Journal of Neural Transmission (2023) 130:181–184
https://doi.org/10.1007/s00702-023-02596-8

EDITORIAL

Neurodevelopmental disorders: research and interventions beyond classifications

Paul Olivier[1] · Pierre Gressens[1,2] · Catherine Barthelemy[1,3]

Received: 10 January 2023 / Accepted: 27 January 2023 / Published online: 9 February 2023

Neurodevelopment covers the mechanisms that contribute to the establishment of neural networks in the central nervous system. In the 1970s, Peter Huttenlocher discovered that synapses are created in the first months of a child's development. He was the first to describe the evolution of neuronal and synaptic density in human cerebral cortex over the span of a lifetime (Huttenlocher 1979). Further studies explored the complex cellular and molecular mechanisms driving neurodevelopment. In particular, Peter Riederer and collaborators underlined the role of neurotransmission on neuronal outgrowth and differentiation starting with earliest embryonic stages (Retz et al. 1996). From childhood to old age, neurotransmitters play a central role in neurodevelopmental phenomenon and associated disorders (Konradi et al. 1992; Kornhuber et al. 1989). Thus, neurodevelopment is now acknowledged to be a process spanning from embryonic development to adolescence and even adulthood (Stiles and Jernigan 2010), with many temporal windows of vulnerability (Chelini et al. 2022; Sisk and Gee 2022).

According to the classifications that are still the most commonly used (DSM-5 (Diagnostic and Statistical Manual of mental disorders—fifth edition), ICD-11 (International Classification of Diseases—11th edition)), the different Neurodevelopmental Disorders (NDDs) (Autism spectrum disorder (ASD), ADHD (Attention Deficit/Hyperactivity Disorder), Disorders of communication, speech, and language, intellectual disability, etc.) used to be described in a "categorical" way (distinct disorders, with a description based on symptoms), leading to the development of scientific and clinical communities working "in silo". There is commonality in that symptoms, that manifest as disruption in physical, intellectual, emotional, behavioral, and cognitive functioning, typically first apparent in early childhood. However, there are vast quantities of situations for the NDD spectrum, and the symptoms of each individual disorder on the spectrum may be unique, or overlap, which can contribute to diagnostic ambiguity (The American Psychiatric Association's 2013).

Research on NDD has been marked by major changes during last years. In addition to this paradigm shift, one major challenge consists of translating the scientific discoveries, particularly in the fields of early identification of NDDs and for lifelong non-invasive interventions. Responding to the priorities of people with NDDs implies a better evaluation of existing solutions (following international good practice recommendations and the most recent scientific consensus). It is also critical to intensify the transfer of technologies generated by researchers to industrial stakeholders. The objective is to accelerate the development of an industrial sector dedicated to disability and its prevention, involving individuals with NDDs, their families, as well as the actors of the civil society.

With this in mind, France proposed in 2019 to federate the forces of research, all disciplinary fields combined, by structuring a national network: the Autism and NDDs Scientific Interest Group (Groupement d'Intérêt Scientifique (GIS) Autisme et TND) called Autism and NDDs GIS. 3 years after its creation, the Autism and NDDs GIS is an international network gathering more than 120 French research teams (450 researchers) involved in collaborations with more than 400 research teams worldwide (autisme-neurodev.org/en/). Through its actions, the GIS promotes the emergence of new scientific research synergies, bringing together scientific and clinical expertise with multidisciplinary expertise, beyond classifications.

Among the actions implemented, The GIS organized a scientific event: the webinar "Neurodevelopmental Disorders (NDD) without boundaries" on June 2022, whose synthesis is presented in the following special issue

✉ Paul Olivier
paul.olivier@aviesan.fr

[1] Autism and NDD Scientific Interest Group (GIS Autisme et TND), Paris, France

[2] Université Paris Cité, NeuroDiderot, Inserm, Paris, France

[3] Faculty of Medicine, University of Tours, Tours, France

(Louveau et al.). Speakers were invited to present their researches discussing classifications in NDD. Both genetic and environmental factors, along with clinical and imaging features, argued toward a continuum between NDDs but also with adult psychiatric presentations. On this occasion, a particular focus was made on the ASD–schizophrenia continuum.

Gillberg suggested the concept "ESSENCE" (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) to reflect the co-existence of neurodevelopmental disorders that rarely present as discreet disorders in children (Gillberg 2010). Because of the complexity of the developmental processes involved, NDD has multiple, often associated and mutually reinforcing, impacts. The frequency of concomitance of these disorders (Septier et al. 2019) suggests common underlying mechanisms. Moreover, the progression of our understanding of the mechanisms involved in psychiatric disorders (schizophrenia, depression, etc.) show that in many cases, they are manifestations of disorders occurring at early or late stages of neurodevelopment (transitions from childhood to adolescence, adolescence to adulthood). Latest scientific results suggest that the neurobiological similarity and dissimilarity between NDDs need to be investigated in a "dimensional" way, beyond DSM/ICD-based, behaviorally defined diagnostic categories (Choi et al. 2020).

