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Neurophysiology of Social Conduct and Impact of Adverse Exposures

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Abstract

Human social conduct draws upon focal as well as global connected brain mechanisms. These flexible anatomical routes operate in cooperation and coordination for intelligent behaviors. Cues and inputs from human social interaction are processed with reference to innate and acquired mental framework, and inference is drawn toward generation of appropriate output (response).The focal and global connections are being characterized with functional neuroimaging technology. Brain mapping approaches have facilitated comprehensive understanding of network neurophysiology. There is increased knowledge of pollution threats to delicate neural architecture operating the social conduct, which is a challenge to the quality of personal and social life. The most vulnerable periods are early developmental stages and later during aging. Such kind of distortion is speculated as a possible basis for the hatred held by Hitler. This article briefly introduces related neurophysiologic and neurotoxicological perspectives; moreover, the interdisciplinary research perspectives relevant to development of preventive and corrective interventions are deliberated upon.

Keywords: Cognitive Neuroscience, Environmental Toxicology, Neuronal Networks, Neurotoxicology, Social Cognition

1. Introduction

Brain receives and integrates signals and then appropriately responds as survivalist function. Complex assets as cognition, awareness, memory, and language are supported by the brain. Responses include sexual behavior, locomotion, and use of varied tools, and tricks. Human brain consists of over 100 billion neurons, processing and transmitting information as electrical signals. Structural and functional neuronal networks affect information processing and mental representations. Neuronal communication takes place at synapses. The plasticity of synapses forms a basis for learning and memory in the brain. Information in the brain is stored in form of altered structure and chemistry of synapses involving continuous making and unmaking of synapses (1). Precise control of molecular and cellular mechanisms of synapse development and connectivity is crucial for normal network activity and brain function. Inappropriate loss of synaptic stability may lead to disruption of neuronal circuits and brain disease. Understanding brain disorders is 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 influence the function of the nervous system. Toxicant induced aberration in any such organ system would reflect in a changed neurobehavioral output.

Neurotoxicity of environmental chemicals is gradual with early manifestations of mere subjective complaints, eg, lethargy, fatigue, weakness, irritability, headache, and depression. Intelligence, memory, emotion, and other complex neural functions can also be affected. Low level exposures to certain toxicants can inflict subtle functional deficits, which may be examined by available technologies. Alzheimer disease, Parkinson disease, and even cerebrovascular lesions may be associated with ambient pollution. The rapid rise in the environmental pollutants calls for the availability of appropriate medical care against toxic exposures. Toxicant heavy metals, pesticides, plasticizers, endocrine disruptors, and variety of neurotoxicants need timely recognition and attention. Exposure to chemicals, a possible basis of neurobehavioral problems, must be ruled out. Collection of clinical and epidemiological data should be prioritized in every instance of suspected neurotoxic exposure.

2. Neuron Network Pathophysiology

Description of neuroanatomical projection paths in the brain white matter and acceptance of “associationistic” models of cognitive function helped develop the concept of network in neurology (2). A healthy brain self-

organizes toward small world networks, characterized by dense local connectivity and critical long distance connections formed under genetic control, which underlie cognition and intelligence. Disruption of optimal brain network typically characterizes neurologic diseases (3).

Brain is a large complex network of interconnected elements at multiple scales (4). Brain networks are disassortative rather than assortative at the neuron level (5). Brain is organized as a communication network at the cellular level. Brain is organized as a social network at the macroscopic level. A core of white matter network exists, which densely interconnects posterior and medial cortical regions (6) and association cortical hubs (7) and has longer range of white matter connections with the rest of the brain. Network of human brain displays opposite patterns of mixing at different spatial scales. Functional brain network shows evolution from more random (scattered) to more small world like form (8, 9). Optimal small world pattern of adult age is gradually replaced in older age by more random topology again (10). A study of people with schizophrenia showed that their grey matter network was typified by increased physical distance or inefficient wiring between connected nodes. The hierarchical organization of the cortex is attenuated, indicating abnormal neurodevelopment (11).

Findings suggest that structural and functional networks are heritable and change with normal aging. Abnormal network function associates clinical disorders. Network carries a persistent or long memory component (12), but quickly adjusts to behavioural changes or cognitive demands (13). Brain networks are dynamically in critical state on the edge of chaos, which facilitates rapid reconfiguration in response to altered inputs (14).

Interregional synchronization or effective connectivity characterizes healthy brain functioning. Strength of interregional synchronization depends on age. Long distance synchronization is relatively low at birth, but it increases during development with maturation and myelination of long distance association pathways. The strength of synchronization between different brain regions fluctuates due to rapid formation and dissolution of functional connections. Brain networks apparently represent solutions to yet unclearly defined problems of neurophysiology.

