William M. Cruickshank Memorial Lecture Delivered at the 2022 Conference of the International Academy for Research in Learning Disabilities

New Directions in the Study of Neurodevelopmental Disorders

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Abstract

The Conference at the University of Oviedo, Spain, within the 44th Annual Meeting of the International Academy for Research in Learning Disabilities, was an excellent opportunity to share knowledge, explore perspectives and reflect on the study of neurodevelopmental disorders in Europe and elsewhere in the world. The William M. Cruickshank Memorial Keynote Address, *New Directions in the Study of Neurodevelopmental Disorders*, covered a broad range of topics relevant to cognition, intelligence, and achievement. It also provided the opportunity to present parts of our current work pertinent to the study of neurodevelopmental dysfunctions and the Marie Skłodowska-Curie Action (MSCA) ITN Neo-PRISM-C project.

The presentation began by focusing on what we study and how and why we study what we study about neurodevelopmental disorders. This was followed by a discussion about the brain and (learning) behaviour, accompanied by some relevant evidence on the neurological basis for reading difficulties, particularly the phonological and visual deficits pathways in the framework of the magnocellular deficit theory. The session concluded with a discussion of the comorbidity of various disorders and the use of the Research Domain Criteria (RDoC) framework as an alternative to the traditional diagnostic categories for the study of neurodevelopmental disorders. Examples of how neuroscience research can contribute to this endeavour were also provided..

Keywords: Neurodevelopmental disorders, brain development, specific learning disabilities, multifactorial modeling, Research Domain Criteria (RDoC)

Mental Health

Mental health includes our emotional, psychological, and social well-being. It affects how we think, feel, and act. Our relationship with others and our ability to handle stress or make choices also rely on it (World Health Organization [WHO], 2022). Mental health is essential at every stage of life, from childhood and adolescence through adulthood (Otto et al., 2021). Given the importance of mental health in sustainable development, the World Health Organization has developed a staged approach to understanding and treating neurodevelopmental disorders instead of the binary strategy of today's current classification system (Patel et al., 2018).

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Mental health and neurodevelopmental disorders (see below) are interconnected in several ways. Neurodevelopmental disorders, such as specific learning disabilities, attention deficit-hyperactivity disorder (ADHD), or intellectual disabilities, can significantly impact a person's mental health and overall functioning. Conversely, mental health conditions, such as anxiety or depression, can also arise from or in conjunction with neurodevelopmental disorders. Thus, it is important to consider mental health and neurodevelopmental disorders when evaluating an individual's overall well-being and planning interventions and treatments (Michelini et al., 2021). The present paper focuses on neurodevelopmental disorders in particular. The following section looks into neurodevelopmental disorders, describing the current situation of their study.

Neurodevelopmental Disorders

Neurodevelopmental disorders include conditions from childhood to early adulthood affecting mental health (Gustavsson et al., 2011). Delays or deficits usually appear in early childhood, many times before formal instruction begins, and can persist throughout an individual's lifetime. Although neurodevelopmental disorders may be limited in nature, affecting only specific aspects of development, they may also generally affect behaviour, cognition, communication, social skills, language, or an individual's broader day-to-day functioning (Bishop, 2010; Drabick & Kendall, 2010). In either case, the observed symptoms or deficits, for example, in cognitive systems such as perception, attention, or memory, can be present across various known (learning) disorders (Papadopoulos et al., 2020; Spanoudis et al., 2019) as conditions can show multifactorial etiology in which certain aspects of neurodevelopment are selectively impaired. These issues pertain to "what" we study in relation to the emergence, development, and manifestation of neurodevelopmental disorders.

The next question relates to "how" we study what we study. Contemporary research into neurodevelopmental disorders integrates various disciplines, from psychology (clinical, cognitive, educational, or developmental) to neuroscience, genetics, epidemiology or psychiatry (Bishop, 2010; Michelini et al., 2021), the efforts of which were previously distinct and separate. We also use multiple levels of analysis, with an emphasis on (a) individual differences (e.g., Georgiou et al., 2012); (b) continuity or discontinuity of adaptive or maladaptive behavioural or learning patterns (e.g., Biederman et al., 2010); or (c) pathways by which the same developmental outcomes are achieved (Papadopoulos et al., 2012; Toffalini et al., 2022).

