Developmental social vulnerability as the intrinsic origin of psychopathology: A paradigm shift from disease entities to psychiatric derivatives within human diversity

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ABSTRACT

How a social episode is perceived by a person and how the experience affects her/his subsequent behaviors will inevitably and sometimes accidentally vary in each case on the developmental trajectory from the birth of consciousness to death. Both the preceding developmental conditions and the social impact of the episode become a starting point for the following states of human complex conditions, creating the extraordinary diversity that characterizes our complex society. In this evolutionarily carved landscape, genetic factors including stochastic epistasis, environmental modification, and gene-environment interactions are all active. In these processes, interactions between developmental social vulnerability and environmental influences can lead to the emergence and persistence of some derivative states with social maladaptation. In our model, every psychiatric condition including aberrant paranoid-hallucinatory states is classified as a derivative state. The probability distribution curve for these derivative states has a non-linear relationship with the liability in the population, and there is none with probability 1.0 or zero. Individuals with trivial social vulnerability or high resilience may develop the derivative states in tremendously stressful circumstances, and individuals with huge social vulnerability may not necessarily develop the derivative states in the presence of adequate social supports. Social skillfulness/unskillfulness and behavioral flexibility/inflexibility form the core of the vulnerability-related dimensions. The clinical picture of a derivative manifestation is profiled depending on the individual trait levels in the derivative-related dimensions. Each derivative state has a requisite lineup of dimensions and each dimension can contribute to multiple psychiatric conditions. For example, aberrant paranoid-hallucinatory states and bipolar condition may share some developmental conditions as the derivative-related dimensions. Therefore, multiple derivative states can co-occur or be sequentially comorbid. Although the ‘learned strategies’ can ostensibly mask the clinical manifestation of developmental deviations, the change of the true dimensional position to the socially skillful direction is efficiently obtained through social experiences in a supportive environment. The liability-probability model makes it impossible to discriminate individuals with psychiatric diagnosis from individuals without the diagnosis and allows all of us to reside in the same human complex diversity.

Introduction

Categorical ambiguity of disease entities

Approximately a century ago, the conceptual considerations and challenges including an innate social capacity (‘social interest’), ‘premorbid conditions’ for psychosis, ‘child-onset schizophrenia’, Bleuler’s ‘autism’ in schizophrenia, and the neurodevelopmental pathogenesis of schizophrenia were launched [1–3]. The earliest descriptions of autism made the boundary between infantile autism and schizophrenia one of the hot topics [4,5]. In the long-lasting discussion, especially recently, the very early age of clinical onset in autism and the prominence of delusions or hallucinations in schizophrenia had attracted researchers’ attention as the basis of the distinction between these conditions [3,6]. However, varied perspectives or stances on a condition sometimes cause distinct perceptions and interpretations of the condition. If the
perceptions or interpretations were dichotomous or multiple, a single condition could be easily misunderstood to be two or more distinct categorical entities [7]. The recent historical distinction between autism and Asperger’s syndrome [8] may be a typical example. Because social skills and behavioral flexibility can interact to make some behavioral deviations inconspicuous, even a transient manifestation of behavioral deviations may suggest the comorbid presence of a social skills shortfall and behavioral/cognitive inflexibility. As well as social unskillfulness and behavioral/cognitive inflexibility [9], hyperactivity, social detachment, compulsivity, communication problems, and reality distortion can also be seen in individuals with autism [7]. Therefore, the distinctions between autism and hyperactivity disorder [10], autism and schizoid personality disorder [11], autism and obsessive-compulsive disorder, and autism and social communication disorder may be examples of unnecessary differentiation as well as the distinction among autism, schizotypal personality disorder, and schizophrenia [7,11,12].

The difference between social contexts in childhood and adulthood

Both behavioral continuity and discontinuity in individual developmental trajectories between childhood and adulthood are mediated by genes, environment, and influences of acquired conditions from prior experiences [13]. The social context for withdrawal or absorption in unusual preoccupations in children with autism [7] cannot usually become a clinically significant problem under the protective and supportive parents’ (guardians’) umbrella. In contrast, isolative, stressful, traumatic, or complex experiences in adolescent or adult cases of autism may be a trigger for the diagnosis of psychosis [14], which is sometimes accompanied by complex reality distortion (including ‘symptoms of the first rank’). Although the emergent symptoms in such adolescent cases may be explained by the inability to keep pace with increasingly complex developmental demands which overwhelms the individual’s social skills [12], the developmental antecedents have received much less attention in adult clinical settings especially in individuals with a schizophrenia diagnosis [14–17]. The social maladaptation can be revealed by a decrease or cessation of familial- or community-level support. Lack of self-recognition of the phenotypic deviation (lack of disease insight) usually indicates the innate presence of the essence of the condition in individuals with a schizophrenia diagnosis as well as in autistics. The phenotypic similarity between cognition and behavior in autism and positive symptoms in schizophrenia is evident in a comprehensive view and challenges the clarity of the distinction between autism and schizophrenia [7,12].

The developmental origin of schizophrenia

Autistic characteristics are sometimes not recognized in the adult clinical setting even by the families [12]. Therefore, the age of clinical manifestation of autistic characteristics can be quite later until social environmental demands exceed the limited capacities in autistic individuals as described in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [18]. Furthermore, the distinction between autism and schizophrenia on the basis of age of onset is continuously being challenged by the clinical knowledge of a high prevalence of innate autistic characteristics in cases with a schizophrenia diagnosis [12,19,20]. The developmental pathological model for schizophrenia was originally established on the basis of the hypothesized relationships between schizophrenia and some developmental epiphenomena including nonspecific abnormal brain pathologies [1,21–23]. However, both the specific pathological markers and the common molecular causes of schizophrenia remain, strictly speaking, unknown [24]. Biomarkers validated for clinical use in autism are similarly absent [25]. Therefore, human mental conditions including developmental conditions continue to be diagnosed exclusively by behavioral signs and symptoms. That schizophrenia has its origins early in development is now widely accepted [23,24].

The genetic overlap between child and adult conditions

The boundaries between specific disorders are also being challenged by growing genetic evidence revealing the overlap of genes shared by autism, attention deficit-hyperactivity disorder (ADHD), and adult-onset psychosis [26–29]. Importantly, it seems likely that the shared genetic factors had evolutionarily survived for human language, cognitive functions, and creative thinking [30–35]. To explain the genetic overlap between child and adult psychiatric conditions, various models have already been suggested and reviewed [28,36–41]. Although causation models which theorize that autism may predispose to schizophrenia are included in the traditional models, the cause and outcome both remain as distinct entities in the ‘increased vulnerability model’ [38,41]. The blurred phenotypic boundary between autism and schizophrenia led us to add a novel hypothetical model in which schizophrenia is merely one of the secondary derivative conditions in individuals with latent or overt autistic characteristics [12,42]. Our hypothesis cannot be classified in the usual liability models in which both autism and schizophrenia have latent liabilities respectively. The secondary derivative states may involve all mental health problems [7,11]. Because almost all theoretical possibilities are covered in the protein history of various psychiatric hypotheses, our model may be novel in its combination (the unified developmental vulnerability, two sigmoidal structures for symptoms to manifest, and a hierarchical correlated-factors model). Here, the detailed architecture of our model is reconsidered and illustrated with citations of related articles.

