Impact from Early Rings on Rings of Maladjustment in Autism

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Abstract

In ASDs, starting with genetic vulnerabilities which may arise from adaptive mental edging changes on one hand, and perturbed microbiota-gut-brain axis on the other hand, the prenatal setup forms a body core that is in general labile and prone to both mental and physical conditions with functional impairments. The internal processes and external behavior of the brain and body in a self-organized system are mal-set as developmental atypicalities with notable mood and disruptive behavior problems in the neurodevelopmental domain. Modified neuronal networks since early-life depend on the environment and energy/resources provision as well as individual potential and self-regulatory setup for remodeling for emotive or motive activities as these contribute to social engagement, cognitive, social, and emotional growth. The postnatal makeup in ASD is altered during the stages of development from both mental and physical impairments whereby a complexity of atypicalities is developed. Layer upon layer, the rings on rings of maladjustments impair matching capabilities, starting early with visuomotor coordination impairment, suboptimal resource functioning, guarded food selectivity, with related defensive behavior, atypical reward-seeking behavior, and self-stimulatory drives depending on severity. More atypicalities may be derived and evolve further with related guarded social behavior, altered emotion-guided attention in ASD children that may evolve into emotion-evading behaviors, and altered self-relevant reward system that dampens the rewarding nature of social interaction and cognition. Depending on the degree of involvement, this early setup from both mental and physical causality leads to the final ASD symptom complex. This reemphasizes the consideration of physical functional problems, which isolated consideration could have distracted past studies with all along difficulties for finding pathogenesis of ASD. This paper describes the whole problem where the parts aggregate into rings, when rings locked in with another ring, to understand from the parts how they make up the whole autistic spectrum.

Keywords: Autism spectrum disorder; Endowed labile body core; Rings on rings maladjustment; Core and match; Mental-physical causality; Developmental complexity

The Causation for Autism Not Simply Genetic

The knowledge of the strong hereditary of autism is understood 20 years ago. Even not too long ago, progress in the genomics of non-syndromic autism spectrum disorder (nsASD) emphasized investigating rare, large effect, germline, heterozygous de novo coding mutations [1]. Yet after a lot of funded research, deleterious genes are now found surely not contributing to most of the patients. No definite resolute pathophysiology yet can be defined, and it has been exclaimed for “even in the historical present....., a whirlwind of ideas, movements, and positions has littered the autism literature [2].” A report in 2018 showed autistic spectrum disorders (ASD) may fully recover by early treatment [3]. Other modalities like bumetanide used to treat edema may also improve symptoms [4]. Large therapeutic margins may exist postnataally. The time will be
changing with more awareness of postnatal ASD development from early presence of specific combinations of inherited neurobehavioral susceptibilities [5,6]. By reasssembling topical findings, it is found that ASD reality stems from both mental and physical causality [7].

The Endowed Core Make-Up of Autism Is Disturbed

The genetic basis of ASD and its variable phenotypic presentation are complex. The strong heritability is contributed by common genetic variants [8,9] that brought about liabilities for common mental tendencies as well as developmental susceptibilities in individuals prone to ASD. These liabilities express with neurodevelopmental alterations related to a general vulnerability factor for different kinds of neurodevelopmental psychiatric disorders (NDPDs) [10,11]. Notably, such psychiatric disorders were more like each other in genetic profiles, in contrast to neurological disorders that in general markedly vary in genetic background [12,13]. It may be presumed that such neurobiological setup with these common genetic variants, common in human beings, provides a base conducive to development into diversity of phenotypes which by chance would furnish extraordinary abilities on one extreme, but on another end could also be associated with atypicalities often unacceptable in general population norms. These may be called mental edging liabilities, resulting in developmental susceptibilities for NDPDs as well as adaptive phenotypic pliability [7]. An increased dose of deleterious effects of rare inherited, de novo, or somatic mutations contributes to the biased gene sets could also enhance the individual’s susceptibility to ASD [14].

