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The effect of exercise interventions on cognitive functions of neurodevelopmental disorders

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Introduction

Neurodevelopmental disorders (NDD) are a broad group of conditions characterized by disruptions in brain development, often manifesting in early childhood (American Psychiatric Association, 2013). These disorders can significantly impact an individual's life by impairing cognitive processes across various contexts. Recognized as distinct disorders in the DSM-III (American Psychiatric Association, 1980), NDDs today encompass a wide range of conditions outlined in the latest edition, the DSM-5 (American Psychiatric Association, 2013).

This thesis explores the categorization approach of the DSM and compares it with a new model that conceptualizes NDD as traits rather than distinct disorders. This comparison provides insights into future clinical approaches by attempting to capture the complexity of these conditions within this new framework. The presence of comorbidity and shared characteristics, such as executive dysfunction, underscores the heterogeneity of these disorders and highlights the need for innovative clinical and research approaches.

The primary focus of this thesis will be on Autism Spectrum Disorder (ASD) and Attention-Deficit Hyperactivity Disorder (ADHD). These disorders will serve as examples of how NDD can be perceived within a spectrum model and how they significantly impact cognitive functioning. One crucial aspect of cognitive functioning to be examined is executive dysfunction, which arises from deficiencies in supervisory functions that are part of the Executive Functions. Analyzing executive dysfunction in ASD and ADHD will highlight new cognitive models and strategies essential for future clinical interventions.

The thesis will also explore interventions centered around exercises and physical activity, emphasizing the physiological and cognitive benefits these interventions offer to individuals with NDD. It will focus on how such interventions can mitigate executive dysfunction and enhance cognitive functioning in affected individuals.

The biological, social, and cognitive aspects of NDD will be also examined, analyzing how these conditions influence an individual's life and how various interventions can prove beneficial. By connecting the neurodevelopmental spectrum model with exercise interventions, the thesis will discuss strategies to address executive dysfunction and other symptoms affecting patients globally.

Chapter 1 - Clinical aspects of neurodevelopmental disorders (NDD)

1.1 - Clinical and developing aspects of NDD

Neurodevelopmental disorders (NDDs) are characterized by executive dysfunction, learning disabilities, and poor cognitive abilities (American Psychiatric Association, 2013). These disorders include Intellectual disabilities, Communication disorders, Autism Spectrum disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), Specific Learning disorder, Motor disorders (i.e Tic disorders), and other similar conditions.

The brain function of individuals with NDD differs significantly from that of neurotypical individuals. In these disorders, various areas of the prefrontal cortex often exhibit altered organization (Hrvoj-Mihić & Semendeferi, 2019). These regions are responsible for information processing, higher-order cognitive and emotional functions, and executive functions. Additionally, the cerebellum plays a crucial role in developmental disorders, as it reflects changes in implicit and procedural learning (Stoodley, 2016). The cerebellum is increasingly recognized for its connections with circuits that support language and social cognition, attention, and literacy acquisition (Stoodley, 2016). Even though specific brain areas are correlated with the disorders, these impairments must be understood as the communication between the entire brain structure, as they depend on neural circuits, cortical regions, and overall brain physiology (Stoodley, 2016).

The clinical assessment is related to the evaluation of abnormalities in achieving expected cognitive milestones, which are key cognitive stages that an individual develops throughout life (American Psychiatric Association, 2013). For instance, an infant begins to recognize familiar faces around 3 months old, and a toddler develops a sense of self-awareness by around 2 years old. However, in NDD, these milestones may be disrupted. For example, ASD is clinically characterized by excessive and repetitive behavior in restricted interests and/or life activities (excess cognitive milestone), intellectual disabilities, and impaired intellectual functions such as reasoning, problem-solving, planning, and learning (delayed cognitive milestones).

NDD are usually diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 criteria, which categorizes and explains clinical and developing conditions of mental disorders.

The DSM 5 serves as a manual to categorize disorders, for clear identification and diagnosis, providing easier communication among healthcare workers, and enabling precise treatment related to the specific disorder. Indeed, for current purposes they attempt to standardize treatment approaches, providing a framework, rather than as fundamental truths for determining patient care (Thapar et al., 2017).