Terminology and fundamental perspectives

Critical perspectives for the re-consideration and re-conceptualization of psychiatric conditions have already been proposed as summarized below. A functional element of behavior or cognition is referred to as a ‘construct’ following the terminology in psychology [43]. Each construct usually has continuous (dimensional) diversity of individual measured values in population studies. Such constructs or dimensional traits are usually referred to as ‘dimensions’ [43]. Because the liability concept has been originally developed to explain a dichotomous (disease or non-disease) entity by a continuous distribution of susceptibility values to the condition, liability or susceptibility can also be described as a ‘dimension’. With respect to the term ‘dimension’, it should be noted that there are technically two directions of ‘dimensional approaches’ in this field [44,45]. Dimensions, which are predicted through the use of multivariate statistical methods, are originally assumed to be relatively independent each other [44]. Then in hierarchical liabilities (correlated-factors) models, the correlations between liability dimensions are underlined [46] as described below. Therefore, the term ‘dimensional approach’ is intentionally not used to avoid confusion in this article. A dimension, whose default distribution is sometimes skewed in population studies, can be a mathematically transformed to a bell-shaped phenotypic distribution in the population. Both liabilities and dimensions can be characterized by a continuous distribution with an evolutionary significance as human complex diversities and reciprocal interactions between related dimensions. These interactions can include correlations, inverse correlations, and nonlinear interactions in manners of pleiotropy and/or multifactorial relations [47]. Although phenotypic characteristics of a tail of the dimension are sometimes used as the name of the dimension in this article, the dimension still involves entire diversity including the border
zone, the majority, and another tail with opposite characteristics. To avoid unnecessary conceptual bewilderment, our hypothesis covers only idiopathic developmental conditions and functional psychoses. Symptomatic psychoses including autoimmune encephalopathies and menopausal psychosis are mentioned only as informative and suggestive information in this article. To avoid terminological confusion concomitant with interdisciplinary consideration, definitions of important terms or phrases are summarized in Box 1.

**Box 1**

Glossary of important terms and phrases

| **Construct:** | In the field of psychology, a functional element of behavior or cognition is customarily referred to as a ‘construct’. |
| **Dimension:** | Each construct usually has continuous (dimensional) diversity of individual measured values in population studies. Such constructs or dimensional traits are usually referred to as dimensions. The framework of the National Institute of Mental Health’s (NIMH’s) research domain criteria (RDoC) has five domains of functioning, each of which contains several specific dimensions. |
| **Endo-phenotype:** | In the hierarchical model for comorbidity between common forms of psychopathology, there are some profound underpinnings. Some hierarchical structures have intermediate risk distributions (liabilities) toward each psychopathology. Both the profound underpinnings and the intermediate liabilities are referred to as endo-phenotypes. |
| **Epistasis:** | In the field of complex trait genetics, the difficulty in detecting susceptibility loci is partially explained by the presence of epistasis (interactions between different genes). |
| **Hyper-systemizing theory:** | In the empathizing-systemizing view by Simon Baron-Cohen, systemizing is the drive to analyze or construct systems including collective, mechanical, numerical, abstract, natural, social, and motoric systems. Autism is explained not just by below average empathy but also with reference to hyper-systemizing. |
| **Instructive accommodations:** | In Convention on the Rights of Persons with Disabilities (United Nations), reasonable accommodation means necessary and appropriate modification and adjustments not imposing a disproportionate or undue burden, where needed in a particular case, to ensure to persons with disabilities the enjoyment or exercise on an equal basis with others of all human rights and fundamental freedoms. Instructive accommodation can provide what is needed for the promotion of personal growth. |
| **Mentalizing:** | The capacity to understand the self and others in terms of intentional mental states is referred to as ‘mentaling’. It is assumed that impairments in the domain of mentalizing or social cognition are a common denominator of conduct problems. |
| **Mentoring:** | Mentoring programs are sometimes provided in companies or schools for newcomers or students who are having difficulties. In the programs, the mentee, one who is mentored, is paired with more experienced peer or tutor, the mentor. Supporting instructions are provided from the mentor to mentee and the necessity of mentor’s assists for autistic mentees usually lasts throughout life. |
| **Missing heritability:** | The difficulty or impossibility to identify all susceptibility genes in complex human conditions is referred to as ‘missing heritability’. This phenomenon is evident in autism and schizophrenia. The gap between twin study-based heritability and genome-wide association study (GWAS)-based heritability is used as a marker of missing heritability. |
| **Open dialogue:** | The open dialogue approach is a family-centered early intervention in the treatment of first-episode psychosis. This multidisciplinary approach is characterized by rapid response to crisis, daily meetings including the patient’s wider social network, the case by case manner, and flexibility. It has gained international attention because both the need for neuroleptics and hospital institutionalization may be minimized by this intervention. |
| **Perceptual memory/perceptual thinking:** | Perceptual memory is common in toddlers and autistics, whose manner of memory is not changed to semantic memory. Perceptual thinking can bring real sensations, that is associated with photographic, voice-recorder, and video-clip memory. |
| **Pleiotropy:** | The phenomenon where a single gene influences multiple phenotypic traits is referred to as ‘pleiotropy’. It can be used as the manner of multiple effects produced by one origin. |
| **Proband case:** | In the field of genetics, family study sampling over generations is performed from an index case in a family. The index case is referred to as ‘proband case’. |
| **Reality distortion:** | Confusion between imagination and perception is closely associated with hallucinations and distortions of social perception may result in psychopathological imagination. Because distorted recognition of the real world causes distorted imagination, reality distortion is important in psychopathological processes. |
| **Social interest:** | The central concept of personality theory by Alfred Adler (1870–1937) is often translated as ‘social interest’, which was described as ‘an innate disposition for spontaneous social effort’. Social environment is still important for the development of social interest, which results in empathy and connectedness. |
| **Stochastic epistasis, stochastic factors, stochastic interactions, stochastic outcomes, and stochastic switching:** | As an inherent property of biological systems, the unpredictable and random manner is represented by the word ‘stochastic’ in genetic phenomena. |
| **Tailored intervention:** | The flexible use of interventional approaches, which is specific for an individual, is referred to as a ‘tailored intervention’. Open dialogue is one of the tailored interventions. |
| **Taxometric studies:** | Taxometric analyses were developed to distinguish between categorical and dimensional models of latent variables in psychiatry and psychology. Although discovering clinical qualitative entities (taxa) or distinguishing them from latent dimensions may have important implications, there is still no validated taxon in this field. |

**Nature and nurture**

In the psychiatric field, ‘nature’ might be involved in innate ‘social interest’ by Adler [2] and ‘nurture’ had been emphasized as ‘personal experiences’ by Meyer [48] and as ‘interpersonal relationships’ by Sullivan [49]. All behavioral and cognitive conditions are subjected to genetic influence and no conditions are 100% heritable under the influence of environment [50]. Both the chronological changeability and
robustness of the phenotype may also be affected by genetic factors [51], and there may be age-related changes in involvement of genetic factors [50]. Additional involvement of symptom-specific genetic factors had been considered in some hypotheses regarding schizophrenia-related conditions [36,37,52,53]. Regarding environment, childhood-specific, adolescence-specific, and adulthood-specific environments may affect phenotypic manifestations. The personal experience of an environment is not the same for each individual [54] and for each developmental stage in a person. Even in a monozygotic twin pair, whose genetic factors are identical, experiences in the same environment can sometimes be different from one another by chance. Small chance differences in experiences might lead to large differences in outcomes [54]. Some environmental deviations can delay the manifestation of a phenotypic extreme or make it latent and childhood negative experiences can have a delayed effect on the liability of psychiatric conditions [55,56]. Although genetic factors have an important role in psychiatric conditions [57,58], the additional involvement of symptom-specific environmental factors had been considered as a critical cue in some hypotheses regarding schizophrenia-related conditions [36,53,59].

