Neurodevelopmental Disorder Associated

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I Introduction

Neurodevelopmental disorders (NDDs) refer to a large, heterogeneous group of childhood-onset conditions that result from disrupted brain development and/or functioning. NDDs can impact an affected individual in many domains including cognition, self-help, social communication, behavior, and motor control. NDDs are often diagnosed based on clinical descriptions of developmental impairments, such as autism spectrum disorder (ASD), intellectual disability (ID), language disorder, specific learning disorder, and attention-deficit hyperactivity disorder (ADHD) (American Psychiatric Association et al., 2013). A subset of NDDs are genetically defined diseases, such as Rett syndrome (RTT), tuberous sclerosis complex (TSC), and fragile X syndrome (FXS), which are commonly associated with variable developmental impairments (Sahin & Sur, 2015).

Collectively, NDDs have a tremendous financial and clinical impact on patients and their families/caretakers. In the United States alone, from 2006 to 2008, around one in six children had a diagnosis of an NDD (Boyle et al., 2011). In addition to limiting a child's ability to function in

everyday life throughout their life, NDDs are known to cause significant parental distress (Craig et al., 2016). The financial costs associated with these disorders is also substantial, taking into account both direct and indirect health-care expenses (Buescher, Cidav, Knapp, & Mandell, 2014; Olesen et al., 2012; Cohen et al., 2012). For example, one study estimated the lifetime cost of raising a child with ASD and ID as $2.4 million in the United States and £1.5 million in the United Kingdom (Buescher et al., 2014). Another study suggested that the total economic cost in 2010 of "brain disorders" in Europe was €798 billion (Olesen et al., 2012).

With an increasing understanding of specific genetic causes and therefore improved insight into the possible mechanisms underlying NDDs, the potential role of effective targeted treatments continues to grow. Current treatments for NDDs, whether behavioral or pharmacological, primarily address specific symptoms rather than targeting disease-specific pathophysiology. Nonpharmacological interventions, such as applied behavioral analysis therapy, can be effective strategies for improving maladaptive behavior, but they require a deep investment of time and effort that even leads to occupational burnout (Hurt, Grist, Malesky, & McCord, 2013). Based on the prevalence of burnout for professionals choosing to work with individuals with NDDs, the burden for parents—who may live with affected individuals throughout their life span—may be overwhelming. As a result, both behavioral and psychopharmacologic interventions aim to measure clinical improvement for affected individuals and the impact on family members and caretakers.

In the realm of psychopharmacology, there are broad categories of medications—such as antidepressants, anxiolytics, stimulants, mood stabilizers, and antipsychotics—that are widely used to target certain symptom clusters prevalent in individuals with NDDs. Existing pharmacological interventions may reduce target symptoms, but they may be only partly effective. They can also have nonspecific mechanisms of action, contributing to negative side effects that might not be as prevalent with more specific and targeted treatments. Because of their side effect profile, they may require numerous empirical trials adjusting dose or family of medication before an optimal regimen becomes apparent. Even with this trial-and-error approach, there is no guarantee of success or ability to predict who will respond to which medication at what dose (Bousman & Hopwood, 2016). At best, current psychopharmacologic treatments address

symptoms but not the underlying cause of specific behavioral challenges for individuals with NDDs.

Not surprisingly, within NDDs, the prospect of better understanding specific disease pathophysiology to develop specific, targeted treatments is a tantalizing one. As the genetic landscape of NDDs expands to include a growing number of pathogenic single-gene changes, chromosomal copy number variants, trinucleotide repeat

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A systematic review of behavioral and neurobiological profiles associated with coexisting attention-deficit/hyperactivity disorder and developmental coordination disorder

Marija PranjićNavin RahmanAdelia KamenetskiyKaitlin MulliganStephen PihlAnne B. Arnett, in
Neuroscience & Biobehavioral Reviews, 2023

1 Introduction

Neurodevelopmental disorders (NDDs) impact millions of children, unfold early in life, and encompass a broad spectrum of symptoms across multiple domains of functioning (Thapar et al., 2017). Although each condition is defined by a distinct constellation of features, NDDs are often comorbid with one another, posing challenges in treatment planning and care (American Psychiatric Association, 2013). Attention-deficit/hyperactivity disorder (ADHD) and developmental coordination disorder (DCD) are among the most common NDDs, with ADHD present in approximately 7% (Polanczyk et al., 2014; Sayal et al., 2018) and DCD in 6% of school-age children (APA, 2000; Zwicker et al., 2012). While ADHD is characterized by inattention, hyperactivity and impulsivity, children with DCD exhibit difficulties with motor control, including motor planning, coordination, and learning (APA, 2013; World Health Organization, 2019). In addition, children diagnosed with either ADHD or DCD are at higher risk for anxiety, depression, lower academic achievement, and less favorable psychosocial outcomes in

adulthood (Cairney, 2015; Omer et al., 2019; Rasmussen and Gillberg, 2000; Sibley et al., 2010).