In addition, we employ multiple levels of examination in labs or naturalistic environments. Thus, our methods include a large variety of measures related to neuropsychology or psychophysiology (e.g., Christoforou et al., 2021; Fella et al., 2023), observations and survey/self-reports or ecological assessment (e.g., Dockrell et al., 2022), imaging (e.g., Al Dahhan et al., 2020), or genetics and neural circuity (Church et al., 2021; Ozernov-Palchik & Gaab, 2016).

By reviewing the relevant research carefully, we aim to understand the basic dimensions of functioning underlying the full range of (learning) behaviour from typical to atypical (Rutter et al., 2011). In addition, theoretical and predictive models aim to address the heterogeneity and comorbidity in neurodevelopmental disorders (Ozernov-Palchik et al., 2022; Pennington, 2009). Likewise, our analysis methods involve advanced statistical approaches (e.g., Papadopoulos et al., 2021), machine learning (e.g., Christoforou et al., 2022), randomized control trials (e.g., Vanden Bempt et al., 2021), or big data and open science (e.g., Eising et al., 2022).

The above developments have advanced our understanding and likely helped detect the mechanisms contributing to the emergence and course of neurodevelopmental disorders. As a result, several questions are slowly being addressed about where the dysfunctions come from, how they develop, why they are common among conditions, and how they can be treated or even eventually prevented.

In practice, however, despite impressive developments in psychology, neuroscience, genetics, and other basic sciences, research, its applications, and the training of young scholars in the field of mental health remain fragmented in that the implicated brain mechanisms and potential biomarkers have been discussed as part of specific disorder entities of traditional taxonomic systems (Diagnostic and Statistical Manual of Mental Disorders, DSM-5; American Psychiatric Association, 2013, or ICD-11; WHO, 2019). Moreover, the categorical models based on these systems aim at unique disorders with clear borders, either present or absent, in an effort to identify unique causes and biological substrates.

However, in reality, they fail to detect unique causes (e.g., Papadopoulos et al., 2012) because individuals who meet the criteria for one disorder often also meet criteria for other conditions (e.g., Landerl & Moll, 2010). Thus, traditional taxonomic systems or categorical models (a) result in high comorbidity between disorders (e.g., McGrath et al., 2019) or a

marked heterogeneity (O'Brien et al., 2012; Protopapas & Parrila, 2018); (b) accept the existence of a continuum from normal to subclinical conditions (Spanoudis et al., 2019); and (c) result in inconsistent success in treating and management (see Connor et al., 2013, for a discussion).

This fragmented approach makes it difficult for researchers and end users alike (e.g., psychologists, educators, psychiatrists or pediatricians) to comprehend the processes implicated to different degrees in a large array of phenotypic dysfunctions (Etkin & Cuthbert, 2014). For instance, a significant challenge emerges among conditions with the highest prevalence in school-age children, as in the case of Specific Learning Disorders (SLDs) (Catts & Petscher, 2022; Swanson, 2015). As used here, "SLD" refers to any neurodevelopmental disorder that interferes with learning academic and/or social skills.

Research on SLD based on diagnostic categories can suffer particularly from problems with heterogeneity because of the varied ways individuals can qualify for a symptom-based disorder diagnosis. For example, in some instances, two children may be diagnosed with the same disorder despite having few symptoms in common. On the one hand, low school attainment and failure may signal the presence of a condition affecting basic psychological processes, such as attention, memory, language, or executive functioning (e.g., Papadopoulos et al., 2005; Papadopoulos et al., 2020), or language processes, such as reading, orthographic processing, and comprehension (Constantinidou & Evripidou, 2011; Papadopoulos et al., 2014). On the other hand, poor school attainment may be an epiphenomenon of dysfunctions in other systems, such as motivation and emotion, social, cognitive and communication difficulties (e.g., Sideridis et al., 2006) or may relate to neurophysiological or structural abnormalities of the brain (e.g., Breier et al., 2005). These variations make it difficult for researchers to pinpoint specific conditions because the neuro-cognitive or -biological mechanisms may differ significantly among individuals with little to no symptomatology.

