURON: The discipline of systems neuroscience encompasses identification of cognitive units, their specific organization in different anatomical locations (e.g. in cerebral cortex, thalamus, cerebellum etc.) and their mode of interaction. The concept of 'connectome', which in the brain represents a complete map of geographical and functional connectivity, remains incomplete without inclusion of the role of glial cells both in single synapse as well as in circuits [88]. Both neurons and glia, although, have similar voltage-sensitive ion channels and similar kind of receptors for neuro-transmitters with long range communication systems, glial cells lacks the membrane properties that characterizes specifically the neurons [29]. That is why neurons fire by means of action potential! Glial cells do not! Astrocyte is highly permeable to K^+. Its K^+-equilibrium is extremely stable and therefore it is electrically cold! However, both neurons and glia participate in information channeling as a mosaic system inside the brain. The roles of different glia are described below.

Microglia has minimal direct role in this communication system. However, in active state, microglia releases inflammatory cytokines, which seriously interfere with communication network locally and/or globally. Activated microglia also participates in structural renovation and in remodeling of synapse and establishing new connection.

Oligodendrocytes form myelin sheath for the axons. Myelin sheath makes the conduction much faster (thus evolutionarily reducing the size of the brain in proportion to body) and insulates the conduction from the surrounding cells. At the periphery, Schwann cell takes up the task of both oligodendrocytes and astrocytes. Schwann cell makes myelin for the peripheral nerves. The terminal Schwann cell also ensheathes the junction of motor neuron with the target organ (e.g. muscle) and thus enabling them to participate in the junctional activities.

The study of Kang et al [89] first demonstrated that astroglias have direct role in synaptic transmission. Astrocyte has stem processes with secondary and tertiary branching, ending in branchlets and then leaflets, which contact synapses. Regarding the number of astrocytes, astrocyte territory and number of synaptic contacts, there is regional variation. Astrocytes listen to and talk to inter-neuronal synapse [90]. Neurons are interconnected by these astrocytes [91]. Astrocytes coordinate synaptic networks [92,93]. Astrocytes look after the details of firing by neuron so that this does not become directionless or misdirected, but remains sustained as desired and reinforced or weakened as required for appropriate duration of time. How? Most likely by differential elimination of K^+ ion from the milieu, differential mopping up of glutamate and adding in the synapse other neuromodulating molecules. In short, astrocyte's role is to minimize chaos and facilitate information transmission in a way that all stakeholders can access the desired information with evolution of time! Where the possibility of misfiring, directionless firing or ill-timed or ill-sustained firing by neuron is very low e.g. in a monosynaptic reflex pathway or in a peripheral ganglion, astrocytes remain irrelevant. The same is true for the 'mini brain' inside the wall of gastro-intestinal tract where cognitive function operates at very low level since there is no requirement of complex discrimination, judgment and decision making faculty. Even in the cerebellar cortex where neurons greatly outnumber astrocytes there is no overarching cognition and consciousness, as we understand these processes in the context of the brain. To make cognition effective, unidirectional and optimally sustained, astrocytes are relevant for neurons. That is why the retina, the end organ receptor for vision, contains not only neurons but also Müller glia and astrocytes to facilitate perhaps discrimination of bandwidth of light received. Organ of Corti in Cochlea also has supporting glia probably for the same reason.

Systems of Neuron-neuron-glia-neuron Communication Network: Connectivity is the power. The systems of networking and information exchange amongst brain cells is the most fascinating, most complicated, most weird and is envy to all communication technologists! Communication involves channelization of information between two or more communicators. Information transmission and communication amongst multiple participants requires different networks. The networking in the brain is an example of multirelational intentional networking. What do we mean by this? The closest analogy could be cited as the relationship of the Director of a Medical Institute who has to maintain intentional relation with Government, funding agencies, his own Faculty, students, residents, nursing and technical staff and other employees. Nature and purpose of communication is different in different network, so also the communication speed. Following paragraphs deal with local and global informational networks within the brain.

Four kinds of Communication Networks: There are four kinds of information channeling within the brain.

1. Neuron-neuron networking through synapses

Neurons communicate with neurons through synapses. One neuron communicates with about 5000-10,000 other neurons. Therefore the number of synapses in the brain is about 500-1000 trillions. Neuro-neuronal network is the most extensive network in the brain.

2. Astrocyte-Neuron communications: three ways

Astrocytes communicate with neurons both at the level of synaptic transmission and at the level of axonal conduction at the node of Ranvier. Besides, there are communications through astrocyte-neuron gap junctions.

Astrocytic process wraps up synaptic cleft. For this reason the synaptic transmission is often called tripartite transmission [94-97]. In human cerebral cortex, one astrocyte is said to modulate approximately two million synapses [30]! Because of the ability of "sensing of neuronal activity by astrocyte" [30], there is reuptake of released neurotransmitters at the synaptic gap. There is also release of various glia-transmitters at the synaptic junction like glutamate, Ca^{++}, ATP and D-serine. Through these wrapping astrocytic processes in the synapse there is cross talk between pre-synaptic and post-synaptic neurons. There is also release of neuro-transmitters-binding protein by astrocyte [98], which regulates their concentration at the synapses.

Neuron-glia interaction at the node of Ranvier is essential for rapid impulse conduction. However, it seems like a chicken-egg paradox whether neuron determines the nodal structure and its function or is it glia, which has been primarily involved in this [29] interaction! Either way, this highlights their dynamic partnership.

In addition to existence of tripartite synapses, astrocytes have been reported to have communication with neurons through gap-junction. This has been detected in in-vitro cell culture system as well as in vivo, in the region of locus ceruleans of medulla [99].

3. Astrocyte-astrocyte communication: two paths

This important but slow-signaling communication between astrocyte and astrocyte happens through intercellular propagation of Ca^{++} waves. This occurs in two ways.

(a) It happens through gap junctions between astrocytes, which also allow diffusion of inositol triphosphate (IP_3). Astrocyte's microdomain (subcellular region) has also been identified which is involved in this Ca^{++}-wave transmission and Ca^{++} release by astrocytes.

(b) It occurs extracellularly through ATP molecules, since Ca^{++} can jump a cell-free lane not exceeding 120 cu. mm. [100]. As neurons carry the electrical impulse, so the astroglial network coordinates several neurons through this 'calcium waves' [101] across astrocytic 'syncitium' [102] or astrocytic 'network' [103]. In average, one protoplasmic astrocyte sends forty processes radially and symmetrically in all directions [30].