Even though they are clinically heterogeneous, the NDDs share many similarities and have the possibility of overlapping with one another and/or other mental disorders. This phenomenon is called comorbidity, as different symptoms could overlap and satisfy different disorders. Numerous studies showed that 22% to 83% of children with ASD have symptoms that satisfy the DSM-IV criteria for ADHD, and vice versa (Morris-Rosendahl & Crocq, 2020). Also, 30% to 65% of children with ADHD have clinically significant symptoms of ASD. Another crucial element is that, although not part of the criteria of ASD, accompanying intellectual or language impairments are recurring in ASD and their presence must be specified (Morris-Rosendahl & Crocq, 2020). Comorbidity factors can lead to a more severe impairment than in single-deficit disorders. For instance, participants with comorbidity involving ADHD and Specific Learning disorder (SLD) revealed worse Executive Function (EF) deficits than those with ADHD alone (Seidman et al., 2001; Mattison & Mayes, 2012).

Another crucial aspect of these disorders is their early onset, typically during childhood. As neurocognitive impairments emerge, particularly in social communication and executive function, a phenotypic analysis is necessary to explain how these impairments develop throughout the lifespan, since NDD tends to exhibit a consistent pattern of symptoms over time. This is why early diagnostic assessments and treatment can significantly influence later cognitive outcomes (Thapar et al., 2017).

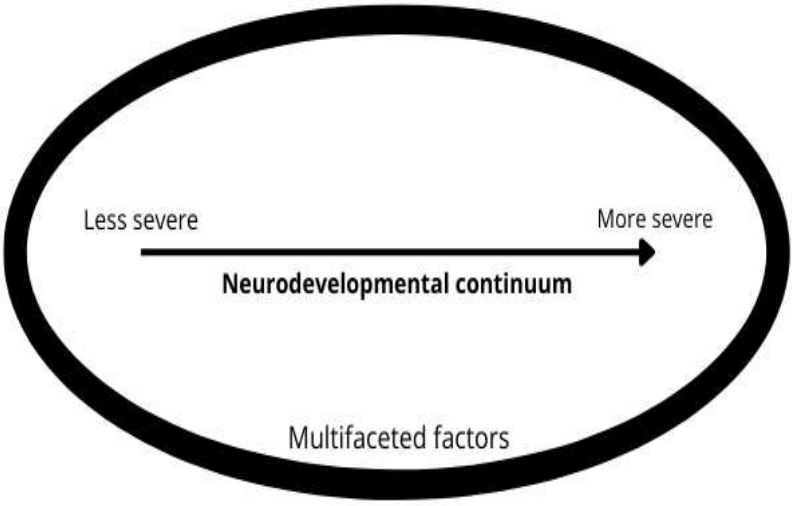
These impairments are the consequence of multifaceted etiological causes: they are highly heritable and are influenced by emotional and behavioral

development as well as social environmental adversities and stresses. Evidence over the past decade has shown that childhood neurodevelopmental disorders such as intellectual disability (ID), ASD, and ADHD share specific genetic risk alleles, including those associated with psychiatric disorders, particularly schizophrenia (Owen MJ et al., 2011).

Multimorbidity is common in clinical practice, and it can be problematic if clinicians focus solely on the diagnostic process of a single condition, thereby ignoring important features of other disorders. The clinical approach to NDD needs to be revised to incorporate more inclusive and flexible assessments, viewing these disorders as a continuum rather than discrete categories. By grouping them into a continuum and perceiving them as traits, it is possible to transcend the diagnostic boundaries implied by the DSM, embrace the complexity of these deficits, and address patients' subthreshold symptomatology.

1.2 - Neurodevelopmental disorders conceptualized as traits

Historically, categorical diagnoses have caused difficulties in clinical practice. They do not emphasize individual differences but instead focus on the boundaries of disorders, allowing symptoms to potentially overlap between disorders. Consequently, treatment is often standardized according to the impairment rather than tailored to the individual. The goal of a new approach to diagnosis is to address these disadvantages and acknowledge the variety of symptom presentations.



Conceptualizing NDD as traits involves presenting them along a spectrum or continuum without distinct boundaries or categorization. Traits and symptoms are presented dimensionally and can vary in degree within the spectrum, being conceptualized as less or more severe. Behavioral and cognitive impairments are represented on a continuum scale, emphasizing the severity of traits rather than distinct diagnostic labels. (see Figure 1).

The neurodevelopmental continuum model relies on shared genetic and environmental risk factors (Morris-Rosendahl & Crocq, 2020). It includes aspects that can directly impact the severity of the impairment, such as age of onset, severity of cognitive impairment, persistence of the impairment, sets of related genes, individual environmental characteristics, and coping strategies (Morris-Rosendahl & Crocq, 2020). These factors determine an individual's position within the continuum, where traits are assessed according to the degree of impairment.