Phenotypic Performance Profiles and Diagnosis

For nearly 30 years (1960–1998), neurodevelopmental disorders such as reading difficulties (RD), developmental language disorders (DLD), and attention deficits (ADHD) have been studied as distinct conditions. This approach focused on a modular, single-deficit model (SDM; Pennington, 1991), positing that a single cognitive deficit is sufficient to explain a given neurodevelopmental disorder's symptoms and that different disorders have different single deficits. Albeit simplistic, the SDM approach provided the required "internal consistency" defined by groups' homogeneity, the reliability of the classification procedures, or the replication of the observations in similar samples (Ramus et al., 2003). However, the model failed to provide valid explanations for the likely co-occurrence of neurodevelopmental dysfunctions (e.g., Pennington et al., 2005).

Thus, relevant research continued to focus on heterogeneity or possible comorbidity for another 15 years (1998–2013). Heterogeneity mattered because it was noticed that even among individuals with similar cognitive profiles, various neuropsychological deficits were likely, as some individuals had the disorder but had only a single or no identifiable deficits. For example, recent work shows that children with reading difficulties have deficits in verbal fluency, particularly in action fluency (Shareef et al., 2018). Also, deficiencies in the speech production of children with DLD or dyslexia may be associated with attention, which affects performance in language/literacy without a causal link between these deficits (Halliday et al., 2017).

Likewise, comorbidity mattered because of the frequent presence of partially etiological and neurocognitive factors (e.g., Moll et al., 2014) between learning disorders, even when stricter cutoff criteria were applied. This means that a profile of cognitive factors could specify a disorder, but another disorder could share some of the same factors, resulting in comorbidity. For example, reading difficulties and attention have a partial genetic and cognitive overlap (Gooch et al., 2011), as do reading difficulties and developmental language disorders (Spanoudis et al., 2019). Add to these challenges that understanding learning disorders and most psychiatric disorders requires recognizing the symptoms' heterotypic continuity across time, and it is quickly realized that a different approach was deemed necessary.

Brain and (Learning) Behavior

Studying the developing brain and methods for assessing cognitive performance via experimental and neuropsychological testing is critical in our quest to determine how neurodevelopmental disorders emerge and may be treated. Central to this endeavour is integrating biological underpinnings into cognitive-linguistic development (Gray & Thompson, 2004).

The developing brain undergoes rapid neurobiological changes in the child's ability to acquire language and communicate effectively while demonstrating significant gains in motor, perceptual, and cognitive skills in infancy and early childhood (Pennington, 2009, 2014). The proliferation of neuronal

and synaptic growth at certain stages of development is associated with academic milestones during the school years, ranging from learning how to read and write (e.g., Schlaggar & McCandliss, 2007) to developing active memory strategies and abstract reasoning abilities in the pre-adolescent and adolescent years to support the more complex academic demands in secondary school (Dumontheil, 2014; Spaniol et al., 2009). Disruptions at any point across the developmental continuum may hamper typical development in acquiring academic abilities and place children at risk for academic and social-communication failure.

There is an ongoing discussion of the relationship between the brain and behavior, as the brain plays a central role in learning behavior (Fuster, 1997). The relationship between the brain and learning behavior is complex and dynamic, shaped by the interplay of neural activity and plasticity, genetic, and environmental factors (Gray & Thomson, 2004).

Fuster (1997) proposed a model for studying the brain and learning behavior. The model assumes that human behavior draws on processes organized along three axes in the brain: bottom-up (d: dorsoventral), right-left (l: lateral), and back-front (m: median). Bottom-up pathways are essential in regulating arousal levels and social and emotional functions. Right-left pathways are critical for integrating spatial/simultaneous and temporal/successive processing. Finally, back-front pathways are essential in receiving visual, auditory, and somatosensory information, integrating them across modalities, navigating working memory, and planning.

