

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 postnatally. 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 reassembling 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 liabilities 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 liabilities 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 neurodevelopmental processes, with the many genetic and environmental biological as drivers building up the ASD makeup (Figure 1).

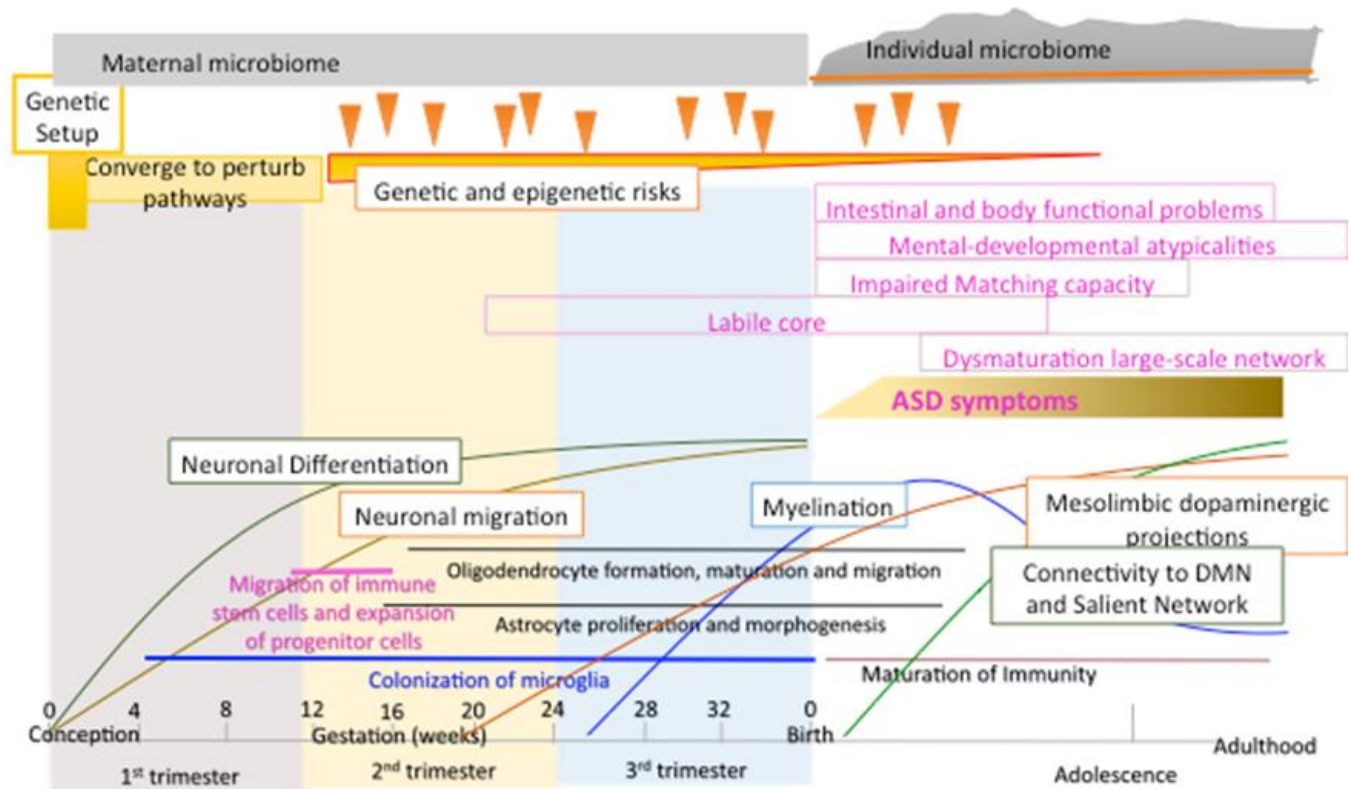


Figure 1: The Genetic and Microbiome Setup towards the ASD mal-development. The genetic setup converges to cause brain pathways causing perturbations in neurodevelopment in utero. The genes affect neural pathways starting mid fetal life. Probably earlier than this is the period of migration of immune 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 immune and neuroimmune perturbations. This labile core features impaired matching capabilities in infancy, and body immune and neuroimmune perturbations. Related autistic atypicalities of repetitive behaviors and disturbed emotion-guided attention started, even manifesting as emotion-evasive 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).