Neuron-Glia synapses : Evidence has been accumulating in favor of existence of neuron-glia electrogenic synapse [104]. This is true for both astrocytes and oligodendrocytes. Neurotransmitters are released not only at synapses but also from the non-synaptic region of neurons. The purpose of such neuron-glia synaptic communication is information sharing, information interaction and trophic function e.g. myelin formation [105]. Beside neurotransmitters, there are neuron-glia communications through cell-adhesion molecules (e.g. MAG and myelin protein NOGO).

Nature and purpose of the Communication: While neurons in the cerebral cortex act in a modular fashion, the glial cells make it intermodular and global. Communication speed also varies from network to network. While inter-neuronal communication speed is in meters/sec., glial communication occurs in the scale of micrometer/sec. Generally, astrocyte functions as slow neuromodulator but covers a large distance.

In the extensive neuro-neuronal network there are feedback positive, feed back negative, feed forward positive and feed forward negative signaling at different junctions which are essentially non-linear and therefore complex and have tendency to become chaotic.

The signals from neurons to astrocytes are meant for a widespread co-ordination of information across several regions of the brain, which, in addition, influences in the long run, glial proliferation or decay, differentiation and myelination

Glial signals direct migration of neurons, axonal growth, dendritic arborization and synaptogenesis. The signal from astrocytes to synapses is engaged in approval (go-ahead), holding back (veto), making it fast or sustained, offering strength or potentiation of on-going function and prevention of precipitation of chaos. In the long run there is either depression or long-term synaptic potentiation (LTP) leading to memory and learning. Even long term potentiation of synaptic function is associated with astroglial health and function. The process of LTP of synapses necessitates astroglial health and the function is associated with increased motility of astroglial leaflets followed by a stability period [106].

Widespread global communication from astrocytes to neurons has two outstanding examples where one group of regional astrocytes has been influencing global brain functions. (i) Astrocytes are supposed to be the probable source of endogenous benzodiazepines-like substance [107] in thalamic reticular nuclei (nRT), and their function is relevant in inducing sleep, allaying anxiety and controlling seizure. (ii) The highly pH-sensitive astrocytes in medulla are the source of ATP signaling to neurons of retrotrapezoid nucleus (RTN) during central chemoreception sensing hypercapnoea [108] and therefore actively involved in the control of breathing through pH-dependant release of ATP.

Information hubs: Different macro- and microcircuits in the brain are manned by physiologically diverse group of astrocytes. In a recent review on diversity of astrocyte function, Khakh and Sofroniew [109], quoting several original researchers, describe seven types of Ca^{++} signaling by a single astrocyte associated with diverse functions.

At the grosser level, there are seven types of cellular cognitive networks in the brain; (i) neuron-neuron networks, (ii) neuron-astrocyte synapses, (iii) astrocyte-astrocyte networks, (iv) astrocyte-astrocyte syncitium, (v) astrocyte-neuron gap

junctions, (vi) astrocyte modulating neuro-neuronal tripartite synapses and (vii) astrocyte modulating nerve conduction at the node of Ranvier. These networks are most abundant in the cerebral cortex but present throughout the brain. Astrocyte-neuron gap junctions are numerous in the upper brainstem/mesodiencephalic region of the brain, the region that is absolutely essential for maintenance of conscious states of the brain.

Pereira (Jr.) and Furlan [110] propose a 'local hub' of information dominated by one local astrocyte and its processes. Also there is a 'master hub' of information, which encompasses a large number of astrocytic domains, which often connect neurons across the two cerebral hemispheres. They also point out that this great communication network could be connected with various morphologic types of astrocytes as mentioned in the work of Oberheim et al. [30]. As mentioned, neuronal discharge is mostly modular, astrocytic network is more widespread and global. Information confined to small simple circuits becomes gradually available to large and complex circuits and eventually gets incorporated in reference to a larger context to determine the final output from the brain.

Astrocytes and Behavior: When astrocytes maintain the BBB, make neural synapses tripartite, participate in ion-homeostasis and have metabolic shuttles with neurons, express receptor for neurotransmitters and secrete gliotransmitters, it is likely that evidence will emerge that neuron-astrocyte networks have a formidable role in behavior of the subject. A recent publication [111] reviews the role of astrocytes in rodent model in four domains of behavior, starting from sensory processing and motor response to the behavior at the level of cognition and emotion. The review cites a number of papers with molecular evidence of the role of astrocyte in depression in rats, motor coordination, in basic sensory function and perception of pain.

In elephant, 97% of cell population of the brain is astrocytes. K^+ equilibrium in astrocyte is extremely stable and that is the reason why astrocytes are electrophysiologically cool! Astrocytes are required where a lot of 'thinking' is going on! Ca^{++} waves in extensive astrocytic network are related to operation of mind. Astrocyte circuits are involved in storage of memory. Could it be the reasons why the elephant is temperamentally so cool-headed, wise and behaves as a thinking animal with stupendous memory! The area remains fertile for the study of comparative histology of the brain in different animals and correlation with their behavior.

Fall-out for the Systems Neuroscience: In the light of the revelations on these neuron-neuron-astrocyte-neuron circuits, traditional description of nervous systems as systems geography is required to be looked into from the viewpoints of systems sociology of cells with deliverance of systems governance, which is reflected in the behavior of the subject.

We have seen while considering the events like metabolic shuttles, ion homeostasis and neurotransmitter clearance it appears in tier/nest I, that the glia-neuron metabolomics, proteomics and genomics together form almost a 'single in double' systems in such a way that they appear as one in two, or two in one. Besides having a common origin, one cell quenches its thirst when the other drinks. One pumps out ions or neurotransmitters and the other readily mops it up! One sends nutrients before the other feels hungry! The nest/tier II covers systems biophysics and informatics of these cells. The operation covers the vast signaling networks, information transfer, computation, analysis of information and production of informational memory etc. This developing frontier has started including computational neuroscience and mathematics. The glia-neuron mosaic in this tier is much more strong although might be less visible as compared to tier I. In this tier II, one cell's signal carries meaning for the other and vice versa. There is a tacit understanding between the two kinds of cells leading to silent collective conclusion. One's thought is the basis of other's action! The relevant points of astrocyte-neuron partnership have been summarized in Figure 1.

