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Review Article

Disruption of Neurosynaptic Physiology and Neuron Network Dysfunction in Brain Disorders: An Environmental and Occupational Health Perspective

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Abstract

Networks of signaling cascades regulate synaptic transmission and morphology. Signaling molecules and their dynamics are subject to impact of environmental insults as well as genes predisposing to disease risks. Pollutants may impact brain through cellular, molecular and inflammatory pathways, causing direct damage or predisposing to damage by other insults, leading to diseases. Disruptions in structure and function of neurotransmission elements and protein networks contribute to pathogenesis of neuropsychiatric diseases. Different affected brain regions and/or synaptic connections between excitatory and inhibitory neurons charecterise specific clinical states. Functional identification of synaptic signaling networks and specific neuronal pathways would facilitate understanding of specific pathomechanisms relevant to preventive and corrective interventions. Physiology of neural networks and pathogenesis, therapeutics and prevention of diseases arising of their disruption, specially with environmental afflictions, deserve holistic and not fragmentary understanding. Present article attempts to present such diverse information with possible coherence to emphasize necessary address in contemporary medical teaching and continuing education for young researchers. The mounting challenge of prevention and management of pollution inflicted disruption of neurophysiology associated with brain dysfunction and diseases in contemporary world may be better addressed by integrated interdisciplinary understanding of the problems.

Keywords: Environmental Neuroscience; Neurotoxicology; Neurosynaptic pathophysiology; Neuron network disorder; Neuroinflammation

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Introduction

Proper brain function is affected through complex and dynamic purposefull biochemistry. Brain physiology is vulnerable to disruption by physico-chemical insults leading to neuropsychologic dysfunction and disease. Natural and anthropogenic mix of chemicals, Particulate Matters (PM), biological materials in ambient environment pose health risks in rapidly developing countries. Pollutants may impact brain causing direct damage and/or predispose to neuro-psychiatric diseases. Nanosized particles and/or toxic compounds adsorbed on them can induce neuroinflammation, oxidative stress, glial activation and cerebrovascular damage [1]. Emerging evidence suggests that certain neurological diseases as alzheimer's disease, parkinson's disease and even cerebrovascular lesions, are associated to ambient pollution. The challenge of polluting heavy metals, pesticides, plasticizers, endocrine disruptors and variety of neurotoxicants, deserves commensurate recognition in teaching for competent address in practice of contemporary medicine.

Synapse Physiology and Disruption

Human brain consists of over 100 billion neurons, processing and transmitting information as electrical signals. Precise control of molecular and cellular mechanisms of synapse development and connectivity is crucial for normal network activity and brain function. Information in brain is stored in form of altered structure and chemistry of synapsaes involving formation of new and elimination of old synapses [2]. Neuronal communication takes place at synapses. The plasticity of synapses forms basis of learning and memory in brain. Inappropriate loss of synaptic stability may lead to disruption of neuronal circuits and brain disease. Understanding brain disorders is partly, a matter of understanding cell biological and biochemical basis of synapse function and plasticity.

Hundreds and thousands of excitatory and inhibitory synapses may be born on dendrites and cell body of single neuron. Neuronal signal processing is mediated by integrating excitatory and inhibitory synaptic inputs. Total input of all the synapses determines event of neuron firing. If reciepient (post-synaptic) neuron receives many strong inhibitory inputs, there is very low chance of action potential generation. Maintaining of balanced excitatory and inhibitory synaptic transmission (E/I balance), requires existence of precise regulatory mechanisms, therefore. Alteration in synapse E/I balance is implied in pathology of disorders as autism and schizophrenia [3,4].

Excitatory synapses are usually situated on dendritic spines and bear glutamate receptors and other components forming the Postsynaptic Density (PSD, thickening), a structure facilitating transmission of electrical signals. There are two types of glutamate recognizing post synaptic receptors. The ionotropic glutamate receptors are ligand gated ion channels. The metabotropic glutamate receptors are G protein coupled receptors. Glutamate binding to ionotropic Amino-Methyl Propionic Acid (AMPA)-type and N-Methyl-D-Aspartate (NMDA)-type receptors leads to excitatory synaptic transmission [5]. The Gamma Amino Butyric Acid (GABA) receptors provide major route for inhibitory transmission. They interact with GABA to allow influx of

negatively charged chloride ions [4]. Glutamate receptors and PSD proteins play a central role in excitatory synaptic plasticity. Intense NMDA receptor activation triggers a signaling cascade in PSD, which recruits AMPA receptors in postsynaptic membrane. This provides Long Term Potentiation (LTP) of synapse strength. The weaker, prolonged NMDA receptor activation causes removal of the AMPA receptors which results in Long Term Depression (LTD) [5]. The trafficking of synaptic AMPA receptors is thus, carefully controlled to modify synaptic strength during plasticity. Incorrect regulation of the process would hamper appropriate synaptic signaling and plasticity, contributing to brain disorders [6].

Dendritic spines are small membranous protrusions that contain postsynaptic machinery. Spines remarkably keep changing in size and shape over seconds to days time patterns [7]. Dynamic changes in spine morphology are closely linked to changes in strength of synaptic connections. Alterations in spine morphology depend on neuronal activity and glutamate receptor activation. Induction of LTP causes enlargement of spine heads, whereas activity patterns inducing LTD cause shrinkage [8]. Abnormalities in spine structure are seen in association with neurological disorders. Several genes encoding factors involved in spine structure and organization exhibit mutations in patients with brain diseases. Molecular mechanisms of spine pathology and relation between alterations in spine and cognitive deficits are of current research interest [9,10].

Glutamate is the most abundant excitatory neurotransmitter mediating 70% of synaptic transmission within nervous system. Learning and memory and drugs of abuse, induce various forms of neuronal plasticity including LTP and LTD mediated by glutamatergic transmission [11]. All drugs of abuse alter glutamate transmission via one mechanism or other. They can cause long lasting neuroadaptation of glutamatergic system in brain. These adaptations may relate to compulsive drug use, loss of volitional control over drug intake and conditioning to drug associated environmental cues or contexts. The changes in glutamate system must be fully charecterised. That may provide critical steps for therapeutic modulation.