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

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.

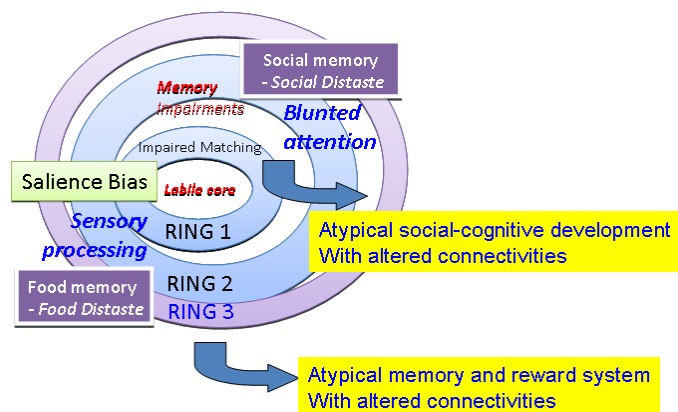


Figure 2: Rings on rings of atypical development with consequent dysfunctional processes.

To recapitulate, impairments first through primary with genetic adaptive mental edging labilities 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

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

1. Sestan N, State MW. Lost in translation: traversing the complex path from genomics to therapeutics in autism spectrum disorder. *Neuron*. 2018; 100: 406-423.
2. O'Reilly M, Lester JN, Kiyimba N. Autism in the twentieth century: an evolution of a controversial condition. In: Taylor S., Brumby A. (eds) *Healthy Minds in the Twentieth Century. Mental Health in Historical Perspective*. Palgrave Macmillan, Cham. 2020.
3. Yu ECL. Neurodevelopment, Intestinal function, and autism. *Neonat Pediatr Med*. 2018; 1000166: 1-8.
4. Zhang L. Symptom improvement in children with ASD following bumetanide administration is associated with decreased GABA/glutamate ratios *Transl Psychiatry*. 2020; 10: 9.
5. Constantino JN. Autistic social impairment in the siblings of children with pervasive developmental disorders. *Am J Psychiatry*. 2006; 163: 294-296.
6. Piven J, Elison JT, Zylka MJ. Toward a conceptual framework for early brain and behavior development in autism. *Mol Psychiatry*. 2017; 22: 1385-1394.
7. Yu ECL. *Developing Autism, The Parts Become The Whole*. Scholars' Press. 2020; 372.
8. Huguet G, Ey E, Bourgeron T. The genetic landscapes of autism spectrum disorders. *Annu Rev. Genomics Hum Genet*. 14: 191-213.
9. Bai D, Yip BHK, Windham GC, Sourander A. Association of genetic and environmental factors with autism in a 5-country cohort. *JAMA Psychiatry*. 2019.