Extensive research on neurodevelopmental disorders, such as reading difficulties, developmental language disorders or attention deficits, covers all these three broad dimensions of human mental functioning (Fletcher & Grigorenko, 2017; Mahone & Denckla, 2017; Papadopoulos et al., 2015). The same applies to the study of intelligence (Demetriou & Spanoudis, 2018). In particular, intelligence assessment may be the key to assessing any individual's potential, but only if used to understand – not evaluate – the cognitive processes involved. This requires focusing more systematically on studying specific neurocognitive functions, such as inhibition/arousal, attention and working memory, and information processing or processing speed (Papadopoulos et al., 2018). This approach is needed if we want to speak about learning competencies or learning problems at a primary or secondary level.

The Neurological Basis for Reading Difficulties

Despite the above, accommodating normal variations in learning and behaviour in explaining individual processes, which, in turn, explain broad domains of behaviour and performance, remains challenging. A suitable example of this challenge is the study of reading difficulties or developmental dyslexia in light of a neurobiological basis according to the magnocellular deficit theory (Ramus, 2003; Stein, 2001). According to this theory, the core deficit of developmental dyslexia is the impairment in the magnocellular pathway of the visual or auditory system, traced back to a more general perceptual dysfunction. This pathway is responsible for processing rapid visual or auditory information, such as movement and contrast, or rapidly changing acoustic information, such as quickly changing phonemes (e.g., Tallal & Gaab, 2006). Thus, it is argued that it plays a critical role in perceiving letters and words.

However, this theory is not universally accepted as an explanation for the underlying causes of dyslexia. Regarding the possible deficits of children with dyslexia in processing dynamic auditory stimuli, such as amplitude (AM) and frequency modulations (FM) in a speech signal (e.g., Goswami et al., 2002; Witton et al., 2002), the findings of the relevant studies are inconclusive. That is, some studies have shown that different tasks measuring the perception of amplitude envelope onsets, such as amplitude rise time discrimination (ARTD) tasks, can tap into the exact underlying impaired perceptual mechanism in children with dyslexia (e.g., Goswami et al., 2002; Muneaux et al., 2004; Richardson et al., 2004). For example, ARTD has been found to account for 8–13% (Goswami et al., 2002) to 22% of unique variance in phonological processing (Richardson et al., 2004) and for 25% (Goswami et al., 2002) to 36% of unique variance in reading or spelling (Muneaux et al., 2004). Other studies have failed to replicate these findings in at least some respect. For instance, some studies have shown that children with dyslexia may differ in some, but not all, ARTD tasks (Surányi et al., 2009) and may not differ at all from their controls (Finnish: Hämäläinen et al., 2009; Greek: Papadopoulos et al., 2012), or differences may appear only when children with dyslexia are tested at a specific age (Halliday et al., 2008).

These results raise the question of whether the theoretical account of low-level deficits in ARTD can explain deficits in phonological skills and reading. At the very least, ARTD deficits are experienced only by a small number of children (Georgiou et al., 2012; Papadopoulos et al., 2012). Also, when orthographic consistency is factored into the equation, they are not equally observed in poor readers learning to read in orthographies more consistent than English

(Hämäläinen et al., 2009; Papadopoulos et al., 2012; Surányi et al., 2009).

Likewise, in the eye and optic pathways, the magnocells respond over a relatively sizeable visual space (Stein & Talcott, 1999) and follow rapid changes in illumination or visual intensity and colour, as occurs in flickering stimuli (Skottun, 2000) or coherent motion of objects in a consistent direction (Boden & Giaschi, 2007). However, compared with controls, individuals with dyslexia have shown less sensitivity in (a) detecting coherent motion (e.g., Conlon et al., 2004; Witton et al., 1998), (b) processing flickering stimuli (e.g., Martin & Lovegrove, 1988), or (c) focussing visual attention (e.g., Bosse et al., 2007; Dubois et al., 2010), thus, limiting the number of visual elements that can be processed in sequence or simultaneously during reading.

