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Brain-Gut Molding Aberrant Development Trajectory in Autistic Children

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Review

Autism spectrum disorders (ASDs) are neurodevelopmental disorders. Many divergent pathogenetic views are currently present. Atypicality's of structural and functional development of the brain have been used to explain ASD, but yet inconclusive. A recent paper tried to demonstrate these prenatally and perinatally (hypoplasia of the pons just after neural tube closure; and a deficient GABA developmental switch in the perinatal period) [1]. Nevertheless, these specific prenatal and perinatal causes are expected to be infrequent. Yet ASD is common, affecting up to 2.25% of children [2,3], even prevalent with parents highly educated. Pathogenesis is also sought for genetic and environmental factors yet ASD etiology remains unknown [4].

The difficulty to find the etiology throughout the years may imply complex causes that work together in bringing forth an autistic child. And these factors may sequentially perpetuate the problem. Assembly of the developing nervous system for a final functional neural circuitry is dependent on a series of temporally regulated developmental processes.

Explaining Autism Neurologically

Development follows senses and stimulation. Thus, as past socio-medical approach to ASD became more sophisticated, the social motivation theories were used to explain the ASD manifestations of stereotypical behavior, communication, and social interaction deficits. The hypothesis suggests that early neurobiological difference in response to social input could lead to weakened social motivation, and in time motivation for restricted interests increases [5].

Carried these up the brain, cognitive models developed. These include domain-specific models elaborating primary deficit in social cognition, and domain general models elaborating primary deficit in nonsocial or domain-general processing. The disrupted cerebral connectivity hypothesis postulates that its clinical symptoms originate from deficiencies in the way the brain coordinates and synchronizes activity amongst different brains regions [6].

More understanding starting from Gut Microbiota

The gut microbial community is dynamic during the first 3 years of life and then stabilizes to an adult-like state [7]. Gut bacteria influence the central processes through their ability to synthesize neurotransmitters including gamma-aminobutyric acid, noradrenaline, and dopamine, modulate activation of the immune system, and produce metabolites, such as short-chain fatty acids that possess neuroactive properties [8]. Research has demonstrated the association between gut microbiota and early cognition in human infants. Fecal microbial community diversity in infants affects later Mullen score (scale of early learning), visual reception scale, and expressive language scale at two years of age [9].

Early life stress during this critical period can induce alterations in many body systems. Time windows of microbial community might be critical in shaping the brain function and have long-lasting effects on behaviors. Perturbations in the delicate synergetic host- microbiota relationship may have serious consequences and lead to brain, digestive, and metabolic disorders [10].

The microbiota–gut–brain axis exerts a profound influence on key brain processes, such as neuroinflammation, activation of the stress axes, neurotransmission, and neurogenesis, in addition to modulating complex behaviors, such as sociability and anxiety [11].

Neuroinflammation-related brain injuries are associated with [12] and cytokine imbalance is involved in ASDs [13]. Neuro-inflammation contributes to a significant subset of ASDs [14].

Gut - more than just Microbiota

During rapid volume growth of cortical gray matter in the first 2 years of life, certain brain regions, notably those around information processing sensory modalities, develop faster. These regions include the inferior frontal gyrus and angular gyrus, cortical regions involved with language, the fusiform gyrus, involved with face recognition and color processing and the inferior temporal gyrus, involved with higher-order visual processing, including shape and faces. Oddly, the insula is also one of the most rapidly growing regions. In fact, the insula is involved with awareness of interoceptive or visceral sensations, pain, body movement, emotions, vocalizations, and perhaps even consciousness [15-16]. Visceral sensations develop as the enteric nervous system (ENS) develops during interactions of the neural crest-derived precursors (mostly vagal neural crest cells [17]) with the enteric microenvironment.

Luminal stimuli activate mucosal enteroendocrine cells and initiate peristaltic and secretory reflexes [18]. Besides the mainframe brain, some called ENS the 'little brain'. The ENS is a division of the autonomic system put in close apposition to effector systems it controls; enterohormones also co-working.

Memory also related to Gut feelings

Hippocampal volume rapidly increases in the first two years of life [19], though less in the first year compared with the other subcortical structures. With more mobility of the child in the second year of life, hippocampus becomes one of the faster growing structures, as it supports the acquisition of episodic memory [20] as well as spatial working memory and path integration abilities [21].

The hippocampus is activated by enteric signals through the vagus nerve between the intestinal tract and the brain [22]. The hippocampus is linked with learning and memory control and with feeding behavior [23]. Vagus nerve stimulation enhances memory [24], facilitates hippocampal neurogenesis, increases hippocampal expression of brain-derived neurotrophic factor [25] and induce neuronal plasticity [26]. Neurogenesis with new neurons continues in the hippocampus to play an important role in learning and memory and responses to stress, even till adulthood [27].

Dopamine dysfunctions have been reported in ASD, and autistic-like behavior could arise from dopamine dysfunctions in midbrain dopaminergic modulatory systems affecting social motivation and goal-directed motor behavior [28]. Dopamine affects plasticity, synaptic transmission and the network activity in the hippocampal circuitry for memory [27]. Findings suggest that while memory representations are processed and activated by the hippocampus in both ASD and controls during successful retrieval, these are not searched for, transferred, or monitored in an efficient way during episodic memory retrieval as a result of widespread disrupted connectivity [29].

