What are neurodevelopmental disorders?

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Purpose of review
The purpose of this review is to highlight the origin and evolution of the field of neurodevelopmental disabilities and describe the main construct(s) upon which the current classification of neurodevelopmental disorders is based.

Recent findings
We address the following questions: Are neurodevelopmental disorders independent entities? Why is it desirable to understand the neurobiological substrate for these disorders? What new knowledge have we generated by leveraging advances in neuroscience, genetics, and neuroimaging? And finally, is the current construct, that is based on functional classification, still useful?

Summary
As our biological understanding of brain-behavior disorders evolves, we ought to re-evaluate the current classification system and expand it into a multidimensional classification that takes into account behavioral profiles and underlying mechanisms.

Keywords
disability, genetics, neurobiology, neurodevelopmental disorders, neuroimaging

INTRODUCTION

Origin and evolution of the term

Catalyzed by the societal demand for civil and legal rights for individuals with disabilities in the United States, the term 'developmental disabilities' originated in law in 1970. The term replaced 'mental retardation and related disabilities' and served as an administrative description that facilitated the design and implantation of policies and services targeted to a subset of individuals that were long overlooked. As the legislative efforts evolved to organization and access to services, the term expanded in 1978 to include any chronic disorder of childhood onset that resulted in generalized and substantial functional limitations and required life-long support.

The current definition of developmental disability is 'severe, chronic disability that occurs before an individual is 22 that is likely to continue indefinitely, and results in substantial functional limitations in three or more of the following areas of major life activity: self-care, receptive and expressive language, learning, mobility, self-direction, capacity for independent living, economic self-sufficiency' [1]. Emphasizing the range of functional limitations served as a roadmap for establishing specialized programs and services. Under this definition, both central nervous system (CNS) and non-CNS functionally impairing disorders that may be congenital or acquired before age 22 were included.

Subsequently, the term neurodevelopmental disabilities (NDD) came to define chronic disorders that affected CNS function during the developmental period in the domains of motor skills, cognition, communication, and/or behavior [2▪▪]. The term excluded childhood disorders of the peripheral nervous system and disorders of musculoskeletal origin (e.g. muscular dystrophy and spina bifida). Under this definition, a group of disorders were characterized by their most obvious functional/behavioral impairment(s), which included developmental delay and regression, intellectual disability, cerebral palsy, epilepsy, autism, specific learning disabilities,

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KEY POINTS

- The current classification of neurodevelopmental disorders is based on behavioral and social constructs.
- The current construct falls short of identifying the underlying neurobiology.
- Advances in neuroanalytic tools (neuroimaging, neurogenetics) allowed better understanding of underlying disease mechanisms.
- A multidimensional classification that includes behavior profiles and underlying mechanisms might inform biomarker and therapeutic targets discovery.

language disorder, attention deficit/hyperactivity disorder, deafness and blindness. Enclosing these disorders by the NDD label was not meant to reflect biologically distinct entities but rather to identify group of patients that required distinct services. The disorders may result from many causes. Hypoxic-ischemic injury, trauma, toxic exposure, infections, immunologic, nutritional, metabolic, genetic, structural, aging/maturation, oncologic, and iatrogenic disorders may cause the functional limitations that define NDD.

Because of the overlap between NDD and mental health disorders of childhood, the diagnostic criteria for NDD are based on a constellation of behaviors/symptoms that are specified in the diagnostic and statistical manual of mental disorders (DSM) and are also coded in the WHO international classification of disease (ICD). Although revisions to the DSM and ICD have been made to bring the neurodevelopmental disorders into alignment and improve diagnostic reliability, the behavior-based and symptom count cutoffs approach is subjected to variability in diagnostic threshold between clinicians and bias in identifying coexisting conditions [3▪].

Are neurodevelopmental disorders independent entities?

It is uncommon for NDD to occur singly. Dysfunction in one area is often accompanied by dysfunction in other areas often leading to multiple diagnoses. In population-based studies, intellectual disability [4], and communication disorder [5] is present in half of the children with cerebral palsy. The majority of children with attention deficit hyperactivity disorder (ADHD) have language disorder [6▪] and there is substantial overlap in autism and ADHD [7]. Hypotonia and developmental coordination disorders are common in children with intellectual disability [8▪]. Because of some diagnostic overlap, high rate of coexisting disorders and, to a large extent, similar treatment strategies, the clinical and biological independence of disorders enlisted under NDD has been questioned. As a result, treatment programs may fail due to misdiagnosis and/or not addressing associated dysfunctions.

