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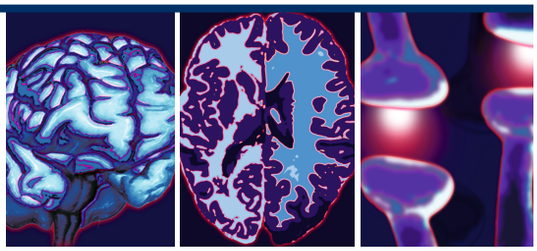

Classification issues in the developmental disorders: the case of autism and schizophrenia

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Practice points

- Autism and schizophrenia are distinct developmental disorders of the immature brain with different courses and sex distribution and some shared behavioral symptoms.
- Classification of developmental disorders is largely based on the severity of the individuals' deficient-for-age acquisition of complex skills.
- Diagnostic margins between developmental disorders and normalcy are statistically based, rather than binary based, which causes diagnostic dilemmas.
- Individuals with autism or schizophrenia vary greatly in symptoms and severity, even when they fulfill behavioral diagnostic criteria or share some genetic abnormalities.
- Neither autism nor schizophrenia is a specific biologically defined disease; each has many genetic and environmental causes.
- Behavioral and biologic classifications of developmental disorders are distinct and nonoverlapping.
- Separate diagnoses of anxiety or attention disorder should not exclude an autism diagnosis because autism spectrum disorders are complex and affect multiple brain networks.
- Progress in genetics, brain imaging and electrophysiology mandates reconsideration of the classifications.

SUMMARY New information continuously alters scientific classifications and their applications. A revision in progress of the DSM-IV-TR, which concerns classification of disorders, predominantly of behavioral symptoms, suggests reconsideration of overlaps and differences between two broad families of developmental disorders: autisms and schizophrenias. Developmental disorders are classified within two independent domains:

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behavioral/descriptive (level A) and biologic/etiologic (level C). Level A classification is syndromic and based on aggregates of mostly continuous, dimensional features with indistinct margins. Etiologic level C classification is based largely on categorical interacting genetic and environmental factors responsible for level A syndromes. Level B encompasses biologic mechanisms (pathogenesis) linking etiology (level C) to behavior (level A). Many level B hierarchical molecular and cellular networks contribute to the structure and function of the many brain networks responsible for level A behaviors. Autism and schizophrenia share some behavioral and cognitive characteristics, pathogenic mechanisms and etiologies, but major clinical disparities (level A) separate them.

Classification is fundamental to medicine and science; it provides a framework and common language for the study of and communication on phenomena or patients. Classification requires common operational rules or criteria for identification and investigation. The two reigning, roughly parallel, classification schemes for human behavioral disorders (mental disorders) are the DSM-IV-TR [1] and the tenth edition of the WHO International Classification of Diseases (ICD 10) [2]. Both are based on clinical/behavioral descriptions. Revision of the DSM-IV-TR towards DSM-5 is important due to the DSM's overwhelming influence on research and the allocation of resources for care and education of affected individuals, and for their eligibility for medical and disability insurances. The revision will have a worldwide impact as revision of the relevant sections of the ICD will likely follow those of the DSM-5.

Neither the DSM nor the ICD classifications consider directly the biologic causes of the disorders they define, not because they deny them, but for historical reasons. Modern research has made it abundantly clear that all complex physical and behavioral disorders are multidetermined. Biology and behavior belong to distinct domains with distinct determinants and metrics. Biologic and behavioral classifications are thus independent, although related. Attempts at unified hybrid classifications spanning both domains have only engendered confusion. We emphasize the important differences between clinical/descriptive and causal biologic classification schemes and the complex biologic pathophysiologic mechanisms intervening between them. We use autism spectrum disorders (ASDs) and schizophrenia spectrum disorders (SSDs) to demonstrate the impossibility of complete categorical separation between descriptively and dimensionally defined disorders, such as those defined in the DSM/ICD systems. We are also stimulated by new interest in the relationship between ASD and SSD. Are they subtypes of one overarching developmental disorder [3] or should their separation continue?

Classification levels

Developmental disorders are defined as difficulty in acquiring complex cognitive/behavioral skills at the expected age if severe enough to interfere with everyday living and attributable to atypical brain development. Their potential causes are many and often undefined, both at the brain and etiologic (basic cause) levels. Even when a specific etiology, such as a particular gene mutation, is causal, it is insufficient to fully explain the disorder because other causal factors, both genetic and, especially, environmental, modify its expression. Most developmental disorders are static although their symptoms often improve with age. Developmental disorders include the consequences of acquired perinatal insults, but not those of progressive disorders or later infection, trauma or other insult to the brain, even though their phenotypes overlap those of developmental disorders.

The classification of developmental disorders is hierarchical and includes two independent domains: behavior/clinical observation (level A) and the fundamental causes (etiologies) of level A (level C) **(Figure 1)**. Level B comprises the hierarchy of biologic (epigenetic, molecular, cellular and brain) mechanisms that link biology to behavior. Level A developmental disorders include attention deficit disorder (ADD) with/without hyperactivity, several subtypes of developmental language disorders, DSM ASD and SSD subtypes, and many others, each of which are also hierarchical.