Genetic factors can affect not only developmental conditions but also the individual responses or stances to social environmental factors [60–62]. In the stress-diathesis model, such genetic factors for individual responses were described as "another diathesis" for a trigger [63]. This additional diathesis can be age-related [60]. The genetic factors which increase the risk of stressful life events and psychotic experiences may partially overlap [64]. Environmental exposure interacting with genetic risk may predict poor prognosis in terms of persistence and clinical need [59]. The responses to environmental factors or cues may include psychopathology as derivative conditions of developmental conditions [63,65]. Stochastic outcomes as results of chance occurrence in genetic effects [66] and experiences through social environments [52,67] are also important origins of human complex diversity.

**Qualitative dichotomy versus quantitative continuum (category versus dimension)**

Two decades ago, the smooth and overlapping behavioral continuum between individuals with autism and the non-autistic majority was noted [68,69]. Although the qualitative dichotomy concept was preserved in DSM-IV for autism, population studies demonstrated that autism is best characterized as an extreme tail of a continuous behavioral dimension that distributes quantitatively from normal development to autistic development [70–80]. Almost all identified genetic risk factors for autism to date can be found in the general population and the same genetic differences may underpin neuropsychiatric variation in the general population [81]. In DSM-5 for autism, it is specified that a balance between social demands and individual limited capacities is critical for the diagnosis [18]. If social demands do not exceed limited capacities in an individual, autistic symptoms may not become clinically apparent (Criterion C), and if educational or social support is not required, the condition cannot fulfill the criteria for the lowest severity level of autism (level 1). Thus, in contrast to DSM-IV, that the sociocultural setting explicitly influences the diagnostic threshold is importantly introduced in DSM-5 [82].

Taxometric studies demonstrated that many other psychiatric symptoms associated with mood disorders, anxiety disorders, eating disorders, or externalizing disorders, have a dimensional distribution in the population [83]. Because the effect size of each modifier variant for complex traits is small and/or the mean phenotypic value of the variant-carrier population might be the same as that of the entire population [66], it may be impossible to depict the boundary between the population continuum and the diagnosed extreme cases with one of the genetic factors. Both the populations with developmental or psychiatric diagnoses and the high-risk populations for these diagnoses are all present in each tail of the entire continuous distributions (normal, skewed normal, or half-normal).

The liability-threshold model in schizophrenia was introduced more than 50 years ago [84], and the quantitative continuum model had been suggested on the grounds of continuous phenotypic heterogeneity in hallucinations and delusions [85,86]. As is the case with the clinical implementation of developmental and other psychiatric diagnoses, the manifestation of psychotic episodes depends on the balance between social stressors and individual capacities [65]. If the social burden of challenging events does not exceed the individual threshold for tolerating it, the crisis can be contained or latent even in high-vulnerability individuals. Although withstanding a crisis is thus a dichotomous manner, everyone is endowed with a varying degrees of vulnerability which establish their unique threshold for resilience [65]. Major challenging events may be necessary for the expression of psychiatric illness in individuals with very low vulnerability, and individuals with very high vulnerability living in non-stressful circumstances may completely avoid illness (a sigmoid threshold model). Border cases, whose position is flanked between the majority and the extreme tail in the liability distribution, have transitional values between low and high vulnerability. Schizophrenia is a derivative diagnosis emanating from the extreme end of the liability spectrum in the liability-threshold model [65] and a developmental model for schizophrenia [63].

A liability-probability model, whose range of individual probability for the clinical manifestation does not include both 0 and 1.0, was applied as a quantitative continuum model of liability to explain the difference of distribution between population and clinical settings [82]. In spite of the converging evidence that autism is best characterized as an extreme of a bell-shaped behavioral distribution by population studies as described above, it can still be captured as a categorical or dichotomous entity in clinically ascertained samples [87]. In clinical settings, both proband (index case-oriented) studies and case-control studies with limited control sampling cannot depict the entire continuum of the population distribution, which can be illustrated by random sampling not related to psychological or psychiatric measured values (population studies). The reason why the case series in clinical settings looks categorical is that the relationship between the liability and probability for the clinical manifestation is non-linear and sigmoid with the maximum probability tail [82]. In addition, possible unpredictability of clinical outcomes might be explained by the liability-probability model.

**Endo-phenotypic layers (correlated-factors model)**

Multifactorial underpinning by the endo-phenotypes (intermediate phenotypes) for a psychiatric condition, partial overlap of the multifactors among psychiatric conditions, and a hierarchical structure of the endo-phenotypes were introduced to interpret the sequential comorbidity of psychopathology [46,88]. The risk distribution (liability) of endo-phenotypic hierarchical constructs for psychopathology can also be depicted as a normally distributed continuous dimension [45] as well as the measured values distribution of the endo-phenotype. Some of the endo-phenotypic constructs including internalizing and externalizing spectra bear a notable resemblance to personality traits, and both personality traits and liability constructs can be the latent entities that explain the psychological coherence of individual differences in almost all psychopathology [46,89]. The complex hierarchical interactions between multiple dimensions can suitably be captured by a general risk factor (general psychopathology dimension: the p factor), which is correlated with childhood brain integrity and whose early developmental feature may be degree of childhood self-regulation [90]. Each endo-phenotypic dimension may have evolutionary significance and implications like personality traits [91]. In the multifactorial and hierarchical structure, a psychiatric condition has multiple (derivative-related) dimensions as endo-phenotypes which correlate with the condition and the requisite lineup of the dimensions can be partially shared.
among psychiatric conditions.

**Psychosis spectrum including developmental conditions**

The case for replacing the Kraepelinian dichotomy system for schizophrenia and affective psychoses with a continuum concept originated with Kraepelin in 1920 [92]. Thus, the categorical distinction between psychiatric conditions has been challenged for approximately one hundred years [93–98]. The presence of shared and symptom-specific additive genetic factors was assumed in a liability-threshold model with the presence of shared and symptom-specific environmental factors [36,37,53]. On the other hand, the idea that abnormalities of neurodevelopment are likely to be involved in the pathogenesis of schizophrenia stems again back to Kraepelin [1]. Although the developmental model for schizophrenia was reconsidered on the basis of the hypothesized relationships between schizophrenia and some developmental epiphenomena including nonspecific abnormal brain pathologies [1,21,22], both the specific pathological marker and the common molecular cause of schizophrenia remain, strictly speaking, unknown [24]. In a discussion on the continuum model of the schizophrenic diathesis, the vulnerability to schizophrenia had been presented as merely the extreme end of a spectrum of central nervous system function [63]. In this decade, growing genetic evidence is suggesting the presence of additive genetic factors shared by child-onset developmental conditions and adult-onset psychiatric conditions [26–29]. To explain these data, various models including the hierarchical multivariate models have already been addressed and reviewed [28,38–41,46,99]. The chronological relationship between developmental conditions and the adult-onset psychiatric spectrum and symptomatic similarities between autism and schizophrenia [7,100] still remain as the main points which require explanation.