Abnormal regulation of protein turnover, chromatin remodeling and genomic imprinting are also suggested to cause synapse pathology [12]. Failure of cellular machinery in novel upstream pathways of synapse, leads to disordered synaptic physiology and neuropsychiatric phenotypes. Small non-coding microRNAs, that repress translation of target mRNAs, contribute also to pathophysiology [13]. Many disorders of genetic determinants involving synapse dysfunction manifest in different ways and many variants may give rise to similar picture.

Nitric Oxide Mediation in Neurosynaptic and Neuron Network Function

During brain development, vast numbers of synapses are established. These undergo activity dependant refinement, which is guided by target derived signals [14]. The signals act as trophic or toxic to synapses and pre-exhisting synaptic contacts are either consolidated or lost. Adult brain is able to rewire mature neural circuits in response to environmental changes, brain damage or sensory and motor experiences. Two plastic processes synaptic remodeling and neurogenesis are involved in maturation of nervous system. Mode of their reactivation during adulthood may be relevant for therapeutic exploitation [15].

NO is unique extracellular neurotransmitter and acts as universal modulator of diverse physiological functions.These include, interneuronal communication, synaptic plasticity, emory formation, receptor functions, intracellular signal transmission, mediator release and regulation of gene expression. Endothelial eNOS and neuronal nNOS are constitutively expressed and activated by elevated intracellular calcium. Immunologic inducible iNOS is induced to express by new RNA and protein syntheses under immune stimulation. The glial cells in CNS can produce NO in response to stimulation by cytokines, via iNOS. NO activates soluble guanyl cyclase and cGMP synthesis. NO regulated guanyl cyclase has ubiquitous presence in brain and its distribution is complementary to nNOS. Goldberg et al., [16] postulated the reciprocal effects of cGMP and cAMP in controlling cellular processes, the "yin-yang" hypothesis cGMP mediates many of physiological NO actions. NO is involved in synaptogenesis during development and synaptic remodeling in adulthood. Learning, memory and restoration of lost sensorimotor functions in adult mammals require specific neuronal reorganization via communication between presynaptic and postsynaptic structures mediated by diffusible intracellular messenger NO [17].

Nitric Oxide (NO) is synthesized in activity dependant manner and would mediate synapse formation, segregate afferent inputs or cause collapse of growth cone, leading to retraction in immature neural systems. Endothelial NO affects synaptic plasticity, mitochondrial biogenesis and function of neuronal progenitor cells. NO mediates activity dependant control of intrinsic neuronal excitability through signaling targets, the ion channels, particularly voltage gated K^+ channels [18]. Such changes may serve mechanisms of synaptic plasticity across neuronal networks. Endothelial NO is key molecule linking vascular and neuronal functions in brain [19]. Genetical inactivation of endothelial NO Synthase (eNOS) causes activation of microglia and promotes a proinflammatory phenotype in brain. Diffusion of NO in to nervous system, formed by endothelial Nitric Oxide Synthase (eNOS) or/and that produced by inflammation induced Nitric Oxide Synthase (iNOS) in immune cells carries pathologic potential requiring due control. Abnormal NO signaling contributes to varied neurodegenerative disorders [20,21].

Synaptotoxic action of NO for synaptic withdrawal and prevention of synapse formation, are mediated by cGMP dependant and possibly S-nitrosylation mediated mechanisms. Neuronal nNOS or NOS1 is concomitantly upregulated with axonal injury that disconnects motoneurons and muscle causing withdrawal of synaptic inputs to motoneurons. After recovery of neuromuscular function, synaptic coverage is re-established and NOS1 is downregulated [22].

Neuronal expression of NO Synthase (NOS1) is upregulated in chronic neurodegenerative diseases and increases susceptibility to neurodegeneration. Signaling pathways of iNOS induction in glial cells and cytotoxic actions of NO on neurons are important from neurotoxicological aspect of neuro-glial interaction [23]. Chronic activation of NO/cGMP pathway suppresses TWIK-related Acid Sensitive K^+ (TASK) currents, through a Protein Kinase G (PKG) dependant mechanism. The NO/cGMP/PKG mediated modulation of TASK conductance leads to hyper excitability and sensitizes neurons to excitotoxic damage [24]. The commonest mechanism leading to neuron loss is glutamate induced excitotoxicity. Even normal levels of glutamate may become lethal with persistent enhancement of neuronal excitability [25]. In the CNS activation of NMDA type glutamatergic receptor induces Ca^{2+} dependant NOS activity and NO release. NO activates cyclo-oxygenase and lipo-oxygenase, leading to production of physiologically relevant quantities of PGE2 and leukotrienes that

cause toxic effects. Such recurrences play significant role in aging process [26]. The CNS pathology of AIDS patients resembles aging associated neurodegeneration, and is also caused by actions of iNOS.

Other signaling molecules probably work with NO. Brain Derived Neurotrophic Factor (BDNF) is a synaptotrophin synthesized and released post synaptically in an activity dependant form. BDNF protects F-actin from depolymerization by NO, thus preventing the collapse and retraction of growth cone under NO effect. Variations in NO/BDNF balance constitute a common hallmark leading to synapse loss in progression of diverse neurodegenerative diseases [27].

NO overproduction directly or indirectly promotes oxidative and nitrossative stress [28]. One of the second messenger pathways having role in learning and memory is NO/cGMP signaling cascade. This is demonstrated in studies on electrophysiological correlates of neuroplasticity i.e., the LTP and LTD phenomena in brain [29]. LTP and LTD phenomena of physiologic plasticity may transform in to pathological, consequent to disturbed equilibrium between neuroprotective and neurotoxivc effects of NO. Drug research focuses on ways to block pathologic NO production to limit neuropathology. Also ways of increasing NO availability are of interest to elicit neuroprotection [30].

Neuroinflammation

CNS can encode and retain memories, based on activity dependant forms of synaptic plasticity [31]. The nervous and immune systems are engaged in intense bi-directional communication. Upon injury, circulating immune cells infiltrate CNS, resident cells are activated and proinflammatory mediators e.g., cytokines and Nitric Oxide (NO) are produced and released [32]. The glial cells participate in CNS immune response and act as third cell element of neurosynapses [33].