10. Dell'Osso L, Lorenzi P, Carpita B. Autistic Traits and Illness Trajectories. *Clinical Practice & Epidemiology in Mental Health*. 2019; 1745-0179/19.
11. Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, Duncan L. Analysis of shared heritability in common disorders of the brain. *Science*. 2018; 360.
12. Brainstorm C, Anttila V, Bulik-Sullivan B. Analysis of shared heritability in common disorders of the brain. *Science*. 2018; 360.
13. Ayhan F, Konopka G. Genomics of autism spectrum disorder: approach to therapy. *F1000 Research*. 2018; 7: 627.
14. Bakken TE, Miller JA, Ding SL, Sunkin SM, Smith KA, Ng L, et al. A comprehensive transcriptional map of primate brain development. *Nature*. 2016; 535: 367-375.
15. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genome wide meta-analysis identifies genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. 2019.
16. Merikangas KR, Calkins ME, Burstein M, He JP, Chiavacci R, Lateef T, et al. Comorbidity of physical and mental disorders in the neurodevelopmental genomics cohort study. *Pediatrics*. 2015; 135: e927-e938.
17. Lahey BB, Krueger RF, Rathouz PJ, Waldman ID, Zaid DH. A hierarchical causal taxonomy of psychopathology across the life span. *Psychol Bull*. 2017; 143: 142-186.
18. Palacios-García I, Parada FJ. Measuring the Brain-Gut Axis in Psychological Sciences: A Necessary Challenge. *Frontiers in Integrative Neuroscience*. 2020; 13: 73.
19. Rogers SJ. What are infant siblings teaching us about autism in infancy? *Autism Res*. 2009; 2: 125-137.
20. Kim SH, Macari S, Koller J, Chawarska K. Examining the phenotypic heterogeneity of early autism spectrum disorder: Subtypes and short-term outcomes. *J Child Psychology Psychiatry*, 2016; 57: 93-102.
21. Hertz-Picciotto I, Schmidt RJ, Krakowiak P. Understanding environmental contributions to autism: causal concepts and the state of science. *Autism Res*. 2018; 11: 554-586.
22. Bölte S, Girdler S, Marschik PB. The contribution of environmental exposure to the etiology of autism spectrum disorder. *Cell Mol Life Sci*. 2019; 76: 1275-1297.
23. Tick B, Bolton P, Happé F, Rutter M, Rijdsdijk F. Heritability of autism spectrum disorders: a meta-analysis of twin studies. *J Child Psychol Psychiatry*. 2016; 57: 585-595.
24. Ronald A, Hoekstra RA. Autism spectrum disorders and autistic traits: a decade of new twin studies. *Am J Med Genet Part B Neuropsychiatr Genet*. 2011; 156: 255-274.