Level B mechanisms consider epigenetic orchestration of gene expression and complex interacting networks at the molecular, cellular and brain sublevels, each one in turn with its own sub-sublevels. Medical disorders are regularly defined as level A by their time course and recognizable groupings of clinical findings (syndromes). They may have a specific level C

etiology, such as tuberculosis, melanoma, or tuberous sclerosis. The clinical picture may be profoundly modulated by other genes and by complex level B pathophysiologic mechanisms, for example, environmentally driven epigenetic changes, immune responses and altered cell proliferation and survival, all of which contribute to the function of organs like the heart or kidney.

Level A, the clinical/behavioral classification of developmental disorders, is descriptive and dimensional, and sorts patients into syndromes (groups of physical and behavioral deviations). It divides both ASDs and SSDs into diagnostic subtypes, developed for the DSM-IV after extensive field trials and discussions (Table 1). These diagnoses and subtypes are pseudodichotomous diagnostic categories defined statistically by the size of departures from the expected mean scores of unaffected matched populations.

Quantitative analysis of behavioral phenotypes is more precise than a yes/no clinical diagnosis, but the resulting boundaries are indistinct and often overlap [4]. The margins of level A symptoms and diagnoses are indistinct, therefore, individual diagnoses are often controversial. Human behavior and society are complex; for example, hallucinations are considered normal in some cultures and pathological in others. Biological level C variables such as genes, infections and other environmental influences, have variable effects depending upon the host's developmental stage, cell type and genotype. Both genes and psychosocial variables modulate the effects of biologic etiologies on level A behaviors [5].

Normal and abnormal behaviors often overlap because of blurred common margins. Shared biologic characteristics are more likely to be approximately similar than identical. No human or animal behavior or specific feature depends on a single skill or component. There are overlaps between related abilities, any one (or several) of which may result in the success or failure on a given task. This is an important difference between humans and machines [5]. When it comes to scoring tests or observations, subjective clinical judgments may be distorted by prejudice, yet observations and clinical diagnoses of experienced clinicians may be more reliable and insightful than standardized tests that assume optimal patient motivation, comfort and cooperation.

Overt postpubertal SSD is usually an obvious clinical diagnosis. The younger the child, the more diagnostic expectation is biased toward the more prevalent ASD. Neurologists may be reluctant to diagnose SSD without hallucinations and other positive symptoms or to diagnose an ASD, unless children are symptomatic by 5 years of age. The current 'official' subtypes of ASD and SSD listed in Table 1 cover a broad range of symptom severities and differences among affected individuals, leading to the concept of spectra – ASD, SSD, dyslexia and attention deficit spectra, among others. No single symptom, even if suggestive, is unique or diagnostically specific for a particular developmental disorder. Table 2 lists some clinical differences and similarities between ASD and SSD.

Seemingly normal relatives of ASD or SSD patients often share some behavioral traits with them (intermediate phenotypes). Kanner and Asperger, who described ASD independently in the 1940s, commented on aloof and eccentric relatives of their patients [6,7]. Gottesman and Shields proposed in the 1960s that SSD is a threshold disease, with incomplete forms in relatives [8]. These phenotypic fragments (e.g., aloofness) or endophenotypes may share common

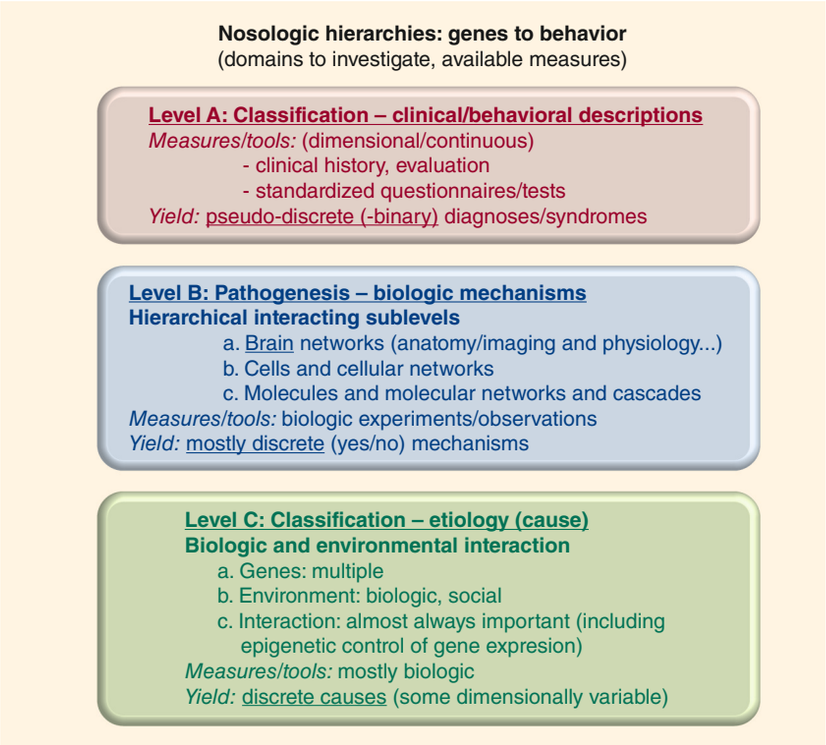

Figure 1. Levels of classification/investigation of developmental disorders. Classification of developmental disorders spans two domains: clinical/behavioral level A and biologic level C. Level A diagnoses are descriptive/observational and essentially dimensional and level C diagnoses are etiologic/causal and mostly discrete. Level B – biologic pathophysiology – links the two diagnostic domains.