When does clumsiness become a developmental coordination disorder and when does developmental coordination disorder transition into cerebral palsy? How wide or narrow is the spectrum of autism or ADHD? How much social dysfunction distinguishes autism from social (pragmatic) language disorder? And finally, what is the definition of functional limitation? Is it driven by the individual? Or the society? Or our medical convention of what constitutes 'abnormal'?

In the current NDD model, the terminologies used to describe behavioral symptoms are often a source of variability. Below are few examples of how terminology can complicate the process of linking functional imitations to the underlying neurobiology. These examples also raise questions about the utility of symptom checklists for diagnosis.

The same functional limitations may arise from different mechanisms (e.g. motor impairment in cerebral palsy may result from prematurity, hypoxic ischemic injury, trauma, or genetic causes).

The same mechanism may result in a different pattern of functional limitations (e.g. outcomes of prematurity range from almost normal development to severe diffuse impairment).

A behavior can have different names (e.g. developmental coordination disorder, motor clumsiness, and specific developmental disorder of motor function all denote some level of qualitative motor impairment; in the cognitive domain perseveration, persistence, or 'stick-to-it-iveness' may all refer to the same behavior).

Different behavioral impairments can have the same name (e.g. stereotypic behavior in Tourette's syndrome vs. autism spectrum disorder).

Manifestations of the same disorder change over time (e.g. hyperactivity/impulsivity in preschool age may transition into inattention and executive dysfunction in older children with ADHD).

The severity does not necessarily distinguish one disorder from the other (e.g. severe social impairment may be seen in children with language disorders and children with ASD).

Additionally, the lack of diagnostic and therapeutic biomarkers, the almost universal subclinical dysfunction, high rate of diagnostic overshadowing, and the establishment of diagnoses that have overlapping symptoms have caused some authors to question the validity of the current construct.

Recognizing the frequent coexistence of NDD and the overlap of symptoms of dysfunction especially in young children, new constructs were proposed. Some authors suggested that NDD should be thought of as a spectrum with varying severity of impairment ranging from minimal brain/cerebral dysfunction to most severe forms of impairment, and as a continuum where all domains of development can be affected with varying degrees of involvement [9,10]. Others proposed Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE) to describe the multiple areas of dysfunction especially in preschoolers [11] and deficits in attention, motor control, and perception (DAMP) which encompasses ADHD and developmental coordination disorder [12]. Informed by new genetic discoveries of shared certain copy number variants and single-gene mutations, other authors proposed that term 'developmental brain dysfunction' denoting that NDD disorders should be considered as a group when evaluated under the genetics lens [13▪].

Why is it desirable to understand the neurobiological substrate for neurodevelopmental disabilities?

As the biological links between brain and behavior are carefully scrutinized, shortcomings of behavior-based classification in understanding mechanisms of NDD have become more apparent. Neurodevelopmental disorders may be a manifestation of connectopathies, synaptopathies, dendritopathies, disorders of neurotransmission and intracellular signaling, neurodegeneration, defective genes, and epigenetic machinery. How these biologically defined mechanisms directly cause behavioral dysfunction or whether they trigger upstream and/or downstream changes that ultimately lead to behavioral dysfunction is not yet fully understood.

At our current level of understanding brain-behavior disorders, we are not able to cure NDD. Treatment strategies and interventions work to ameliorate intercurrent and intermittent symptoms, minimize functional limitations, and increase participation, rather than address the underlying mechanisms of the disease.

Furthermore, the dynamic nature of brain development and its selective vulnerability over time, across neuronal networks, functions, and contexts, impacts the behavioral profile. For example, the severity and extent of motor impairment following perinatal brain injury varies between patients based on the timing of injury in relation to stage of sensorimotor tracts development (in utero stroke vs postnatal stroke) [14]. Other examples of selective vulnerability are region-specific susceptibility to hypoxic-ischemic injury, trauma, or metabolic insult, and region-specific brain volume loss in amygdala, accumbens, and hippocampus in children with ADHD [15].

Another unique aspect is the effect of brain maturation on identification of dysfunction over time. In premature children, for example, cognitive and academic difficulties are not evident at the time of premature birth or soon after, but rather later when normal-for-age cognitive faculties fail to emerge. Similarly, the diagnosis of cerebral palsy is not made until a clear behavioral phenotype is identified. However, this may be too late for effective interventions. As a result, interventions around the time of injury (e.g. hypoxic ischemic event) rarely predict long-term outcomes.

