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Environmental Cognitive Neuro-toxicology: A Perspective

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ABSTRACT: Human asset of social brain is an evolved system that draws upon focal as well as global connected brain mechanisms. These are dynamic and flexible anatomical routes operated for co-operation and co-ordination in intelligent behaviors. Different cues and inputs from environmental and human social interaction are understood by refereeing to mental assets which determine the appropriate response. The focal and global connections are now subject to view with functional neuro-imaging technology. Brain mapping approaches are now adding to the comprehensive understanding of neurophysiology. The technology driven scientific advances have disclosed serious threat of environmental pollutants for the complex, dynamic but delicate neural architecture operating the social brain. The dreads are worst at early developmental stages and later in aging phase of population. It is a huge challenge of quality of human beings, society and life. There is myth also that Hitler's hatred arose in such very contexts. The need for befitting response to the challenge by medical fraternity is urgent. This narrative attempts to briefly introduce neuro-physiological and neuro-toxicological perspectives in this context for general reading among medical basic science and clinical educators and students. The descriptive review is based on PubMed search with single keywords as well as phrases relevant to real life domain. The interdisciplinary perspectives also indicate the research vistas and development of preventive and corrective interventions.

Keywords: Social cognition, Cognitive neuroscience, Neuronal networks, Environmental toxicology, Neurotoxicology

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INTRODUCTION

There are near 1000 chemicals in environment with tested neurotoxic potential. Early and gradual stages of neurotoxicity of environmental chemicals are often vague and ambiguous, involving largely subjective complaints e.g. lethargy, fatigue, weakness, irritability, headache, depression. The potential is therefore large, for occurrence of subtle, undetected effects with important bearing on higher nervous functions. Low level exposures to certain toxicants produce deleterious effects on nervous system requiring appropriate procedures to detect. There are still episodes of large scale poisonings. Concern has however shifted to the more subtle deficits that reduce functioning of the nervous system, in less obvious but still important in ways, so that intelligence, memory, emotion and other complex neural functions are affected. Emerging evidence suggests that certain neurological diseases as Alzheimers disease, Parkinsons disease and even cerebrovascular lesions, bear strong association to ambient pollution (Calderon-Garciduenas et al., 2015; Kubik and Philbert, 2015 and Wilker et al., 2015). Rapid rise in kind and quantum of environmental pollutants, calls for an intelligent medical care of accrued toxic substances. The challenge of polluting heavy metals, pesticides, plasticizers, endocrine disruptors and variety of neurotoxicants, deserves commensurate recognition and address in grass root teaching and practice of contemporary medicine. It is important that role of exposure to chemical must be taken in to account, whenever a person presents with neurobehavioural problems and priority must be given to obtaining clinical and epidemiological data. Brain receives and integrates signals and then appropriately responds to them to maintain bodily functions. Complex human assets as cognition, awareness, memory and language are supported by brain. Responses mounted by brain include sexual behavior, locomotion and use of vast kinds of tools and tricks. Structural and functional neuronal networks provide the physiological mechanism for sensory processing and mental representations. Human brain consists of over 100 billion neurons, processing and transmitting information as electrical signals. Information in brain is stored in form of altered structure and chemistry of synapses involving formation of new and elimination of old synapses (Yuste and Bonhoeffer 2001). 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. Complex brain disorders involve structural and functional

abnormalities in multiple brain areas, involving several distinct functional systems in brain. Precise control of molecular and cellular mechanisms of synapse development and connectivity is crucial for normal network activity and brain function. Understanding brain disorders is partly, a matter of understanding cell biological and biochemical basis of synapse function and plasticity. Functioning of other organ systems as, liver, cardiovascular, endocrine etc also influences function of nervous system. The toxicant induced aberration in any such organ systems would reflect in changed neurobehavioural output.

Neuron network pathophysiology

The concept of network in neurology was fostered by developments in related fields, viz: **i)** the movement from characterization of surface morphology to description of neuroanatomical projection paths in brain white matter and **ii)** the widespread acceptance of "associationistic" models of cognitive function (Bassett and Bullmore 2006). Healthy brain self-organizestoward "small world networks", characterized by the combination of dense local connectivity and critical long distance connections, which most likely arise under genetic control serving cognition and intelligence. Optimal brain network organization becomes disturbed in neurologic diseases in characteristic ways (Stam and van Straaten 2012).