The rate of ADHD and DCD co-occurrence is around 50% (Blank et al., 2012; Farran et al., 2020; Gillberg et al., 2004). Despite this, clinicians have only recently recognized that motor difficulties in children with ADHD are not simply secondary to attention and behavior dysregulation (Sergeant et al., 2006). As a result, the intersection of ADHD and DCD has largely been understudied. The concept termed "deficits in attention, motor control and perception" (DAMP) was introduced in the 1970 s in Scandinavia to describe the overlap between ADHD and DCD (Gillberg, 2003; Gillberg and Rasmussen, 1982). Stemming from clinical observations of children with combined symptomatology, the DAMP concept highlights the link between perceptual abilities and difficulties in attentional and motor domains. The role of perceptual timing is especially intriguing given that both DCD and ADHD have high comorbidity rates with other NDDs associated with perceptual vulnerabilities, including autism spectrum disorder and dyslexia (Arnett et al., 2018; Falter and Noreika, 2014; Gomez and Sirigu, 2015; Goswami, 2011; Lense et al., 2021; Noreika et al., 2013; Pranjić et al., 2023). Nonetheless, the question of whether ADHD and DCD have shared or separate neurobiological mechanisms continues to be debated (Goulardins et al., 2015; Sergeant et al., 2006). In the current review, we summarize the extant literature related to the co-occurrence between ADHD and DCD in the context of these competing hypotheses.

Considering that children with co-occurring ADHD and DCD tend to have more severe outcomes (Pitcher et al., 2003; Visser, 2003), understanding the performance features that characterize the comorbid presentation could have important clinical implications. In addition, relatively little neuroimaging research has directly compared DCD and ADHD (Bishop, 2010), and the relationship between the two has predominantly been studied from an ADHD perspective (for a review of existing neuroimaging evidence on either ADHD or DCD, see: Brown-Lum and Zwicker, 2015; Bush, 2011; Cortese et al., 2012; Langevin et al., 2014; Norman et al., 2016; Parlatini et al., 2023; Sutcubasi et al., 2020; Wilson et al., 2013, 2017). Studies focusing on treatment of motor difficulties in ADHD have been synthesized in recent reviews (Kaiser et al., 2015; Kleeren et al., 2023). Kleeren and colleagues (2023) found positive effects of motor-based interventions on motor skills in children with ADHD, and Kaiser and colleagues (2015) demonstrated positive effects of ADHD medication on motor

performance in 28–67% of children. Considering that a proportion of children with ADHD continued to display motor difficulties while on medication, Kaiser and colleagues argue that motor control challenges in ADHD cannot only be attributed to inattention. Altogether, the effects of medication on both attentional and motor difficulties indicate that ADHD and DCD share some common neural circuits; however, the link between the two remains unclear. In an attempt to explain the etiology of comorbidity, several conceptual frameworks have been proposed. The *shared etiology hypothesis* suggests that NDDs

Neurodevelopmental Disorders as Model Systems for Understanding Typical and Atypical Mathematical Development

Marcia A. Barnes, Kimberly P. Raghubar, in
Acquisition of Complex Arithmetic Skills and Higher-Order Mathematics Concepts
, 2017

Conclusions and future directions

In this chapter we proposed that neurodevelopmental disorders associated with high rates of mathematics disability at school age and that are diagnosed before or at birth provide the field with model systems for testing hypotheses that may be more difficult to test in populations without clear neurological disorders. The longitudinal studies of children with SBM and their typically developing peers provide support for the importance of domain-general abilities—working memory and language—not just in the *performance* of mathematical tasks, but in the *development* of mathematical competencies. They also provide support for the idea that early number knowledge is an important developmental precursor of later mathematical achievement. Furthermore, these number-specific precursors show some developmental continuity and differentiation; for example, the early ability to perform arithmetical manipulations on

nonsymbolic quantities uniquely predicts the later ability to perform complex manipulations (calculations) on symbolic quantities.