Additionally, the profile of brain (dys)function is fluid which complicates standardized assessments and limits prognostication. In some disorders and as a function of brain maturation, a primary behavioral dysfunction may improve (e.g. hyperactivity in ADHD), worsen (e.g. adaptive function in intellectual disability and complications from motor impairment in cerebral palsy), fluctuate (e.g. developmental regression in neurometabolic disorders) or remain unchanged (e.g. visual and auditory impairment). Therefore, the ability to identify reliable biomarkers and targets for therapies is challenging. Consequently, our treatment approaches range from rigorously studied interventions such as therapeutic hypothermia for neonatal hypoxic ischemic injury to less systematically investigated ones such as early intervention programs.

What new knowledge have we generated by leveraging advances in neuroscience, genetics, and neuroimaging?

Significant strides were made in the field of neurodevelopmental disorders owing to advances in research approaches and tools spanning animal models to breakthroughs in genetic, neurophysiologic, and neuroimaging technologies. A prominent example of the power of multimodal approach in deciphering a complex phenotype is drawn from the field of pediatric epilepsy. Over the past few decades, we began to move from a pure functional classification of seizures and epilepsy to a more specific etiological classification that is based on molecular genetics. This approach paved the way for targeted therapies based on underlying cause.

A similar approach is evolving for the other neurodevelopmental disorders. For example, Advances in next-generation sequencing technology allowed high-throughput evaluation which

identified more than 700 genes to date that are associated with, or causal to, intellectual disabilities [16▪]. Autism research is also enriched by genetic-based approaches allowing deeper understanding of the effect of genetic mutations on molecular pathways, synaptic morphology, and function. Mechanism-based treatments in animal models of Fragile X and Tuberous Sclerosis Complex and Angelman syndrome are showing promising preclinical results in reducing the burden of the phenotype [17].

Understanding the upstream and downstream effects of epigenetic modifications on brain development in primary disorders of epigenetic machinery (e.g. Angelman, Prader-Willi, and Rett syndromes) and in acquired neurological disorders (traumatic brain injury and stroke) [18,19] is gaining momentum. New evidence suggest that epigenetic changes may explain sex-based differences in susceptibility and clinical expression of some NDD [20].

Advances in brain imaging and neurophysiology enabled a new approach that draws on the understanding of structural and functional connections between brain areas and how they change as a function of time, task, or a pathologic process. The dynamic approach of neuronal networks takes into account the effect of maturation on structural and