Particulate Matter (PM) carries numerous biocontaminants that are capable of triggering free radical production and cytokine response. PM may irritate airway sensory nerve endings activating vanilloid receptors and causing release of neuropeptides that induce neurogenic inflammation [34]. Chronic pollutant induced epithelial and endothelial injury can lead to systemic inflammation with release of proinflammatory cytokines acting on brain blood vessels via constitutive or induced receptors [35]. The cytokines stimulate neuronal afferents and peripheral innate immune cells with synergistic pathologic impact for neurons [36]. Circumventricular organs located around third and fourth ventricles are highly vascular and lack blood brain barier allowing direct uptake of circulating toxicants [37]. IL1b and Tumor Necrosis Factor (TNF) are major cytokines modulating neuronal responses, effecting neuroimmune integration in neurotransmission and synaptic plasticity. Excitatory glutamatergic cytokine link may inflict excitotoxic neuropathology [38].

Microglia activation during neuroinflammation leads to release of mediators like NO, chemokines, proinflammatory cytokines, Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), all deleterious to the brain structure and function [39]. Glia actively contribute to neurotransmission, neuronal excitability and several forms of synaptic plasticity, i.e., LTP [40,41].

An active neuro-immune cross-talk occurs during induction of LTP. Immune cytokines and MHC (Major Histocompatibility Complex) molecules actively modulate synaptic memory processes. LTP along with LTD provide consensus model of learning and memory process. LTP manifests as a persistent increase in the size of the synaptic component of the evoked response, following repeated synaptic activation. This occurs through out at excitatory synapses in brain. Induction of LTP requires synaptic activation of post synaptic NMDA receptors. Subsequent steps involve, post synaptic Ca^{2+} entry, several signal transduction systems and in late phases, gene transcription and new protein synthesis [42].

Abnormalities in the induction, maintainance and reversal of the main forms of neuroplasticity may occur in neuroinflammatory pathologies with cognitive impairment as in alzheimer's and parkinson's diseases. The proinflammatory cytokines adversely affect neuronal function, viability and plasticity [43]. Impaired synaptic plasticity destabilises neuronal networks.

In "uninjured" brain, when pro and anti-inflammatory cytokines are expressed at low basal levels, they serve essential physiological role in the regulation of bidirectional glioneuronal communication and in modulation of synaptic plasticity [44,46]. The final downstream effect of cytokines on plasticity and neuronal survival depends on their synaptic concentration. At low, "physiological" levels, these immune mediators may be essential for the induction and maintenance of neuroplasticity [45]. They are over expressed during neuroinflammation, when they may impaire synaptic plasticity and cause neurodegeneration. Net synaptic and neuronal effect of cytokines depends on the synaptic balance of pro and anti inflammatory molecules. The hippocampal LTP is impaired in elderly, in association to decreased concentration of anti inflammatory IL4 and increased concentration of proinflammatory IL1beta [47]. IL1b has inhibitory effect on induction of LTP in hippocampus [48]. IL1 appears to be involved in maintenance of LTP in hippocampus [45].

Tumor Necrosis Factor alpha (TNFa) has pivotal role during physiological cross talk occurring between neurons and astrocytes [49]. TNFa mediated modulation of glia-neurone communication involves prostaglandin PGE2, having crucial role in synaptic plasticity [50]. Among other cytokines, IL6 may exert inhibitory effect on LTP induction by modulating MAPK-Extracellular signal regulating Kinase (Erk) pathway [51].

The class I Major Histocompatibility Complex (MHC) molecules are also expressed by neurons and regulated by spontaneous and evoked neural activity [52]. Post synaptically localized MHC has central role in homeostatic regulation of synaptic function and morphology. It acts in retrograde manner across the synapse to translate activity in to lasting structural change [53]. Downstream effects triggered by inflammatory insult also include the release of NO [54], and cyclo-oxygenase products. Their role in neurotransmission and plasticity is established [55].

Implications of Immune Control of Neuroplasticity in CNS Disease

LTD, LTP and synaptic, "depotentiation" have all been described at corticostriatal synapses [56]. Parkinson's disease related pathological process disrupts all of these. Immune mechanisms are implicated in pathogenesis of parkinson's disease, including striatal upregulation of MHC molecule expression [57,58]. Alzheimer's patients suffer glial activation and neuroinflammation triggered through Amyloid beta (Ab). Inflammatory mediators TNF, NO, super oxide, may mediate the LTP depression. Alzheimer's disease, at least in early stages, represents a synaptic failure [59]. An active CNS inflammatory process deeply affects synaptic development with marked downstream consequences for cognitive and even motor functions.

Neuron Network Pathohysiology

The concept of network in neurology was fostered by developments in related fields. There has been advance from characterization of surface morphology to description of neuroanatomical projection paths in brain white matter and acceptance of "associationistic" models of cognitive function [60]. Healthy brain self organizes toward "small world networks", charecterised by combination of dense local connectivity and critical long distance connections. This complex architecture underlies cognition and intelligence and arises under genetic control. Optimal brain network organization becomes disturbed in neurologic diseases in charecteristic ways [61].

Brain is large complex communication network of interconnected elements at multiple scales [62]. At neuron level, brain networks are disassortative rather than assortative [63]. At macroscopic level, brain is organized as a social network. The complex network of human brain therefore, displays opposite patterns of mixing at different spatial scales. Topology of human functional brain network shows evolution from more random (scattered) to more small world like form [64,65]. Optimal small world pattern of adult age is gradually replaced in older age by more random topology, again [66]. Brain network topology also differs in two sexes.There is higher connectivity and shorter path lengths in females [64,67]. The complex network is more than sum of the constituting blocks. It is also more than the sum of its pair-wise interactions. Complex systems have "emergent" properties and should be viewed in general, as large collections of interacting elements, displaying a hierarchial organization [68]. Network theory influences notions of localization of brain function and global effect of local lesion. The graph theory of network analysis [69], describes network as a set of nodes connected by ridges (lines). Microscopically, the nodes will be neurons and the edges will be axons connecting neurons to each other. Human brain network at macroscopic scale will have nodes as major subcortical nuclei and regions. The edges shall be represented with hypothetic or verified measures of association.