Although these findings are intriguing and add to a rapidly changing knowledge base on the development of mathematical cognition and the factors associated with difficulties in acquiring mathematical abilities, there are a few caveats with our longitudinal approach that merit consideration. First, although our findings converge with many others in the literature, phenotypic similarities in performance on mathematical tasks between groups (SBM vs. TD; younger vs. older children) need not mean that underlying neurocognitive processes are identical (Ansari, 2010). For example, the fact that the relation of working memory to mathematics may be larger in children whose MLD is associated with other developmental disorders than for those with MLD only (Peng et al., 2015) could also mean that the large contributions of early working memory to later mathematics that we found in our studies may not be generalizable to all other groups of children with MLD. Second, our studies were neither initially nor primarily designed to test models of mathematical development and disability even though they yielded data amenable to investigating aspects of these models over long developmental time windows. This means there are several model-driven hypotheses about mathematical development that our studies were not equipped to test. Based on our findings, but also these caveats, we think there would be benefit in conducting studies that begin assessment in infancy and follow

Social Cognition in Individuals With Intellectual and Developmental Disabilities: Recent Advances and Trends in Research

Daniela Plesa Skwerer, in
International Review of Research in Developmental Disabilities, 2017

Abstract

This chapter provides an overview of recent research on social cognition and social functioning in people with intellectual and developmental disabilities (IDDs), with a particular focus on neurodevelopmental disorders associated with distinctive social-cognitive and behavioral phenotypes. We review the main experimental paradigms that have been used to probe social cognition in both typically and atypically developing populations and discuss findings primarily from research on two neurodevelopmental disorders that have been extensively studied in the last 3 decades: Autism spectrum disorders (ASD) and William's syndrome (WS). Viewed in the past as diametric opposites in their social phenotypes, the two disorders have been intensely researched for their potential to provide

Common mechanisms in intellectual disabilities: a challenge for translational outlooks

Daniela Valenti, ... Rosa Anna Vacca, in
Neuroscience & Biobehavioral Reviews, 2014

6 Concluding remarks and future perspective

In the present review we have shown that some neurodevelopmental disorders such as Down, RTT and Fragile X-related syndromes, as well as ASD, though different in their genetic origin and aetiology, share significant clinical and neuropathological overlaps (see Table 1) as well as common alterations of key proteins of mitochondrial OXPHOS apparatus (Fig. 1). Oxidative stress and abnormal mitochondrial metabolism seemingly represent a common molecular underpinning of these neurodevelopmental disorders associated with mental retardation and intellectual disability.

Several factors make the brain exceptionally vulnerable to oxidative degeneration. Due to its high energy request, brain has extremely high OXPHOS activity, accompanied by correspondingly high electron leakage. The brain is also particularly loaded with unsaturated fatty acids in the myelin sheath and long-chain fatty acids in cell membranes, which are highly susceptible to peroxidation; finally, the brain is poorly equipped with antioxidant enzyme defenses (Kovacic and Somanathan, 2012; Natelson, 2013). In this context, the evidence is

persuasive that mitochondrial function inadequacies could be a central etiologic mechanism in the poor brain function leading to ID. Since OS biomarkers are related to neurological symptoms severity in particular in RTT (Durand et al., 2013) and in DS syndromes (Lott et al., 2011), speculatively, mitochondrial impairment would promote a downward spiral of bioenergetic capacity that progressively contributes to disease progression. This hypothesis would be compatible with the potential reversibility of some clinical features demonstrated at least in RTT patients (De Felice et al., 2012c).