Aberrant development Trajectory in Autistic children

The developmental trajectory before the preschool years is determined by a combination of internal biologic variables and environmental influences [30]. It depends on the performance level at the onset and the rate of change and direction of deviation. Memory deficits in ASD driven by retrieval-related impairments reduce their probability of recollection success [29]. As it biases the individual's social motivation in a more or less fixed environmental structure, the individual conforms with a self-concept and self-worth in a fairly fixed trajectory pertaining to himself. Though parenting style and learning environment can have significant effects, the individual developmental trend of mental functioning at a different level and discrimination tends to be fixed. This could lead to diminished social motivation and increased activation to stimuli associated with their restricted interest and thereby the typical ASD manifestations.

Developmentally, visceral sensations and the enteric nervous system develop together. Stimulation with external or internal (visceral) information is important for developing functional networks and refining synaptic plasticity. A study noted infants with sleep restlessness starting after 3 months old can recover with peaceful sleep by 3-5 courses every 7-10 days of chlorpheniramine 1mg and duphalac 2.5ml daily for 3 days [31]. During early development, time windows shaped by enteric microbial assembly and cortical neuro connectivity may shift developmental trajectories for brain function and behaviors.

ASDs having neuro-inflammation with deviations in gut microbiota, and problems in acquisition of memory and path integration abilities related to affected hippocampus neurogenesis, could set up an aberrant developmental trajectory.

Successful treatment of ASD children with herbs, senna and chlorpheniramine, by improving intestinal transit time, relieving inflammation and improving sleep, noted first and early recovery of the enteric system (appetite, speed of finishing feeds) [32]. Subsequently there was improvement in sleep restlessness, concentration, temper, and school acceptance. Finally, the children had restoration of normal school work and social interaction. Together with the restoration of the internal environment and the management of abnormal processes, ASD children could recover with treatment and restore their useful activities and normal development trajectories.

Aberrant development Trajectory perpetuated in Autism

Aberrant connectivity may lead to structural demonstrable differences in many brain areas, especially for developmental process involved in response to rewarding social input, which in turn may lead to the diminished social motivation. Apart

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from the aberrant connectivity, other issues in ASDs may perpetuate the problem. Brain development including brain cell proliferation, apoptosis, myelination, neurogenesis, maturation and differentiation depend on nutrition and immune development from the gut [33]. The temporal series of adaptive mechanisms would pave the developing nervous system for a final functional neural circuitry.

The treatment report, after enteric restoration, noted that improvement of sleep precedes improvement of other problems [32]. ASD tends to be associated with difficulty in falling asleep, wake up in the night frequently and a low frequency of saccadic eye movement during REM sleep [34]. Slow wave sleep is also shortened in ASD, and sleeping time, particularly the proportion of REM sleep, is reduced [35]. Cerebral plasticity has an important relationship with sleep [36].

Inadequate or poor sleep may foster lasting neural changes as well as changes in functional connectivity after perceptual, motor, or emotional learning tasks [37]. Hippocampus and the ventral striatum are activated during NREM sleep [38], and this may help subsequent performance improvement [39] and consolidate associative memory-reward information [40].

Noted in rats, REM sleep deprivation impairs hippocampal neurogenesis and related memory formation [41]. Emotional off-relevance and motivational biases may misdirect this overnight consolidation of declarative memory and skill learning [42].

Poor sleep, probably disturbed ENS visceral sensations, memory deviations, emotional off- relevance and motivational biases, associative memory-reward value-system, and neuro- inflammation as well as habituated responses to environment make up a set of factors in ASDs that perpetuate the aberrant development trajectory. It deters useful interactions with the environment, leads to the diminished social motivation, biased social skills and restricted interests. Whether due to a circuit dysfunction in reward and motivation, autistic brains would fail to register social experiences as rewarding, further reducing social interactions and social abilities, ultimately leading to heterogeneous social deficits with this “aberrant development trajectory” [32].

Conclusion

ASD may arise from deviated hippocampus memory processing related to brain-gut dysregulation. There is a critical window in early life, when the cerebral cortical networks from neuroconnectivity is adapting to changes, that microbial colonization can influence neurogenesis, including that in the hippocampus. ASDs are associated with neuro- inflammation, and alterations in the gut microbiota can change the developmental trajectory of brain function and behavior.

The vagus nerve of the intestine, with which the enteric microenvironment inputs related memory to hippocampus, will affect neural development for hippocampus. ASD children have memory retrieval-related impairments that reduce the probability of recollection success. These aberrant memory processes, resulting in restricted interest and diminished social motivation. It explains how ASD children have stereotypic interest and behavior, their characteristic communication and social interaction deficits, as well as the presence of atypical mixed picture of neural connectivity.

The developmental trajectory of ASD with perpetuating brain-gut dysregulation, working memory and path integration deviations, poor restoration from sleep all result in related brain function and behavior deviating from normal. A course of Chinese and western medicines has been successful to restore intestinal function, improve sleep, restore normal school work and social interaction. Treatment that normalizes microbiota relieving neuro-inflammation and management of the enteric system can be useful in maintaining signals to the hippocampus and brain for neurogenesis. Together, with improving sleep, restoration of the internal environment and the management of abnormal processes, it is very likely that ASD can be treated to restore their useful activities and normal development trajectories of life.

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