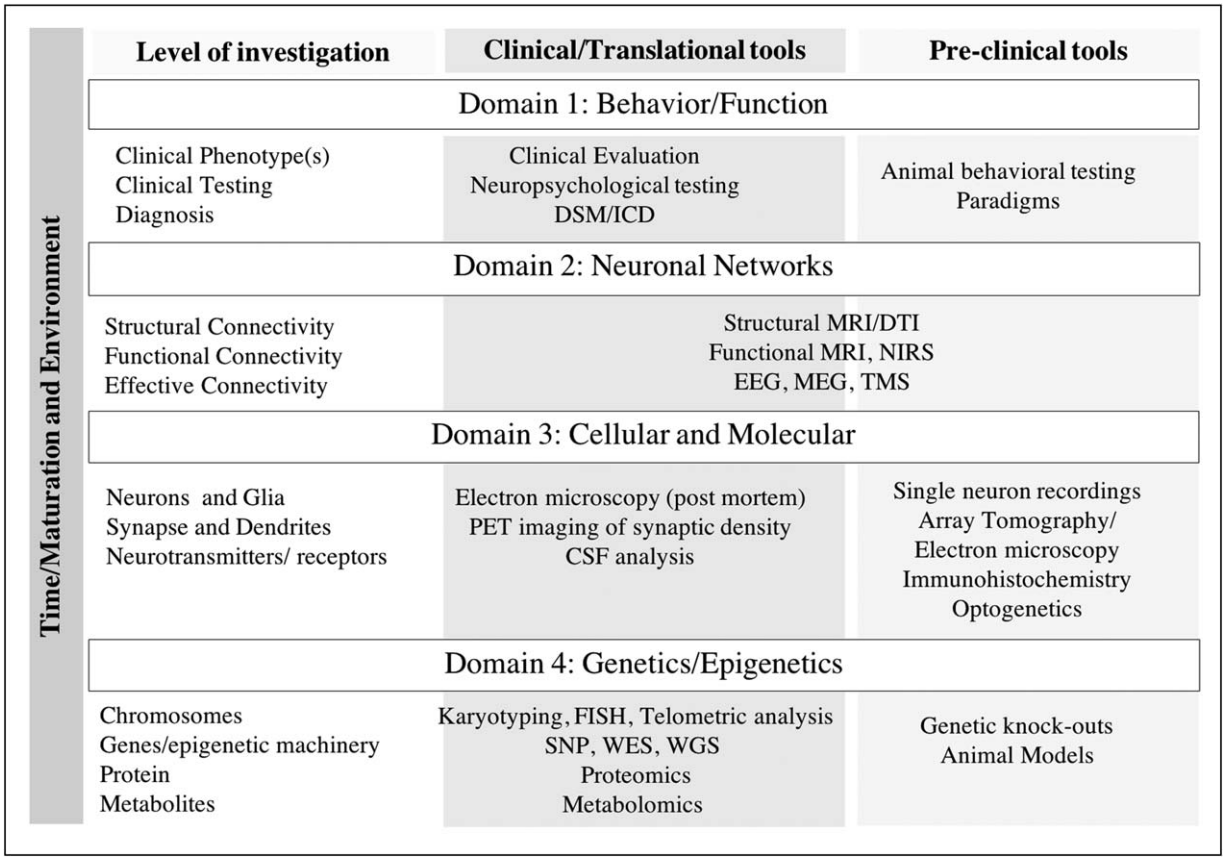

FIGURE 1. Clinical and research approaches to investigating the spectrum of neurodevelopmental disabilities. Deciphering the link between biological mechanisms underlying brain development and behavior in health and disease requires careful evaluation and integration of the multiple organizational domains through which these mechanisms operate and manifest. This figure represents four major research domains that investigate neurodevelopmental disorders ranging from the behavioral/functional analysis of the phenotype to evaluating the underlying neuronal networks and examining the cellular and molecular foundations of these networks and identifying their genetic and epigenetic underpinnings. Within each domain, there are levels of investigations that address the structure and/or function of the nervous system at that particular domain (left column). The central column lists the clinical tools that are used to investigate each of these levels within a domain. The right column lists examples of corresponding preclinical tools. The column labeled (Time/Maturation and Environment) brings focus to the fourth dimension, development, and the processes that affect its progression across all domains. DSM, disease and statistical manual; DTI, diffusion tensor imaging; EEG, electroencephalogram; FISH, fluorescence in-situ hybridization; ICD, international classification of diseases; IPSC, induced pluripotent stem cells; MEG, magnetoencephalography; MRI, magnetic resonance imaging; NIRS, near-infrared spectroscopy; PET, positron emission tomography; SNP, single-nucleotide polymorphism; TMS, transcranial magnetic stimulation; WES, whole exome sequencing; WGS, whole genome sequencing.

functional connectivity and changes in neuronal oscillations and their synchronization on a local and global level. Networks dynamics approach is being used to understand brain-behavior interaction in ADHD [21] and Autism [22].

Theoretical models of brain and cognition have long been pursued to explain the complex, dynamic, multifaceted nature of brain development. An old view of nativism proposed that brain function is made of independent innate modules that are predetermined, prespecified, and domain-specific. A dysfunction in one module does not necessarily affect other independent modules. By leveraging advances in neuroscience, artificial intelligence and big data, new models are generated. A recent model is neuroconstructivism which views development as the progressive elaboration of increasingly complex structures and seeks to understand the neural mechanisms underlying behavior using computational modeling [23].

Taken together we are better equipped than ever to study brain-based disorders using a multimodal approach that seeks to explain the heterogenous phenotype (Fig. 1).

CONCLUDING REMARKS

The timely question is whether 'NDD' is still a useful construct. As mentioned earlier, the term originated to identify a group of children and adults with special needs to allow planning at the population level, facilitate individual and societal advocacy efforts, increase social interventions that increase participation (e.g., structural adaptations, living, vocation, inclusion). However, the construct falls short of a biologically based categorization that may enable deciphering the underlying mechanisms of these disorders.

It is also a source for heterogeneity because it does not firmly establish the borders of these disorders nor validate their distinctiveness, which negatively affect biomarkers and therapeutic targets discovery.

We are not yet at the point of abandoning functional diagnosis of NDD, but we have to be careful when drawing conclusions from research studies that are based on functional diagnoses. As our biological understanding of brain-behavior disorders evolves, we ought to re-evaluate the current classification system and expand it into a multidimensional classification that takes into account behavioral profiles and underlying mechanisms.

Seeking a deeper molecular, genetic and biological understanding of neurodevelopmental disorders is an important step to transform the current model of NDD into a multidimensional biologically-informed model for prevention, identification, prognostication and planning and, most importantly, development of effective interventions that may lead to amelioration or cure.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Developmental Disabilities Assistance and Bill of Rights Act, Public Law 95-602, 92 Stat. 1978 3004-5.
2. ■■ Mullin AP, Gokhale A, Sanyal S, *et al.* Neurodevelopmental disorders: mechanisms and boundary definitions from genomes, interactomes and proteomes. Transl Psychiatry 2013; 3:e329–e336.