Defects in OXPHOS complexes are consistently linked to dementia (Rhein et al., 2009; Damiano et al., 2010). In particular, a deficit of complex I activity occurs in RTT syndrome (Grosser et al., 2012), autism (Tang et al., 2013; Ghanizadeh et al., 2013) and Down syndrome (Valenti et al., 2011), (Fig. 1 and Table 1) as well as in several human neurological disorders including primary mitochondrial diseases, Parkinsons' and Alzheimer's diseases (for refs see Papa and De Rasmo, 2013). Complex I is the major entry-point for electrons into the OXPHOS system and regulates mitochondrial ATP production (Distelmaier et al., 2009). In addition, complex I is the main mitochondrial site of free radical production in the case of its impairment (Koopman et al., 2010); thus it has a key function in neuronal cells which require large amounts of ATP for their excitability and are highly susceptible to radical species. Since complex I activity, as well as the activity of the other proteins involved in OXPHOS, are governed by cAMP/PKA-dependent phosphoregulation (Horbinski and Chu, 2005; De Rasmo et al., 2010), the cAMP/PKA signaling pathway is supposed to regulate the functional capacity of OXPHOS and the oxygen free radical balance in mitochondria. Thus, a primary alteration of cAMP/PKA signaling pathway, rather than mitochondrial defects, could be the cause of mitochondrial energy impairment. Indeed, in several neurological diseases with mitochondrial respiratory chain dysfunction, such as DS and Parkinson's disease, stimulation of cAMP-dependent phosphorylation by dibutyryl-cAMP, a derivative of cAMP, rescued OXPHOS activity and prevented ROS accumulation in cultured fibroblasts obtained from patients (Piccoli et al., 2008; Valenti et al., 2011; Papa and De Rasmo, 2013). Compounds able to activate cAMP cascade by acting on the activation of cAMP production by adenylyl cyclase (β-adrenoreceptor molecules, EGCG *etc.*) and/or on the inhibition of its degradation by phosphodiesterase (EGCG, resvaretrol, rolipram *etc.*) should be considered interesting potential candidates for treating ID-linked neurological diseases.

Table 1. Main mitochondrial alterations and clinical phenotypes associated to mitochondrial dysfunction in Down syndrome, Rett syndrome, Fragile X-related syndromes and autism spectrum disorders.

Disorders	**Mitochondrial alterations**	**Clinical phenotypes (associated to mitochondrial dysfunction)**	**Refs.**
Down syndrome	Defective cAMP/PKA-dependent phosphorylation; deficit of complex I, ATP synthase, ADP/ATP translocator and adenylate kinase activities; mtDNA depletion; altered mtDNA repair system; mitochondrial ROS overproduction; altered mitochondrial morphology and biogenesis	Developmental delay; hypotonia; lactacidosis; ophthalmoplegia; cardiomyopathy; dendritic abnormalities; neurodegeneration; oxidative stress	Arbuzova et al., 2002; Coskun and Busciglio, 2012; Helguera et al., 2013; Valenti et al., 2010, 2011
Rett syndrome	Decrease in complexes I, II, and IV protein subunities and activities; up regulation *ANT1;* disturbances in cAMP homeostasis; altered mitochondrial morphology	Hypotonia; abnormal movements; subclinical myocardial dysfunctions; neurological regression; oxidative stress	De Felice et al., 2012a,b,c Gibson et al., 2010b; Forlani et al., 2010; Heilstedt et al., 2002
Fragile X-associated syndromes	Decrease of NAD- and FAD-linked oxygen uptake rates, electron transport; OXPHOS	Gait ataxia; peripheral neuropathy; muscle weakness;	de Diego-Otero et al., 2009; Kaplan et

	capacity; decrease of mitochondrial number and mobility	exercise intolerance; neuropathology;	al., 2012; Ross-Inta et al.,

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A systematic-review of olfactory deficits in neurodevelopmental disorders: From mouse to human

Ariel M. Lyons-Warren, ... Benjamin R. Arenkiel, in Neuroscience & Biobehavioral Reviews, 2021

3.2 Neurodevelopmental disorders with olfactory deficits as part of the diagnostic criteria

A total of 60 % of patients with hypogonadotropic hypogonadism also present with anosmia or hyposmia, and are diagnosed with Kallmann Syndrome (Balasubramanian and Crowley, 2007). Like ASD, Kallmann syndrome is a heterogeneous disorder associated with numerous genetic mutations (Stamou and Georgopoulos, 2018). A systematic study of types of olfactory deficits in Kallmann syndrome has not been published. However, Ragancokova et al. nicely demonstrate the power of linking animal models with patient mutations. In their study, a role for *Tshz1* in OB development was identified. Mice lacking *Tshz1* have impaired odor detection, but no deficits in odor discrimination. Similarly, patients with *Tshz1* mutations have reduced odor sensitivity, as well as difficulties with odor discrimination (Ragancokova et al., 2014). Similar to ASD and Kallmann syndrome, Bardet-Biedl syndrome (BBS) is a clinically heterogeneous, multi-gene ciliopathy and

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Imitative and contagious behaviors in animals and their potential roles in the study of neurodevelopmental disorders

Amtul-Noor Rana, ... Hye Young Lee, in
Neuroscience & Biobehavioral Reviews, 2022