Which developmental period these gene sets carrying the mental edging liabilities are activated could be important. For schizophrenia, related genes are activated later, from infancy through adulthood [14]. For ASD, these are likely to occur prenatally, when early developmental “windows” open to the environment and during which important connections are formed. The pleiotropic loci are located within genes that express diversely in the brain, beginning in the second trimester prenatally, and together with a suite of neurodevelopmental processes, they regulate behavior formation throughout life [15]. The neurodevelopmental manifestations vary as they are subject to developmental molding of the body core and environmental incompatibilities at matching. Individuals affected with ASD may manifest ASD symptoms and impairments with phenotypic diversity.

Lability in ASD affects both physical and mental makeup. The body having neurodevelopmental disorders is also more prone to physical conditions and functional labilities with impairments [16]. Mental lability in disposition is manifested as having mood and anxiety disorders, disruptive behavior disorders, and when older, substance use disorders [17]. The lability set should be better viewed as involving the interdependent brain-body, as the dynamic and complex brain is tightly coupled and integrated with the rest of the body as a self-organized system [18]. Phenotypes are shifted towards having the atypical features of ASD, with phenotypic diversity of ASD symptoms and impairments and with variabilities in autistic traits [19,20]. Environment takes a certain role [21,22]. With the heritability of ASD being between 64 and 91% [23] and estimates never reaching well above 90% [24] even with concordant MZ twins, it suggests a role for non-shared effects such as epigenetic, gene expression, other environmental and/or stochastic factors [25,26]. Environmental effects from air pollutants [27-30] and valproic acid [31] in pregnancy are well noted. While most would tend to agree that autism is caused by a combination of genetics and the environment, there is no specific dominant causation environment.

Prenatal Development of a Disturbed Endowed Core in Autism

Genes relating to neurodevelopment could have effects on synapse formation, neuronal proliferation, growth, transcription and splicing, and chromatin remodeling [32-34]. While these shapes the neural pathways by molecular convergence and specificity towards certain patterns of neuro-connectivity, biased gene sets activated prenatally at developmental “windows” are open to the environment. The final neurobiological architecture has certain lability in disposition. Genes for the individual to react with microbiota may even be affected. Among gene mutations most widely associated with ASD are mutations in genes related to the mTOR pathway [35], which apart from its important role in neurological disorders, is also involved in directing immune responses. ASD-risk factors such as advanced parental age [36,37], low birth weight [38] and multiple births [39] may be related to, at the body core of ASD individuals, their related immune changes, as well as the whole lability in disposition.

Related to deviations in gut microbiota [40,41], brain reactions and neuroinflammation are seen early even since pregnancy [42,43]. Neuroimmune changes in ASD [44] would further enhance core lability, resulting in many functional problems. As immunological dysregulation is not necessarily correlated with the severity of autistic traits [45], it could be more a sign of core lability. The state of the gut and its microbiota priming immune and metabolic functions have a long-lasting modification for developing several physical conditions, including gastrointestinal, allergic, autoimmune, and metabolic diseases [46] as a kind of

altered adaptive neuro-immune function. Maladaptive functional GI problems are particularly common in ASD [47,48].

**Postnatal Developmental Alterations in ASD**

This bias of autistic individuals towards formation of a labile core, being prejudiced by postnatal gut microbiome on the brain as well as by mental edging labilities from genetic makeup, could have subsequent lifetime effects on the development of a full-blown ASD. Each phase of neurodevelopment would produce a set of neurological and somatic base for the next phase of development cascading onto further neuropsychological functions [49-51] along with the common highway of neuro-developmental processes, with the many genetic and environmental biological as drivers building up the ASD makeup (Figure 1).

![Figure 1: The Genetic and Microbiome Setup towards the ASD mal-development. The genetic setup converges to cause brain pathways causing perturbations in neurodevelopment in utero. The genes affect neural pathways starting mid fetal life. Probably earlier than this is the period of migration of immune stem cells and expansion of progenitor cells. Then, maternal microbiota is associated with ASD development. A labile body core is developed consequent from the genetic setup related to other mental-neurodevelopmental disorders and to body immune and neuroimmune perturbations. This labile core features impaired matching capabilities in infancy, and body functional problems especially marked in the intestine. Related autistic atypicalities of repetitive behaviors and disturbed emotion-guided attention started, even manifesting as emotion-averse behavior, social guardedness, food selectivity, food intolerance and food allergy occur in the body-brain domain, while poor development of self-relevance, poor neuro connectivity to large scale brain network occur in the brain-body domain. ASD symptoms and signs become more obvious after infancy (purple).](image)