This paper proposed reconceptualization of neurodevelopmental disorders based on understanding underlying genetics, proteomics and interactomics.

3. ■ Reiersen AM. How should we classify complex neurodevelopmental disorders? Scand J Child Adolesc Psychiatry Psychol 2017; 5:1–2.

This reference highlights limitations of current classification of neurodevelopmental disorders.

4. Reid SM, Meehan EM, Arnup SJ, Reddihough DS. Intellectual disability in cerebral palsy: a population-based retrospective study. Dev Med Child Neurol 2018; 60:687–694.
5. Zhang JY, Oskoui M, Shevell M. A population-based study of communication impairment in cerebral palsy. J Child Neurol 2015; 30:277–284.
6. ■ Korrel H, Mueller KL, Silk T, *et al.* Research Review: Language problems in children with attention-deficit hyperactivity disorder - a systematic meta-analytic review. J Child Psychol Psychiatry 2017; 58:640–654.

This is a systematic meta-analytic review of language disorders in children ADHD.

7. Avni E, Ben-Itzchak E, Zachor DA. The presence of comorbid ADHD and anxiety symptoms in autism spectrum disorder: clinical presentation and predictors. Front Psychiatry 2018; 9:717.
8. ■ Houwen S, Visser L, van der Putten A, Vlaskamp C. The interrelationships between motor, cognitive, and language development in children with and without intellectual and developmental disabilities. Res Dev Disabil 2016; 53–54:19–31.

This paper highlights the developmental comorbidities in children with intellectual disabilities.

9. Capute AJ, Palmer FB. A pediatric overview of the spectrum of developmental disabilities. J Dev Behav Pediatr 1980; 1:66–69.
10. Capute A, Accardo P. A Neurodevelopmental perspective on the continuum of developmental disabilities. In: Capute A, Accardo P, editors. Developmental disabilities in infancy and childhood. Baltimore: Paul H Brookes Publishing Co; 1991.
11. Gillberg C. The ESSENCE in child psychiatry: early symptomatic syndromes eliciting neurodevelopmental clinical examinations. Res Dev Disabil 2010; 31:1543–1551.
12. Gillberg C. Deficits in attention, motor control, and perception: a brief review. Arch Dis Childhood 2003; 88:904–910.
13. ■ Moreno-De-Luca A, Myers SM, Challman TD, *et al.* Developmental brain dysfunction: revival and expansion of old concepts based on new genetic evidence. Lancet Neurol 2014; 12:406–414.

This study proposed updating current classification of neurodevelopmental disorders based on understanding of shared genetic causes.

14. Jaspers E, Byblow WD, Feys H, Wenderoth N. The corticospinal tract: a biomarker to categorize upper limb functional potential in unilateral cerebral palsy. Front Pediatr 2016; 3:112.
15. Hoogman M, Bralten J, Hibar DP, *et al.* Subcortical brain volume differences of participants with ADHD across the lifespan: an ENIGMA collaboration. Lancet Psychiatry 2017; 4:310–319.
16. ■ Vissers L, Gilissen C, Veltman JA. Genetic studies in intellectual disability and related disorders. Nat Rev Genet 2015; 17:9–18.

This study reviews the impact of genetic discoveries on diagnosis and therapy of intellectual disabilities.

17. Ebrahimi-Fakhari D, Sahin M. Autism and the synapse: emerging mechanisms and mechanism-based therapies. Curr Opin Neurol 2015; 1:1–12.
18. Wong VS, Langley B. Epigenetic changes following traumatic brain injury and their implications for outcome, recovery and therapy. Neurosci Lett 2016; 625:26–33.
19. Felling RJ, Song H. Epigenetic mechanisms of neuroplasticity and the implications for stroke recovery. Exp Neurol 2015; 268:37–45.
20. Chung WCJ, Auger AP. Gender differences in neurodevelopment and epigenetics. Pflugers Arch 2014; 465:573–584.
21. Bos DJ, Oranje B, Achterberg M, *et al.* Structural and functional connectivity in children and adolescents with and without attention deficit/hyperactivity disorder. J Child Psychol Psychiatry 2017; 58:810–818.
22. Mohammad-rezazadeh I, Frohlich J, Loo SK, Jeste SS. Brain connectivity in autism spectrum disorder. Curr Opin Neurol 2016; 29:137–147.
23. Sirois S, Spratling M, Thomas MSC, *et al.* Precis of neuroconstructivism: how the brain constructs cognition. Behav Brain Sci 2008; 31:321–356.