The new network associated with attention demanding tasks is called task related network. The network operating stimulus independent thought at rest is called default network. The 2 networks are negatively correlated (anticorrelated). Anticorrelated networks are complementary ways of understanding, self- monitoring, and task performance. The default mode is defined as baseline condition of the brain function. The magnitude of default network connectivity correlates with psychopathology. Hyperactivation (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 to executive functions. These neurons are latest to evolve, and hence lack genetically fostered defence against stress. They are most susceptible to oxidative damage (15). VENs are instrumental in switching between the default mode resting state and task related attention and executive networks. Network switching is disturbed in neuropsychiatric disorders (16). Most such disorders are linked to neuroinflammation and glutathione depletion. Anything that calms the inflammation in VENs will help normalize network transformations, free the VENs to process higher nervous functions and reduce progression of many neurocognitive disorders.

Understanding of the pathogenesis of human disorders associated with axonal or synaptic lesions requires the understanding of synaptic neurobiology (17). Several biochemical steps of synaptic transmission eg, calcium signal, glutamatergic, and NO dependent mechanisms were shown to be altered upon exposure to ubiquitous pollutant bisphenol-A via mediation of non- classical estrogen receptors (18-21). Direct in vitro neural effects of bisphenol-A may indicate a wider impact on synapse physiology and neuron network function and its consequences to health (22, 23). Additional effects on synaptogenesis regulated by genes products and epigenetic factors need understanding of the pathogenesis of conditions in which morphology appears normal, but with functional disorder (24).

3. Social Cognition

Social cognition is exemplified as we look at somebody and speculate on his/her intentions/action agenda. This does not happen when one looks at inanimate objects. Social cognition implies the processing of information about and directed toward other people. Cognitive processing includes perception, reasoning, memory, attention, motivation, and decision- making that underlies social functioning. Social functioning is a broader concept than social behavior. It refers to long- term contextualized ability of an individual to interact with others.

Specialized brain cells called mirror neurons moderate our observations and interpretations of other people actions to speculate about their intentions. The later serves the inputs that govern our reaction/ response (25, 26). Dysfunction of the mirror neurons is associated with autism spectrum disorder (ASD). Afflicted individuals lack

the knowledge for appropriately interacting with other people and lack the ability to empathize (share thoughts and feelings) and imitate. Typically, they fail to make eye contact, which is vital for interaction. Mirror neurons provide understanding of the actions, thoughts, and emotions in others through an ability to see actions and behavior of others as conveying the following message: like me. The mental simulation allows the observer to understand another person's behaviors and feelings, or to have a theory of mind, which the autistic child lacks. The mirror neuron dysfunction implies pathophysiological role of various neurochemicals. There is manifest loss of Purkinje cells and associated physiologic dysfunction (27).

Psychiatric disorders involve difficulties in social functioning that result in further changes in the brain and cognition (28). Stress of alienation in city life involves specific changes in regional brain activation and increases risk of schizophrenia (29, 30). Social cognition is implemented by social brain networks and the cognition causes social behavior. Social cognition is highly context dependant, involving critical depths of abstraction, inference, and counterfactual thinking. Extended tuning with particular social context and culture during development is needed for social cognition. Social cognition is highly variable and communal in nature. Thus, to an extent, social functioning can be compensated by behavior of others in a supportive environment. The network function generally depends on rapid, efficient, and interactive processing. Even mild dysfunction in any structural component can result in network impairment. The wider spread of brain components/regions involved in social cognition makes it vulnerable to damage. Compensation through unaffected components of network can help in recovery.

Sharing a focus of attention with other individuals bestows socially learned and exercised skills such as language. Autism is a state of severe social disconnect. Autistic children are deficient in attention sharing ability and consequent learning. They cannot focus their attention on the same object to grasp their own perspectives and those of others. The disability for joint attention is the result of mirror neuron dysfunction.

4. Organic Brain Disease and Social Cognition

Social behavior is learnt through a prolonged period of development amid social context. Social impairments are seen after damage to prefrontal cortex or amygdala. Most severe impairments happen when damage occurs during early development (31-33). Bilateral damage causes more profound social impairments 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 (34), especially the value related to social emotions (35, 36). Studies of lesions in prefrontal cortex and amygdala have revealed the role of emotions in social cognition that motivate and guide complex social behaviours (37).

Neuropsychiatric disorders may be understood in the context of anatomically distributed networks comprising several structures. They also feature a prospect for compensation in the event of single structure damage. Damage to connecting white matter can also compromise network integrity and function (38, 39). The consequences are more severe when more medial structures accrue lesion than lesions of lateral structures (40).