ASD certainly develop early [52]. However, characterizing behavioral signs are not present early in life and do not emerge until the second year [53], even after attention to subtle representations of autistic traits [54]. Rather than simply genetics forming a dysfunctional ‘social brain network’ [55,56], ASD individuals start with atypical development in early life involving perceptual, attentional, motor, and social systems before the emerging autism phenotype [53]. The margins in developing ASD during postnatal development [6] may be related to core capacity and matching capabilities that influence the fully developed formation [57], as environment and energy/resources provision as well as individual potential and self-regulatory setup allow for internal and external remodeling.

**Developmental Complexity of the ASD Brain-Body Whole**

The genetic convergence on synapse formation, neuronal proliferation, growth, transcription and splicing, and chromatin
remodeling is one part of the starter processes. With general vulnerability prone to mental-neurodevelopmental disorders and starting additionally with influence from deviations in gut microbiota, the body is labile and prone to both mental and physical conditions and functional labilities including intestinal and immunological dysregulation. These physical conditions include gastro-intestinal (GI) dysfunction [58], functional psychogenic abdominal pain in children [59], migraine and primary headaches [60], learning disabilities, attention deficit disorder [61] and sleep problems [62]. Physical and mental processes together on the developmental highway contribute to an aberrant trajectory. There are certainly some atypicalities to start with, yet none singly can account for ASD to develop. Furthermore, oddly for determinists, ASD is not a fixed outcome. The outcome is related to vulnerability to a spectrum of traits: the biological mechanisms being associated with vulnerability starts early in life, to be shaped by postnatal drivers [63]. The final manifestations can be heterogeneous. In fact, at best ASD diagnosis requires a co-aggregate whole [64] or a gestalt [65].

On the highway for this aberrant developmental trajectory, parts contribute to the whole [7]. In this complex disorder, the patterned behavior, the shaped internal patterns in functioning, the stored memory, the further adaptive re-tuning, and the microbiota–gut–brain axis, all exert a profound influence on key brain processes [7]. Not simply a "social brain" pathology to explain for the social development in ASD [53,57], not singly a hippocampal perturbation to explain for ASD memory function impairment [66]. ASDs develop from widespread brain atypicalities, remodeling for internal and external dysmaturation as well as biased emotive or motive activities [7]. In fact, with multiple parts that contribute to ASD, it is not so surprising to see such report that the frequency and severity of nausea and vomiting during pregnancy can affect ASD severity [67].

**Rings Over Rings of Maladjusted Development In ASD**

**Early complexity developmental rings**

Manifested impairments start early with impaired visuomotor weaknesses from subtle proprioceptive and integration-coordination matching problems associated with a labile core [68-70]. The drivers are subtly perturbed. Many seem just functional. Joint attention ability is atypical in ASD, rather than simply being delayed [71,72]. Visuomotor coordinative setup is essential for matching in real time [73]. The worse the onset profile of exteroceptive dysfunction, the more would be the ASD development and abnormal social communication [74].

Dispositional tendencies are ill framed by the labile core and its functional problems as well as by memory mechanisms that are impaired in ASD. The hippocampus expands rapidly in the first two years of life [75], developing at the age when gut development and microbiota are established as visceral sensations and the enteric nervous system develop together. The hippocampus is activated by enteric signals through the vagus nerve between the intestinal tract and the brain [76]. The vagus itself mediates GI-sensory signaling to dorsal hippocampal glutamatergic neurons, facilitates hippocampal neurogenesis [77], and promotes hippocampal-dependent learning and memory function [78]. Functional GI disorders start early. At the same time, the insula cortex, as it expands rapidly in the first year of life, may be perturbed by interoceptive or visceral sensations that it maps.

During development, exteroceptive and interoceptive functions progress and advance together. The body modules, each as subsystems supporting specific functions, are mutually interacting dynamically. Programmed organization upon programmed organization will be reinforced through repeated use and developed further, while social, emotional, and cognitive brain domains develop in parallel. Functional gut dysfunction would have consequent internal resource handling problems. Energy and glucose metabolism are associated with and regulation products can affect synaptic function [79].