PART - II, Section B

TIERS II & III: ASTROYTE - NEURON MOSAIC IN SUPPORTING COGNITIVE AND CONSCIOUS STATES: Consciousness is the final frontier in the science of the brain. "Consciousness is the guarantor of all we hold to be human and precious. Its permanent loss is considered equivalent to death, even if the body persists in its vital signs" [112]. Consciousness, simply, is what looks after and is in-charge of what all have been going on in mind self and life! The question remains, can the phenomenon of consciousness (if it were a phenomenon!) be explained by contemporary theories of consciousness? The present section deals with this issue, picks up theories relevant to the goal of this review and steer clears the path for Part III.

The Network Theory: There are several variants of network theories, the essence of all of which is emergence of consciousness from neural networking. The detail discussion on this is outside the scope of this review. The network constituted by only neurons, howsoever complex its nature and character might be, fails to explain this phenomenon as evident from the several results of experimental neural network. Glias are absolutely necessary to complete such network [91]. The network, now we know, is that of Neuron-Neuron-Astrocyte-Neuron. We concentrate on some areas, which seem relevant from the perspectives of systems neuroscience and systems psychology.

AC/DC Magnetic Fields and Consciousness protectorate: Banaclocha [28] has emphasized that while steady state (DC) magnetic field is the result of astrocytic network, time-varying (AC) magnetic field is the product of neural network. Astrocytic magnetic field has also been implicated in storage of memory as preservation of content of consciousness. Also, this would be interesting to know how the magnetic field generated by glia can influence the techniques like NMR and magneto encephalography and the vice versa. Alfredo Pereira (Jr.) [113], inspired by the architecture of a large scale ion trap quantum computer [114] proposed a mechanism for consciousness where calcium ions trapped within astrocyte is surrounded by electrical fields of neural circuitry creating a quantum protectorate-like situation. The proposition of consciousness-protectorate intends to verify consciousness within the verifiable scale of nature. The proposal merits attention for further research since disturbed calcium wave within astrocytes has been implicated in temporary loss of consciousness in epileptic seizure [96], in concussion of brain [115] and even during administration of general anesthesia [116].

Role of Astrocytes in Dream and Sleep: Like many other

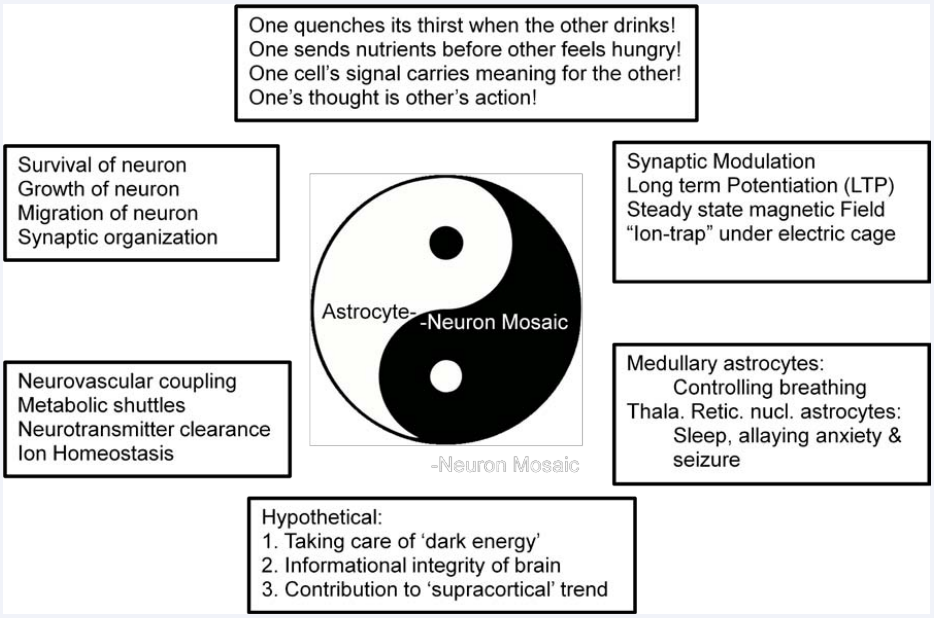

Figure 1 Functions of Astrocyte in the Glia-Neuron mosaic.

animals human beings regularly go through three states of consciousness; wakefulness, dreamy sleep and dreamless sleep. Do glial cell have any role in sleep and dream? Accumulated evidence suggests in favor of affirmation. Bernhard J. Mitterauer [117] has posted his article in the net titled, "Do glia play a comparable role in dream states and schizophrenic delusions?" Robertson has commented on this page, "This would be a very interesting experiment to perform…..Neuro-glial interactions occur during slow-wave sleep." Further, Petit et al [118] have identified a circadian rhythm in expression of m-RNA of protein targeting to glycogen in astrocytes, which gets reversed during deprivation of sleep. We have already mentioned about endogenous benzodiazepine production by astrocytes in thalamic reticular nuclei [107].

Hard-ware-Soft-ware Metaphor: While the brain's vast neuron-neuron-astrocyte-neuron network, in the metaphor of computer acts as 'hardware' (unlike material hardware, this network consists of a live-hardware) and the mind as software, in the advanced science of these non-localizable entities such as mind and self etc., mind might be considered the hardware and consciousness remains the ultimate software!

The role of the hardware in communication cannot be underestimated in the glamour of software, which is engaged with signal/information. The problems in the hardware affect operation of both mind and consciousness. Extensive neuron loss reduces synaptic density and concurrent impaired astrocytic activity deprives the patient's function of 'mind' resulting in dementia, Alzheimer's disease. Memory is an important content of consciousness and astrocytes have been implicated in storage of memory [119]. Conditions and disease affecting astrocytes lead to memory loss. External agents, like LSD, which seriously interfere with neurotransmitters and/or glia-transmitters, leads to altered states of consciousness. Compromised blood-brain-barrier due to sick astrocyte explains fluctuation of mood, development of stress-related irrational behavior and depression. Microglial destruction by HIV virus contributes to loss of mental function in neuro-AIDS. Thrombospondin secreted by glia [120] determines the complexity of the neuropil in human brain, which is characterized by its language function and social cognition (theory of mind) [121].That glia are involved also in feelings is also supported by the fact that astrocytic and microglial network has been used to explain persistence of feelings of chronic pain long after the disappearance of the organic disease process [76].

Astrocytes are proposed to handle "dark" energy generated from information-split: The author has a proposition that the glial cells manage the "dark" energy within the brain [122,123]. The source of dark energy inside the brain is information itself. Mind is extremely fertile to be impregnated by information. Mind splits information to generate 'form'/ signal (form is a space-time structure, signal is frequency, space per unit time), and releases energy, which being unobservable, comes under category of dark energy.