**Hypothesis**

**An overview of the model**

**The unified developmental vulnerability**

Because age-appropriate sociality or better social skills than the age-level and enough behavioral flexibility can interact to make concomitant behavioral/cognitive deviations or problematic reactions inconspicuous, overt clinical manifestation of the deviations or reactions may suggest the presence of individual shortfall in social skills and social flexibility. The shortfall also causes the manifestation of the shortfall itself. Social skills and flexibility are developmental conditions whose levels distribute dimensionally in the population. In our model, such developmental dimensions are classified as vulnerability-related dimensions. Here, vulnerability can be defined as the probability that an individual will experience an episode of a psychiatric derivative condition. The distributional continuity of the probability between derivative-prone and derivative-resistant individuals suggests that the high vulnerability is an extreme in a continuum of a normally distributed trait [57]. The social unskillfulness and behavioral inflexibility form the core of the basis of this vulnerability in our model (Fig. 1). The developmental variations themselves can ostensibly be masked by ‘learned strategies’ as described in DSM-5 (autism spectrum disorder) [18]. Individuals whose vulnerability-related conditions are perfectly masked by ‘learned strategies’ are not necessarily resistant or resilient to derivative states, and the vulnerability-related conditions act like the intrinsic core of human nature in such individuals. An accidental transient occurrence of relatively selective damage to the function of ‘learned strategies’ or an abrupt decline of learned strategy-protective factors can cause manifestation of the intrinsic core. Anti-N-methyl-D-aspartate (NMDA) receptor antibodies can induce this transient selective damage [101], and neuroprotective factors including estrogens may have a role in the maintenance of ‘learned strategies’ [102]. Although the acquired strategies are usually hard to ameliorate the true individual position on the social skill dimension, interpersonal experiences or individual own efforts under supportive instructions can change her/his position to the skillful direction. Unsupportive educational environments including unusually overprotective circumstances can also cause a change of the position on the dimension. However, the direction of this possible shift in unconstructive environments can be bidirectional sometimes by chance, to more skillful or unskillful, depending on the individual primed conditions at the time. Individuals in difficult educational environments may not necessarily have high vulnerability.

**Two sigmoid structures for a derivative state to manifest**

In our model, there are two sigmoid structures for a derivative state to arise or remit. The level of deviation in each vulnerability-related dimension is not necessarily the same in an individual under the influence of the domain-specific genetic and environmental factors, and complex interactions between the dimensions nurture the phenotypic individuality at each age. The multiple-dimensional distribution of the core vulnerability-related dimensions can depict a liability distribution for psychiatric derivative states. The liability distribution has a non-linear sigmoid relationship with the probability of derivative manifestation (social vulnerability) (Fig. 1). The probability is neither zero nor 1.0, but ranges from low to high. The majority of the population is endowed with a low degree of probability (not zero). The boundary cases between the majority and the extreme tail have modest probabilities and the borderlines are unclear. Psychiatric derivative states can be clinically expressed in an individual in the border zone and even in the majority when she/he is left in a severe social environment without supports (strong environmental cues). Furthermore, an individual in the extreme tail with a very high probability (not 1.0) can continuously enjoy a derivative-free latent situation in a supportive and instructive environment with no or trivial social demands. Therefore, everybody has the possibility to develop the psychiatric derivative states and everybody can enjoy the derivative-free latent situation. The second sigmoid threshold (upper-light square in Fig. 1), regionalizing the derivative manifestation and latency, was conceptualized more than 40 years ago as the denominator of schizophrenia psychopathological models [65]. As long as the environmental cue level, which is usually increased by the high social demands and/or stressors, stays below the threshold, the derivative state remains latent. When the cue level exceeds the threshold in association with deteriorating situations, isolation from supportive accommodations, or an increase in social demands, the psychiatric derivative state is clinically manifested. The coordination between developmental social vulnerability and environmental cues can make multiple derivative states manifested. The relation between state probability and environmental cues is never fixed but time-limited [65]. When the environmental situation is modified for the better, the manifested state can become immediately latent. When the social vulnerability is decreased by a change of the developmental conditions in supportive environments or by the acquisition of coping strategies from prior experience, it is possible for the psychiatric state to become clinically latent. The possible effect of environmental modifications can be rapid but it sometimes takes a long time for supportive interventions to exhibit the effect without any environmental modifications.

**Factors which profile the clinical presentation**

The hypothetical mechanisms which profile the clinical presentation are closely associated with the concomitant manifestation of multiple derivative states, the sequential comorbidity, and/or sequential changes of clinical pictures. The level of deviation in each derivative-related dimension is also not necessarily the same in an individual under the influence of the genetic and environmental factors. The clinical picture of a derivative state is profiled depending on the preceding individual positions of the trait levels in the population distributions of the derivative-related dimensions which form a
hierarchical structure for the manifestation (Fig. 1). Although both the
lineup of the dimensions and the pattern of trait levels in the lineup
dimensions are unique to the derivative state, each lineup for different
derivative states can be partially overlapping among psychiatric condi-
tions. Upper layers in the hierarchical structure may include unique
or relatively unique dimensions for the derivative state and bottom
layers may include relatively common (shared) or non-specific dimen-
sions. The layers can also be classified as premorbid measures of the
derivative state, subjective layers, and psychological layers [103]. The
psychological layers may be theoretically segregated to conscious and
unconscious (subconscious) layers. Trait levels in some derivative-re-
lated dimensions can be fluctuating like mood swings and vigilance/arousal levels and there may be an interaction with state-specific en-
vironments. Fluctuation range or pitch (cycle) can be one of the deri-
vative-related dimensions. Multiple derivative states can co-occur or be
sequentially comorbid following the concurrent or sequential occurrence of the state-unique patterns of trait levels. The level of the environmental cues is depicted by
a solid longitudinal line stringing the derivative-related lineup from the individual position in the threshold square. The manifestation of the psychiatric derivative state is illustrated by an open head arrow. Double-headed arrows indicate changeable or modifiable factors as described in the text. Anywhere in this evolutionarily
survived landscape, genetic influences including stochastic epistasis, environmental modification, and gene-environment interactions are all active [47].

Vulnerability-related developmental dimensions

Each developmental condition varies quantitatively and the quan-
titative dimension may be surviving evolutionarily as an inter-in-
dividual diversity [30,35,104]. The genetic and environmental me-
chanisms for phenotypic diversity may be evolutionarily beneficial and
increase population performance [105]. Hence, the genetic mechanism for phenotypic variability including environmental phenotypic switching should be evolutionarily fixed (selected) in the population. Developmental plasticity is underpinned by such genetic mechanisms and can individually make a developmental trajectory in behavioral and mental conditions. If extreme cases in a tail of a developmental diversity (dimension) are linked to decreased reproductive competence, the shape of the population distribution will be undermined and the prevalence of the extreme cases will not be maintained thorough generations [66]. Because developmental and mental deviations are still prevalent [106,107] and the extreme characteristics in these conditions are associated with reduced opportunity to have offspring [108–111], the presence of an intergenerational fitness fluctuation or randomized (stochastic) switching between hypo- and hyper-fertility in each generation is plausible [47,66,112]. The interactions of developmental conditions in an individual determine the social vulnerability level (Fig. 1). Social unskillfulness and behavioral inflexibility are core characteristics of autism [9] and also form the foundation of vulnerability-related dimensions.