5. Psychiatric Diseases and Social Cognition

Autism spectrum disorders (ASD) are a collection of neurodevelopmental disorders (41). Many people with ASD have above average IQ, yet have severe difficulties in social interaction due to disorder of brain connectivity (41, 42). Several studies have shown abnormal connectivity precisely between the components of social brain (43, 44). Williams syndrome (WS) is opposite social phenotype of autism and afflicted patients' approach to strangers. ASD victims in contrast avoid strangers (45, 46). WS patients abnormally rate faces as trustworthy, while ASD patients do not (47). Such phenomena provide evidence that representation of other peoples' mental states and recognition of their faces may be 2 distinct and dissociate processes (48).

6. Environmental Challenge to Social Cognition

Many novel disorders have emerged over the last century in parallel with rise of manufactured chemicals and drugs (over 3000 numbers), electromagnetic fields, and widespread application of diverse technologies. Chemicals at levels below safety thresholds can act by mimicking hormones and other signaling and regulating molecules (49). Combined toxic exposures impact in unique fashions over the years. They can adversely affect fetal neuronal circuits at critical stages of development. Excess oxygen radical generation, impaired synthesis, and enhanced degradation of long chain fatty acids, which are promoted by many pollutants, compromise cognitive function. Many pollutants impair synthesis and function of thyroid and gonadal steroid hormones with adverse consequence to cognitive function.

Persistent organic pollutants cause neuroinflammation and are associated with chronic diseases as obesity, diabetes, and atherosclerosis. The modern lifestyle diseases, eg, obesity, diabetes etc. increase the risk of dementia (50). Diabetes may increase 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 (51, 52). Inflammatory disruption of insulin signaling in the brain may contribute to abnormalities that are commonly observed in Alzheimer disease, eg, impaired glucose metabolism and acetyl choline synthesis. In uninjured brain, pro- and anti-inflammatory cytokines are expressed at low basal levels. They serve an essential physiological role in the regulation of bidirectional glioneuronal communication and in modulation of synaptic plasticity (53-55). 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. Net synaptic and neuronal effect of cytokines depends on the synaptic balance of pro- and anti- inflammatory molecules. Pollutants trigger inflammation, cytokine production, and activation of microglia, with secretion of added set of cytokines. Exposure to air pollution results in occurrence of brain inflammation at early age and accompanies early cognitive impairment.

7. Environmental Impacts on Social Brain Structures

Combined chemical influences can be infinite and vulnerability of exposed individuals may vary. Identification of culprit chemicals in affected individuals to devise unique treatment strategies against resultant disorder like autism is a major indispensable challenge. Mirror neuron dysfunction concept helps narrow down the investigation of what may have caused dysfunction at biochemical level. The concept also facilitates coherent understanding of the imbalances caused in brain function vis-a-vis detected invasive chemicals and their quantity in tissue and body fluid.

Normal functioning of cerebellum is most critical during early stages of development; and performance requires deliberate thought facilitated by cerebellar activity before the associative learning occurs and specific neural connections are established to allow automatic performances (56). Neuronal dysfunction within cerebellum including Purkinje cells occurs in early development of an autistic individual (57). In the cerebellum, Purkinje cells are exceptionally large inhibitory neurons, which receive profuse inputs (over 200,000 connections) from parallel and climbing fibres; 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. The postnatal period involves synapse formation and processes of network development, which is defective in autism. Mirror neurons may be affected by improper connectivity or wiring problems in the brain and serve an example to prove that dysfunction of any one particular neuronal group may contribute to symptoms of autism.

Acquisition of new social skills requires the construction of new neuronal structures with sufficient plasticity for synaptic rearrangements. Amygdala is a cerebral region involved in emotional integration of daily experiences and is closely associated with hippocampus. Active neurogenesis in amygdala and hypothalamus is known to occur in adults, who are integrated with emotional process. Toxic substances can directly or indirectly affect neurons altering function of the natural neurotransmitters, growth factors, and hormones. Toxicants may deregulate neurogenesis, neuronal differentiation, axon myelination, and synaptogenesis. Disruption of neurogenesis in amygdale contributes to autism. Decrease of gray matter and under connectivity in prefrontal motor cortex bearing mirror neuron system as well as malformation of neural networks in other cortical areas impairs empathy(shared thinking) (58).