The modular organization of human brain structural networks reflects the known functional specialization of the brain regions [70]. The networks of regional structural associations are under robust genetic control [71]. Small world network can provide a topological substrate for both, local specialized/segregated processing in the neighbourhood of highly clustered nodes and global distributed/integrated processing on a highly efficient network with characteristic short path length [72]. EEG and EMG data provide information of brains electromagnetic activity over a wide frequency renge (1 to 100Hz), with millisecond time resolutions. Transition from childhood (8-12 years) to adulthood (21-26 years) is charecterised by a reduction of overall connectivity (decreased clustering and increased path lengths) [65].

A core of white matter network exhists which densely interconnects posterior and medial cortical regions [73], association cortical hubs [74], and has longer range white matter connections with rest of the brain. A study of people with schizophrenia showed that their grey matter network was typified by increased physical distance between connected nodes, indicating inefficient wiring. The hierarchial organization of cortex was attenuated, indicating abnormal neurodevelopment [75]. Interdependance of network organization and behavior has already been studied for several specific tasks. Findings suggest that structural and functional measures are heritable, abnormal in clinical disorders and change in context of normal aging.

While network dynamics seems to have a persistent or long memory component [76], they can also adjust quickly to behavioural changes or cognitive demands [77]. Brain networks are dynamically in critical state, "on the edge of chaos", that facilitates rapid reconfiguration for adapting in response to altered environmental inputs [78]. Ferri et al., [79], reported that through progression from light to deeper sleep small worldness became steadily greater in frequency bands less than 15Hz. That indicates a definite configuration, which may be related to neural plasticity during sleep. Leistedt et al., [80] analysed the sleep networks of acutely deppressed patients. They were charecterised by an increased path length i.e., randomization of the network topology, likely to directly impact cognitive capacity during wakefulness. Collectively, structural and functional metrices are important in brain organization and neurobiology. Current challenge is to evaluate the convergence of structural and functional networks, to provide a more integrated account of brain network organization.

Functional connectivity [81], refers to the interdependency of neurophysiological (global and local), time series [82]. An important concept for understanding communication in brain networks is, synchronization. The most important linear measure of correlation between time series is coherence. Coherence describes the strength of correlation between two time series, as a function of frequency. Inter regional synchronization or functional/effective connectivity conveys important information about healthy brain functioning. In healthy subjects, the strength of inter-regional synchronization depends upon age. Long distance synchronization is relatively low at birth. It increases during development, possibly due to maturation and myelination of long distance association pathways. The strength of synchronization between different brain regions shows characteristic fluctuations. The fluctuations may be due to rapid formation and dissolution of functional connections. This dynamic nature of synchronization, even during resting state is called fragile binding [83]. Inter-regional synchronization is also clearly influenced by behavioural state and cognition. Tasks that involves working memory is associated with increased EEG synchronization especially, in the theta band and possibly also in alpha band. Gamma band synchronization is important neurophysiological mechanism underlying binding, attention and even cociousness [84-87]. Charecteristic "fragile binding" of dynamic synchronization can be disturbed in two ways. There can be excessive connectivity or disconnection. Excessive synchronization menifests in epilepsy [88].

Network Disorder and Neuropsychiatric Diseases

Increased local and decreased global connective efficiency suggests abnormally regular networks [89]. Destruction or loss of anatomical connectivities between brain regions would reflect in diminished functional connectivity implicated in broad category of disorders charecterised by cognitive and psychiatric symptoms. Delbeuck et al., [90], refered alzheimer's disease as disconnection syndrome. In a large fMRI study, depressed patients had lower normalized path length and increased node centrality of their functional brain networks, compared to controls [91]. Some of the altered node centrality measures correlated with duration and severity of disease. Structural and functional network changes (of genetic origin) are implicated in Attention Deficit Hyperactivity Disorder (ADHD) [92], similarly, complex genetic and developmental factors are implicated in schizophrenia where in, normal development of long range fronto-temporal connection is disrupted [93,94].

Autism is a neurodevelopmental disorder charecteterised by impairment in social interaction, verbal and nonverbal communication and repeatitive behavior. Functional network analysis of delta band

EEG, revealed increased short-range fronto-lateral connectivity and loss of long range fronto-occipital connections [95]. Loss of global (ALPHA band) coherence and increase in local (THETA band), connectivity was reported in ASD in another EEG study [96]. An association was found between estimated concentration of metals and solvents in ambient air around the residential area at birth and autism development in SanFransisco epidemiological study [97].

Epilepsy is charecterised by unexplained and unpredictable emergence of an abnormal dynamic state of brain with excessive neuronal firing and synchronization. The changes in the organization of brain networks lower the threshold for pathological synchronization and facilitate spread of abnormal activity throughout the brain [98].

Dementia in parkinson's disease may result in loss of connectivity, particularly between frontal and temporal areas [99]. Following varied local lesions, connectivity in different frequency bands i.e., alpha versus theta, may be increased, as well as decreased [100]. This may suggest attempts for compensation. Connectivity changes are also related to cognitive changes in patients [101]. Alzheimer's disease is commonest cause of dementia in the aged. MEG of resting state functional brain networks in these patients, were charecterised by a lower normalized clustering co-efficient and path length, especially in the lower alpha band [102]. Decreased clustering coefficient indicates loss of local connections. The alzheimer's patients show relative lower connectivity in parietal and occipital but higher in the frontal cortical area [103]. Loss of functional connectivity in alzheimer's dementia correlates both with structural changes as well as cognitive impairements that might improve the prediction of progression from MCI (Minimal Cognition Impairement) to AD [104,105]. The deposition of amylod-beta peptide in brain is not random, but most concentrated in multimodal association areas. These areas exhibit considerable overlap with the "Default mode" network, as revealed by resting state fMRI studies [106-109]. These are areas that show the highest activity level at rest. These also have the highest connectivity [40,110,111]. Disordered network is a pattern that has been observed in many different types of brain diseases, ranging from alzheimer's disease, brain tumors, depression to schizophreni [112-114]. Network randomization (disorganization) charecterises relatively severe and advanced brain disease.