Several studies present strong evidence that grouping NDD can lead to better clinical outcomes. For instance, over 70% of people with autism also experience medical, developmental, or psychiatric conditions (Simonoff et al., 2008). Certain co-occurring conditions, like epilepsy and depression, may emerge during early life (Lai et al., 2014). Typically, the presence of more co-occurring conditions increases the severity of an individual's disability (Mattila et al., 2010). Underlying pathophysiology, developmental impacts on autism, common symptom domains and associated mechanisms, or overlapping diagnostic criteria may lead to high comorbidity rates (Lai et al., 2014).

Since co-occurring conditions are associated with poor diagnostic approaches and lead to comorbidity, recognizing them as part of the continuum can predict better life outcomes. A meta-analysis demonstrated that individuals with autism have a mortality risk 2.8 times higher compared to their counterparts in the general population of the same age and sex (Woolfenden et al., 2012). This difference is mostly related to co-occurring medical conditions (Lai et al., 2014). These studies emphasize the complexity and multifaceted nature of these disorders, and by recognizing these connections, it may become easier to understand, diagnose, and treat neurodevelopmental disorders more effectively.

Emphasizing individual differences is a key element in conceptualizing NDD

as traits. This approach allows for the consideration of sub-threshold diagnoses, which involve assessing individuals who exhibit signs of impairment but do not fully meet diagnostic criteria. These sub-threshold diagnoses are common and clinically significant in predicting poorer mental health and functional outcomes in adulthood (Copeland et al., 2015). They are often overlooked during early childhood because they do not fulfill the DSM criteria for a disorder. However, early interventions for individuals just below the diagnostic threshold can be beneficial, potentially reducing developmental impairments and delaying the onset of later symptoms.

Because neurodevelopmental deficits share common factors, a unified intervention can enhance treatment, improve well-being, and minimize developmental challenges. Early interventions can be broadly applied to the disabilities represented within the continuum, targeting executive functions, social communication, and cognitive impairments. Physical activity and community engagement are examples of accessible interventions at a group level, highlighting the advantages of viewing NDD as traits.

This raises the question: is it beneficial to disregard the DSM and the International Classification of Diseases (ICD)? No, because they provide distinct categories that are crucial for clear communication and understanding of disorders, as well as for prescribing medication and other clinical purposes. It is impractical to rely solely on one approach. Instead, a holistic approach that integrates both the spectrum of neurodevelopmental traits and the structured perspectives presented by the DSM and ICD is necessary. Determining the optimal use of these approaches, such as positioning disorders at the most severe point of the spectrum, requires further research, along with exploring other factors that could directly influence disorder assessment and addressing challenges identified by these analyses.

1.3 - Current challenges for clinicians and researchers

The proposed model and the overall characteristics of NDD highlight the need for further research to inform clinical analysis. Studies that integrate new models and demonstrate reliable validity can serve as a foundation for future clinical interventions, such as the Research Domain Criteria (RDoC) and the genotype-first approach.

The RDoC, a project proposed by the National Institute of Mental Health, aims to analyze genetic, molecular, phenotypic, and multiple levels of measurement for mental disorders. This project is significant due to the rapid research advances in classifying neuropsychiatric disorders based on their biology, particularly the genes and variants involved (Morris-Rosendahl & Crocq, 2020). The genotype-first approach focuses on the etiological level of the individual, driven by new evidence of copy number variants (CNVs) and disruptive gene variants in ASD (Morris-Rosendahl & Crocq, 2020). This approach identifies specific genetic subtypes shared by many individuals. For instance, disruptions in the CDH8 gene result in genetic subtypes characterized by distinct physical traits, common in ASD (≥87%) and also in intellectual disability (ID) (~60%) (Morris-Rosendahl & Crocq, 2020).

It is crucial to emphasize research and clinical practice that considers the genetic approach. Further analysis is needed to understand the clinical and psychosocial benefits of this approach, which could improve diagnosis and prognosis (Morris-Rosendahl & Crocq, 2020). Support group interventions are also part of this analysis, as family members of individuals with the same genetic subtype can share experiences and insights, contributing to research and clinical practice for better outcomes (Morris-Rosendahl & Crocq, 2020).

Maintaining distinct diagnoses alongside the conceptualization of NDD as traits can enhance treatment in clinical practice. Specific diagnoses can influence medication prescriptions, leading to better clinical outcomes based on symptom severity. For instance, stimulant medications can alleviate ADHD symptoms (The MTA Cooperative Group, 1999), as can atomoxetine (Bushe & Savill, 2014). Atypical antipsychotic drugs can also alleviate severe tics (Leckman & Bloch, 2015). These medications do not affect core NDD symptoms (Thapar et al., 2017)

and could not be prescribed if distinct disorder categories did not exist. Moreover, clear diagnostic labels improve clinical communication, helping clarify difficulties and provide explanations about the disorder (Thapar et al., 2017).