Table 1. American Psychiatric Association's DSM behavioral classification: types and subtypes of autism and schizophrenia spectrum disorders[†].

ASD[‡] and PDD	SSD
Autistic disorder	Schizophrenia ▪ Paranoid ▪ Disorganized ▪ Catatonic ▪ Undifferentiated ▪ Residual
PDD not otherwise specified	Schizophreniform disorder
Asperger's disorder	–
–	Schizoaffective disorder
Disintegrative disorder	COS[§]

[†]The parallels are those of the authors; DSM-IV-TR does not compare its three autism spectrum disorder subtypes to its schizophrenia spectrum disorder subtypes, each of which is treated as a discrete entity.
[‡]Rett syndrome omitted because it is a level 3 (biologic) diagnosis, not primarily a level A (behavioral/descriptive) dimensional diagnosis.
[§]Childhood onset schizophrenia added because of its overlap with disintegrative disorder.
–: Not applicable; ASD: Autism spectrum disorder; COS: Childhood onset schizophrenia; PDD: Pervasive developmental disorder; SSD: Schizophrenia spectrum disorder.

biologic bases, such as DNA sequences, brain structure and connectivity.

Classification, based on level A continua contrasts starkly with classification based on discrete, yet often, multiple level C biologic etiologies responsible for the many causally distinct developmental disorders [9,10]. Level C studies seek discrete molecular/cellular (genetic) alterations or defined environmental variables such as premature birth, infection or gross neglect in orphanages, which influence individual level A endophenotypes and syndromes. Level C metrics are primarily dichotomous (i.e., yes/no, particular etiology present/absent), although the size/severity of the causative variables can differ and gene dosage effects are important [11].

Genetic disorders may be linked to structural chromosome anomalies, whether microscopically detectable (cytogenic) or submicroscopic (copy number variants [CNVs]), both of which involve multiple genes. Other genetic etiologies, more prevalent in ASD than SSD, involve single gene mutations, some exceedingly rare, others not. Mendelian genes with large ASD-related effects include, among others, two tuberous sclerosis genes that control different steps in the same molecular pathway, or the Fragile-X gene in which expansion of the DNA trinucleotide CGG inhibits production of the Fragile-X protein required for normal brain (and body) development. Highly penetrant disorders (e.g., Huntington's disease) are largely impervious to environmental effects, whereas most genetic factors identified in psychiatric disorders have small and variable effects that become clinically evident only in the context of other alterations in particular networks [11].

Level C etiologies encompass many genetic factors, environmental impacts on the immature brain, such as drug effects (e.g., fetal thalidomide, ethanol and valproate exposure), physical trauma and certain infections, as well as on-going life experiences and stresses. High-resolution brain imaging (level B research) and molecular genetic techniques (level C research) are revealing novel factors linked to ASD and SSD. Environmental and psychosocial influences shape brain development through level C epigenetic mechanisms, including DNA methylation changes and other transcriptional effects of noncoding RNAs on gene expression and its timing [12,13]. Without historical clues or physical findings, most cases of ASD and SSD remain unexplained today. Imaging and genetic studies are crucial for research, but are rarely helpful today for counseling or management of the individual. Their costs and benefits for individuals and families must be considered in view of potentially misleading results and the expense of testing all patients.

Level B pathogenesis highlights the interconnected biologic cascades that link causation (level C) to clinical symptoms and behaviors (level A) [14], including very complex abilities like recognition of faces and reading social cues, 'psychological' functions, such as inner language, reasoning, decision-making, weighing expectations and anxiety, among others. They all result from integrated activities in neural networks. The many pathophysiologic complexities that explain how gene products and exogenous factors, such as trauma and infection, regulate the structure and function of dynamic circuitry within and between cells are now being tackled. Behaviors and brain connectivity cannot be reduced to single genes or molecules, but molecular understanding of chemical networks may suggest treatment strategies. Level B has to do with mechanisms of connectivity between biology and behavior, not classification.

Historical perspective: ASD & SSD, one or two developmental disorders?

Whereas SSD has been known as a severe 'classic psychosis' for well over a century, it was not until 1980 that ASD was included in the DSM-III as one of the pervasive developmental disorders (PDDs) [15], a behaviorally defined

Table 2. Behavioral comparisons between autism spectrum disorders and schizophrenia spectrum disorders†.