In the same way, this special issue of Journal of Neural Transmission: "NDD—research and interventions beyond classifications" presents original articles and reviews that are part of this scientific paradigm shift.

Medical and scientific research in the field of NDD must, therefore, aim to better understand these complex mechanisms, occurring in the earliest developmental stages. This special issue shed new light on the pathophysiology of NDDs:

- Namba et al. suggest an alternative accessible in vivo mouse model system to study human neocortical development and its pathogenesis.
- In a systematic review, Schmitt et al. underline the complex interplay between multifactorial genetic and environmental risk factors involved with NDDs and psychiatric disorders.
- NDDs, and particularly autism, are over-represented in males compared to females (Zeidan et al. 2022). A systematized review by Amestoy et al. questions the hypothesis that perinatal factors associated with sex differentiation (e.g., steroid hormone pathways) could play a role in the emergence of autism.
- Yde Ohki et al. present an original cellular model suggesting that a decrease in neural stem cell proliferation could be associated with NDD, such as ADHD pathophysiology.
- Klein et al. present a new approach to explore the origin, both at the cognitive and neural level, of dyscalculia, a specific learning disorder that persists over life-time.
- The brain is not an isolated organ, it maintains privileged links with the digestive system via the enteric nervous system. Thus, the microbiota–gut–brain axis could be a determining factor in the occurrence of NDDs. Hill et al. suggest the gut-associated lymphoid tissue (GALT) as a new insight connecting inflammatory disorders and gastrointestinal dysfunction in neurodevelopmental disorders such as autism.
- A better understanding of cellular phenomena underlying NDD pathophysiology opens the way to potential therapeutic strategies. The original study by Bokobza et al. suggests that modulating the activity of a serotoninergic receptor could prevent brain white matter damages associated with preterm and perinatal inflammation.

A better understanding of genetic, molecular, mechanisms is needed to identify early biomarkers and behavioral measures to determine risk status, even before the emergence of clear behavioral symptoms. This is crucially important to identify a targeted early intervention with the objective to prevent disabilities with a maximized impact (Micai et al. 2020).

It is also critical to better characterize the diversity of clinical and functioning situations to implement adapted interventions. In a prospective study, Rosello et al. explore the developmental trajectories of children with autism spectrum disorder (ASD) throughout adolescence. Müller et al. underline that co-occurring disorders are often neglected among older adults with ADHD, leading to unmet interventions.

Understanding the evolution of such disorders offers opportunities to improve long-term outcomes. This special issue underlines the importance to take into account the atypical sensory experience commonly associated with NDDs, such as ASD (Balasco et al. 2019). Latest diagnostic criteria, according to DSM-5 (Diagnostic and Statistical Manual of mental disorders—fifth edition), now include sensory issues among the four restricted/repetitive behavior features defined as "hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment":

- Gonçalves et al. examined research evidence of the integrity of the cognitive function in auditory-related tasks, the integrity of the peripheral auditory system, and the integrity of the central nervous system in persons with ASD.
- Chokron et al. focused on the possible overlap between cerebral visual impairments and NDDs. This review interestingly raises the question of the need for systematic evaluation for disorders of visual perception and cog-

nition in children with a NDD and/or previously born under adverse neurological conditions.

Furthermore, this special issue explores the functioning characterization of NDDs through 2 reviews:

- Despite mounting evidence showing significant motor impairments in ASD that strongly contribute to its pathophysiology (Craig et al. 2021; Lim et al. 2021); (Cook et al. 2013), motor impairments are not currently included in the diagnosis criteria of such disorders. Basing on experimental studies made with 3 mouse models of autism, Jaber et al. bring additional elements linking ASD and motor deficits.
- Schaeffer et al. reviewed the current knowledge state on language abilities in autism. In particular, they explore and discuss the association between language impairment and autism through categorial and dimensional approaches.

This special issue of Journal of Neural Transmission emphasizes the importance to connect scientific and the priorities of persons with NDDs and families though the implementation of participatory research. Participatory research involves incorporating the views and partnership of the persons with NDDs about what research gets done, how it is done and how it is implemented (Cornwall and Jewkes 1995). Burger et al. present GenIDA: involving the direct participation of persons with intellectual disabilities, GenIDA is an international online participatory database that aims to better characterize the clinical manifestations of rare NDDs with genetic origin. Through several examples, this article demonstrates how participatory research is relevant to improve the clinal characterization of the disorders. Beyond that, this approach is very interesting to increase the adherence of patients and families to the solutions provided by research.

All of the studies presented in this special issue illustrate the dynamism of the scientific community, bringing together researchers, practitioners, people affected by NDDs and their families. They call for the federation of all scientific expertise to support multidisciplinary research aimed at improving mental health heavily impacted by NDDs, and transcending the barriers of a classification that often wrongly divides the communities. It is necessary to get out of the categories that separate communities of researchers and stigmatize the persons with NDDs, to consider all the dimensions of the individuals who present disabilities, but also forces which should not be forgotten.