In other conditions, brain networks shift from global to local connectivity. In developmental disorders [95] and in early stages of neuropsychiatric disease [115,116], there is pathological increase in "network regularity". A syndrome among gulf war veterans described as TILT (Toxicant Induced Loss of Tolerance), also increasingly seen in Chinese industrial work force, is understood to result from exposure to chemicals with cognitive deterioration and multisymptom illness. Brain networks must be "solutions" and the nature of problems that they envisage to solve requires better understanding and clarity. Imperative emerges that subtle health effects, such as delays in functional brain maturation and impairment of neurobehavioural competences should be included in studies of chronic pollution effects [117].

The Von Economo Neurons and Default Mode Network Dysfunction

Creatures with complex social organization and self consciousness, posses Von Economo Neurons (VEN) in anterior cingulate, fronto insular and dorsolateral prefrontal cortex, which are home for executive functions. These neurons are latest to evolve and hence lack genetically fostered defence against stress. They are most susceptible to oxidative damage [118].

The new network associated with attention demanding tasks is called task related network. The network associated at rest with stimulus independent thought is called default network. The two networks are negatively correlated (anticorrelated). Regions of brain associated with default network, overlap with regions important in motivation. These are activated by memory retreaval, auditory hallucinations and ketamine. Normal people exhibit task related suppression of activation of default network. The patients exhibit abnormally high functional connectivity within the default network during rest and task. The magnitude of default network connectivity correlates with psychopathology.

Task related networks are necessary for performance of neurocognitive tasks. On these, the schizophrenic patients perform poorly. Anticorrelated networks are complementary ways of understanding self monitoring and task performance. The default mode is defined as "baseline" condition of brain function. Its component brain regions become abnormal due to abnormal activation and connectivity in schizophrenia. Neuron network mediating default mode of brain function, typically exhibits greater activation during rest than during task, in patients in early phase of schizophrenia. Hyper activation (reduced task related suppression) of default regions and hyperconnectivity of default network cause thought disorder and increased risk of illness.

VENs are instrumental in switching between the "Default mode", resting state, attention and executive networks. Such network switching is disturbed in neuropsychiatric disorders [119]. Most such disorders are linked to neuroinflammation and glutathione depletion. More accurate characterization of mechanisms underlying immune mediated control of synaptic plasticity could represent basis for novel immune centered therapeutic approach for neurological disorders. Disturbance of VENs, e.g., in Autism, leads to obscessive desire for maintaining sameness. Similar is case with addiction including addiction to own personality. 5HT2b serotonine receptors present on VENs mediate anticipation of punishment, while the D3 dopamine receptors mediate anticipation of reward, in state of uncertainty. Schizophrenia has network switching dysfunction mediated by inflammation. Efficiency of neurofeedback depends on neuroprotection and neuroplasticity. Enhancing anti-inflammatory and antioxidant intracellular resource of glutathione through N-acetyl cystein supplement, significantly and rapidly improves cognition in schizophrenia and bipolar disorder. Any thing that calms the inflammation in VENs, will help to

- Normalize network transformations;
- Reduce the etiological factors for many neurocognitive disorders and particularly
- Free the VENs to process higher nervous functions

Neuropsychiatric Impact of Pollution

Exposure to air pollutants can cause stroke related sickness and death, as well as brain damage, neuroinflammation and neurodegeneration. Environmental pollutants, chemicals, metals and drugs have negative impact on developing central nervous system. The cognitive and emotional functions develop during early childhood. The process slows after age of 4 to youth. Plateau phase is reached by fourth to fifth decade of life. This is followed by small decline which accelerates after seventh decade [120]. Maturation of cortex (i.e., wiring synaptic changes and axonal myelination), during the first years of life is very intensive. Frontal cortex is last to mature [121]. Children are a

population at risk since; childhood and adolescence are crucial periods of brain development associated with dynamic behavioural, cognitive and emotional changes. If cognitive abilities are reduced during the critical childhood developmental years as a result of air pollution, detrimental consequences for society are enormous.

Hazardous air pollutants include hundreds of metals, particulate and volatile organic compounds. Deposition of Ultra Fine Particle (UFP) containing metals in olfactory bulb or frontal cortical and subcortical areas, or alternatively, the neuroinflammation following the systemic inflammatory responses secondary to oxidative stress triggered by air pollution, could result in white matter lesions and vascular pathology in these areas. That could be, basis for cognitive deficits and behavioural impairment, both in children and the old people. The cognitive deficits result from reduced brain connectivity [122-124], in highly exposed children. The deficits match the localization of the substantive white matter differences remaining consistent with impairments of parietal and temporal lobe functions [125]. Different neurodegenerative diseases often share common mechanisms, such as protein aggregation, oxidative stress injury, neuroinflammation, microglial activation, apoptosis and mitochondrial dysfunction, leading to ultimate loss of specific neurons [126].

Exposure to airborne Ultra Fine Particulate matter (UFPs) associates mitochondrial damage as indicated by increased copy number of mitochondrial DNA [127]. Damaged mitochondria would cause increased oxidative stress and overwhelm antioxidant defence. The UFPs perturb permeability of mitochondrial transition pores. This can result in release of pro-apoptotic factors and apoptosis [128]. Nanoparticles may target neuronal presynaptic terminals, affecting glutamatergic neurotransmission and leading to neuronal damage [129]. Mitochondrial dysfunction impacts endoplasmic reticulum homeostasis. Perturbed ER calcium homeostasis contributes to neuronal dysfunction and degeneration [130]. Although each pollutant has its own mechanism of toxicity, several air pollutants like, ozone, sulfer dioxide, volatile organic compounds and PM are oxidants, capable of directly acting on cellular components and disrupt physiological function [131-133]. Animals exposed to high levels of air pollution, such as fine and ultrafine particulate matter, lipopolysaccherides associated with PM, ozone and dissel engine exaust, show an increase of proinflammatory cytokines in brain tissue [134-137].

General intelligence exhibits significant association with damage to frontal and parietal cortex network. White matter association tracts and frontopolar cortex are critically included in the network [123]. White matter integrity of the target regions is key for a correlation to performance on the Wechsler Intelligence Scales, both in young and adults [138,139]. The study in Mexico city, children exposed to pollution projects possibility of differential regional effects of inflammatory cytokines in brain. Cognitive deficits may have not only structural basis in CNS, but also a systemic inflammatory component [140]. Strategies for prevention of pollution inflicted neuroinflammation should start crucially, early in exposed child populations.