Although this evidence has gradually become more compelling, as the development of mangocells seems to be impaired in many – but not all – individuals with reading difficulties or developmental dyslexia, it remains controversial (Stein, 2021). In addition, similar deficits, particularly regarding visual attention span, are detected in several other neurological or neurodevelopmental conditions besides developmental dyslexia, such as alexia following a stroke or ADHD (see Habekost, 2015, for review). Nevertheless, these outcomes underscore the heterogeneity of neurodevelopmental disorders and the need for a multifactorial approach to studying such conditions.

Comorbidity of Learning Disorders

To further understand how a multifactorial approach can better inform research and practice in neurodevelopmental disorders, it suffices to consider the challenges observed in comorbid deficits. For example, neurobiological impairments can exist alongside other neurocognitive deficits in information processing skills, attention, working memory, or other executive functions. Furthermore, these deficiencies are related to specific aspects of reading difficulties (Papadopoulos et al., 2014; Papadopoulos et al., 2020), weaknesses in word problem-solving, calculation skills (Math Difficulties-MD; e.g., Kroesbergen et al., 2003), or ADHD (e.g., Papadopoulos et al., 2005). Notably, these impairments are observable even among children with typical intelligence who have RD, MD, or ADHD. Therefore, the concept of SLD, in particular, rests on two assumptions. First, SLDs are not due to inadequate opportunity to learn, general intelligence, or physical or emotional disorders but to primary dysfunctions in specific neurobiological or neurocognitive processes. Second, these particular processing deficits reflect neurological and/or environmental factors (e.g., Berninger et al., 2015; Swanson, 2015).

These assumptions are supported by several studies (e.g., Kirby et al., 2015; Kroesbergen et al., 2015; Papadopoulos et al., 2020; Papadopoulos et al., 2021). The overarching conclusion from these studies is that the viability of a multifactorial model relies on its potential applications, which, in turn, provide the means for explaining and understanding individuality at the level of neurodevelopmental dysfunctions. Likewise, behavioral phenotypes, defined as cognitive, linguistic, or social observations consistently associated with neurodevelopmental disorders, do not provide an adequate means of diagnosing SLD. As a result, the simple collection of symptoms, which happen to co-occur with sufficient regularity to convince us that this co-occurrence is meaningful and has implications for the diagnosis of SLD, may be only the first step of the diagnostic procedure.

The aim of diagnosis must be to determine if congruence exists between an individual's neurobiological or neurocognitive processing competence and academic requirements. Thus, the real question is what kind of theoretical underpinnings and evidence-based applications would be required of a multifactorial model to align with emerging demands for the study of neurodevelopmental disorders. As mentioned earlier, since learning disorders and most neurodevelopmental disorders result from genetic and environmental risk factors that act early in development and influence the developmental trajectory in particular domains of functioning, understanding them requires a developmental perspective. Indeed, the developmental course of specific domains of functioning in SLD changes as children encounter different developmental tasks. In this respect, a legitimate cycle of learning problems would show how impairments in underlying neurocognitive processes can gradually lead to primary or secondary learning deficits. Specifically, problems at any early level of neurocognitive functioning can cause problems at follow-up levels.

Also, the higher the source of the problem, the broader the problem. For instance, inappropriate attention or arousal disrupts planning (Papadopoulos et al., 2005), disrupting working memory or processing speed (Swanson, 2015), and, consequently, achievement areas. Even if attention or arousal is within tolerable limits, planning problems could disrupt lower levels of processing. Similarly, if one or many general

cognitive skills are weak, they can produce a particular learning problem across achievement areas, with significant impairments in processing speed. For example, poor information processing could affect word decoding, resulting in overemphasizing visual cues in spelling and an inability to follow a plan in problem-solving. Finally, learning problems can give rise to secondary affective issues, which can feed back upon the higher levels of processing.