The consensus concept of brain is that of a large complex network of interconnected elements at multiple scales (Srinivasan et al., 2013). At neuron level, brain networks are disassortative rather than assortative (Bettencourt et al., 2007). At the cellular level, brain is organized as a communication network. 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 (Boersma et al., 2011 and Micheloyannis et al., 2009). Optimal small world pattern of adult age is gradually replaced in older age by more random topology, again (Knyazev et al., 2015). A core of white matter network exists which densely interconnects posterior and medial cortical regions (Hagmann et al., 2008), association cortical hubs (Iturria-Medina et al., 2008), 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, (Bassett et al., 2008). Interdependence of network organization and behavior has already been studied for several specific tasks. Findings suggest that structural and functional measures are heritable. They are abnormal in clinical disorders and change in context of normal aging. While network dynamics appear to have a persistent or long memory component (Achard et al., 2008), they can also adjust quickly to behavioural changes or cognitive demands (De VicoFallani et al., 2008). This adaptivity to changing environmental contingencies may be related to brain networks, being dynamically in critical state, "on the edge of chaos" (Kitzbichler et al., 2009).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. Brain networks must be "solutions" and the nature of problems that they envisage to solve requires better understanding and clarity.

Task related network refers to that associating attention demanding task. The network associated at rest with stimulus independent thought is called Default Network. The two networks are negatively correlated (anti-correlated). Anti-correlated networks are complementary ways of understanding self monitoring and task performance. The default mode is defined as "baseline" condition of brain function. The magnitude of default network connectivity correlates with psychopathology. Hyper activation (reduced task related suppression) of default regions and hyperconnectivity of default network cause thought disorder and increased risk of illness.

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 (Allman et al., 2005). VENs are instrumental in switching between the "Default mode", resting state, attention and executive networks. Such network switching is disturbed in neuropsychiatric disorders (Broyd et al., 2009). Most such disorders are linked to neuro inflammation and glutathione depletion. Anything that calms the inflammation in VENs, will help to **1)** normalize network transformations; **2)** reduce the etiological factors for many neurocognitive disorders; and particularly **3)** free the VENs to process higher nervous functions (Allman et al., 2005).

Understanding of the pathogenesis of human disorders associated with axonic or synaptic lesions will probably depend on research concerned with the synthesis and turnover of biological membranes and the packaging and selection of neurotransmitters, elucidation of mechanisms of cytoplasmic streaming and axoplasmic flow and biophysical and biochemical characteristics and functions of fibrous proteins (Gonatas and Moss, 1975). Study of direct exposure of nervous tissues in vitro to Bisphenol-A, revealed non-classical estrogen receptor mediated alterations in several biochemical steps of

synaptic transmission, e.g. calcium signal, glutamatergic and nitric oxide dependant mechanisms (Pandey and Deshpande, 2012; 2015). Synapse formation is complex and incompletely understood. Direct in vitro neural effects of ubiquitous pollutant, Bisphenol-A deserve elaboration on synapse physiology and neuron network function, with serious health concerns. Exploration of synaptogenesis, particularly the influence of genes products and epigenetic determinants on synapse maturation, will facilitate understanding of the pathogenesis of conditions in which, "morphology" appears normal, but function is abnormal (Becker, 1991).