25. Plomin R. Commentary: why are children in the same family so different? Non-shared environment three decades later. *Int J Epidemiol*. 2011; 40: 582-592.
26. Ronald A, Happé F, Dworzynski K, Bolton P, Plomin R. Exploring the relation between prenatal and neonatal complications and later autistic-like features in a representative community sample of twins. *Child Dev*. 2010; 81: 166-182.
27. Volk HE, Kerin T, Lurmann F, Hertz-Picciotto I, McConnell R, Campbell DB. Autism spectrum disorder: interaction of air pollution with the MET receptor tyrosine kinase gene. *Epidemiology*. 2014; 25: 44-47.
28. Ivon Ehrenstein OS, Aralis H, Cockburn M, Ritz B. In utero exposure to toxic air pollutants and risk of childhood autism. *Epidemiology*. 2014; 25: 851-858.
29. Raz R, Roberts AL, Lyall K, Hart JE, Just AC, Laden F, et al. Autism spectrum disorder and particulate matter air pollution before, during, and after pregnancy: a nested case-control analysis within the Nurses' Health Study II Cohort. *Environ Health Perspect*. 2015; 123: 264-270.
30. Kalkbrenner AE, Windham GC, Serre ML, Akita Y, Wang X, Hoffman K, et al. Particulate matter exposure, prenatal and postnatal windows of susceptibility, and autism spectrum disorders. *Epidemiology*. 2015; 26: 30-42.
31. Ornoy A. Valproic acid in pregnancy: how much are we endangering the embryo and fetus? *Reprod Toxicol*. 2009; 28: 1-10.
32. Gilman SR, Iossifov I, Levy D, Ronemus M, Wigler MVD. Rare de novo variants associated with autism implicate a large functional network of genes involved in formation and function of synapses. *Neuron*. 2011; 70: 898-907.
33. Hu WF, Chahrour MH, Walsh CA. The diverse genetic landscape of neurodevelopmental disorders. *Annu Rev Genomics Hum Genet*. 2014; 15: 195-213.
34. Kiser DP, Rivero O, Lesch K. Annual research review: the (epi) genetics of neurodevelopmental disorders in the era of whole-genome sequencing—unveiling the dark matter. *J Child Psychol Psychiatry*. 2015; 3: 278-295.
35. Ivan Sadelhoff JHJ, Pardo PP, Kraneveld AD. The Gut-Immune-Brain Axis in Autism Spectrum Disorders; A Focus on Amino Acids. *Front Endocrinol*. 2019; 10: 247.
36. Durkin MS, Maenner MJ, Newschaffer CJ, Lee LC, Cunniff CM, Daniels JL, et al. Advanced parental age and the risk of autism spectrum disorder. *Am J Epidemiol*. 2008; 168: 1268-1276.
37. Sandin S, Schendel D, Magnusson P, Hultman C, Suren P, Susser E, et al. Autism risk associated with parental age and with increasing difference in age between the parents. *Mol Psychiatry* 2016; 21: 693-700.