Current Trends in the Study of Neurodevelopmental Disorders

This (vicious) cycle has brought up the need to interface any multifactorial theory with newer trends in the study of neurodevelopmental disorders. Contemporary research on neurodevelopmental disorders favours a Multiple Deficit Model (MDM; McGrath et al., 2020; Pennington, 2014) or a broader framework such as the Research Domain Criteria framework put forward by the National Institute of Mental Health, USA (Insel et al., 2010).

Both propositions are agnostic about certain diagnostic entities. According to the MDM model and the RDoC framework, the etiology of neurodevelopmental disorders is multifactorial. This means multiple etiological protective and risk factors may shape an individual's cognitive development and difficulties in everyday functioning. In this line of thinking, no single cognitive deficit can readily explain the emergence and trajectory of a neurodevelopmental disorder. Instead, each cognitive deficit is thought to have a contributory effect on the development of a condition. For instance, as a primary index of SLD, working memory deficits are usually observed in combination with deficiencies in inhibition, attention, or planning (Friso-Van den Bos et al., 2013; Papadopoulos et al., 2020), phonological and naming speed deficits (e.g., Swanson, 2015). Such evidence shows how a cognitive deficit interacts with others for a disorder to manifest. It also supports the contention that cognitive mechanisms underlying known DSM-related conditions (e.g., dyslexia, developmental language disorder, ADHD, or math difficulties) may cut across diagnostic boundaries. The real question, then, is whether MDM or RDoC, with their theoretical foundations and evidence-based applications, can encompass multiple levels of functioning and causation in the study of neurodevelopmental disorders.

The MSCA ITN Neo-PRISM-C Project

The MSCA ITN Neo-PRISM-C project (Papadopoulos, 2018; http://www.neoprismc.org/) aims to provide pertinent answers to the above questions. First, we argue that probabilistic multiple deficit models are necessary to provide realistic accounts of neurodevelopmental disorders. Second, the non-deterministic relationship between neurodevelopmental disorders and their presumed causes requires a radical change in how scientists and clinicians are trained to study and combat such conditions. Finally, markers for clinically relevant phenomena may cut across diagnostic boundaries. Thus, approaches such as the RDoC are relevant to accelerating research that significantly impacts individuals and families affected by neurodevelopmental disorders.

To understand the probabilistic relationships between multiple levels of analysis (e.g., genetics, neural systems, cognition, environmental influences) and different remedial outcomes, Neo-PRISM-C relies on the RDoC. The RDoC research framework integrates multiple levels of data (from genomics to self-report) to understand the basic dimensions of functioning underlying the full range of behaviour from normal to abnormal. Furthermore, theoretical and predictive models adhering to the RDoC help address the heterogeneity and comorbidity in various neurodevelopmental disorders. Indeed, training a new generation of researchers within this framework seems to (a) improve the understanding of the brain and behaviour (Amora et al., 2022; Christoforou et al., 2021; Fanti et al., 2022), (b) enhance diagnosis and clinical formulation (Khanolainen et al., 2022; Kouki et al., 2023; Papadopoulos et al., 2021; Verwimp et al., 2021), and (c) develop personalized treatments, support prevention of NDD, and eliminate the disparities in underserved populations (https://www.neoprismc.org/research-outcomes/).

A Final Word

We do not know if neurodevelopmental disorders will continue to fall within the dimensions we have been accustomed to studying for at least five decades as a continuation of William M. Cruickshank's significant legacy. Still, we must explore the approaches they represent for future research. In the framework of this memorial IARLD keynote address, I attempted to underscore that the topics of focus for future studies will likely be influenced by the growth and modification of new multifactorial models, such as the RDoC, and by significant advances in research made within this or similar frameworks. Using the RDoC matrix as a starting point instead of a definitive guide, future research may reveal developmental variations not captured currently (Casey et al.,

2014). The way forward is to seek new/revised constructs or interactions between multiple constructs. In addition, we should continue carefully selecting the units of analysis that best fit the study questions.

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