8. Compensation and Recovery: The Network View of the Social Brain

Network concept is being widely applied in study of neurological and psychiatric disorders (23, 59, 60) and represents the shift of emphasis from specific brain regions to specific brain networks. Considerable advances have been made in defining components of functional brain networks. Resting state functional neuroimaging is used to identify networks that are activated during the performance of specific social tasks (61, 62). Social neuroscience research is focused on defining subcomponents of the default mode network (63). Abnormal individual components of default mode networks have been implicated in many psychiatric and neurologic illnesses (16, 23, 64). Disordered network is a pattern that has been observed in different types of brain diseases, ranging from Alzheimer disease, brain tumors, and depression to schizophrenia (65-67). Network randomization (disorganization) characterizes advanced brain disease. In other conditions, brain networks shift from global to local connectivity. In developmental disorders (68) and in early stages of neuropsychiatric disease (69, 70), there is pathological increase in network regularity.

9. Clinical Perspectives

Environmental pollutants, chemicals, metals, and drugs have a negative impact on developing central nervous system. The cognitive deficits result from reduced brain connectivity (71-73) in heavily exposed children. The deficits correlate the localization of the substantive white matter changes in parietal and temporal lobe with impaired functions (74). Childhood and adolescence are crucial periods of brain development associated with dynamic behavioral, cognitive, and emotional changes. If cognitive abilities are reduced during the critical developmental yeas, detrimental consequences to the society are enormous.

Compensation mechanisms through centralateral homologue structures as well as through top down strategies such as lateralized activation and recruitment of prefrontal regions should be further studied and understood. These mechanisms may also explain greater dependency on prefrontal region with less lateralized brain activation in normal aging (75, 76). Across the neuropsychiatric disorders, ranging from frontal lobe damage (77) to amygdale lesions (78), autism (79), and Williams syndrome (80), social behavior could be disproportionately affected relative to nonsocial behavior. Knowledge of the relationship between specific brain region/s and specific brain function/s helps understand such disorders. Knowing which brain networks are activated during a particular task (and genes associated with particular process) is very useful in this respect.

10. Research Perspectives

Functional neuroimaging technology (eg, fMRI) helps identify regions involved in or sufficient for a particular function in a healthy brain. The lesioning studies reveal which nodes of the network are necessary for a function. Protracted changes in one brain region affect the structure of other functionally or anatomically connected brain regions with distal effects in peripheral as well as the central nervous system (81). Research in to social dysfunction associating neurological and psychiatric disorders should focus on the core structures that constitute the social brain and their connectivity. Continuous additions to list of such structures and networks would refine the definition of neural basis of social cognition

Mental disorders have environmental etiologies, and there is heterogeneity in response to them among the exposed people (82). Gene-environment interaction approach assumes that a disorder occurs due to environmental agent and the genes influence the susceptibility to the agents. Genotypic susceptibility to pollutant induced neurotoxicity is exemplified in ApoE deficiency and other types of susceptibilities to oxidant stress (83). Pollution can impact gene expression through variety of mechanisms. Epigenetic effects lead to imprinting, gene silencing, and suppression of expression (84, 85). Epigenetic mechanisms of pollutant mediated neurological damage have been demonstrated (86).

Genotype interaction with environmental exposure may create phenotype with typical neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, emotional, or neuropsychological measures. The later have been examined with functional neuroimaging (87) and assessed indirectly by EEG, electrodermal and heart rate reactivity, and hormonal responses. States of protein, calorie, vitamin and/or mineral undernutrition are associated with a range of neurodevelopmental, neurological, and psychiatric disorders involving both central and peripheral nervous system. Undernutrition can modify the risk of chemical induced neurologic disease and may even be a prerequisite for manifestation of neurotoxicity (88-90). Epidemiological cohort studies should collect neurophysiologic measurements of individual differences, which should help the integration of epidemiological and experimental research observations (91).

Risk assessment technology should identify and assess progressive and cumulative neurotoxicity of mixed pollutants that may selectively affect different regions of the brain as per gender and age (92). The multi-hit hypothesis of neurotoxicity assumes that the brain may readily compensate for an insult caused by a singular agent on the 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 and/or multiple risk factors), the limited homeostatic capabilities of the brain are overwhelmed and sustained, or cumulative damage accrues as consequence (93). A prospective mother- child cohort following the participants since prenatal period until adulthood could facilitate the relating data from neurotoxic exposure to information on behavioural development throughout life with particular focus on disconnecting behaviors. Significance of differences in dose, time, and length of exposure as well as critical windows need to be determined in neurotoxic exposure, especially during early development. Human developmental neurotoxicity can be delineated better by databases that continuously integrate any exposure data and report toxicity testings.

To enhance and maintain normal synaptic connectivity, effective treatment should provide both trophic and neurochemical support. Optimal functioning of cortical circuits for effective network function may then be rein-

stated by proper chemical signaling. Relevant drugs currently available for regulating plasticity include inhibitors of glutamate release, NMDA antagonists, cAMP phosphodiesterase inhibitors, and glucocorticosteroid receptor antagonists, etc.

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