**Social skillfulness/unskillfulness**

Dimensional diversity in sociability and social skills may be evolutionarily necessary for humans to maintain a large and complex society [104]. Timely exposure to postnatal interpersonal or social circumstances during the developmental critical period may be quite important for efficient imprinting and priming of subjectivity and sociability [113]. The social skillfulness/unskillfulness is not a single dimension but a hierarchical complex of endo-phenotypic dimensions. Complex interactions between the endo-phenotypic dimensions also include correlations, inverse correlations, and non-linear interactions in manners of pleiotropy and/or multifactorial relations [47], that may contribute to the difficulty in detecting the net vulnerability level in each case. Because early stage memory retention is non-semantically mediated (perceptual memory), profound layers in the hierarchical structure consist of non-semantic constructs. Social/self interest, social motivation, empathy, willingness to communicate, distinction between self and non-self (others), recognition of social contexts (social reality), social sense, and affiliation/attachment may all be included in the non-semantic layers. Social reality is tightly associated with reality distortion and dysregulated reality perception seriously affects social skills. Cognitive domains including face recognition may also be an important construct of the layers [114]. The later semantic acquisition of social skills may be underpinned by the perinatal priming of subjectivity and sociability and the preceding non-semantic layers. Public order and morals are shaped and varied personally in the individual semantic and conceptual circumstances. The semantic layers include social communication, language achievement, social artfulness, skills for intentional superficial engagement, deception skills, and response intensity to social stresses. Sense of social prioritization, social logic, social allowance, ‘theory of mind’, and self-control skills can be continuously developed through social experiences, semantically and non-semantically. Poor sense of social prioritization may effectively undermine social executive functions. A social skillfulness/unskillfulness condition is only a point on the chronological developmental trajectory in an individual. A change for the better of motivational conditions in association with appropriate support accelerates the efficient acquisition of social skills (a catch-up phenomenon) especially in childhood. Although it is more difficult to measure non-semantic social skills both subjectively and objectively than semantic social skills, the core of the vulnerability-related social skills may be non-semantic and it may require considerable time to change the non-semantic conditions, especially in adulthood. Acquired ostensible masking of developmental conditions, including autism and hyperactivity, may usually be accessible in the semantic social skills.

The unskilful tail of the dimension is highly associated with social vulnerability (Fig. 1). However, the extreme tail is not necessary for phenotypic variability including environmental phenotypic switching to be evolutionarily fixed (selected) in the population. Developmental plasticity is underpinned by such genetic mechanisms and can individually make a developmental trajectory in behavioral and mental conditions. If extreme cases in a tail of a developmental diversity (dimension) are linked to decreased reproductive competence, the shape of the population distribution will be undermined and the prevalence of the extreme cases will not be maintained thorough generations [66]. Because developmental and mental deviations are still prevalent [106,107] and the extreme characteristics in these conditions are associated with reduced opportunity to have offspring [108–111], the presence of an intergenerational fitness fluctuation or randomized (stochastic) switching between hypo- and hyper-fertility in each generation is plausible [47,66,112]. The interactions of developmental conditions in an individual determine the social vulnerability level (Fig. 1). Social unskillfulness and behavioral inflexibility are core characteristics of autism [9] and also form the foundation of vulnerability-related dimensions.

**Behavioral inflexibility/flexibility**

Human inflexibility can look like a product of behavioral imprinting in a changeless environment [113]. It is characterized by or associated with unfamiliarity with changes, attachment to sameness, tendency to detachment, a preference for one’s own style, and closed-mindedness. These tendencies are respectively extreme tails of dimensional constructs which compose a hierarchical architecture of inflexibility. Individuals in the other side tail of the dimension can easily apply their experiences to novel situations, elicit a generalized concept or lessons from a few trivial experiences, respect a broad perspective, and eventually seek to modify behavior to fit the situation. Although the inflexible extreme tail is sometimes associated with motor and/or conceptual mannerisms, it also promotes rites, rituals, tradition, and customs which have cultural and religious significance. Because the bilateral tails of the dimension can be meaningful for human society, the entire flexibility/inflexibility diversity may have an evolutionary implication in association with human cultural civilization in the large and complex society. Such diversity may be critical for responsibility assignment or appropriate allocation of social roles in the population. The inflexible tail of the dimension is sometimes associated with strong attachment or preoccupation, repetitive patterns of interests, and obsessive-compulsive behaviors. The central/peripheral coherence dimension may also be one of the endo-phenotypic dimensions for the hierarchical architecture of inflexibility and the apparent peripheral coherence may undermine social executive function. Because social vulnerability results from the interaction between social skillfulness/unskillfulness and behavioral flexibility/inflexibility and most inflexible persons may have sufficient social skills, a considerable number of behaviorally inflexible individuals can enjoy low social vulnerability (Fig. 1) and contribute to human cultural diversity. Behavioral inflexibility may be associated with prolongation of the derivative state duration as a vulnerability-related trait. When inflexibility is involved in derivative-related dimensions, it may also affect the duration of the derivative state. In addition, the inflexibility can be associated with resistance against preventive and therapeutic interventions.

**The secondary derivative states**

Clinical psychiatric conditions are all classified as derivative states in our model. Social maladaptation in the absence of supports or helpful accommodations is a common feature of these derivative states. Actually, the prerequisites for the manifestation of the derivative states are not so simple. Of course, the most important prerequisite is the interaction between the social vulnerability (probability of derivative manifestation) and the environmental cues as described above. The coordinate point in the regionalized square must be within the ‘manifested’ region for the derivative state to manifest (Fig. 1). For the manifestation of a derivative state, the preceding lineup of deviated or un-deviated dimensions should have the unique pattern for the derivative state. In some derivative states, the environmental influences can change the phase of fluctuating dimensions including mood swings and vigilance/arousal levels and the requisite lineup fulfills the pattern. With respect to the social significance of the manifestation, the social significance of the phenotypic presentations have an additional sigmoid threshold relationship with the acceptability (or tolerability) of the
community (social environments). As long as the social significance of the behavior stays below the threshold of social un-acceptability, the derivative state remains socially latent or hidden. When the social significance exceeds the threshold and the social circumstances cannot accommodate the presentations, the derivative state is socially manifested. For antisocial behaviors which are classified in the tertiary derivative conditions, a further additional threshold relationship is involved. When the social significance exceeds the threshold of legal and/or ethical acceptability, the derivative state is referred to as an antisocial behavior. Because reported endo-phenotypic constructs in already existing models including the correlated-factors model are candidates of the derivative-related dimensions in our model, the candidates are briefly listed below with the references for some derivative states. Prolongation of the environmental cues causes chronicity of the state.

Aberrant paranoid-hallucinatory states

The prominent manifestation of delusions or hallucinations in schizophrenia has captured researchers’ attention as the basis for the distinction between autism and schizophrenia [3,6]. This distinction suggests that autistic characteristics are phenotypically indistinguishable from the schizophrenic features other than overt hallucinations and delusions in cases with diagnoses of both autism and schizophrenia. These autistic phenotypes may be the neurodevelopmental core of schizophrenia [3,117], and the current operational definitions diagnose individuals with a chronic paranoid-hallucinatory variant (accessory phenotypes) as patients with schizophrenia [3]. The discrimination between the core and accessory phenotypes and the classification of the observed accessory phenomena as derivatives are basic and traditional views [3,117]. Because the core of schizophrenia itself is effectively the same as autistic developmental traits [7,11,12], there is little reason for the diagnostic entity of schizophrenia to be used for the social manifestation of latent accessory phenotypes. The derivative states should strictly be referred to as aberrant paranoid-hallucinatory states.