Information →[Mind]→Signal (space per unit time) + dark Energy

This dark energy, if not managed appropriately, may ruin the sensitive neurons. On the other hand, dark energy can be managed only by 'life'. Here, come into play the orchestras of live glial cells, astrocytes in particular. The astrocytes 'absorb' this invisible dark energy and convert this into visible energy (Figure 2). The proposition stimulates for formulating research questions and hypothesis generation.

Circumstantial evidence for such proposition comes from a well-established fact. As referred earlier, astrocyte is the only cell in the body so far recognized which in healthy condition releases its "cash" energy, ATP, in substantial amount for the utility of other cells such as neurons. The cell which has been dealing with dark energy (unaccountable cash) can afford to donate cash

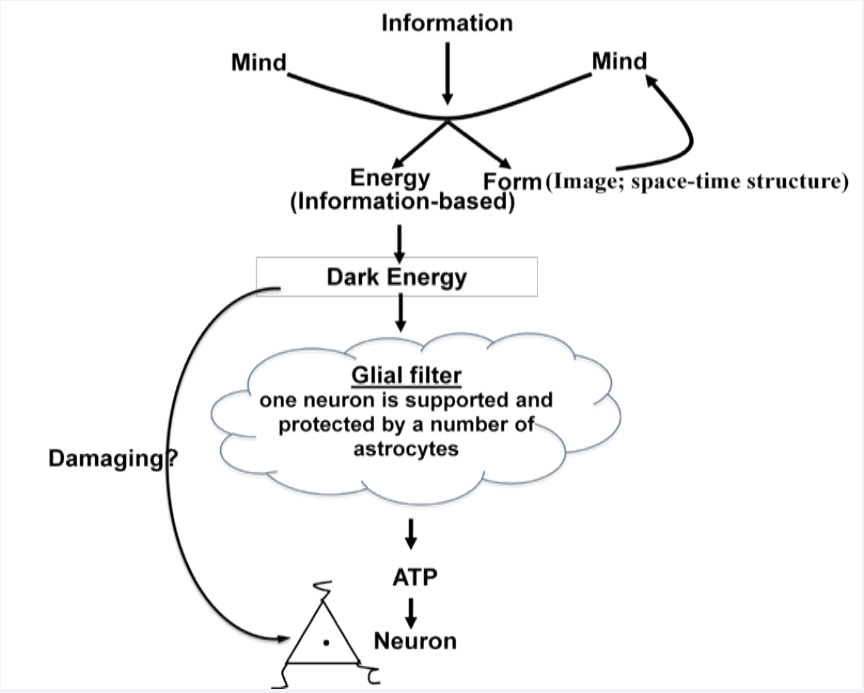

Figure 2 Astrocytic filter for protection of Neurons.

substantially to the nearby needy in accountable form, in form of ATP.

Are astrocytes responsible for informational integrity of the systems brain?: The systems brain is informationally integrated. Contrary to signal-structure transfer between two software devices by 'blue tooth' technology, transmission of 'Thoughts' from one brain to adjacent another brain normally does not happen perhaps because of healthy astrocytes guarding such transfer. There is no evidence yet in favor of this speculation. If proved true, astrocytes would be held responsible in maintaining informational integrity of the brain. This kind of transfer, at least partially, might happen in some specific conditions where such guarding has been altered (altered state of consciousness), manipulated chemically (schizophrenia), or willfully overcome (e.g, in higher states of consciousness) in between partners.

Sub-cellular Structure in supporting Consciousness: It is Stuart Hameroff [124] who first digressed from the mainstream thinking by proposing the role of microtubules of neurons as the sub-cellular structure in the context of generation of conscious state. Following his first publication in this regard in 1980s regarding anesthetic agents working on neuronal microtubules for controlled loss of consciousness during surgical anesthetic procedures, and subsequent development of his theory with Roger Penrose, he has been active since 1994 through his yearly conference, "Towards Science of Consciousness" to nurture development of a science of consciousness, where microtubules are the discussed time and again. However, Pereira, Jr. and Furlam [110] have suggested that anesthetic effect of halothane is based on the astroglial gap junctions and not on neural gap junctions. Ketamine and other NMDAR blockers interfere with this astroglial network. Hameroff [125] in 2010, although, implicated neuron-astrocyte syncitium through gap junctions in generation of consciousness, his latest (2014) formulation goes beyond this, as stated in the review of his and Penrose's Orchestrated Objective Reduction theory in *Physics of Life Reviews* [126]. The review follows an important publication by Bandopadhyay and his colleagues [127] in 2013 on vibration of microtubular protein in kilo, giga and mega hertz scale leading to wireless communication between nerve fibers through resonance bands of multiple locks in imaginary space and imaginary time.

For cell biologists, cytoskeleton is an extraordinary feat of mechanical, electrical, electronic and information engineering within biological system of cell in general and neuron and glia in particular. Non-multiplying neurons have relatively stable microtubules, which are involved in production of spindle during mitosis. The ultrastructure of microtubules is conducive for holding information. This offers a characteristic situation to neurons to be the hub of information transit. On the other hand, cytoskeleton in general is at the center of systems biology since it, through cytoskeleton-gated ion-channels, connects cell membrane (the receptor and transducer for environmental information) with other organelles of the cell, maintains connectivity between five important cellular operations at endoplasmic reticulum, Golgi apparatus, lysosome, nucleus and mitochondria at mechanical (spatiotemporal distancing and appropriating), electrical, electronic and molecular informational levels. Intercellular connectivity is achieved through cytoskeleton in two ways: (i) through gap-junctions between cells, astrocyte-astrocyte and astrocyte-neuron, and (ii) through integrin receptor family of molecules and ECM. In addition, "Microtubules have been regarded as critical structures for stable neuronal morphology because they serve as tracks for long-distance transport, provide dynamic and mechanical functions, and control local signaling events" [128].

In search of a more comprehensive mechanism for consciousness: Contemporary theories of neurocentric consciousness hold consciousness as property emerging from complex networking itself or from the dynamics in microtubules. On the other hand, many philosophical theories such as non-dual philosophy consider consciousness as more fundamental. Integrated Information Theory (IIT) of Tononi accepts conscious experience as primary and in its latest version Tononi and Koch [129] analyze the physical structure and mechanism, which can support consciousness. The theory also considers consciousness being here, there and possibly 'everywhere' including cosmos!