Indoor levels of particulate matter pollution strongly associated attention defdiciet hyperactivity syndrome [141]. Windham et al. [97], found a significant association of autism spectrum disorders with higher ambient air concentration of metals as, cadmium, mercury and nickel. Relatively low exposures to lead and mercury impair cognitive function in children. Lead exposure also associates behavioural problems. Some studies have pointed out potential relationship between air pollutants and language delay [142].

Glutathione S-Transferase P1 (GSTP1) gene that represents the most strongly expressed glutathione 5 transferase isoenzyme in the human brain during early life protects against oxidative stress. GSTP1 variant coding less active enzyme made brain cells more susceptible to changes due to early life air pollution exposure leads to poor mental development [143]. Research on individual susceptibilities may reveal mechanism of ultrafine particle induced neurological effects and identification of susceptible phenotypes. Oxidative stress following deposition of UFP containing metals in olfactory bulb or frontal cortical and subcortical areas or the systemic inflammatory response secondary to air pollution can induce white matter lesions and regional vascular pathology. This may be the basis of cognitive and behavioural impairement. Wilker et al. [144], examined association between residential long term exposure to ambient air pollution and markers of brain aging using MRI. Exposure to elevated levels of PM 2.5 (under 2.5 micron), was associated with smaller total cerebral volume, a marker of age associated brain atrophy and with higher odds of covert brain infarcts. Air pollution is associated with insidious effects on structural brain aging even in persons free from dementia and stroke.

Understanding of the pathogenesis of axonic or synaptic lesions would follow advanced understanding of synthesis and turnover of biological membranes, the selection and packaging of neurotransmitters, the mechanisms of cytoplasmic streaming and axoplasmic flow and biophysical and biochemical charecteristics and functions of fibrous proteins [145]. Polychlorinated biphenyls are ubiquitos and poorly biodegraded pollutants, of modern environment. They cause changes in dopamine and serotonine neurotransmission impacting fronto-striatal function, critical to executive competence [146,147]. Adults exposed to high PCB load through fish consumption, suffered impaired memory and learning [148]. Exposure of pregnant rats to PCBs caused reduction of LTP in hippocampal neurons in offsprings at later age [149]. Direct *in vitro* exposure of nervous tissues to Bisphenol-A, the organic plasticizer, caused alterations in several biochemical steps of synaptic transmission, e.g., calcium signal, glutamatergic and NO dependant mechanisms [150,151]. Such effects raise multiple health concerns as synapse formation is complex and incompletely understood. Exploration of synaptogenesis, particularly the influence of genes products and epigenetic factors on synapse maturation, will increase our understanding of the pathogenesis of conditions in which, "morphology" appears normal, but function is abnormal [152]. Pre and postnatal exposures to environmental factors predispose to the onset of neurodegenerative diseases later in life.

Amylloid beta (Ab) Homeostasis as a Target of Environmental Factors

Neurotoxic metals, such as lead, mercury, albumin, cadmium and arsenic, as well as some pesticides and metal based nano particles have been involved in alzheimer's disease due to their ability to increase beta amyloid peptide and phosphorylate Tau protein (P-Tau), causing senile amyloid plaques and neurofibrillatory tangles, characteristic of AD. Environmental factors such as diet (fat rich), heavy metals, biogenic metals and pesticides, disrupt metabolic pathways involved in homeostasis of Ab, thus leading to development of alzheimer's disease [153]. Many of environmental pollutants are oxidative agents acting through different mechanisms. Brain is particularly vulnerable to oxidative stress due to its highly glucose based metabolic rate, low levels of antioxidants, high levels of polyunsaturated fatty acids and high enzymatic activities related to transition metals that catalyse formation of free radicals [154].

The exposure to lead, manganese, solvents and some pesticides has been related to hallmarks of PD such as mitochondrial dysfunction, alterations in metal homeostasis and aggregation of proteins, such as alpha-synuclein (a-syn), which is key constituent of Lewy bodies, crucial in pathogenesis of PD [155]. Neurodegenerative diseases as AD, PD and huntington's disease involve gradual neuronal death leading to decline in movement control, memory and cognition. Autism Spectrum Disorders (ASD), are diagnosed before 2nd to 3rd year of age i.e., the period of synapse formation and maturation in humans [156]. Alzheimer's disease is charecterised by loss of neurons and synapses in hippocampus, cerebral cortex and subcortical regions. Amyloid beta peptide is released from neuronal membrane in to the interstitium and then triggers signaling cascade on post synaptic membrane. Altered synapses predispose to developing ASDs, GABAa receptor mediated inhibitory synaptic transmission is selectively enhanced in ASD, causing a shift in the E/I balance in the synapse [157]. Alzheimres disease in the early stage appears as disorder of synaptic receptor trafficking and dysfunction. Remarkable similarity with LTD is displayed, including increased synaptic endocytosis of AMPA receptors and loss of dendritic spines [158].

Drug addiction has genetic, psychological and environmental dimensions with causative powerfull long lasting memories of drug experience. The synaptic plasticity mechanisms, that are normally employed to reinforce associated behavior, become pathologic in patients of drug addiction. Chronic drug use consistently causes changes in dendrite spines and synaptic proteins. Several synaptic mechanisms, e.g., AMPA receptor trafficking, mGluR signaling and dynamics of actin in spine, are affected by chronic drug taking [159]. Parkinson's disease is a chronic and progressive neurological disorder. Only fraction of cases exhibit familial trait, and 90% of cases have no attributable genetic basis. Aging is main risk factor. Epidemiologic evidence suggests that the exposure to environmental toxicants, mainly pesticides, metals and solvents could increase risk of developing PD [160]. PD is characterized by selective loss of dopaminergic neurons in substantia nigra, pars compacta. Additional to neuronal loss, the main hallmark is presence of Lewy Bodies (LB) in the surviving neurons, containing aggregates of proteins such as a-syn [161]. Several molecular mechanisms of neuronal death in PD pathogenesis have been described. These include mitochondrial dysfunction, impairment of protein quality mechanisms, oxidative/nitrative stress, microglia activation and inflammation. These mechanisms converge and are consistent with a major role of oxidative stress in PD. Oxidative stress damages organelles and proteins leading to increased protein aggregates (e.g., a-syn), that in turn, overload degradation systems leading to a self perpetuating cycle of further oxidative stress [162,163].