Characteristics	ASD	SSD
DSM-IV-TR core deficits		
1. Social impairment, poor insight and 'theory of mind'	Universal, variable severity	Almost universal, variable severity
2. Impaired language use/ communication (pragmatics)	Universal, prominent	Common, variable severity
3a. Rigidity, perseveration, overly narrow focus, preoccupation	Common, variable severity and type	Common, variable severity and type
3b. Stereotypies (motor, verbal)	Common, variable severity and type	Less frequent than in ASDs
Other salient level A features		
Motor abnormalities (unmedicated)	Frequent toe walking, hypotonia, dyspraxia and stereotypies	Frequent soft signs and extrapyramidal difficulties, correlated with cognitive abnormalities
Catatonia	Yes, rare	Frequent
Sensory dysfunction	Common, multimodal, often significant, both hypo- and hyper-reactivity	Common, related to hallucinations, often apparently reduced pain perception
Self-injury	Highly variable, picking, biting and gouging	Suicide attempts, sometimes bizarre self-mutilation
Deficient attention and error monitoring	Common, variable	Common, variable
Cognition	Highly variable, very low to above average, irregular profile of abilities and rare savants	Highly variable, lowest level better than ASDs
Anxiety	Common and often significant	Common, less overt than ASDs
Paranoia	Seen in high functioning adolescents [90]	Common and significant
Mood	Variable, labile	Often flat, depression, anergia, anhedonia
Aggressive behavior	Severe in some	Severe in some
Poor judgment and self awareness	Common, often severe	Common, often severe

†The table reflects the authors' clinical experience, investigations and the published literature.
ASD: Autism spectrum disorder; SSD: Schizophrenia spectrum disorder.

overarching category that included classic ASD and other related disorders. The PDD family was subsequently broadened to include intellectually capable individuals, such as those with Asperger's syndrome who, by definition, speak at normal ages and have at least borderline cognitive competence (full scale intelligence quotient [IQ] >70). **Table 1** displays clinically defined subtypes of PDDs and SSDs in the current DSM-IV-TR [1].

King and Lord recently proposed that similarities between the broad ASD and SSD phenotypes may justify "reconnecting these phenotypes" at some levels of classification or analysis [3]. They aptly point out that, whereas typical ASD is easily distinguished from typical childhood-onset schizophrenia (COS), this is not so at the margins of either spectrum where symptoms may blend or overlap with normality or with those of other disorders, such as ADD/ADHD, developmental language disorders or bipolar disorder. A large NIH study indicated that 30–50% of individuals diagnosed with COS fulfilled criteria successively or simultaneously for both ASD and SSD [16]. We review the history of their successive connections and separations before considering some of the similarities and differences between ASD and SSD.

Autism was first conceived as related to schizophrenia. Bleuler of Zurich coined both terms in the early 20th century [17], replacing Kraepelin's dementia praecox. Bleuler saw autism (avoidance of social contact) as a cardinal symptom of schizophrenia. De Santis had reported in 1906 that overtly brain damaged children may show 'psychotic' behaviors (e.g., hallucinations and delusions), while other 'psychotic children' seemed neurologically and intellectually intact [18]. He called the first group dementia praecocissima (very early onset of dementia praecox). Kanner, a German-educated child psychiatrist, described infantile autism in 1943 in Baltimore [6] and, in 1944, Asperger, a Viennese pediatrician, labeled similar children independently as suffering from autistic psychopathy [7]. Kanner stressed differences between this 'new' disorder and COS. He wrote that his first 11 patients had all shown their extreme aloneness "from the very beginning of life" [6]. They had powerful desires for monotony and being alone, yet seemed purposeful and intelligent in relating to inanimate objects. Benda wrote in 1952: "The

great question is whether autism is a part of the schizophrenic syndrome complex or should be considered a separate entity" [19]. The Canadian psychiatrist Cappon used both ASD and SSD as diagnoses – the earlier and more severe the problem, the more likely it would be ASD [20]. Bender from New York wrote about a 'pseudodefective form of childhood schizophrenia' in the 1940s, one that often began before 5 years of age [21].

Kanner revisited historical concepts of childhood 'psychosis' in 1971 [22]. He opposed combining all major early childhood behavioral disturbances (e.g., ASD, childhood SSD, and more) into a single category of disturbances of the mother–child bond. He had lost confidence in his original psychosocial explanations for ASD. Rutter and Bartak's British paper strongly supported Kanner's separation of ASD and SSD [23]. "For many years autism was regarded as a particularly early manifestation of schizophrenia. The consensus today is that this view is wrong. Autism and schizophrenia differ in terms of sex distribution, social background, family history of other developmental and psychiatric disorders, intellectual level, cognitive pattern, presence of delusions and hallucinations, and course of disorder" [23]. This opinion agreed with Kolvin's report of qualitative differences between English children with disease onset before the age of 3 years who had severe speech abnormalities and often striking stereotypies, and those with 'late-onset psychosis', after 5 years of age, whose hallucinations and 'adult schizophrenic symptoms' compromised affect, motility, and volition [24]. Only 22% of Kolvin's early onset patients had intelligence quotients above 70, whereas 83% of late-onset patients did [25]. Rimland's book added a strong voice against psychogenic theories of ASD [26].