The excessive preoccupation with unusual interests in children with autism and the ‘withdrawal to fantasy life’ in individuals with a schizophrenia diagnosis [3] can both be referred to as reality distortion [7]. The difference between the autistic and schizophrenic reality distortions is just their age-related contents and the social contexts depend on individual social experiences and demands. Autistic reality distortions are associated with less-experienced (childish) social contexts and the episodic manifestations including the excessive preoccupation with unusual fantasy worlds can usually be covered by a parents’ umbrella. In contrast, schizophrenic reality distortions are associated with complex and severe social contexts and the episodic manifestations are occasionally beyond a supporter’s control. Therefore, the derivative-related dimensions for aberrant paranoid-hallucinatory states are the vulnerability-related dimensions (autism). The absence of self-recognition of the psychotic deviation (disease insight) in circumstances without social conflict is a common feature between autism and schizophrenia, suggesting the developmental origins for aberrant paranoid-hallucinatory states. Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment, which is re-introduced in DSM-5 as autism criteria, may be the extreme tails of the derivative-related dimensions for aberrant paranoid-hallucinatory states. Individuals with hyper-sensitivity (perceptual thinkers), non-semantic perceptual (photographic or voice-recorder) memories can be the basis of the episodic manifestation of hallucinations in challenging circumstances [7,12]. The rapid recall of the perceptual or intuitive memories is referred to as a ‘flash back’. Photographic or voice-recorder ‘flash backs’ sometimes cannot be phenotypically distinguished from hallucinations [7,12]. In individuals with social reality distortion, which may be one of the extreme tails in the hierarchical structure of social unskilfulness, difficult experiences can easily cause paranoid states. Paranoid states in association with ‘flash back’ may exaggerate the hallucinatory symptoms. Unusual spatial sensitivity [115] may be associated with hyper-arousal conditions without social reality and a sense of social prioritization in individuals with autism [7]. Fluctuation of the arousal conditions, which is affected by innate pitch (cycle) and environmental changes in autistic individuals, may also contribute to episodic features like catatonia and loss of inhibition [7]. Behavioral inflexibility has reciprocal interactions with the hyper-arousal state. As level of vigilance fluctuates (arousal level), a hyper-arousal state can trigger overt clinical manifestations of the behavioral inflexibility and an inflexibility-associated episode can heighten the arousal level.

Related environmental contributions include social life disruption, social isolation in the transition period between childhood and adolescence, decrease or cessation of familial and/or community supports, and increases in social demands. Excessively pampering environments can be a hotbed for paranoia.

Depressive and manic conditions

Internalizing spectra and distress intolerance may be involved in derivative-related dimensions [45,46,89,90]. The measures of one of the subjective well-being (positive affect) may be a specific depression-related dimension which is negatively correlated with depressed mood [118]. Mood swings and the fluctuation of vigilance or arousal levels may be associated with phase pitch and continuity (duration). If the innate pitch (cycle) is too long, the phase can be monopolar. A hyper-arousal state may co-occur with a manic state. Autistic characteristics may be included in the derivative-related dimensions for manic conditions and bipolar conditions. The severity of the depression may depend on positivity/negativity or optimism/pessimism dimensions. Related environmental triggers for depression include bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability [18].

Anxiety, phobia, panic attack, and stress-related conditions

Internalizing spectra, fear bias, and distress intolerance may be involved in the derivative-related dimensions for anxiety and phobia [45,46,89,90]. Risk factor analyses for panic attack onset in adolescence reveals the presence of a wide range of internalizing and externalizing dimensions as risk factors, suggesting a wide repertoire of derivative-related dimensions [46,119]. The close link of panic attacks to social problems [119] may suggest the credibility of our social vulnerability model. A pessimism dimension may have a role in anxiety. Recall or retention of stressful stimuli is associated with perceptual or intuitive thinking dimensions. Clear memory retention can intensify effects. Hyper-reactivity to sensory input and a hyper-arousal state can be associated with anxiety reactions and hyper-reactivity to stress [118].

Dissociative (conversion) conditions

Self-perception, avoidance, negative reactivity, alexithymia, and emotional dysregulation are involved in the derivative-related dimensions [120,121]. Hypochondriasis, emotional dependence, and impulsivity should be evaluated as the related dimensions.

Eating problems

The derivative-associated genetic loci overlap between anorexia and variation of body mass index [122]. It is possible that anorexia and bulimia may be the bilateral extreme tails of a continuous distribution whose latent spectrum is the main derivative-related dimension. Immaturity, perceptual or intuitive thinking, body image, and compulsivity may be included in the derivative-related dimensions for eating problems.

Dependence syndromes

Brain reward circuitry is one of the evolutionary modules for us to survive and reproduce. The natural rewards include food, sex, and social interaction [123]. Dysregulated feelings of reward or pleasure to the natural or unnatural rewards are associated with dependence.

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 syndromes or addiction. Externalizing spectra, impulsivity, compulsivity, attachment, and novelty-seeking may be included in the derivative-related dimensions [45,46,89,90,124–126].

Other derivative-related dimensions

Hyper-reactivity to sensory input may be associated with lowering of pain threshold. Self-esteem, self-control skills, self-advocacy (or help-seeking) skills, and behavioral inflexibility are associated with the state duration in all derivatives. The personality trait neuroticism may be a common derivative-related dimension for almost every psychiatric derivative state [29]. An extreme tail of the neuroticism dimension is characterized by emotional instability, nervousness, irritability, worry-proneness, and subjective negative affect [91,118]. This common dimension may be also involved as the vulnerability-related dimensions.

The tertiary derivative conditions

There is no direct causal link between shortfall in social skills and the tertiary derivative conditions. Individuals with trivial social vulnerability have the possibility to develop the derivative states in tremendously stressful circumstances, and individuals with huge social vulnerability may not necessarily develop the derivative states in supportive interpersonal relationships. In order to develop the tertiary derivative states for individuals with the secondary derivative state(s), the individual positional pattern on the additional derivative-related dimensions for the tertiary derivatives must fulfill the pattern prerequisite. Even in individuals with severe paranoid-hallucinatory states, if the tertiary derivative-related dimensions have a different pattern from the prerequisite, they are free from tertiary derivative states. When secondary and tertiary derivative-states are comorbid in an individual, for example depressive conditions and suicide, derivative-related dimensions for both are backgrounds of the clinical pictures of the tertiary derivative-state. As described above, for antisocial behaviors which are classified in the tertiary derivative states, a further additional threshold relationship must be involved. When the social significance exceeds the threshold of legal and/or ethical acceptability, the derivative state is referred to as antisocial behavior. The self-esteem dimension, self-control skills, self-advocacy (or help-seeking) skills, and behavioral inflexibility are associated with the state duration. Social isolation is an important derivative-related environmental factor for the tertiary derivative conditions.

Antisocial behaviors (conduct problems)

Developmental conditions are involved as both the vulnerability-related and derivative-related dimensions of antisocial behaviors. Therefore, in multiple pathways to conduct problems, chronic or temporary deviations in the domain of social cognition or mentalizing are a common denominator [127]. Externalizing spectra [45,46,90] and negative and positive valence systems and cognitive systems [127] may be listed as the derivative-related dimensions. The sense of public policy, conscientiousness, unfriendliness, impulsivity, aggressiveness, and self-centeredness should be evaluated as the related dimensions.

Suicide attempt

Reward and threat processing may represent independent related dimensions in the development of suicidal ideation [128]. In addition, Negative valence systems may also be involved in the derivative-related dimensions [129]. Internalizing spectra, impulsivity, negativity, pessimism, and threat sensitivity should be evaluated as the derivative-related dimensions.