Social cognition

Social cognition is exemplified as we look at somebody, but simultaneously contemplate about his/her likely behavioural agenda. This doesn't happen on looking at inanimate objects. Social cognition is the processing of information elicited by, about and directed toward other people. Cognitive processing includes perception, reasoning, memory, attention, motivation and decision making that underlies social ability or social behavior. Social functioning is broader concept than social behavior. It refers to long term contextualized ability of individual to interact with others. The social brain performes social cognition and in turn effects social behavior. Specialized brain cells called "mirror" neurons, moderate our observations and interpretations of other peoples' actions and our deduction of their intentions, providing essential input that governs our interactions with others. Dysfunction of the mirror neurons is associated with autism spectrum disorders (ASD).The afflicted individuals lack the knowledge of interaction with other people, and also the abilities to empathise (sharing thoughts and feelings) and imitate behaviors (Oberman, et al., 2007 and Rizzolati et al., 2006). Typically, they fail to make eye contact as vital for interaction. Mirror neurons can explain the reciprocation of observation and perception in understanding actions, thoughts and emotions in others. These are necessary also for normal development of recognition, theory of mind and language. Understanding human actions and internal status, relies on the ability of the observer to see others as being "like me", both in their actions and behaviours. There is also the ability to simulate these observed actions and states with observers' own cognitive, motor and emotional demonstrations. The mental simulation allows the observer to understand another person's behaviours and feelings, or to have a "theory" of mind, which the autistic child is incapable of. While mirror neuron dysfunction is primary in autistic disorder, pathophysiological role of various neurochemicals involving loss of Purkinje cells becomes evident (Pellicano, 2007). A key feature of psychiatric disorders is the difficult social functioning that over period of time, also leads to changes in brain and cognition (Eisenberger and Cole, 2012). Stress of alienation in city life, increases risk of schizophrenia, involving specific changes in regional brain activation (Lederbogen et al., 2011; Mwyer-Lindenberg and Tost, 2012). Social cognition is implemented by "social brain" networks and the cognition causes social behavior with following general features:

1. Social cognition is supported by large number of different brain structures and their connectivity. Their network function generally depends on rapid, efficient and interactive processing thus, even mild dysfunction in any structure, or anatomically nonspecific diffuse dysfunction or white matter damage, can result in impairment.
2. The distributed (involving multiple brain components/regions) nature of social cognition makes it vulnerable to damage. The arrangement for recovery, e.g. compensation through unaffected opponents of network, is seen.
3. Social cognition is highly context dependant, involving a deep level of abstraction, inference and counterfactual thinking, which should be least, compromised.
4. Extended tuning during development, with particular social context and culture is needed for social cognition
5. High variability and communal nature of social cognition (To some extent, social functioning is compensated by behavior of others in a supportive environment).

Autism is a severe state of social disconnectedness. Sharing a focus of attention with other individuals, enables one to acquire skills that are only socially learned and exercised, such as language. The ability to jointly focus attention with others is also at the root of theory of mind, in which autistic children are deficient. They are thus unable to form representations of self and those of other persons, focusing attention on the same object. The disability for joint attention is a result of mirror neuron dysfunction, which is pervasive in social interactions and cognitive perception of self and others.

Organic brain disease and social cognition

Social behavior depends critically on a prolonged period of development amid social context. Social impairments are seen after damage to prefrontal cortex or amygdala. Most severe impairments result when damage occurs early during development (Anderson et al., 1999; 2000 and Shaw et al., 2004). Damage that is bilateral and affects both right and left brain structures results in more profound social impairments than do the unilateral damages. This is because the homologous structure is unable to compensate for damage. Ventromedial prefrontal cortex is necessary for acquisition and storage of associations between stimuli and their value (Chib et al., 2009), especially value related to social emotions (Krashich et al., 2009 and Shamay-Tsoory et al., 2003). Studies of lesions in prefrontal cortex and amygdala have revealed the role of emotions in social cognition that

motivate and guide complex social behaviours (Koenigs et al., 2007).

Neuropsychiatric disorders necessarily require explanation in the context of anatomically distributed networks comprised of many structures. They feature compensation prospect by other structures, when a single structure is damaged. They can also be compromised by damage to the "connecting" white matter (Philipps et al., 2009 and Paul et al., 2007). Brain modeling has helped to explain how lesions of particular network-nodes impact network function. The consequences are more severe when more medial structures accrue lesion, than lesions of lateral structures (Alstott et al., 2009).