Studies of pathogenesis (level B) and biologic mechanisms of both ASD and SSD, in particular increased prevalence of epilepsy in ASD, began in the 1970s and rapidly discredited psychogenic theories. Comprehensive biologic studies highlighted aberrations linked to the behavioral features of both disorders; new tools pinpointed neurologic, cellular and molecular abnormalities, notably those affecting neurotransmitters and their receptors; spectacular advances in genetics leave no current doubt about its critical role in brain development and its aberrations. These new data have yet to be integrated into coherent nosologies of either ASD or SSD, in part because some investigators still treat ASD and SSD as 'diseases' rather than complex multidetermined syndromes, and attempt to bypass pathophysiology at the brain level when seeking to correlate genes, molecules and behaviors. To this day, views on the relationship of ASD to SSD fluctuate.

ASD & SSD: some clinical/behavioral (level A) commonalties & differences

The DSM and ICD nosologies are rooted in behavior, with impaired sociability and communication, and narrow repetitive interests and behaviors as core deficits. **Table 2** lists some of the major overlaps and differences in DSM-IV-TR clinical and behavioral characteristics of ASD and SSD. Considering the variety and broad range of manifestations of each, including language behaviors compiled in **Table 3**, it is crucial to keep in mind that neither ASD nor SSD is a single entity or 'disease'. Substantial clinical/behavioral differences between ASD and SSD groups argue against lumping them into a single continuum. We agree that their symptoms are often parallel. Among the differences, early language and behavioral regression, epilepsy [27], physical features, such as atypical head and brain growth [28], and association with identifiable genetic disorders [29], all suggest ASD rather than SSD. The symptoms that differentiate ASD and SSD vary with age and rarely affect all group members.

Table 3 reviews language abnormalities, which are important in both ASD and SSD. With increasing attention to 'theory of mind' (TOM) [30] has come the realization that brain networks involved in TOM issues overlap with those used in comprehension of verbal stories and irony [31]. The idea of TOM began with ASD, but also clearly involves SSD and other disorders [15,31]. Psychic abnormalities are prominent and varied in both ASD and SSD. Although both are deficient in empathy, social adjustment and communication skills, individuals with ASD rarely exhibit frankly psychotic features or strong paranoia. The profound mood disorders of SSD, often evident as apathy and anhedonia, are rare in unmedicated ASD. Overactivity or ADHD is so prevalent in ASD that a recent paper asks whether the autistic spectrum includes ADHD [32]. Differences notwithstanding, many recent papers stress overlaps between ASD and SSD [3,16,33,34].

The reliability of diagnostic criteria for defining level A subtypes of ASD and SSD has increased over successive revisions of the

Table 3. Language comparisons: autism spectrum disorders versus schizophrenia spectrum disorders†.

Characteristics	ASD	SSD
Age at speaking	Often delayed, others speak precociously or may speak in sentences after a prolonged nonverbal period	Usually normal, some mildly delayed
Pragmatics (verbal and nonverbal communication)	Universal, permanent, often major impairment, few communicative gestures, speak to self or 'the room', avoid eye-gaze, may not respond to name or do not need communicative partners	Impaired, less obvious than ASD but common, neglect social cues, speech noncommunicative and disorganized
Amount of speech	Variable, from none or sparse when prompted to verbose; meaningless jargon or repetitive questioning in some	Variable, usually decreased with impoverished content and complexity
Phonology (speech sounds)	Highly variable, from severely impaired to over precise imitation (delayed echolalia) to fluent jargon	Usually normal, rarely with echolalia and/or verbigeration
Prosody (melody at sentence level)	Usually abnormal, wooden, robotic, high pitched tone; sing-song; raising intonation of assertions	Abnormal, monotonous and flat
Grammar (grammatical markers), use of small invariant words (articles, prepositions), word order	Variable and very impoverished (single words) to normal	Usually normal, but often impoverished with short truncated sentences
Semantics (meaning of words, sentences, discourse)	Variable, impoverished to over sophisticated, unusual word choices and tangential speech	Disorganized sparse speech, perseveration, incoherence and neologisms
Comprehension	Impaired in young children, variable later; may be worse than expression; difficulty with wh-questions; miss jokes; inferences; sarcasm; overly literal interpretation	Similar problems understanding stories and irony, narrow focus and often colored by paranoid ideation
Major diagnostic features or red flags	Early language/behavioral/play regression or prolonged stagnation Perseveration, echolalia, pronoun reversal and incessant questioning Impaired pragmatics or aberrant prosody Scripted discourse	Perseveration Sparse communication Tangential incoherent communication Neologisms

†The table reflects the authors' clinical experience, investigations and the published literature.
ASD: Autism spectrum disorder; SSD: Schizophrenia spectrum disorder.