38. Schendel D, Bhasin TK. Birth weight and gestational age characteristics of children with autism, including a comparison with other developmental disabilities. *Pediatrics*. 2008; 121: 1155-1164.
39. Croen LA, Grether JK, Selvin S. Descriptive epidemiology of autism in a California population: who is at risk? *J Autism Dev Disord*. 2002; 32: 217-224.
40. Xu M, Xu X, Li J, Li F. Association between Gut Microbiota and Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. *Front Psychiatry*. 2019; 10: 473.
41. Iglesias-Vázquez L, Van Ginkel Riba G, Arijia V, Canals J. Composition of Gut Microbiota in Children with Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. *Nutrients*. 2020; 12: E792.
42. Lombardo MV, Moon HM, Su J, Palmer TD, Courchesne E, Pramparo T. Maternal immune activation dysregulation of the fetal brain transcriptome and relevance to the pathophysiology of autism spectrum disorder. *Mol Psychiatry*. 2018, 23: 1001-1013.
43. Minakova E, Warner BB. Maternal immune activation, central nervous system development and behavioral phenotypes. *Birth Defects Res*. 2018.
44. Salter MW, Stevens B. Microglia emerge as central players in brain disease. *Nat Med*. 2017; 23: 1018-1027.
45. Pan Py, Tammimies K, Bölte S. The Association between Somatic Health, Autism Spectrum Disorder, and Autistic Traits. *Behav Genet*. 2019.
46. Goulet O. Potential role of the intestinal microbiota in programming health and disease. *Nutr Rev*. 2015; 73: 32-40.
47. Fruta GT, Williams K, Kooros K. Management of constipation in children and adolescents with autism spectrum disorders. *Pediatrics*. 2012; 130: S98-S105
48. McElhanon BO, McCracken C, Karpen S, Sharp WG. Gastrointestinal symptoms in autism spectrum disorder: a meta-analysis. *Pediatrics*. 2014; 133: 872-883.
49. Narzisi A, Muratori F, Calderoni S, Fabbro F, Urgesi C. Neuropsychological profile in high functioning autism spectrum disorders. *J. Autism Dev Disord*. 2013; 43: 1895-1909.
50. Kana RK, Uddin LQ, Kenet T, Chugani D, Müller RA. Brain connectivity in autism. *Front Hum. Neurosci*. 2014; 8: 349.
51. Constantino JN. Early behavioral indices of inherited liability to autism. *Pediatric Res*. 2019; 85: 127-133.
52. Szatmari P. Prospective longitudinal studies of infant siblings of children with autism: lessons learned and future directions. *J Am Acad Child Adolesc Psychiatry*. 2016; 55: 179-187.
53. Elsabbagh M, Johnson MH. Autism and the Social Brain: The First-Year Puzzle. *Biol Psychiatry*. 2016; 80: 94-99.
54. Bussu G, Jones E, Charman T, Johnson MH, Buitelaar JK. BASIS Team Prediction of autism at 3 years from behavioural and developmental measures in high-risk infants: a longitudinal cross-domain classifier analysis. *J Autism Dev Disord*. 2018; 48, 2418-2433.
55. Misra V. The Social Brain Network and Autism. *Ann Neurosci*. 2014; 21: 69-73.
56. Moessnang C, Baumeister S, Tillmann J, Goyard D, Charman T, Ambrosino S, et al. Social brain activation during mentalizing in a large autism cohort: the Longitudinal European Autism Project. *Mol Autism*. 2020; 11: 17.
57. Yu ECL. CORE-vs-MATCH MODEL for Autism and Neuro-Developmental Disorders. *J Paediatr Neonatol*. 2020; 2: 112.
58. Visser RE, Latzer Y, Gal E. Eating and feeding problems and gastrointestinal dysfunction in Autism Spectrum Disorders. *Res Autism Spectr Disord*. 2015; 12: 10-21.
59. Levenson JL. *Pediatrics*. In, *Textbook of Psychosomatic Medicine and Consultation-Liaison Psychiatry*, 3/e. Levenson JL, (Ed) p.2016. The American Psychiatric Association. 2019.
60. Bruijn J, Locher H, Passchier J, Dijkstra N, Arts W-F. Psychopathology in children and adolescents with migraine in clinical studies: a systematic review. *Pediatrics*. 2010; 126: 323-332.
61. Genizi J, Gordon S, Kerem NC, Srugo I, Shahar E, Ravid S. Primary headaches, attention deficit disorder and learning disabilities in children and adolescents. *J Headache Pain*. 2013; 14: 54.
62. Cohen S, Conduit R, Lockley SW. The relationship between sleep and behavior in autism spectrum disorder (ASD): a review. *J Neurodev Disord*. 2014; 6: 44.
63. Livingston LA, Happé F. Conceptualising compensation in neurodevelopmental disorders: reflections from autism spectrum disorder. *Neurosci Biobehav Rev*. 2017; 80: 729-742.
64. Mous SE, Jiang A, Agrawal A, Constantino JN. Attention and motor deficits index non-specific background liabilities that predict autism recurrence in siblings. *J Neurodevelopmental Disorders*. 2017; 9.
65. Fitzgerald M. The broader autism phenotype: expanding the clinical gestalt of autism and broadening DSM V criteria of autism spectrum disorder. *J Psychol Clin Psychiatry*. 2018; 9: 316-324.