Discussion

Developmental vulnerability and the heritability of each condition

Developmental conditions including autism have twin-study-heritability estimates as high as 90%, and the heritability for schizophrenia is also considerably high (70–90%) [57,58]. In other psychiatric conditions, the discrepancy from the highest estimate of heritability may mirror the distance from developmental premorbid conditions. For the clinical manifestation of the derivatives, it may be critical for the at-risk individuals to be subjected to additional environmental effects including changes in social demands, an increase of social stresses, and isolation from supportive circumstances. The necessity of such additional environmental prerequisites may reduce the heritability and underline the distinction between derivative- and vulnerability-related dimensions. Therefore, the reported heritability data may provide supporting evidence for our model. The similarity of the twin-study-heritability for schizophrenia with that for autism may be consistent with our hypothesis that the derivative-related dimensions for aberrant paranoid-hallucinatory states are autistic characteristics. Because the heritability for bipolar disorder is also considerably high (60–90%) [57,58], the derivative-related dimensions for bipolar conditions may include autistic characteristics as important components. Recently, a quantitative transcriptomic profiling study showed that the brain co-expression patterns of some functional gene modules are shared by autism, schizophrenia, and bipolar disorder [130]. As supporting evidence, the shared molecular underpinnings may suggest the presence of common neuronal networks across these conditions and underline the significance of autistic characteristics as the derivative-related dimensions in bipolar conditions as well as in aberrant paranoid-hallucinatory states. In most human complex traits, genome-wide association study (GWAS)-based heritability is much less than twin study-based heritability (missing heritability) [131]. The heritability gap is much greater for childhood behavioral problems including autistic conditions than for other domains [132]. Because the gap can be explained by stochastic interactions between segregating loci (epistasis) and this stochastic epistasis has a significant role for human evolution [47,66,112,133], the greatest missing heritability in autistic traits may also suggest the intrinsic role of the developmental conditions for other psychiatric conditions.

Clinically supporting evidence for the unified presence of developmental vulnerability

Despite the several revisions of the operational diagnostic criteria during the past half century, understanding of the intrinsic role of the developmental conditions and interrelationships between mental constructs remains rudimentary [43]. The chronological link between developmental conditions and derivative psychiatric conditions is repeatedly suggested by recent studies. The greater the number of early autistic traits a child has, the greater is her or his risk of developing psychotic experiences [134]. According to the results of a parental retrospective review, the rate of autism diagnosis was strikingly high especially in the group with paranoid type schizophrenic psychosis [20], and individuals with a schizophrenia diagnosis have implicit social cognition impairment with the same severity as autism cases [135]. In addition, contextual social cognition impairments has been demonstrated in both schizophrenia and bipolar disorder [136], and the most significant risk of panic attack was reported to be developmental social problems in a risk factor analysis [119]. Because developmental conditions can be ostensibly masked by ‘learned strategies’ as described in autism criteria of DSM-5 [18], the clinical detection of the deviated developmental conditions may be partial in individuals with psychiatric conditions. These recent results are consistent with our social vulnerability model. The facts that multiple psychiatric syndromes can co-occur or be sequentially comorbid [45,46,88,118] and the recently-reconsidered ‘psychosis spectrum concept’ [93–98] may come from the clinical aspects of the unified vulnerability model. The clinical ambiguity of the boundary between personality pathology and psychiatric conditions and endo-phenotypic roles of liability constructs including personality traits for psychopathology [46,89] may also provide...
support for our model.

Explanations why hypo-reproductive extremes including developmental conditions can survive

The continuous prevalence of hypo-reproductive extreme conditions has been interpreted in an evolutionary perspective [137–139]. Even if the extreme behavioral deviations including overt psychiatric conditions are associated with a decline in the birthrate or an increase of suicide, they are viewed either as eventually advantageous or neutral conditions or as disadvantageous by-products of normal brain evolution [140]. There are several explanations for the relationship between evolutionary costs and benefits in association with the genetic factors which underpin the behavioral extremes. First, a part of the population may include unaffected carriers of the genetic factors and be enjoying the benefits. In the extreme male brain theory (hyper-systemizing theory) of autism, people who are enjoying the benefits are placed in the adjacent part (border cases) to the extremeness in the population [141]. The extreme imprinted brain theory was proposed as a genetic basis of the extreme male brain theory [142]. The second is the possibility of the ubiquitous load of the genetic factors in the population. In the mutation-selection balance theory, everyone alive has minor brain deviations associated with the mutation load, and the reproductive majority of the population is also a little bit abnormal in behavioral and cognitive functions [138]. In the third explanation, which was established for autism and schizophrenia, it is speculated that the selection of the deviation-related genetic factors has had a profound impact on the reproductive success, adaptability and evolution of ancestral hominid populations [31–35,143]. The fitness-value of the genetic factors in the ancestral environment can actually be either beneficial or neutral [144,145]. In the fourth framework, a group selection theory has been introduced to bring sense into the link between autism and exceptional creativity [146]. In this population benefit theory, the creativity, which can be sometimes concomitant with autism, benefits all members of the human community and the community can survive. The fifth is the possibility that the individuals carrying the genetic mechanism can randomly or stochastically develop either the extreme behaviors or reproductive benefits [47,66,112]. In this fifth model, the genetic architecture is surviving evolutionarily with the phenotypic quantitative diversity and critical for the phenotypic changeability and robustness [66]. Because persons who can enjoy the reproductive benefits are everybody other than the hypo-reproductive cases in the fourth and fifth models, the presence of extreme cases is altruistic.

Human diversity and the unified vulnerability model

Although the complex derivative states may include even criminal conduct behavior as a result of educational failure or lack of support, it was speculated that efforts to eliminate or change the deviation-related genetic factors have a risk of eradicating genetic factors that may be over-represented in altruistic and creative individuals [30,146,147]. The evolutionary costs might be outweighed by the advantages conferred by expanding the range of genetic diversity involving the genetic factors for the behavioral/cognitive extremes [148]. Dimensional diversity may be evolutionarily necessary for humans to maintain our complex society [104], and the genetic and environmental mechanisms for the phenotypic diversity may increase population performance [105]. If there is no diversity, there may be no humanity (no diversity, no humanity). Our model for psychiatric conditions may provide some structures which can enhance the inter-individual diversity. In both vulnerability-related and derivative-related dimensions, the complex interactions between related dimensions inflate the diversity. In most dimensions, each individual position on the population distribution is only one of the passing points on the developmental trajectory and the following developmental direction is determined by genetic, environmental, and stochastic factors. There may be no one whose developmental trajectory is identical to someone else. The concomitant manifestation of multiple derivative states and the sequential comorbidity can be available depending on the fulfilled prerequisites as described above. There also may be no one whose psychiatric trajectory is completely the same as that of someone else. In addition, the developmental conditions can be masked by acquired strategies, suggesting the presence of two-sides of sociability, latent (true) and observable. These structures may ensure that the human population is diversified enough to maintain complexity. In this model, both individuals with the diagnosis of psychopathology and without the diagnosis all reside in the human complex diversity, because the liability-probability model never qualitatively distinguishes the diagnosed individuals from the majority without diagnoses.