DSM [35,36], but so have criticisms of the standard approach, which attempts to carve categorical syndromes out of severity continua [37]. Hyman reports that family and genetic data do not match categorical boundaries of the DSM-IV disorders [36]; biologically discrete and dimensionally/behaviorally defined entities cannot be superimposed. A recent Korean study illustrates the indistinct margins of behavioral diagnoses [38]. It assigned ASD diagnoses to some children who seemed normal in most respects and would not have been counted without detailed research evaluations. More sensitive diagnosis explains part of the present 'autistic epidemic' [39]. Fuzzy boundaries between successfully treated individuals with full blown SSD and the general population parallel the indistinct boundaries of mild ASD [40].

The DSM-III classified ASD among the developmental disorders and SSD among the psychoses, implying that they are fundamentally different nosologies. This controversial dichotomy persists [1]. Some individuals with ASD qualify for a diagnosis of SSD (or bipolar disease) by the late teens or early twenties [41,42]. Mouridsen and colleagues identified many (35% of 89 individuals) with SSD diagnoses among Danish adults previously diagnosed with ASD as children [42]. However, Volkmar and Cohen detected only one case evolving into SSD and argued for a chance association [43].

ASD & SSD: major shared & differing biologic (level B) pathophysiologies

In addition to the many behavioral differences between ASD and SSD, they differ in age of onset, sex distribution, clinical course and many other biologic characteristics, few of which are understood **(Table 4)**. Their clinical/behavioral similarities are more likely to indicate common

Table 4. Selected biologic characteristics: autism spectrum disorders versus schizophrenia spectrum disorders†.

Biologic characteristics	ASD	SSD
Prevalence	1–2% of children	1% of adolescents/adults
Large sex discrepancy	Yes, males >> females	No
Age of onset	Rarely after 2 years of age	Usually teens or adults
Course	20–30% early regression; most improve with age and intervention; complete recovery rare	More variable than ASDs; episodic; remissions occur; some patients static, others deteriorate
Epilepsy	Frequent; may precede clinical ASD	Rare
EEG, electrophysiology	Variable and nondiagnostic; event-related potentials often abnormal	Usually normal; event-related potentials often abnormal
Pattern of brain growth (group studies)	Abnormal trajectory of head growth (see text)	Normal head growth; mild microcephaly
Clinical brain imaging abnormality	Rare without clinical clues (e.g., Rett phenotype, tuberous sclerosis, perinatal insult, others)	Rare
MRI abnormalities in group studies	Common; variable; often enlarged white matter; many others in selected areas	Common but variable; gray matter loss often reported
Abnormal connectivity in group studies	Common at dendritic and tract level	Common at dendritic and tract level
Abnormal GABA interneurons	Yes (autopsy, imaging)	Yes (autopsy, imaging)
Multiple neurotransmitters and modulators, overlapping but nonidentical	Yes	Yes
Neuroinflammation at autopsy	Yes, not all cases; limited data	Yes, not all cases; limited data
Level C: etiologies		
Cases with large gene effects	Yes, approximately 10% (e.g., Rett, tuberous sclerosis, Fragile-X, others)	Very rare (e.g., *DISC1*)
Multiple gene effects	Estimated common	Estimated common
Identifiable environmental causes	Yes	Yes, data less strong

†The table reflects the authors' clinical experience, investigations and the published literature.
ASD: Autism spectrum disorder; SSD: Schizophrenia spectrum disorder.

neural pathophysiologies (level B) than common etiologies between the many ASDs and SSDs (level C).

The most productive current investigations focus on pathophysiology, striving to link etiology and the cascades of molecular and cellular abnormalities to particular brain pathways and behaviors. The discussion in this article is limited to four major clinical areas of active investigation.

■ Epilepsy

Deykin and MacMahon's early report of a prevalence of epilepsy up to 28-times higher compared with unaffected controls was incompatible with psychogenic theories of ASD [44]. Recent studies with many more mildly affected children report a lower prevalence, still considerably higher than in typically developing children [45]. The prevalence of epilepsy is especially high in Rett syndrome and childhood disintegrative disorder, but epilepsy is not essential for the diagnosis of any ASD. The prevalence of epilepsy in SSD is much lower [46]. There is continuing interest in the interictal psychoses of some epileptic patients, particularly those with temporal lobe epilepsy. SSD and epilepsy may share genetic susceptibility [47]. Some epilepsies, SSD and ASD are linked, in rare cases, to a handful of genes or submicroscopic CNVs, supporting common pathogenic mechanisms for all three in some individuals [48].