66. Cooper RA, Simons JS. Exploring the neurocognitive basis of episodic recollection in autism. *Psychon Bull Rev.* 2019; 26: 163-181.
67. Whitehouse AJO, Alvares GA, Cleary D, Harun A. Symptom severity in autism spectrum disorder is related to the frequency and severity of nausea and vomiting during pregnancy: a retrospective case-control study. *Mol Autism.* 2018; 9:37.
68. Gray KM, Tonge BJ. Screening of autism in infants and preschool children with developmental delay. *Aust N Z J Psychiatry.* 2005; 39: 378-386.
69. Ament K, Mejia A, Buhlman R, Erklin S, Caffo B, Mostofsky S, et al. Evidence for specificity of motor impairments in catching and balance in children with autism. 2015; 45: 742-751.
70. Dawson G, Campbell K, Hashemi J, Lippmann SJ. Atypical postural control can be detected via computer vision analysis in toddlers with autism spectrum disorder. *Nature Sci Rep.* 2018; 8: 17008.
71. Charman T. Why is joint attention a pivotal skill in autism? *Philosophical Transactions of the Royal Society B.* 2003; 358: 315-324.
72. Perry CJ, Sergio LE, Crawford JD, Fallah M. Hand placement near the visual stimulus improves orientation selectivity in V2 neurons. *J Neurophysiol.* 2015; 113: 2859-2870.
73. Watson LR, Crais ER, Baranek, GT, Dykstra JR, Wilson KP. Communicative gesture use in infants with and without autism: A retrospective home video study. *American Journal of Speech-Language Pathology.* 2013; 22: 25-39.
74. Rujuta WB, Peter EG, Rinehart NJ. Motor development and delay: advances in assessment of motor skills in autism spectrum disorders. *Current Opinion Neurol.* 2018; 31: 134-139.
75. Gilmore JH, Shi F, Woolson SL, Knickmeyer RC, Short SJ. Longitudinal development of cortical and subcortical gray matter from birth to 2 years. *Cereb Cortex.* 2012; 22: 2478-2485.
76. Suarez AN, Hsu TM, Liu CM, Noble EE, Cortella AM. Gut vagal sensory signaling regulates hippocampus function through multiorder pathways. *Nature Comm.* 2018; 9: 2181.
77. Ogonnaya ES, Felice D, Levone BR, Conroy L The Vagus Nerve Modulates BDNF expression and Neurogenesis in the Hippocampus'O'Leary OF. *Eur Neuropsychopharmacol.* 2018; 307-316.
78. Lauritzen KH, Morland C, Puchades M, Holm-Hansen S, Hagelin EM, Lauritzen F, et al. Lactate receptor sites link neurotransmission. 2014.
79. Gonçalves CA, Rodrigues L, Bobermin LD, Zanotto C. Glycolysis-Derived Compounds From Astrocytes That Modulate Synaptic Communication. *Front Neurosci.* 2019; 12: 1035.
80. Yerys BE. Modulation of attentional blink with emotional faces in typical development and in autism spectrum disorders. *J Child Psychol. Psychiatry.* 2013; 54: 636-643.
81. English MCW, Maybery MT, Visser TAW. Autistic-traits, not anxiety, modulate implicit emotional guidance of attention in neurotypical adults. *Sci Rep.* 2019; 9: 18376.
82. Corden B, Chilvers R, Skuse D. Emotional modulation of perception in Asperger's Syndrome. *J Autism Dev Disord.* 2008; 38: 1072-1080.
83. Gaigg SB, Bowler DM. Brief report: Attenuated emotional suppression of the attentional blink in Autism Spectrum Disorder: another non-social abnormality? *J Autism Dev Disord.* 2009; 39: 1211-1217.
84. English MCW, Maybery MT, Visser TAW. Threatening faces fail to guide attention for adults with autistic-like traits. *Autism Res.* 2017; 10: 311-320.
85. Sasson NJ, Pinkham AE, Weittenhiller LP, Faso DJ, Simpson C. Context effects on facial affect recognition in schizophrenia and autism: behavioral and eye-tracking evidence. *Schizophr Bull.* 2016; 42: 675-683
86. Constantino JN. Infant viewing of social scenes is under genetic control and is atypical in autism. *Nature.* 2017; 547: 340-344.
87. Young GS, Merin N, Rogers SJ, Ozonoff S. Gaze behavior and affect at 6 months: predicting clinical outcomes and language development in typically developing infants and infants at risk for autism. *Dev Sci.* 2009; 12: 798-814.
88. Rogers SJ, Hepburn S, Wehner E. Parent reports of sensory symptoms in toddlers with autism and those with other developmental disorders. *J Autism Developmental Disorders.* 2003; 33: 631-642.
89. Leekam SR, Nieto C, Libby SJ, Wing L, Gould J. Describing the sensory abnormalities of children and adults with autism. *J Autism Developmental Disorders.* 2007; 37: 894-910.
90. Baranek GT, Boyd BA, Poe MD. Hyperresponsive sensory patterns in young children with autism, developmental delay, and typical development. *Am J Mental Retardation.* 2007; 112: 233-245.
91. Balasco L, Provenzano G, Bozzi Y. Sensory abnormalities in autism spectrum disorders: a focus on the tactile domain, from genetic mouse models to the clinic. *Frontiers Psychiatry.* 2020.
92. Schaaf RC, Lane AE. Toward a best-practice protocol for assessment of sensory features in ASD. *J Autism Developmental Disorders.* 2015; 45: 1380-1395.