March 1st 2023,
Paul Olivier, PhD, Guest Editor.

Funding This study is funded by Ministère de l'enseignement supérieur et de la recherché (Stratégie Nationale pour l'Autisme au sein des Troubles du Neuro-Développement).

References

Balasco L, Provenzano G, Bozzi Y (2019) Sensory abnormalities in autism spectrum disorders: a focus on the tactile domain, from genetic mouse models to the clinic. Front Psychiatry 10:1016. https://doi.org/10.3389/fpsyt.2019.01016

Chelini G, Pangrazzi L, Bozzi Y (2022) At the crossroad between resiliency and fragility: a neurodevelopmental perspective on early-life experiences. Front Cell Neurosci 16:863866. https://doi.org/10.3389/fncel.2022.863866

Choi EJ, Vandewouw MM, Taylor MJ, Arnold PD, Brian J, Crosbie J, Kelley E, Lai M-C, Liu X, Schachar RJ, Lerch JP, Anagnostou E (2020) Beyond diagnosis: cross-diagnostic features in canonical resting-state networks in children with neurodevelopmental disorders. NeuroImage Clin. 28:102476. https://doi.org/10.1016/j.nicl.2020.102476

Cook JL, Blakemore S-J, Press C (2013) Atypical basic movement kinematics in autism spectrum conditions. Brain J Neurol 136:2816–2824. https://doi.org/10.1093/brain/awt208

Cornwall A, Jewkes R (1995) What is participatory research? Soc Sci Med 1982(41):1667–1676. https://doi.org/10.1016/0277-9536(95)00127-s

Craig F, Crippa A, Ruggiero M, Rizzato V, Russo L, Fanizza I, Trabacca A (2021) Characterization of Autism Spectrum Disorder (ASD) subtypes based on the relationship between motor skills and social communication abilities. Hum Mov Sci 77:102802. https://doi.org/10.1016/j.humov.2021.102802

Gillberg C (2010) The ESSENCE in child psychiatry: Early symptomatic syndromes eliciting neurodevelopmental clinical examinations. Res Dev Disabil 31:1543–1551. https://doi.org/10.1016/j.ridd.2010.06.002

Huttenlocher PR (1979) Synaptic density in human frontal cortex—developmental changes and effects of aging. Brain Res 163:195–205. https://doi.org/10.1016/0006-8993(79)90349-4

Konradi C, Kornhuber J, Sofic E, Heckers S, Riederer P, Beckmann H (1992) Variations of monoamines and their metabolites in the human brain putamen. Brain Res 579:285–290. https://doi.org/10.1016/0006-8993(92)90062-E

Kornhuber J, Konradi C, Mack-Burkhardt F, Riederer P, Heinsen H, Beckmann H (1989) Ontogenesis of monoamine oxidase-A and -B in the human brain frontal cortex. Brain Res 499:81–86. https://doi.org/10.1016/0006-8993(89)91136-0

Lim YH, Licari M, Spittle AJ, Watkins RE, Zwicker JG, Downs J, Finlay-Jones A (2021) Early motor function of children with autism spectrum disorder: a systematic review. Pediatrics 147:e2020011270. https://doi.org/10.1542/peds.2020-011270

Micai M, Fulceri F, Caruso A, Guzzetta A, Gila L, Scattoni ML (2020) Early behavioral markers for neurodevelopmental disorders in the first 3 years of life: an overview of systematic reviews. Neurosci

Biobehav Rev 116:183–201. https://doi.org/10.1016/j.neubiorev.2020.06.027

Retz W, Kornhuber J, Riederer P (1996) Neurotransmission and the ontogeny of human brain. J Neural Transm 103:403–419. https://doi.org/10.1007/BF01276417

Septier M, Peyre H, Amsellem F, Beggiato A, Maruani A, Poumeyreau M, Amestoy A, Scheid I, Gaman A, Bolognani F, Honey G, Bouquet C, Ly-Le Moal M, Bouvard M, Leboyer M, Bourgeron T, Delorme R (2019) Increased risk of ADHD in families with ASD. Eur Child Adolesc Psychiatry 28:281–288. https://doi.org/10.1007/s00787-018-1206-0

Sisk LM, Gee DG (2022) Stress and adolescence: vulnerability and opportunity during a sensitive window of development. Curr Opin Psychol 44:286–292. https://doi.org/10.1016/j.copsyc.2021.10.005

Stiles J, Jernigan TL (2010) The basics of brain development. Neuropsychol Rev 20:327–348. https://doi.org/10.1007/s11065-010-9148-4

The American Psychiatric Association's (2013) Diagnostic and statistical manual of mental disorders: DSM-5

Zeidan J, Fombonne E, Scorah J, Ibrahim A, Durkin MS, Saxena S, Yusuf A, Shih A, Elsabbagh M (2022) Global prevalence of autism: a systematic review update. Autism Res 15:778–790. https://doi.org/10.1002/aur.2696