Psychiatric diseases and social cognition

The neurological disorders generally feature more precise neuroanatomical structure function relationship. The psychiatric disorders are generally lacking in neuroanatomic descriptions. ASD are a collection of neurodevelopmental disorders (Geshwind and Levitt, 2007). ASD shows that general intellectual function can be dissociated from social behavior and social functioning. There are many people with ASD having above average Intelligence Quotient (IQ), yet having severe difficulties in social interaction. Investigations to identify structures responsible for impaired social cognition in ASD, has revealed it to be a disorder of brain connectivity (Geshwind and Levitt 2007 and Anderson et al., 2010). Several studies have shown an abnormal connectivity, precisely between the components of social brain, and not all over (Gotts et al., 2012 and von dem Hagen et al., 2012). Williams syndrome is the social phenotypic opposite of autism. Some of the most valuable insights regarding social abilities and other dissociations have come from careful comparisons of people with Williams syndrome and those with other disorders, e.g. autism (Riby and Hancock, 2008). The afflicted people approach to strangers in contrast to avoidance exhibited by ASD people (Jarvinin Pasley et al., 2010 and Porter et al., 2007). They tend to abnormally rate faces as trustworthy, while ASD patients do not (Bellugi et al., 1999). These, and neurological illness such as prosopagnosia (Duchaine et al., 2010) together, provide evidence that representing other peoples' mental states and recognizing their faces may be two distinct and dissociate processes (Tager-Flusberg and Sullivan, 2000).

Environmental challenge to social cognition

Several diseases/disorders have emerged over last century in parallel with rise of chemical manufactures, drugs (over 3000 numbers), electromagnetic fields and widespread application of technology. Chemicals in environment are measured as part per million/trillion. These chemicals that fall below safety thresholds, can act upon the body by mimicking hormones and other signaling and regulating molecules (Herbert, 2006). Varied mixed toxic exposures, over years impact in unique fashions. Many of such pollutants are blamed as teratogens. They can negatively affect fetal neuronal circuits at critical stages in development. Many pollutants promote excess oxygen radical generation and degradation of long chain fatty acids, as well as impairment of their synthesis. These effects compromise the cognitive function. Many pollutants impair synthesis and function of thyroid and gonadal steroid hormones with adverse consequences to cognitive function. Persistent organic pollutants are the major agents of neuroinflammation as well as chronic systemic inflammatory diseases as obesity, diabetes, and atherosclerosis. All these conditions themselves are risk factors for cognitive decline. Inflammatory disruption of insulin signaling in brain may contribute to abnormalities that are commonly observed in Alzheimers disease e.g., impaired glucose metabolism and acetyl choline synthesis. The modern lifestyle diseases, e.g., obesity, diabetes etc increase the risk of dementia (Steen et al., 2005). Diabetes may increase the neuronal damage by increasing oxidative stress and advanced glycation end products; reduced acetyl choline synthesis due to defective glucose availability and insulin effects on amyloid-beta metabolism and vascular pathology (Talbot et al., 2012). Exposure to air pollution results in occurrence of brain inflammation at early age and accompanies early cognitive impairment. Pollutants trigger inflammation, cytokine production and activation of microglia, with secretion of added set of cytokines. The latter promotes inflammation as well as neurodegeneration. 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 (Bezzi et al., 2001 and Schneider et al., 1998 and Avital et al., 2003). 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. They are over-expressed during neuroinflammation, when they may impair synaptic plasticity and cause neurodegeneration. Synaptic balance of pro and anti inflammatory molecules determines synaptic and neuronal effect of cytokines.

Environmental impact on social brain structures

There are infinite possible combinations of chemical influences and there are differences in vulnerability to their effects in individuals. Identification of specific etiological culprit chemical in affected individuals is a major challenge. This is however indispensable to find, to then tailor unique treatment strategies against resultant disorder, like autism. Mirror neuron dysfunction concept helps to narrow down contemplations. Thus, what may have caused dysfunction at biochemical level? Are there imbalances caused in brain function, what invasive chemicals are detected and in what quantity in tissue and body fluid, etc.