93. Sinha P, Kjelgaard MM, Gandhi TK. Autism as a disorder of prediction. *Proc Nat Acad Sci United States of America*. 2014; 111: 15220-15225.
94. Lawson RP, Rees G, Friston KJ. An aberrant precision account of autism. *Frontiers Human Neurosci*. 2014; 8.
95. van de Cruys S, Evers K, van der Hallen R. Precise minds in uncertain worlds: predictive coding in autism. *Psychological Review*. 2014; 121: 649-675.
96. Kaldy Z, Giserman I, Carter AS, Blaser E. The mechanisms underlying the ASD advantage in visual search. *J Autism Developmental Disorders*. 2016; 46: 1513-1527.
97. Henderson HA, Zahka NB, Kojkowski NM, Inge AP, Schwartz CB, Hileman CM, et al. Self-referenced memory, social cognition, and symptom presentation in autism. *J Child Psychol*. 2009; 50: 853-861.
98. Grisdale E, Lind SE, Eacott MJ, Williams DM. Self-referential memory in autism spectrum disorder and typical development: exploring the ownership effect. *Conscious Cogn*. 2014; 30: 133-141.
99. Sumiya M, Okamoto Y, Koike T. Attenuated activation of the anterior rostral medial prefrontal cortex on self-relevant social reward processing in individuals with autism spectrum disorder. *Neuroimage Clin*. 2020; 26: 102249.
100. Mosner MG, McLaurin RE, Kinard JL, Hakimi S, Parelman J. Neural mechanisms of reward prediction error in autism spectrum disorder. *Autism Res Treat*. 2019; 2019: 5469191.
101. Balsters J, Mantini D, Apps MAJ, Eickhoff SB, Wenderoth N. Connectivity-based parcellation increases network detection sensitivity in resting state fMRI: an investigation into the cingulate cortex in autism. *Neuroimage Clin*. 2016; 11: 494-507.
102. Cermak SA, Curtin C, Bandini LG. Food selectivity and sensory sensitivity in children with autism spectrum disorders. *J Am Diet Assoc*. 2010; 110: 238-246.
103. Schreck KA, Williams K. Food preferences and factors influencing food selectivity for children with autism spectrum disorders. *Res Developmental Disabilities*. 2006; 27: 353-363.
104. Bandini LG, Andersen SE, Curtin C, Cermak S, Evans EW, Scampini R, et al. (2010). Food selectivity in children with autism spectrum disorders and typically developing children. *J Pediatrics*, 2010; 157: 259-264.
105. Hubbard KL, Anderson SE, Curtin C, Must A, Bandini LG. A Comparison of food refusal related to characteristics of food in children with autism spectrum disorder and typically developing children. *J Acad Nutrition Dietetics*. 2014; 114: 1981-1987.
106. Suarez MA, Nelson NW, Curtis AB. Longitudinal follow-up of factors associated with food selectivity in children with autism spectrum disorders. *Autism*. 2014; 18: 924-932.
107. Nadon G, Feldman DE, Dunn W, Gisel E. Association of sensory processing and eating problems in children with autism spectrum disorders. *Autism Res Treat*. Epub. 2011.
108. Chaidez V, Hansen RL, Hertz-Picciotto I. Gastrointestinal problems in children with autism, developmental delays or typical development. *J Autism Dev Disord*. 2014; 44: 1117-1127.
109. Smith AM, Roux S, Naidoo NT, Venter DJL. Food choices of tactile defensive children. *Nutrition*. 2005; 21: 14-19.
110. Lapate RC, Rokers B, Li T, Davidson RJ. Nonconscious emotional activation colors first impressions: A regulatory role for conscious awareness. *Psychol Sci*. 2014; 25: 349-357.
111. Gurney JG, McPheeters ML, Davis MM. Parental report of health conditions and health care use among children with and without autism: National survey of children's health. *Arch Pediatr Adolesc Med*. 2006; 160: 825-830.
112. de Theije CG, Wu J, da Silva SL, Kamphuis PJ, Garssen J, Korte SM, et al. Pathways underlying the gut-to-brain connection in autism spectrum disorders as future targets for disease management. *Eur J Pharmacol*. 2011; 668: S70-80.
113. Lyaal K, Van de Water J, Ashwood P, Hertz-Picciotto I. Asthma and allergies in children with autism spectrum disorders: Results from the charge study. *Autism Res*. 2015; 8: 567-574.
114. De Groot K. Non-clinical autistic traits correlate with social and ethical but not with financial and recreational risk-taking. *Front Psychol*. 2020; 11: 360.
115. Washington SD. Dysmaturation of the default mode network in autism. *Human Brain Mapping*. 2013.
116. Hoff GA-J, Van den Heuvel MP, Benders MJ, Kersbergen KJ, De Vries LS. On development of functional brain connectivity in the young brain. *Front Hum Neurosci*. 2013; 7: 650.
117. Wiggins JL. The impact of serotonin transporter genotype on default network connectivity in children and adolescents with autism spectrum disorders. *Neuroimage Clin*. 2012; 2: 17-24.
118. Doyle-Thomas KA. Atypical functional brain connectivity during rest in autism spectrum disorders. *Ann Neurol*. 2015.
119. Cheng W. Autism: reduced connectivity between cortical areas involved in face expression, theory of mind, and the sense of self. *Brain*. 2015; 138: 1382-1393.
120. Olivito G, Clausi S, Laghi F, Tedesco A. Resting-state functional connectivity changes between dentate nucleus and cortical social brain regions in autism spectrum disorders. *The Cerebellum*. 2016; 16.