An international change of the research framework and the unified vulnerability model

The framework of the National Institute of Mental Health’s (NIMH’s) research domain criteria (RDoC) has five domains of functioning, each of which contains several specific dimensional constructs (psychological functional elements of behavior or cognition) [43]. These dimensions may have complex interactions each other and sometimes form a hierarchical structure as an evolutionary module. The complex interactions may include correlations, inverse correlations, and non-linear interactions in manner of pleiotropy and/or multifactorial relations [47]. In our model, there are two types of constructs, vulnerability-related dimensions and derivative-related dimensions and the social vulnerability is emphasized as the intrinsic origin of psychopathology. The vulnerability-related dimensions are the members of the domain ‘social processes’ and associated with the domain ‘cognitive systems’ in the RDoC components. The vulnerability-related dimensions also act as the derivative-related dimensions and every RDoC domain provides the derivative-related dimensions. The emphasized developmental dimensions as the core of vulnerability-related dimensions are social skillfulness/unskillfulness and behavioral flexibility/inflexibility whose extreme tails are the characteristics of autism [9].

Factors which can mask the clinical manifestation

It is well known that there are two factors that can mask the clinical manifestation of autism as described in DSM-5 as described above [18]. Semantically and/or culturally acquired social skills (learned strategies) may ostensibly mask the clinical manifestation of the developmental conditions. A shortage of social demands in the balance with individual social capacities may also mask the clinical manifestation. Sex differences in the clinical manifestation of developmental conditions and the relative difficulty in detecting the correlation between developmental and psychiatric conditions [29] may be associated with this acquired masking of developmental deviations. The masking does usually not affect the true intrinsic vulnerability, but possibly influences the clinical pictures of the derivative states. In our model, there are three prerequisites for the manifestation of secondary psychiatric derivative states, the coordination between the social vulnerability and the environmental cues, the presence of a state-specific pattern in the lineup of deviated or un-deviated dimensions for the clinical manifestation, and the coordination between the social significance of the clinical expression and the un-acceptability of the community. As long as the social significance of the pictures stays below the threshold of social unacceptability, the derivative state remains socially latent or hidden. When the social significance exceeds the threshold and the environment cannot accommodate the behavior, the derivative state is socially manifested. The social manifestation is different from the clinical manifestation. If there is no opportunity for the individual with apparent clinical manifestation to access treatment but helpful and supportive environments are available, she/he will usually not come to attention as a clinical case with the diagnoses [82]. Cultural or social
accompaniment for children is another example. There are some phobic objects or situations which are relatively specific to childhood, including ghosts, monsters, separation from parents, and sleeping alone. Even if the fear, anxiety, or avoidance causes clinically significant impairment in daily-life functioning in the form of crying, tantrums, freezing, or clinging, the parents may not consult a psychiatrist but ask a parenting expert. In addition, withdrawal or absorption in children with autism is usually not a clinical topic or problem under the protective and supportive parents’ (guardians’) umbrella as described above. The social manifestation depends on the mismatch in acceptability or tolerability of the inter-personal or social environments.

Preventive and interventional strategies in the unified vulnerability model

In our model, the priority for preventive strategies should be given to instructive accommodations to individuals with social vulnerabilities. Because everyone shares a possibility to develop psychiatric crises in highly stressful circumstances [65], the instructive accommodations should be universally available. At least, support programs which are requested by individuals with stress should be available appropriately. With consideration for human complex diversity which is underpinned by the vulnerability- and derivative-related dimensions in our model, both the preventive strategies and clinical concerns for psychopathology should be tailored interventions. Such preventive approaches may be quite important to decrease the number of the tertiary derivative cases with antisocial behaviors or suicide. Interventional targets are shown by double-headed arrows in Fig. 1. In vulnerability-related dimensions, individual positions on the social skill dimension are changeable to the skillful direction by experience or efforts under supportive instructions including behavioral approaches and mentoring [10,149]. The enhancement of motivation in children with autism is one of the central strategies of behavioral interventions, which are among the only evidence-based interventions for autism [150]. However, the positional change on the social skill dimension usually takes time in adulthood. The derivative-related dimensions also include changeable constructs. It may again sometimes take a long time for psychological and/or instructive programs to reach an effective result in the changeable derivative-related dimensions. A regular daily routine with family (e.g. family meal), which has a prophylactic effect against the secondary and tertiary derivative states [151], may ameliorate both the social skills and the derivative-related dimensions. Because increased social demands or stressors are the cue of derivative manifestations and chronicity, the modification of the pathways may bring a positive effect in both preventive and therapeutic settings. Family-level or community-level easy accessibility to a supportive and inclusive atmosphere is one of the safety-nets for stress management. Community-level programs for family support are also important [152]. Solitary living without instructive programs in family or community settings may be particularly toxic for some individuals at risk. In short, interventional strategies after the clinical manifestation of derivative states should involve both provisions of the immediate modification of the environment and the longer-term access to supportive interventions. Isolation from substantial interpersonal or social interactions may be exacerbation factor and regular daily routine with support can exert a prophylactic effect. Medication therapy or institutionalization has usually takes time in adulthood. The derivative-related dimensions also include changeable constructs. It may again sometimes take a long time for psychological and/or instructive programs to reach an effective result in the changeable derivative-related dimensions. A regular daily routine with family (e.g. family meal), which has a prophylactic effect against the secondary and tertiary derivative states [151], may ameliorate both the social skills and the derivative-related dimensions. Because increased social demands or stressors are the cue of derivative manifestations and chronicity, the modification of the pathways may bring a positive effect in both preventive and therapeutic settings. Family-level or community-level easy accessibility to a supportive and inclusive atmosphere is one of the safety-nets for stress management. Community-level programs for family support are also important [152]. Solitary living without instructive programs in family or community settings may be particularly toxic for some individuals at risk. In short, interventional strategies after the clinical manifestation of derivative states should involve both provisions of the immediate modification of the environment and the longer-term access to supportive interventions. Isolation from substantial interpersonal or social interactions may be exacerbation factor and regular daily routine with support can exert a prophylactic effect. Medication therapy or institutionalization has only an accessory role in this model. The implications of our model for psychological and/or instructive programs to reach an effective result in the changeable derivative-related dimensions. A regular daily routine with family (e.g. family meal), which has a prophylactic effect against the secondary and tertiary derivative states [151], may ameliorate both the social skills and the derivative-related dimensions.

Conclusion

The categorical diagnostic boundaries for psychiatric conditions have never had any biological validity [158]. A considerable fraction of individuals with psychiatric conditions exhibit autistic characteristics, and there is a phenotypic similarity between autism and schizophrenia [7]. In addition, developmental deviations and psychiatric conditions may share genetic factors [159] and genetic factors link between developmental conditions and human brain functions [30–35]. Although our liability-probability model was developed through our clinical experiences (authors), it can provide a helpful framework for viewing the development and prevention of psychopathology. In the traditional probability models, most of the typical majority population has probability zero and the maximum probability in the extreme cases is 1.0 [160]. However, the range of probability of a derivative manifestation (social vulnerability) in our model includes neither zero nor 1.0. Therefore, everyone has some degree of social vulnerability and there is no one whose risk is 100%, and individuals with or without a diagnosis of psychopathology all contribute diversity to the human condition. The vulnerability diversity may be evolutionarily conserved to ensure the complexity of society, and the presence of extreme cases is thus necessary for the intrinsic compatibility between distributional robustness and phenotypic changeability [66]. Population-based studies to detect multi-dimensional endo-phenotypes of the derivative states may elucidate both the unified vulnerability structure and the hierarchical structure of the derivative-related dimensions.

Conflict of interest

All authors declare no conflicts of interest.

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