In the cerebellum, Purkinje cells are exceptionally large inhibitory neurons, which receive input from parallel and climb fibers at over 200,000 connections. This makes these cells particularly sensitive and also selectively vulnerable to changes in the environment. Purkinje cell loss in the cerebellum is one of the most consistent neurological abnormalities found in autistic individuals. Normal functioning of cerebellum is most critical during early stages of development, before significant learning takes place. A performance requires deliberate thought facilitated by cerebellar activity, before associate learning has occurred and specific neural connections are established, that allows automatic performances (Courchesne, 1997). Neuronal dysfunction within cerebellum, including Purkinje cells occurs early in development of an autistic individual (Kern, 2003). The postnatal period involves the development of network processes and synapse formation, which is altered in autism. Mirror neurons may also be affected by improper connectivity or, "wiring problems" in the brain. The dysfunction may arise if neurons become incapable of sending signals to appropriate destinations. The mirror neurons provide an example of the fact that dysfunction of any particular neuronal group may cause some symptoms of autism. Purkinje cells demonstrate neuronal vulnerability to environmental insults, specially chemical and biochemical toxins (Kraskov et al., 2014 and Coude et al., 2016).

The acquisition of new social skills requires the construction of new neuronal structures including sufficient plasticity for synaptic re-arrangements. Active neurogenesis in amygdala and hypothalamus is known to occur in adults. Amygdala is a cerebral region associated with emotional integration of daily experiences and is closely associated with hippocampus. The active neurogenesis in amygdale is integrated with emotional process. Dysfunction of neurogenesis in amygdale is thus, a contributory cause of autism. Toxic substances can directly affect neurons or indirectly produce consequences by altering the natural neurotransmitters, growth factors and hormones. They may cause deregulation of neurogenesis, neuronal differentiation, axon myelination and synaptogenesis. Altered levels of neurotransmitters, eg GABA, may affect neuronal integration and inter-neuron migration. Under-connectivity and decreased gray matter is caused in prefrontal motor cortex, belonging to mirror neuron system, as well as "malformation of neural networks", in other cortical areas associated with empathy (shared thinking) (Hadjikhani et al., 2007).

Compensation and recovery: The network view of social brain

Network perspectives are now being widely applied in study of neurological and psychiatric patients (Menon, 2011; Castellanos and Proal, 2012), representing shift of emphasis from specific brain regions to specific brain networks. Considerable advances have been made in dissecting the brain in to functional network components, using resting state functional neuroimaging profile (Yao et al., 2011), and particularly, identifying networks that are activated during performance of specific social tasks (Simmons and Martin, 2012). The recent focus of social neuroscience has been on dissecting the default mode network in to subcomponents (Mars et al., 2012), partly because the individual components overlap with those assigned to the "social" brain and partly because, abnormal default mode networks have been implicated in many psychiatric and neurologic illness (Buckner et al., 2008 and Broyd et al., 2009). Disordered network is a pattern that has been observed in many different types of brain diseases, ranging from Alzheimers disease, brain tumors, depression to schizophrenia (Micheloyannis et al., 2006; Rubinov et al., 2009 and DeHaan et al., 2009).Network randomization(disorganization) charecterises the relatively severe and advanced brain disease.In other conditions,brain networks shift from global to local connectivity. In developmental disorders (Barttfeld et al., 2011) and in early stages of neuropsychiatric disease (Sendina-Nadal et al., 2011 and Pijnenburg et al., 2004),there is pathological increase in "network regularity".A syndrome among gulf war veterans with cognitive deterioration and multisymptom illness, described as Toxicant Induced Loss of Tolerance (TILT), is also increasingly seen in Chinese industrial work force. It is understood to result from exposure to chemicals.