1.3 Imitative and contagious behaviors in neurodevelopmental disorders

Imitative deficits and their consequences have been greatly studied in patients with autism spectrum disorders (ASDs) and other neurodevelopmental disorders associated with autistic-like symptoms. Children with ASDs show difficulty in performing emotional contagion —such as automatic mimicry of whole-body fear and facial expressions (Hadjikhani, Joseph et al., 2009; Drimalla, Baskow et al., 2021)—as well as impaired mirroring—such as imitation of object use and body movements (Smith and Bryson, 1994; Forbes, Pan et al., 2016; Li, Sharma et al., 2017)—compared to their age-matched, neurotypical peers. Additionally, contagious behaviors, specifically yawning, are reduced in children with ASDs (Senju, Maeda et al., 2007). However, instructing children with autism to maintain eye-contact (Senju

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Understanding autism and other neurodevelopmental disorders through experimental translational neurobehavioral models

Judith R. Homberg, ... Allan V. Kalueff, in
Neuroscience & Biobehavioral Reviews, 2016

2 Animals models of neurodevelopmental disorders

Since a key function of the nervous system is to produce behavior, behavioral analyses provide the most meaningful assessment of the central nervous system (CNS) and its deficits. For example, rodent tests are commonly used to measure neural phenotypes in behavioral genetics, developmental psychobiology, psychopharmacology and

neurotoxicology (Buelke-Sam and Kimmel, 1979; Butcher, 1976; Elmazar and Sullivan, 1981; Reiter, 1978; Vorhees et al., 1979). However, because of multiple limitations inherent in experimental modeling of complex human brain disorders (Cachat et al., 2011; Kalueff and Tuohimaa, 2005b; Kalueff et al., 2007d), targeting the entire spectrum of clinical NDDs is impossible (Table 1). Nevertheless

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Amtul-Noor Rana, ... Hye Young Lee, in
Neuroscience & Biobehavioral Reviews, 2022

4.1 The mirror neuron system and atypical activity in autism spectrum disorders

The large body of literature in both animals and humans suggests that imitative and contagious behavior abilities are involved in learning motor skills, social cooperation, and communication. Impairments in imitation are seen across various neurodevelopmental disorders and intellectual disabilities, as described earlier, which leads to deficits in learning and social interaction. However, the mechanisms behind imitative deficits in patients with neurodevelopmental disorders associated with autistic-like symptoms remains unclear. Empirical studies have found abnormal MNS activity in ASD patients, which might explain their imitative difficulties (Khalil, Tindle et al., 2018). Transcranial magnetic stimulation studies have shown that the motor cortex, a major component of the MNS, has reduced activity in ASD patients compared to neurotypical controls when performing imitative tasks that involve finger movement, while controlling for basic motor abnormalities (Théoret, Halligan et al., 2005). Interestingly, another study found that children with ASDs can mirror facial expressions; however, functional magnetic resonance imaging (fMRI) results

displayed little activity in the inferior frontal gyrus, a major component of the MNS. This finding ultimately suggests that alternative pathways involving visual and motor attention may be unchanged in ASD children; however, the empathetic significance of emotional expressions may not be experienced (Dapretto, Davies et al., 2006). In other words, some patients with ASDs might display imitative behaviors by copying the motor movements of an action or gesture, but the emotional implications of that action may not be understood. Interestingly, this study also revealed that ASD children with severe social deficits showed reduced MNS activity compared to higher functioning ASD children (Dapretto, Davies et al., 2006). Subsequent neurophysiological and fMRI studies consistently report that ASD individuals have atypical activity in brain regions involved in the MNS when imitating gestures (Bernier, Dawson et al., 2007; Shih, Shen et al.

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Neuroscience & Biobehavioral Reviews, 2022

4 Discussion

4.1 The mirror neuron system and atypical activity in autism spectrum disorders

The large body of literature in both animals and humans suggests that imitative and contagious behavior abilities are involved in learning motor skills, social cooperation, and communication. Impairments in imitation are seen across various neurodevelopmental disorders and intellectual disabilities, as described earlier, which leads to deficits in learning and social interaction. However, the mechanisms behind imitative deficits in patients with neurodevelopmental disorders associated with autistic-like symptoms remains unclear. Empirical studies have found abnormal MNS activity in ASD patients, which might explain their imitative difficulties (Khalil, Tindle et al., 2018). Transcranial magnetic stimulation studies have shown that the motor

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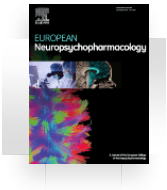

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