In both matter-based study of consciousness and consciousness-based study of matter the point that is missed is the presence of "life" in between! Every unit of life has cognitive properties. An ameba or a paramecium does not have brain but is conscious! Bacteria are small but not stupid [130]! Neurons and glial cells in the brain are alive and individually conscious!

The present author is well known for his 'against the grain' and radical view, that the brain, which includes both neurons and glial cells, or their subcellular structures such as microtubules can neither generate nor use consciousness [131]. It is consciousness, which uses the evolved infrastructures of the live-brain for its manifestation. When 'life' is missing from the brain, no network, nor any substructure of neuron can make the subject conscious! As the brain is unable to use consciousness, so consciousness has no capacity to operate on the life-less brain!

If it is so, how can we bring 'life' in constructing a theory of consciousness? 'Life' cannot be digitized! If it is non-localizable, how do we accommodate both 'life' and consciousness within systems neuroscience? The question remains, is 'life' confined within the system, on the system or outside the system? Here, the scope of speculation remains open on the existence of a third nest/tier, which interacts openly with information and signals coming from outside the living system. The dementia syndrome cannot be explained without taking their operations under consideration.

One common issue, one common thread and one common problem: To make systems science inclusive of consciousness, there is one issue, one thread and one problem! In the network theory, in the microtubular theory of Hameroff, in the IIT of Tononi and in the case of the author, the brain as an organ for manifestation of ground consciousness, the common issue is that of an infrastructure that supports consciousness or from which emerges consciousness. The common thread to climb into the next higher tier/nest seems to be 'information'. The common problem in theorizing consciousness to make it inclusive of systems science is how to go about from information to consciousness?

Infrastructure issue: For one single cell, microtubules are the best set as infrastructure. For the organ like brain as a whole, the patterns of connectivity and synapses (including astrocytes) are of primary importance for generating conscious experience (it might be for only sensory experience). According to author, the immediate infrastructure for intuitive experience is constituted by the non-synaptic spines of the apical dendrites of the cortical neurons and dendritic mat in the superficial layers of the cortex [132].

Interlinking thread: Information is the link between observable and non-observable realm of nature. Conversion of signal into information is the first step. "Information is a prime commodity, and when it is used in biological theorizing it is granted a kind of atomistic autonomy as it moves from place to place, is gathered, stored, imprinted and translated" [133]. Information is one 'entity', which has the ability to connect the nonlocal domain of nature with the local measurable domain. The present author has suggested information connects matter with mind and self, and has a multidimensional geometry looking like a trifoliate leaf [134] and therefore remains as the 'key' in maintenance of conscious state. How the trifoliate leaf like structure of active information at the level of 'abstract' imaginary plane conforms to the symmetry (?triplicate) found in live-visualization of single tubulin protein molecule by atomic scale quantum tunneling [135] and to supposedly three energy-trapping sites in a self-organizing molecule of laboratory chemical behaving like fractal [136] is yet to be seen. Moreover, no information is an island. There is information-manifold and the pattern in information manifold is relevant for conscious experience.

Information to Consciousness: From the data discussed in this essay, it seems, the final optimal geometry in information-manifold related to production of awareness and maintenance of conscious state, is determined by both neurons and astrocytes. Layered spatiotemporal geometry of electrical and magnetic fields determined by topology of different 'connectomes', supports this final optimum geometry of information-manifold from below. The connectome consists of neuron-neuron circuits, astrocyte-astrocyte syncitium and astrocyte-astrocyte networks, neuron-astrocyte synapses and astrocyte-neuron gap junctions, in a multirelational intentional network. Vibrational resonance theory of Bandopadhyay bypasses neuronal communications but leads to layered space-time metrics. How to go from this space-time metrics to consciousness? The signal in space-time metrics is a specific physical frequency, i.e., space per unit time. What converts signal into information is the real issue! It is not possible to advance further without bringing mind in the scenario.

Transformation of space-time metrics to information or vice versa, requires an outside-in and inside-out phenomenon [137], an operation executed through mind by 'self'. The mind alone is incapable of allowing this execution [138]. The issue has been discussed in details in one of author's recent publications [139]. While the capacity to acquire information is directly related to uncertainty the organism lives in, the capacity to organize information is a function of consciousness not directly, but indirectly through operations of 'life' and 'self'. Therefore, all such operations as part of systems psychology have been considered in the tier/nest III.

Do we see any formulation/circumstantial evidence that points towards 'above-the cortex' trend?: There is a developing trend in neuroscience to look at this 'consciousness' having a 'supervening' (e.g. John Searle in The Rediscovery of Mind) or super-ordinating property (e.g. World III of Eccles and Popper). The idea has many similarities with the 'transmissive' view of the brain held by William James, or the brain as a biological reducing valve, a view held by Aldous Huxley, or radio reception theory of consciousness of Henry Bergson and the

television analogy for brain function, a view held by George Wald. This view is equally powerful in the concept of consciousness protectorate from viewpoint of quantum consciousness and also of the author's view of conformational geometry of information over the cerebral cortex in a supra-cortical position! This is also much relevant when one accepts the proposal of the existence of "wireless connections" between various local classical and quantum fields in several active anatomical regions within the brain! This kind of communication could be considered as 'supracortical' and might explain connectivity in the phenomena like cross-modality perceptions (synaesthesia), hysteria and multifocal epileptic seizures.

Consider the neural density and synaptic density within the cortex and then the number of possible neuro-neuronal channels of communications, which is approximately 10^{83} in number, and thereafter add glial density in the picture and then imagine the reality of complexity of conformational facets in the information geometry at the top of the cortex. Consciousness overarching such a complexity, working over the systems could be called supracortical, a position just above the cortex but in physical touch and is in intimate contact with the cerebral cortex. Consciousness has been working from the 'top' of the systems!

While microtubular theory of consciousness by Hameroff and Penrose does not lay emphasis on cell membrane and synapses, in its extension by Bandyopadhyay and his group, the global synchronization of brain activity by cascading resonance [140] originating from single tubular protein vibration and extending in imaginary space and imaginary time has an unspoken acknowledgement of supra system location of neurocentric consciousness. Even Hameroff's and Penrose's 'protoconsciousness' is very close to supracortical consciousness in the context of the brain.