121. Di Martino A, Ross K, Uddin LQ, Sklar AB, Castellanos FX, Milham MP. Functional brain correlates of social and nonsocial processes in autism spectrum disorders: an activation likelihood estimation meta-analysis. *Biol Psychiatry*. 2009; 65: 63-74.
122. Uddin LQ. Salience processing and insular cortical function and dysfunction. *Nat Rev Neurosci*. 2015; 16: 55-61.
123. Alabaf S, Gillberg C, Lundström S, Lichtenstein P, Kerekes N, Råstam M, et al. Physical health in children with neurodevelopmental disorders. *J Autism Dev Disord*. 2018; 49: 83-95.
124. Kohane IS, McMurtry A, Weber G, MacFadden D, Rappaport L, Kunkel L, et al. The Co-morbidity burden of children and young adults with autism spectrum disorders. *PLoS ONE*. 2012; 7: e33224.
125. Aldinger KA, Lane CJ, Veenstra-VanderWeele J, Levitt P. Patterns of risk for multiple co-occurring medical conditions replicate across distinct cohorts of children with Autism Spectrum Disorder. *Autism Res*. 2015; 8: 771-781.
126. Chistol LT, Bandini LG, Must A. Sensory sensitivity and food selectivity in children with autism spectrum disorder. *J Autism Dev Disord*. 2018; 48: 583-591.
127. Parracho HM, Bingham MO, Gibson GR, McCartney AL. Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. *J Med. Microbiol*. 2005; 54: 987-991.
128. Ferguson BJ, Marler S, Altstein LL, Lee EB, Akers J, Sohl K, et al. Psychophysiological associations with gastrointestinal symptomatology in autism spectrum disorder. *Autism Res*. 2016; 10: 276-288.
129. Pine DS, Guyer AE, Goldwin M, Towbin KA, Leibenluft E. Autism spectrum disorder scale scores in pediatric mood and anxiety disorders. *J Am Acad Child Adolesc Psychiatry*. 2008; 47: 652-661.
130. Ivarsson T, Melin K. Autism spectrum traits in children and adolescents with obsessive-compulsive disorder (OCD). *J Anxiety Disord*. 2008; 22: 969-978.