Visuomotor impairment and subtle proprioceptive problems causing matching and lateralization disturbances with problems in multisensory integration, impaired chaining abilities and joint-attention behavior, even with low attention to faces and a salience bias (Figure 2). The salience to act in a multi-stimuli environment is further limited by internal resource functioning needed to simultaneously process sensory input. The poorer emotional valence as emotion-guided attention in ASD children [80] is associated with high levels of autistic traits [81]. When grown up, ASD adults [82,83] or those neurotypical adults with high level of autistic traits [84] have the response flattened, not differing. It could be related to the insufficiency of resources in childhood in ASD for salient attention with multiply increased demand for efforts to cater for the many stimuli, getting better in resource allocation and compensated when they grow older [7].

Variations in infants for saliency by attention allocation to their visual social environment [85,86] affect their active shaping of their own visual experiences and development [87]. The affected individual may be obsessed with social visual engagement in the individual’s own ecological niche or becomes emotionally evading to reduce his inherent risk and adversity by active construction and maintenance of an ecological niche for himself that mediates social attachment. Emotion guided attention is dampened. Reduced salience in attention may bring along many sensory modalities

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being affected. Sensory processing problems are noted later mainly after 2 years of age [88-90], affecting any sensory modality [91] with no one modality uniquely a hallmark for ASD [92]. ASD individuals commonly exhibit inflexible behavior and fixated interests. In terms of capabilities, some are innately limited, and some are functionally capped. Atypical brain prediction errors may maintain behavioral and cognitive inflexibility and rigidity in ASD [93-95]. Sometimes, as gaps need be overcome, enhanced attention to details is common, and visual search in ASD would be enhanced and even becomes robustly efficient as an area of strength in ASD [96].

ASD children have comparatively reduced attention and memory for self-relevant objects [97,98]. Social reward from the self-relevant responses of others is less rewarding for adults with ASD [99]. Reward processing deficits [100] correlate with overall ASD symptom severity [101]. Full reward not really achieved, and resource functional suboptimal, autistic tendencies with dampened emotion-guided attention [80] evolve into emotion-evaded behavior. Impaired memory mechanisms, and functional gut problems with interoceptive-exteroceptive maladjustment and feelings further shape the emotional inclination.

**Figure 2:** Rings on rings of atypical development with consequent dysfunctional processes.

To recapitulate, impairments first through primary with genetic adaptive mental edging liabilities and perturbed microbiota-gut-brain axis, develop a labile body core more prone to both mental and physical conditions and functional labilities (Ring 1). Impaired matching to environment is a maladjustment related to impaired visuomotor coordinative setup as well as impaired memory systems associated with gut-vagal dysfunction and microbiota alterations. These have interoceptive and extractive consequences feeding back into a salience bias with poor emotion-guided attention (Ring 2), leading to further secondary altered internal processes and external behavior. With poor assets of an inefficient memory mechanism, neuroimmune alterations, gastrointestinal dysregulation and functional guardedness, the individual could face integration and adaptive problems for the whole person. The labile core manifest with atypical eating patterns and food selectivity highly associated with ASD. Food guardedness may evolve into distaste. Social distaste manifests in time with on-going reward processing deficits and cumulative atypicalities in behaviors reacting in an individual predisposed to ASD (Ring 3). After these rings, the typical ASD may further develop with widespread brain atypicalities while the social, emotional, and cognitive brain domains are developing at the same time. The complexity contributed by both physical and mental impairment is analogous to rings upon rings with organizational consequences upon consequences.

**At worst if distastes developed**

ASD is highly associated with atypical eating patterns [102] and food selectivity [103-106]. Rather than gratification from food, the net experience would vary and ASD children have problems with taste and/or smell sensitivity mealtime problems [107] and regurgitator reflux commonly [108], all suggesting a reactive enteric nervous system with functional guardedness of the GI system.

Along with food guardedness or defensiveness, even tactile “defensiveness” associated with food selectivity has been reported [102,107,109] in children with ASD. Even their skin conductance changes could change with emotional stimuli such as when presented with defense to faces feared [110]. Along with food repulsion and selectivity, food allergies are observed more often in autistic individuals than in the general population [111-113].