Combining these approaches can result in better and more inclusive clinical outcomes. Future clinical and research practices must capture phenotypes, acknowledge overlaps and subthreshold complexity, consistently consider a psychosocial approach, and maintain a holistic view of the individual for treatment (Thapar et al., 2017). However, it is beneficial to retain different labels for communication in many contexts. It is not reasonable to rely exclusively on one approach, but rather important to conduct more analysis that integrates both, highlighting their impact on future diagnosis.

The lifespan development of impairment, assessments, and clinical perspectives must be considered (Thapar et al., 2017). While early onset is a fundamental characteristic of NDD, later onset cases also appear in clinical practice. Later onset cannot be explained solely by subthreshold cases or by earlier comorbidities, as most adult ADHD cases at age 38 were not preceded by a childhood diagnosis (Moffitt et al., 2015). Patterns of onset and persistence across the lifespan need to be examined, requiring longitudinal studies (Thapar et al., 2017). This longitudinal perspective necessitates multifaceted interventions when assessing patients and predicting outcomes (Leckman & Taylor, 2015) because even if patients present similar diagnoses, they might require different interventions based on co-occurring symptoms, social contexts, and biological factors (Thapar et al., 2017).

Another challenge in clinical development is the availability of resources for assessing and treating these disorders. For example, it is essential to assess people beyond their primary diagnosis and focus on their symptoms, function, and social dimensions (Thapar et al., 2017). The availability of social resources can significantly impact an individual's life, as can early identification and intervention (Lai et al., 2014). The statistics supporting this assumption are compelling. Various studies have shown that 58–78% of adults with autism experience poor outcomes in terms of independent living, educational attainment, employment, and peer relationships (Howlin et al., 2004). The transition from childhood to adulthood is often accompanied by the loss of many resources, such as school support and

mental health services (Lai et al., 2014), leading to poor quality of life and well-being and contributing to the exclusion of neurodiverse people within society. Another strong evidence of this is the average proportion of adults with ASD in employment and full-time education, which is 46% (Howlin & Moss, 2012). This data underscores the importance of recognizing early-onset symptoms and monitoring how they develop throughout the lifespan, as well as having the resources to reduce impairments and provide treatments that can influence the developmental factors of these disorders. Interventions such as sports programs can improve outcomes not only functionally but also socially. Current clinicians need to consider the many aspects that influence, will influence, and should influence the patient's impairment.

Chapter 2 - Executive dysfunction in neurodevelopmental disorders: a focus on Attention Deficit/Hyperactivity Disorder and Autism

2.1 - Cognition and Autism

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by impairments in social communication and interaction, along with restricted and repetitive behavior patterns (American Psychiatric Association, 2013). Executive functions is a term that refers to a set of supervisory functions involved in controlling mental processes, such as working memory, emotional control, organization, and goal-directed behavior. These functions relate to the ability to plan, initiate, and complete tasks, think abstractly, adapt, and perform complex activities.

ASD is highly correlated with executive functions and overall neurocognitive functioning, playing a crucial role in autism symptoms and behaviors (Demetriou et al., 2018). Executive dysfunctions, or deficits in executive functions, are present in many neurodevelopmental disorders, including ASD. These dysfunctions in ASD are linked to several psychological areas and theories, such as the Theory of Mind (Pellicano, 2007), social cognition, and social impairment (Leung et al., 2016). There is a consensus that executive dysfunction plays a crucial role in the development of autism spectrum disorder (Maximo et al., 2014). Additionally, abnormalities have been observed in patients' brain development, such as cortical volume and thickness in both frontal and other brain regions (Nomi & Uddin, 2015).

Many developmental differences in ASD are influenced by individual variables such as cognitive measures, biological factors, and environmental influences. These variables may moderate overall executive function performance, particularly in specific executive function subdomains and brain development (O'Hearn et al., 2008). Although there are not many studies evaluating developmental trajectories (Demetriou et al., 2018), recent studies have attempted to connect clinical aspects of ASD with executive function deficits.

A recent study found that individuals with ASD performed worse in overall executive function tasks than neurotypical individuals (Demetriou et al., 2018).

However, there were no significant differences in effect sizes across executive function subdomains, only moderate differences (Demetriou et al., 2018). This could be related to the tendency of NDD to show a steady course throughout one's life. However, another study highlighted that children with both ASD and ADHD were more significantly impaired in executive function activities than children with only ASD (Dajani et al., 2016), suggesting that comorbidity catalyzes executive dysfunction and other developmental deficits.