Increasing evidence suggests that epigenetic changes in the developing embryo may play important roles in susceptibility to diseases in later life (imprinted disease phenotypes). These changes result from maternal exposures to environmental stimuli at critical periods of development. This suggests that a short exposure to chemicals could be memorized through epigenetic mechanisms long after the chemical trigger has gone. Recent studies suggest an epigenetic component related to environmental factors, involved in neurodegenerative diseases [164]. Environmental factors associated with increased PD risk such as pesticides, may alter the expression of genes through epigenetic mechanisms [165]. The oxidative stress induced by varied neurotoxicants activates/inhibits signaling pathways leading to augmented/diminished activity of enzymes that promote the accumulation of toxic materials in neural cells. The latter include, damaged/aberrant proteins, Ab in AD or a-syn in PD and oxidative by products or the oxidation of DNA that can alter genetic or epigenetic regulation.

Studies on Disruptive Exposure

Animals exposed to high levels of air pollutants, such as fine and ultra fine particulate matter, lipopolysaccherides associated to PM, ozone and diesel engine exhaust, show increase of proinflammatory cytokines in brain tissue [135,136]. Ozone is most important air pollutant in terms of its concentration, persistence and ubiquitous occurrence. Prenatal ozone exposure leads to permanent damage of the cerebellum [166], disruption of cerebellar monoaminergic system [166], and altered level of neurotrophic factors [167]. A study by Chen & Schwartz [168], demonstrated that neurobehavioural effects are associated with long tern exposure to ambient PM and ozone concentration in adults. Adult residents of highly polluted urban area of Mexico-City exhibited significantly higher COX-2 expression in olfactory bulb, hippocampus and frontal cortex. The astrocytes had accumulated greater levels of Amyloid-b as compared to age, gender and education matched subjects from low pollution areas [142]. Life-long exposure to air pollution associated accumulation of alpha-synuclein in brain of young people also [169].

Ultra fine carbon particles (below 100nm) and manganese nano particles were detected on olfactory bulb, cerebrum and cerebellum upon inhalational exposure in mice [170]. Nasally inhaled nanoparticles enter the celiate olfactory neurons by pinocytosis, simple diffusion or receptor mediated endocytosis and can be transported along axonal projections from olfactory bulb, further in to CNS, viz. piriform cortex, amygdala and hypothalamus, or gain access to cerebrospinal fluid, bypassing vasculature route [171]. Changes in cytokine expression in brain were directly linked to intranasal ultra fine carbon exposure [172]. Recent epidemiological studies combined with psychological tests support an association between chronic exposure to traffic related air pollution and decreased cognitive function in both genders [173]. Polycyclic aromatic hydrocarbon exposure of pregnant mothers resulted in babies having lower IQs at 5 year than unexposed peers [174]. Black carbon exposure caused downgrading of IQs in babies at 9 year age [175]. Significant reduction in psychomotor, attention and sensory scales, without cognitive impairment was observed in children studying at school located in area of dense city traffick, compared to those from clean air area [176].

Lead, is neurotoxic, affecting cognitive abilities, intelligence, memory, speed processing and motor functions in children. Mercury disrupts brain development producing cognitive and motor disabilities. There is suspected link between mercury exposure and risk of Alzheimer's Disease (AD). Apolipoprotein E4 phenotype is a risk factor for AD. This protein does not have sulph-hydryl group to scavenge heavy metals like mercury. Over-production of Ab may associate arsenic induced inflammatory response and oxidative stress in brain [177,178]. Lead is most potent Ab inducer, followed by cadmium and minor arsenic effect. Aluminium (Al) is neurotoxic and plausible contributor to AD risk. Transgenic mice fed with 2mg/kg Al in diet for 9 months had increased Ab production. Vitamin E administration reversed it, suggesting role of Al induced oxidative stress [179]. Al exposed mice had increased expression of proinflammatory micro-RNAs also [180]. Deregulated micro-RNA production by xenobiotics as pathogenic factor in AD causation needs further understanding. Administration of nano particles of Al, Cu, Ag at different doses and routes in rats and mice produced motor, sensory and cognitive deteriorations [181,182].

Tau Hyper Phosphorylation by Environmental Factors

Inorganic mercury increased P-Tau (Phosphorylated Tau), by Reactive Oxygen Species (ROS) dependant mechanism. Cadmium increases aggregation of tau protein. Arsenic phosphorylates tau as well. The resultant destabilization of cytoskeleton structure promotes axonal degeneration [183]. Maternal and early post natal lead exposure significantly increases P-Tau, parallel to cognitive impairement in mice. Arsenic inhibits activity of protein-phosphatase 2, involved in dephosphorylation of P-Tau, and so P-Tau level rises [184].

Molecular mechanisms of neuronal death in Parkinson's Disease (PD) converge and are consistent with major pathogenic role of oxidative stress that is self perpetuating [162,163]. Exposure to environmental toxicants especially, pesticides, metals, solvents can increase PD risk. Chronic exposure to iron, lead, manganese and their combinations contribute increased PD risk. These metals accumulate in Substantia Nigra (SN), generating oxidative stress. Miners exposed to manganese suffer a variant of PD, which does not respond to DA replacement treatment [185]. Neuromelanin pigment of SN preferentially chelates metals, particularly iron, inviting occurrence of Fenton and Haber-Weis reaction and ROS generation. Deregulated iron homeostasis contributes PD risk [186]. Many epidemiological studies show increased PD risk with exposure to pesticides, specially dieldrin which crosses BBB and is retained in brain. It is selectively toxic to DA neurons. Herbicide paraquat is also selective DA neuron toxicant. Organophosphate pesticide rotenone is found to raise PD risk 10 fold higher in exposed people [187]. It is mitochondriotoxic and increases oxidative stress. Rotenone induced PD model is employed for experimental studies. Solvents are used widely and some lipophillic solvents easily gain access to nervous system. Acute exposure to n-Hexane and toluene can cause aute parkinsonism. Trichloroethylene chronic inhalation caused 6 fold heightened risk of PD [163]. This agent recapitulates most of known pathologic mechanisms in PD viz. inhibition of mitochondrial function, increased oxidative stress, microglia activation, a-syn accumulation in SN and loss of SN neurons in dose dependant fashion [188]. Nanoparticles are important alternative in developing treatment strategies for neurodegenerative diseases that would easily cross BBB and effectively deliver specific drugs. Their small size however, enables them penetrate the cell and organelles, disrupting their normal function [189].