Social distaste is not an early primer. Poor social reward and retrieval-related memory impairments additionally drift the child’s development gradually into social distaste. Only with the on-going cumulative atypicalities in behaviors reacting in an individual genetically predisposed to ASD would it evolve and fully manifests in time (Figure 2, Ring 3). Layer upon layer, the rings on rings of maladjustments impair matching capabilities, starting early with visuomotor coordination impairment, suboptimal resource functioning, guarded food selectivity, related defensive behavior, atypical reward-seeking behavior, and self-stimulatory drives depending on severity. More atypicalities may be derived and evolve further with related guarded social behavior, altered emotion-guided attention in ASD children that may evolve into emotion-evading behaviors, and altered self-relevant reward system that dampens the rewarding nature of social interaction and cognition.

**Further ASD Formation**

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With the deranged make-up of ASD set for development (from the microbiota-gut-brain axis, the gut-vagus-hippocampus axis, and the brain-social-cognitive axis) [7], as the individual adapts to the environment, the regional and large-scale brain networks become atypical and build up significant cascading effects on neuropsychological development to form the whole ASD problem. Rings on rings of maladjustment trajectory screw in, and the end can be complex and heterogeneous. Guardedness may accentuate and the poor social-reward system could bring up further secondary consequences with altered internal and external processes and behavior, with the characteristic ASD impairments in social development—stereotypical behavior, communication, and social interaction deficits. Deviated mode and different salient whole may manifest as more calculative rational [114]. With problems in processing information about the “self” and self-relevance, the salience network, and the default mode network (DMN) that mature in later childhood would be drifted into dysregulation or delay and dysmaturation. ASD has dysmaturation of the DMN with relatively late DMN maturation and still under-connected [115-118] to achieve the typical cross-network connectivity [119,120]. Insula activation is also involved and reduced in ASD during social processing [121]. These are associated with alterations in social cognition that are characteristic of ASD [122].

The former multiple neural substrates affected along the highway of neurodevelopment, drive the individual into certain ways of behaving and attention, and mold emotion-guided behavior into dysfunctional processes, which during long-term establishment could lead to secondary deranged cerebral connectivity. Altered variations in saliency, skimping away from poor allocation of resource functioning, social distaste, food distaste with food allergies as worse scenario for ASD can be among the atypical development involving multiple systems including perceptual, emotional, attentional, motor, and social systems that precede the emerging autism phenotype [7]. By this time, large-scale brain network is at fault, not a single regional pathology.

**ASD as a Developmental Complexity**

Complex problems are related to multiple causes each with small but pertinent effects that work together additively or synergistically to affect a significant perturbation. ASDs, mainly contributed by common genetic variants in the population, affect individuals with drastically varying phenotypes even with similar genetic variants. As the parts contribute to the whole, after deeper detailed understanding of the parts [7], the full picture how the parts click into each other would manifest. The increase of mental as well as physical conditions and functional impairments in ASD individuals, the increase risk for immune dysregulation, GI disturbances, and neurologic-psychogenic problems [123,124], and sleep problems in an individual, all predict more severe behavioral symptoms in ASD children [125]. They correlate with atypical eating patterns starting early in life [106], food selectivity [126] and associated atypical oral sensory sensitivity [123], even defensive-refusal mechanisms as gastroesophageal reflux disorder in childhood [108] in a form of body-brain dysregulation with functional psychogenic abdominal pain associated with irritability, social withdrawal, stereotypy, hyperactivity, or inappropriate speech [127], and internalizing symptoms [128-130].

Both mental and physical atypicalities contribute to ASD [128-130]. While initially genetically predisposed, all these in a child develop with widespread brain atypicalities and neuro-connectivity related to exteroceptive and interoceptive dysfunction as a co-aggregate sprouting from rings on rings of impairments [7]. The individual outcome in development will be determined by his biological setup of genetic program modulated by epigenetic forces and by engrained patterns over recurrent contexts of the physicochemical and biosocial environment. Then the whole can be mapped more clearly. Postnatal margin for therapy is there.

**References**


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