Clinical perspectives

Varied environmental pollutants have a negative impact on developing central nervous system . 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.The cognitive deficits result from reduced brain connectivity (Glascher et al., 2009; 2010 and Woolgar et al., 2010),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 (Calderon-Garciduenas et al., 2011). Compensation through contralateral homologue structures, as well as through top-down strategies needs to be explored. This may include changes in lateralized activation and in recruitment of prefrontal regions. These mechanisms may also explain less lateralized brain activation in normal aging (Cabeza et al., 2004), with more dependency on prefrontal regions (Park and Reuter-Lorenz, 2009). Various neuropsychiatric disorders, ranging from frontal lobe damage (Dumasio et al., 19940), to amygdale lesions (Adolphs et al., 1994), autism (Yagmurlu et al., 2005) and Williams syndrome (Bellugi et al., 1999) may have much greater social then personal behavior disorder. Additional more specific dissociations in social functioning can be

made without differences in genetic and neurobiological details. Conceptuallization of an impairement now draws input from information of relationship of specific brain region/s and specific brain function/s.

Research perspectives

Functional Magnetic Resonance Imaging (fMRI) helps to identify regions of healthy brain involved in or sufficient for particular function. The lesioning studies reveal, which nodes of the network are necessary for a function and when damaged, compromise that function. Changes in one region of the brain over a period of time affect the functional structure of other brain regions, which are functionally or anatomically connected, with distal effects in peripheral as well as the central nervous system (Waller, 1850). Research goes on to identify sets of brain structures that constitute networks and systems functioning at certain levels in the social brain. Research in to social dysfunction of neurological and psychiatric disorders should focus on the core set of brain structures that constitute the social brain and their connectivity. Continuous addition to list of structures and networks that constitute social brain would help systematic definition of the neural basis of social cognition.

Pollution can impact gene expression through range of mechanisms. Gene-environment interaction approach assumes that disorder results due to environmental agents and genes influence susceptibility to the agents. Mental disorders have environmental etiologies and there is heterogeneity in response to them among exposed people (Moffitt et al., 2005).Genotypic susceptibility to pollutant induced neurotoxicity is exemplified in Apolipo protein E (ApoE) deficiency that causes susceptibility to oxidant stress (Campbell et al., 2009). Epigenetic effects lead to imprinting, gene silencing and suppression of expression (Lu et al., 2006). Epigenetic mechanisms of pollutant mediated neurological damage have been demonstrated (Gong et al., 2010).

Genotype-environmental exposure response can be examined on functional neuroimaging (Hariri et al., 2006), 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 (Collins, 2004). Malnutrition associates with a range of neurodevelopmental, neurological and psychiatric disorders, commonly with involvement of both central and peripheral nervous system. In some cases, under nutrition may be a prerequisite for manifestation of neurotoxicity (Spencer and Palmer, 2012; Pandey and Pandey, 2013 and Pandey et al., 2014). Effective treatment should provide both trophic and neurochemical support to enhance and maintain normal synaptic connectivity for normal effective function 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. (Kalivas and Volkow, 2011 and Chen et al., 2010).

Hazard identification and risk assessment technology should be apt to identify and encompass progressive and cumulative neurotoxicity of mixed pollutants. They interact, not necessarily system wide but by different regions of brain, outcome measure, gender and age (Quaak et al., 2013). "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 (eg. By multiple agents or combined with multiple risk factors),the limited homeostatic capabilities of brain are overwhelmed and sustained or cumulative damage accrues as the consequence (Cory-Slechta, 2005).A prospective mother child cohort, following subjects prenatally until adulthood, could be used to relate data from neurotoxic exposure to information on behavioural development throughout life, focusing upon "disconnect" behaviours. Human developmental neurotoxicity can be delineated better by continuous integration of any exposure data and reports of toxicity testings. Significance of differences in dose, time and length of exposure as well as, critical windows need determination in respect to neurotoxic exposure, specially during early development.

Physical environment, biology, lifestyle, the social environment and health care are the five broad determinants of health (Zhang and Fan, 2013). People respond to hazards according to their perception of risks that they pose. Risk perception is the focus of many social science investigations and actions. Grouping of health risks in to environmental, technological and social may be effective in better "dread" perception. Dread perception of the hazard most facilitates formulation and implementation of environmental policies, especially, effective educational campaigns (Zhang and Fan, 2013). Superior social, mental and physical activities, inversely relate to risk of cognitive decline and dementia. Neurogenesis particularly increases in hippocampus by such enriched environment.

Conflict of interests

There are no conflicts of interests.

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