■ Brain structure & imaging

A variety of imaging abnormalities described in both disorders have not coalesced into a coherent 'core' of characteristic imaging changes for either ASDs or SSDs. Hauser and colleagues reported pneumoencephalographic (PEG) temporal lobe abnormalities in 18 severely impaired children with ASD [49]. The first reported PEG studies of SSD, in 1927, described brain atrophy in patients with a progressive course [50]. Many PEG studies of schizophrenics had appeared by 1975, without consensus on the significance of structural abnormalities or their correlations with symptoms. High-resolution morphometric MRI, analyzing groups of affected individuals and 'normal' controls, has uncovered various

subclinical anatomic correlates in both ASD [51] and SSD [52], but no unique pattern, which is hardly surprising in behaviorally defined disorders with disparate clinical symptoms and biologic etiologies. Imaging studies can neither establish nor refute these behavioral diagnoses, even in individuals with 'idiopathic' ASD or SSD. Longitudinal studies show a changing pattern of cortical thinning and other structural abnormalities in some individuals with ASD and SSD [53,54]. Head growth is accelerated in a significant proportion of infants and toddlers with ASD, followed by premature cessation of growth by the teens [28], and is linked to *PTEN* gene mutations in some patients, in whom it represents a biologic endophenotype (see section 'ASD & SSD: similarities & differences at the etiologic/causal level C').

Functional MRI, diffusion-tensor imaging and a wealth of behavioral studies indicate altered network connectivity in both ASD and SSD, yet standardization of network connectivity studies remain incomplete [55]. Structural changes in the anterior cingulate, thalamic, frontal and temporal regions [53,56] may correlate with shared social and other behavioral inadequacies [57].

■ Neuropathology

Bauman and Kemper's neuropathologic studies implicated cerebellar and limbic neuronal abnormalities in ASD and contributed to major changes in understanding the role of the cerebellum in language and higher cognitive functions [58,59]. The neuropathologic studies are limited by small numbers, variable findings and questions of whether these were 'atypical patients'. Roberts and Bruton said in 1990 that SSD was no longer the 'graveyard of neuropathology' and that a coherent picture was emerging [60]. However, different kinds of schizophrenic neuropathology continue to emerge; inflammatory/immune pathology has been found in some studies of both ASD and SSD, but is unlikely to be universal or to indicate active infection [61,62]. Casanova *et al.* reported underdeveloped neocortical neuronal minicolumns and insufficient inhibitory GABAergic interneurons in ASD and SSD [63], consistent with heightened excitability and excessive glutamatergic effects in both disorders [64].

■ Static versus dynamic course

If exogenous insults to the fetal/infantile brain and maldevelopment are major etiologies of ASD, we would expect a static condition that may improve with maturation and adequate intervention. The many toddlers who lose their language and regress socially, stagnate for weeks or months then improve, although often incompletely, refute an overall static hypothesis. Regressive ASD raises the possibility of exogenous insults, especially in the occasional seemingly normal older child with disintegrative disorder who becomes permanently nonverbal and demented [65]. Autistic regression was largely ignored until Kurita's 1985 paper [66]. It remains unexplained and a major research issue today [67], possibly implicating inflammatory or immune mechanisms in some individuals with ASD [61,67]. Mild cognitive impairment and MRI abnormalities often precede the clinical onset of SSD [68,69], although few patients deteriorate soon after the first-psychotic episode [70,71]. Symptoms of both ASD and SSD often change considerably with time, the trajectories differing among affected persons. The delayed onset of SSD and its frequently fluctuating course suggest an evolving disorder, as do reported brain volume changes in some patients after the onset of psychosis. Autopsy studies of ASD and SSD rarely show active pathology [72], although occasional ASD patients have unsuspected slowly progressive genetic disorders [73]. Some cases of ASD and SSD deteriorate with time, suggesting an 'ever-changing brain', whose structure is shaped by experience throughout the lifespan [74]. Repeated subtle insults, perhaps of environmental origin, may play a role in the often subacute nature of COS, disintegrative disorder and early autistic regression.

ASD & SSD: similarities & differences at the etiologic/causal level C

■ Genetics

Important new data continue to accumulate [75]. A small minority of individuals with ASD and SSD share genes, or CNV deletions or duplications that involve other genes and regulatory factors besides a gene of interest. Examples include *NLGN4*, *NRXN1*, *SHANK3*, *CTNAP2* and others, rarely found in the population at large [8,10]. A number of implicated genes control synaptic development, maintenance or regulation [11,75,76] or general brain growth [77,78]. Shared genes do not imply identical syndromic level A diagnoses; they suggest shared pathogenic influences on particular brain networks, which, in other brains, may be affected by other molecular

mechanisms [14]. The genetic analysis of behavior and its disorders remains immature. Even common genes correlated with specific narrow endophenotypes that ASD and SSD may share cannot explain the overall phenotypes, although they may suggest shared gene defects or pathogenic molecular circuitry [78].

Over 100 well-defined Mendelian somatic and neurologic disorders are responsible for a small minority of individuals with ASD. Among the more prevalent mutations with large effects are tuberous sclerosis genes 1 and 2, Rett syndrome, and fragile-X syndrome. Many rare mutations, some limited to a single family, are associated with ASD symptoms. One of very few genes and CNVs associated so far with both ASD and SSD is the chromosome 22q11 deletion responsible for the velocardiofacial (Shprintzen) syndrome, which has variable somatic abnormalities. Although said to be the single most frequent genetic 'cause' of SSD, only 25–30% of individuals with this deletion manifest SSD [79].