Conscious state is intimately related to delivery of a decision, motor function, action-production, - the view originally held by Roger Sperry [141] dating back 1952 and subsequently supported by other neuro- and cognitive scientists. To deliver a decision for a system in systems science, this is absolutely necessary for consciousness, the decision-maker, to remain above, 'supra' to the system. This collective and supervening consciousness of the human might have co-evolved in the course of development of our Triune brain [142], which had passed through the phase of brain-stem consciousness (manifested as awakening, alertness and orientation), limbic system consciousness (manifested in seeking pleasure and avoiding the unpleasant) and cortical consciousness (development of discrimination, judgment, decision and its execution). Awareness of this supracortical location of consciousness makes consciousness of the subject inexhaustible (within cortical limits). Behavioral expression of it is 'love'. This seems to be an evolutionary imperative for consciousness to occupy this supracortical location to have governance over the whole brain-confined consciousness. The present author coined the term and concept of supracortical consciousness in 1985 and developed the idea in his subsequent publications [143]. The argument is further supported by the results of late neurophysiologist Benjamin Libet's experiment that underpins pre-volitional events [144]. Much before the will of volition there are multiple non-recordable activities, which perhaps (?) happen in the pre-space, pre-time domain and are not initiated by the cortex or not happening within the cortex but which might direct the neurons within the cortex. How astrocytes are linked with such trend? Astrocytic signaling, although slow, is widespread and global. Production of steady state (DC) magnetic field is the result of astrocytic network. Calcium ions trapped within astrocyte are surrounded by electrical fields of neural circuitry and create a quantum protectorate-like situation.

PART - III

SYSTEMS NEUROSCIENCE, SYSTEMS PSYCHOLOGY AND CONSCIOUSNESS: We have described the astrocyte-neuron fabrics of the mind inside the brain. In this nest/tier IIII we come to the subtitle of the paper, systems neuroscience, systems psychology and consciousness. Operations in this tier/nest III are responsible for experiencing, retaining episodic memory, and performing several other complex functions which require intelligence such as differential cognition, complicated learning, discrimination, decision-making and commitment. All such are higher order functions and behaviors and some of those are evolutionarily acquired and cannot be executed merely by a congregation of neurons in absence of astrocytes in tier/nest I. The issue at hand is when the automated cell signaling system in systems biology fails to operate at the desirable level of perfection, how self is called upon for application of mind to take a conscious decision on the remedial measures. Systems neuroscience shares border with systems psychology at biological signaling systems. Systems psychology begins with conversion of signal into information by operations of mind and continues with operations of self and life under stewardship of operations of consciousness (Figure 3).

In contrast to any signal processing software, the mind-ware handles and processes information. Astrocytes, neurons and their networks are observable. Software and mind-ware are not. Their operations are understandable but not visible. Operations of software could be localized in time and space but of mind-ware not. Every cell in the body has its own signaling software as well as mind-ware. For the brain, hundred billions neurons and a far more number of astrocytes create a collective mind-ware for the *individual*. Therefore, the mind does not work alone. Mind works with the self of the individual. Every cell has an uncanny sense of self. The whole immune system works on the basis of division of non-self from self. Inside the brain, on the background of experience and memory, operations of self(s) and minds of hundred billions neurons and far more number of astrocytes create what we call intelligence, which works with a sense of 'I', 'me' and 'mine'. This sense is created because of involvement of self. Its structure may be called the intelligent ware of the brain. In fact, intelligence are of four types, according to involvement of different operations of mind, self, life and consciousness (Table 2). Besides, the astrocyte-neuron ware inside the brain is a live-ware. The signaling in software and the signaling in live-ware are automated. However unlike in software, the signaling in cells are somehow inextricably connected with operation of life. Once life-operations stop, cell signaling fails. Software signaling is obviously independent of presence or absence of any life-operation. Further, operations of mind and self are intriguingly connected with operations of life. It is this presence of life, which

opens multiple logic gates in information processing, transforms the process of integration of information, which is an arithmetic algebraic or geometric combination into an integral process. The process integral is 'feminine' in nature and is responsible for aesthetics and all creativity as mentioned above. In addition to having intelligence, which works with more than a few logic gates, the live-ware has the ability to choose options outside algorithmic pre-specifications. While ordinary software works with signals and its computation, the 'living' ware operates with information and mind. Mind-like properties in ordinary software differ from the properties of mind itself. The former cannot extract meaning out a signal. Mind can extract meaning out of information. Software in non-living entity (e.g. silicon chip) is a finite entity, works with finite energy and does not evolve. Mind, because of its connection with 'life' is not finite, almost endless, operates practically without any constrain of energy and has capacity to evolve! The basic differences between nonliving ware and live-ware are shown in Table 3.

Further, life operates on the support of consciousness. In fact, consciousness is the supporting ground for all operations as mentioned above; operations of information, operations of mind, operations of self and operations of life. If self is stated to be 'son' heir of consciousness, the 'life' could be said the 'daughter-darling' of consciousness-Mother Nature. Fecundity of mind originates from consciousness while its infidelity comes from its attachment to matter. Operation of consciousness, self and mind together are responsible for keeping the individual awake and aware of what all are happening within the systems. Presence of consciousness makes the brain a conscious ware, which can have cognition, feelings (emotion) and will. Conscious ware, like the brain, can create its own logic gate. Consciousness also restricts a situation of multiple divided 'self'. When consciousness takes a decision, it takes all stakeholders on board.

Table 2: Four different types of Intelligence.

S. No.	Categories of Intelligence	Operations involved	Alternative name
1.	Ordinary Intelligence	Mind, Self, Informational Memory	Dry Intelligence
2.	Phenomenal intelligence	Mind, Self, Episodic Memory	Moist Intelligence
3.	Emotional Intelligence	Mind, Self, Memory, Experience and Life	Juicy Intelligence
4.	Intuitive Intelligence	Consciousness, Self, Life, Mind, Memory and Experience	Crystal Intelligence

Table 3: The basic differences between nonliving ware and live-ware.

Nonliving ware	Live-ware
1. Linear causality amongst parts.	Circular causality amongst parts. Every part is connected to other parts by reciprocal cause and effect relationship.
2. Purpose is decided extrinsically. Designer is outside the system.	Purpose is intrinsically decided. Designer is inside the system
3. Not self-sufficient in energy.	Procures its own energy from the environment.
4. Modular independence is absolute.	Because of circular causality amongst modules, modular independence is not absolute.
5. Information transmission from one ware to another is not possible. Signal transmission is possible.	Information transmission from one ware to another is possible.