Gene-Environment Interaction and Epigenetic Vulnerability

Pollution can impact gene expression through range of mechanisms. Main effect approaches assume two possible contexts of gene causing disorders. There can be direct linear relation of gene to syndrome [190]. Genotypes moderate the capacity of environmental stressors to inflict mental disease. Direct inter relation between genes and brain structure has been suggested in depression [191], schizophrenia [192] and addiction [193]. Alternatively, specific neurophysiologic, biochemical, endocrinological, neuroanatomical or neuropsychological components can be examined instead of the whole syndrome for relationship to genes. The components constitute "endophenotypes" [194]. Gene-environment Interaction approach assumes that disorder results due to environmental agent and genes influence susceptibility to the agents. Mental disorders have environmental etiologies and there is heterogeneity in response to them among exposed people [195]. Genotypic susceptibility to pollutant induced neurotoxicity is exemplified in ApoE deficiency and other kinds of susceptibilities to oxidant stress [134].

Epigenetic effects lead to imprinting, gene silencing and suppression of expression [196]. Epigenetic mechanisms of pollutant mediated neurological damage have been demonstrated [197]. Epigenetic DNA modifications include DNA methylation, histone post-translational modification and impact of microRNAs. Increased evidence suggests that epigenetic changes can hold effects of short toxicant exposure, to express long after. Epigenetic mechanisms appear involved in neurodegenerative diseases related to environmental factors [164]. Hypomethylation of Amyloid Precursor Protein (APP) gene increases its expression, driving overproduction of APP and Ab. That in turn facilitates ROS production and DNA damage, toward neuron loss. Hypermethylation, on the other hand, affects gene transcription and DNA repair. Both changes can impact gene expression and cause increased susceptibility to oxidative DNA damage in brain [198]. Pesticides may act via epigenetic mechanisms to increase PD risk [165]. Exposure to environmental neurotoxicants during pregnancy or early life, which are known to increase PD risk, may progressively damage SN and increase vulnerability to other environmental insults (TWO HIT model) [199]. Pollutant exposure might change expression profiles of microRNAs which are crucial mediators of post translational gene regulation [200].

Research Considerations

Probability of experiencing certain exposures may partly be under genetic influence, e.g., tendancies to tobacco, cannabis exposures. Randomised assignment of groups to environmental risk, in epidemiologic studies, can take care of such bias. Environmental exposure is difficult to measure reliably and precisely, in extended periods of life. Only, experimental situation allows control of timing and doses. The harm from naturally occurring exposures frequently accumulates over months and years. Epidemiologic investigation must involve experimental neuroscience investigations, as joint strategy to unravel complex mechanisms underlying disease pathogenesis. Animal models of disease make poor extrapolative sense. However, endophenotypic components of disease and their reactivity to exposure are scientifically more relevant to study [201]. Genotype-environmental exposure response can be examined on functional neuroimaging [202], neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, emotional or neuropsychological measures, as resultant phenotypes. Examples of such application include use of EEG, electrodermal and heart rate reactivity, and adrenocortical responses. Epidemiological cohort studies should collect neuroscience measurements of individual differences to help integration of findings of epidemiological and experimental research [203].

Pollutants, such as pesticides posses crucial neurotoxic potentials. In vitro testing tools, adequately usefull for performing sensitive and practical neurotoxicity screening, are very worthwhile. Cortical neuron network grown on a Multi Electrode Array (MEA) is described as usefull in examining chemicals for effect profile on spontaneous electrical activity of the neuronal network. A set of electrophysiological effect parameters, enables classification of neurotoxicants. The multiparametric description of neuronal network activity is more accurate to indicate toxic potential, in combination with dose response scruitiny [204]. Neurobehavioural tests are increasingly being used in human risk assessment. Most studies examin single agent on single health target. Real life exposures are mostly mixed co-exposures, which may increase, decrease or not affect neurotoxicity. Methods

should be refined to detect subclinical dysfunction.Toxicity in vulnerable population groups e.g., elderly and children must be ascertained. Evaluation strategy for outcomes with lifetime exposure should be feasible. All these are crucial to regulatory thought for preventive action in exposed population.

Hazard identification and risk assessment technology should be apt to identify and encompass progressive, cumulative neurotoxicity of mixed pollutants. They interact, not necessarily systemwide but by different regions of brain, outcome measure, gender and age. "Multi-Hit", hypothesis of neurotoxicity assumes that brain may readily compensate for insult caused by singular agent on finite target system within it. However, when multiple targets or functional sites, within a single system are attacked by different mechanisms (e.g., By multiple agents or combined with multiple risk factors), the limited homeostatic capabilities of brain are overwhelmed and sustained or cumulative damage accrues as consequence [205]. States of protein, calorie, vitamin and/or mineral undernutrition are associated with a range of neurodevelopmental, neurological and psychiatric disorders, commonly with involvement of both central and peripheral nervous system. Undernutrition can modify risk for certain chemical induced neurologic disease and in some cases, undernutrition may be a prerequisite for manifestation of neurotoxicity [153,206,207].

In respect to therapeutic thought as adjunct to preventive measures against pollultant neurotoxicity, attention to glucocorticoid hypothesis of stress induced psychiatric disorders is pertinent. That envisages, hypothalamo-pituitory-adrenal axis dysregulation alongwith memory impairment involving hippocampal damage in affective disorders [208]. Zarate et al., [209], discuss cellular plasticity cascades, as novel therapeutic targets for bipolar disorders. Effective treatment should provide both trophic and neurochemical support to enhance and maintain normal synaptic connectivity. That would allow the chemical signal to reinstate the optimal functioning of cortical circuits, necessary for normal effective function. Plasticity changing drugs may include inhibitors of glutamate release, NMDA antagonists, cAMP phosphodiesterase inhibitors, glucocorticosteroid receptor antagonists, etc.

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