ASD and SSD phenotypes appear to be based on many small gene and environmental effects. None is individually specific. Specific biologic or behavioral traits (endophenotypes) common to patients and 'unaffected relatives' have been linked to particular genes or imaging findings. Early megalencephaly in some ASD patients is linked to *PTEN* gene mutations [80]; Fornito and Bullmore correlated abnormal frontotemporal connectivity with *ZNF804A* polymorphisms [81]. Single gene mutations or CNVs reliably predict some medical illnesses, but not disorders with only behavioral symptoms. Even in medical or multisystem illnesses they often fail to predict severity. Whole-genome sequencing may now provide estimates of the combined risk of multiple gene mutations. Walton used single nucleotide polymorphisms from 34 'SSD risk genes' to calculate a cumulative risk score for SSD, and correlated this score with the function of the dorsolateral prefrontal cortex, studied by functional MRI [82]. This is a promising approach, but problems with interpretation remain to be solved before it can be used clinically [83].

The authors cannot endorse recommendations for extensive genetic studies in routine patient evaluation [75], despite their spectacular contributions to research [84]. Medicine is now asked to reduce spending; money spent on low-yield genetic studies reduces that available for treatment and remedial education.

■ Environmental influences

Environmental causes of ASDs and SSDs have mostly eluded detection. When found, most do not have specific effects. Prematurity increases the risk of both disorders: the more premature, the greater the risk [85]. Intrauterine infections such as rubella and cytomegalovirus and, rarely, neonatal herpes encephalitis, as well as cytotoxic drugs such as thalidomide and valproate, may damage the fetal brain at a crucial stage of development and can cause ASD, among other sequelae. Weinberger argued that fetal injury during the second trimester of pregnancy can distort subsequent brain development [86] and lead to SSD [87]. Several studies report excessive numbers of schizophrenic births during winter and spring, suggesting possible fetal exposure to maternal infection and/or vitamin D deficiency [88]. The births of children with ASD exhibit less seasonal clustering; when present, ASD clusters are more likely to occur in spring and summer [89].

Conclusion & future perspective: ASD & SSD: lumping versus splitting

This paper revisits the debate about modern classification of ASD and SSD, both common and costly developmental disorders of the brain. We and others [40], stress the need to consider separately observational/behavioral classification (level A – dimensional) and etiologic/biologic classification (level C – categorical). These distinct classifications of developmental disorders may be related, but cannot be merged into one common nosology because their domains and their metrics are not isomorphic. Diagnosis is classification. The seemingly discrete diagnoses of the DSM and ICD systems group individuals into a series of clinically/behaviorally defined syndromes on the basis of clinical observations and scores obtained on statistically-defined continuous measures. The resulting level A diagnoses are therefore pseudodichotomous and are often contentious because of overlaps of blurry margins between them and between milder variants and normalcy. Pathophysiology (biologic mechanisms underlying symptomatology – level B) illuminates the complex interacting epigenetic, molecular and cellular mechanisms that alter function of neural networks that link biology to behavior. Biologic investigations elucidate some of the brain bases of behavior, but can not reduce behavior in all its complexity to a single domain. Behavioral commonalities

between ASD and SSD suggest involvement of some common brain networks, without implying identical cellular or molecular mechanisms or etiologies.

The overlap between ASDs and SSDs at level A is strongest for disintegrative disorder and COS. These rare syndromes have relatively similar but atypical ages of onset and poor prognoses, and are not representative of individuals commonly seen with ASDs and SSDs. As groups, individuals with ASDs and SSDs have a number of parallel manifestations, not only those affecting social function, language, attention, impulse–control and a variety of cognitive abilities, and both often have sensorimotor abnormalities and evidence of other widespread brain dysfunction.

Nevertheless, differences in sex distribution, course and symptoms outnumber behavioral similarities. Parallel behavioral abnormalities at level A suggest dysfunction of some common brain and other pathophysiologic mechanisms, but not unitary classification at level C, despite some overlapping genetic and nongenetic etiologies. Common endophenotypes suggest common genes; if found, investigating their molecular and cellular effects on the brain brings hope for the development of novel pharmacologic therapies. None of the small number of known shared genes can account for the complexities of these two families of multidetermined disorders.

We agree with Rutter that both dimensional and categorical evidence should be used in the classification of developmental and other disorders with predominantly behavioral symptomatology, respecting their inherent distinctiveness and complementarity [37]. Appropriately, the new classification in preparation for DSM-5 remains behaviorally based. Users need to know that the DSM entities are pseudobinary, necessary for real-world usage, with inherently blurry margins and overlaps. The DSM-5 and its future editions will accrue both clinical and more refined quantitative behavioral research evidence, which will probably lead to regrouping of some core symptoms and diagnoses.

Biologic considerations belong to another domain altogether. Biologic classifications cannot be asked or expected to map onto behavioral ones. Ongoing work at the many biologic sublevels of pathophysiology offers hope of novel neuropharmacologic agents; it will continue to uncover brain mechanisms of developmental disorders that can provide ideas for new evidence-based interventions.

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