Software, mind-ware, intelligent ware, live-ware and conscious ware are thus five steps in systems engineering for developing a conscious ware [139]. The characteristics of different wares regarding their general properties, sensitivity and operation on number of logic gate have been shown in Table 4. The concept, as tabulated, seems relevant especially in ware construction for biological self-assembly, and 4D printing from neural stem cell [145-148].

Within the terrain extending from the neural fabrics of mind to the supporting and participating ground of consciousness, as described above, there are several operations in phases. The operations are multilayered, stratified, hierarchically nested one within the other, tortuous and labyrinthine in nature (Figure 3). The triangular relationship between self, mind and memory/ experience creates the world of 'I', me and mine. The triangular relationship between mind, information and life is observed by the self as the world of 'they', others and the nature world while at the apex, the triangular operation of consciousness, self and life create awakening and awareness and the world of Spirit! The model thus builds up a finer fabric for answering three fundamental questions raised in *Prasna Upanishad*. Who am I? What is this World? And, what is the Spirit (God)? These are often designated as three Absolutes in philosophical discourse!

From figure 3, it is evident that information as an ontological entity has no access to consciousness. Information's domain ends in the domain of mind. New information is generated by 'life'. Information-manifold in the phase of nature is identified by 'self'. All of mind, life and self have direct communication with consciousness. Mind is to be bereft of information to reach the spectrum of consciousness. Life is to transform its 'emotion' into devotion to have access to consciousness. It is self, which identifies information-manifold and manipulates its geometry to bring the intent of information on notice of consciousness. To become conscious of what all happening in mind, life and self, system-bound consciousness is to be in dynamic concurrence with system-independent consciousness. Finally, Consciousness responds through self by creating phenomenon, through 'life' by creating information and through mind by converting that information into signal.

Do we have any molecular or signal signatures of such complex operations? Author's recent publication [149] attempts to find out this. Molecular signatures of the mind-ware working inside the brain are suggested to be calcium ion channels and the Ca^{++} waves in the astrocyte-astrocyte–neuron network. Evidence for this comes from the discipline developmental psychology when the child is said to clinically conclusively have his own mind as he learns to control his sphincters, and also from the discipline of neurology, when an unconscious patient gives up his mind and starts passing urine and stool in the bed. Molecular signatures of self in cellular biology are MHC-1 molecules and ion–pumps, and when these ion pumps fail, the patient develops brain edema. Pressure (cytoskelton)-gated ion channels are sensitive

Table 4: Important characteristics of different categories of wares.

Ware	Important Properties	Number of Logic Gate	Sensitive to
Software	Processes signal	One or Two	Signal
Mind-ware	Processes information	Multiple	Information
Intelligent ware	Having decision-making ability within algorithmic–pre-specifications	Multiple	Phenomenon as well
Live-ware	Have choice outside algorithmic prespecifications	Almost unlimited	Alteration of symmetry within mind or self of the system
Conscious ware	Have 'Will'	Can create its own logic gate	Surrender of Informational properties

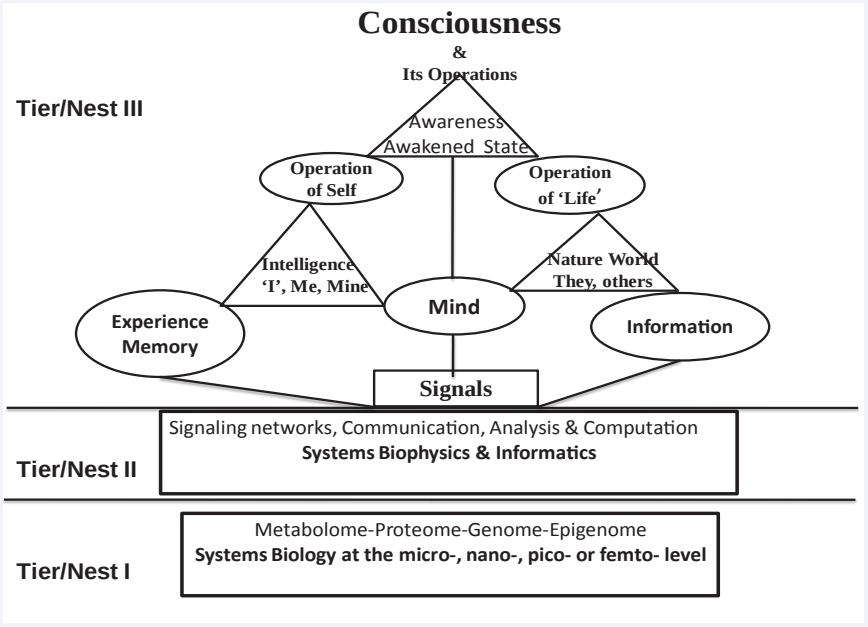

Figure 3 Hierarchically nested integrated systems science of the nervous system.

to life-operations. When 'life' fails to operate the cytoskeleton, the integrating sub-cellular structure crumbles. There is multi-organelle failure of cellular infrastructure leading to death.

The application of these molecular concepts extends in investigating various chanelopathic disorders and their interrelation with psychological and psychiatric illness. This is a fertile frontier for formulating research questions and generation of hypotheses. Signature signals for those individual operation or their joint operations are even yet to be suggested and then could be verified by live-cell imaging and nano-tracer technology.

Examples of Bottom-up and Top-down Systems Failure

Bottom-up Failure: Ordinarily, not all information necessarily reaches the level of consciousness. Three guards of different kinds of threshold are in the gateway to consciousness (Figure 4). When intentional-threshold of any information fails to conform to the concern-threshold of self and the perfection-threshold as decided by consciousness of the system, information is brought to the conscious level for scrutiny. Otherwise, information operates at subconscious level. When intentional threshold of information is not intense enough, it is also left to operate below conscious level. In a perfectly functioning systems brain, cell signaling metabolome-proteome-genome pathways, which have achieved a desirable level of perfection and satisfy the concern-threshold of self, are automated. There is no need of presence or intervention by any operation of mind or consciousness as long as those are perfectly in harmony with the whole. As soon as the perfection in communication fails, there is noise in the brain systems. This is a compelling event for the self to be called upon for application of mind. Following a conscious decision on the remedial measures for the systems, the proposed change in life-style works through the epigenetic mechanism to restore the perfection in genome-proteome-metabolome signaling.

Top-down Failure: Take the example of an unconscious patient. In unconscious patient, consciousness is non-functional within the systems brain because of necessary infrastructure cannot support its functions. However, in the early stage, mind continues to work with information as evident from the subject's control over urinary and anal sphincters. Life operations are active and that is why he is alive. Even his self-sense is functional. However, nothing is there to hold all the operations together to produce a unified effect and so a similar response. The subject

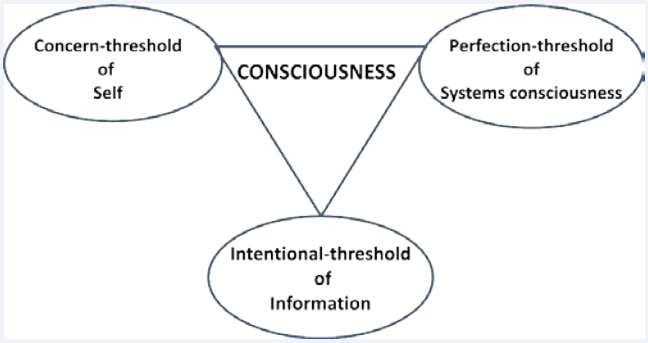

Figure 4 Three guards at the entry point of consciousness.

gradually slips into a situation when he has to be shifted for intensive care. When mind ceases to operate within unconscious patient the subject is said to be deeply unconscious. No longer there is Ca^{++} wave propagation in extensive astrocyte networks of the brain! When self also finds itself in a supportless situation, ion pumps fail. Brain edema develops the progression of which forces 'life' to stop functioning.

PART - IV

PARADIGM SHIFT, NEW PARADIGM AND REVOLUTION: The paradigm shift could be recognized in concurrence with viewing astrocytes much more than the supporting cells for neurons. When we understand that the software, mind-ware and intelligent ware working in the context of the brain are 'alive', we are in for a new paradigm. Biologists want to bring the principles and vocabulary of systems engineering model in cell signaling [150] forgetting the fact that when 'life' comes into the picture, the metaphor of 'bioengineering' requires to be replaced, as suggested by Neil Theis [151], by the metaphor of 'cultivating biology'. In a recent article, Rabinovich et al [152] have tried to conceptualize the cognitive dynamical bridge between the brain as computational device and the mind. They have recognized inhibition and winnerless competition as components of robust cognition. They opine to have a connection between sequential totality with finite capacity and prediction in the mind, without consideration of any interconnection between operation of mind, self and 'life' in the process. If we can develop the dynamical bridge between operations within software, mind-ware, intelligent ware and live-ware, we are entering the gate of a completely new paradigm.

Recognition of consciousness as the final decision-making authority is likely to bring a revolution in cognitive science. How? It would be so, because the center of Power in this scheme is not the brain but is consciousness. It is likely to dissolve several divides in science such as, left brain-right brain divide, outside-inside divide, mechanistic-vitalistic divide, intuitive-rational divide and ghost-real divide. The supracortical location of a ground consciousness, which is active and participating, signifies this revolutionary trend. Recognition of other members of the decision-making body of consciousness is the first step towards realization of this revolution.

CONCLUDING REMARKS AND PERSPECTIVES

So far the systems neuroscience has looked at the brain from anatomical point of view as systems of hind brain, mid brain and fore brain, or from evolutionary point of view as systems of reptilian, mammalian and human brain or as archi-, paleo-, and neo-brain systems. From functional point of view, systems neuroscience consists of systems of sensation and perception, cognition, emotion, decision-making and motor-execution; in short as systems of cognitive, emotional and psychomotor brain. The approach to neuropsychiatric diseases regarding their pathogenesis, classification and management has been accepted accordingly. The present paper lays down the basic foundation for developing a systems psychology and systems consciousness with operations of information, mind, self and life anchored in the systems neuroscience of the glia-neuron systems biology and systems bioinformatics.

However in deciphering the hidden operations from 'will' to signal and from signal to 'will' what required are (i) to define more clearly the individual operation of mind, self, life and consciousness, (ii) their interlinked mosaic of operations. (iii) Since all operations have been happening in phase in the domain of nature beyond Planck's scale of measurement we are to find out their footprints in nature within Planck's scale, as signature signal, signature molecule etc. (iv) Finally, we are to find out the relative importance of individual operation in respective context in delivering the final outcome of 'will' as signal.

In the model presented, one can see small-scale bottom-up connections and large-scale top-down ramifications accommodating almost all the variables within the systems framework. To understand much more of the brain-milieu, which is conducive for development of such dynamic hierarchical nested operations, what is desirable is an advancement in technology with fusion of biotechnology, nanotechnology and information technology.

Generally the talking-molecules of the brain, the neurotransmitters have been classified according to size (small molecules and large molecules), according to whether the neurotransmitter vesicle is electron-lucent or electron-dense, or according to their chemical nature like amine, amino acid, peptides, diffusible gas etc. Is it not easier now to classify different neurotransmitters as molecular signature of specific operations in the systems psyche? Such effort has far-reaching effect in interlinking various synaptopathies and mental disorders.

Reading this article, aspiring mind may ask questions, are we ready for systems engineering of developing a conscious ware? If so, what could be the steps, what could be the material to begin with, and how to go about it logically with appropriate question-weaponry?

The fall-out of publication of this article for the discipline of mental health and psychiatry is expected to be wide, ranging from the very classification of mental illness, their molecular mechanisms, and clinician's approach in managing them from systems neuroscience and systems psychology perspectives.

ACKNOWLEDGEMENTS

The author has profuse thanks for Dr Sudip Dutta, MD,

Asst. Prof. in the department, who has meticulously looked into the flow of thoughts in this review and for fruitful discussion with two other Faculty members of the department, Dr Shyam Prakash, PhD, and Dr. Gaurav Chhabra, MD, during preparation of the manuscript. Our young MD, Dr. Samanyoya Gochhait, did final check up of the write-up. The author also acknowledges the help tendered by his students Dr. Pooja Pallavi, PhD, Dr. Md. Nasim Mansoori, PhD, Dr. Rizwan Alam, PhD, and Ms. Rizwana Qadri, PhD student in organizing the references and Mrs. Pooja Taneja for secretarial assistance. The author expresses his gratitude for the inputs from the reviewers and the editor of the journal.

DECLARATION

The work was not funded by any funding agency. Ethical clearance was not required for publication of this review. It is also stated that there is no conflict of interest with anyone or any agency for publication of this paper.

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Cite this article

Mukhopadhyay AK (2015) Neural Fabrics of the Mind: Systems Neuroscience, Systems Psychology and Consciousness. Ann Psychiatry Ment Health 3(7): 1049.