Biological factors can also impact executive function tasks. One study discussed the comparison of age with working memory (Demetriou et al., 2018). However, this correlation might relate to developmental trajectories, as neurotypical individuals might perform worse due to synapse reorganization (Blakemore & Choudhury, 2006). Although executive function subdomains have weak empirical support, there is an overall effect of executive dysfunction in individuals with ASD compared to the general neurotypical population.

Of note, the validity of current studies is limited by measurement levels (Dajani et al., 2016), mainly due to task characteristics, the severity of impairment, and comorbidities (Demetriou et al., 2018). Regarding comorbidities, anxiety in individuals with ASD has been associated with poor executive function performance (Hollocks et al., 2014). Furthermore, ecological studies related to environmental research on individual differences can align developmental stages of impairment with clinical measures (McGorry et al., 2014), such as the RDoC framework.

Early intervention can improve developmental outcomes in ASD (Demetriou et al., 2018). While cognitive deficits are present throughout the developmental period, adults often perform better in executive functions than younger age groups due to developmental maturity and increased use of compensatory strategies (Demetriou et al., 2018). This highlights the necessity for treatment during early life stages. Diagnostic and intervention approaches need to shift toward more inclusive treatment that accounts for individual differences within the spectrum of impairment or the neurodevelopmental continuum (Demetriou et al., 2018).

2.2 - Evolving cognitive models of Attention Deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by persistent patterns of inattention and/or hyperactivity-impulsivity that interfere with individual functioning and development (American Psychiatric Association, 2013). ADHD is strongly linked to executive dysfunction, as the disorder may affect various subdomains of executive functions. It also impacts the brain's structure and functioning, particularly in regions that support higher cognitive functions (Biederman, 2005).

Researchers have explored how ADHD influences cognitive functions and how these insights can contribute to understanding the disorder's etiology. Over the years, studies have focused on the relationship between ADHD and executive dysfunctions, particularly those related to frontal lobe functions like attentional regulation and working memory (Lyon & Krasnegor, 1996), leading to the development of evolving cognitive models proposed by various scholars.

One cognitive model proposed in the late 20th century emphasized deficits in the inhibitory control system as the core of ADHD's executive function processes (Barkley, 1997). The inhibitory control system, a component of executive functions, is responsible for self-regulation and goal-directed behaviors, allowing individuals to inhibit and select specific stimuli to complete an action. However, several studies have failed to establish a connection between a single core deficit, such as the inhibitory control system, and ADHD's executive function processes. For example, studies using the Go/No-Go task, particularly the Stop-Go task, have only successfully replicated evidence for executive motor inhibition within the broader inhibitory process (Nigg, 2001). Addressing executive dysfunction with a single assessment analysis is challenging, as results depend on many variables, including response anticipation, reaction time, mood, and task instructions (Aron & Poldrack, 2005).

Less than half of the children with ADHD exhibit significant executive function impairment (Nigg et al., 2005), and the correlation between ADHD and executive function deficits, while significant, is relatively low (Nigg et al., 1998). One possible reason for the limited evidence is the inadequacy of assessment tools, as most clinical assessments focus on a single executive functions

component, excluding other variables that could impact individual scores.

Studies involving families and twins suggest small correlations between genetic factors and ADHD executive functions (Doyle et al., 2005). Still, they indicate that most genetic and environmental influences affecting ADHD symptoms are distinct from those influencing EF weaknesses (Willcutt et al., 2005). This suggests that ADHD symptoms cannot be solely attributed to executive dysfunction. Instead, ADHD should be understood through a multifaceted approach that acknowledges cognitive and behavioral heterogeneity.

Cognitive models that embrace heterogeneity are part of the multiple pathways model. These models recognize individual differences in mental processes that may influence executive functions, such as motivation, reinforcement, delay aversion, and sensorimotor perception (Castellanos et al., 2006). They also consider frontal cortex functions related to cognitive processes and executive dysfunction. Zelazo and Muller (2004) proposed two distinct executive function pathways: the "cool" pathway associated with the dorsolateral prefrontal cortex (DLPFC) and the "hot" pathway associated with the orbital and medial prefrontal cortex (OMPFC). The "cool" EF pathway involves cognitive processes related to logical mechanisms, which include many executive functions umbrella terms and assessment tests. Examples of this pathway include working memory, planning, organization, response inhibition, and attentional control (Salehinejad et al., 2021). The "hot" executive functions pathway involves cognitive processes related to emotional and motivational salience, such as rewards and punishments, goal-directed emotions, and social behaviors (Salehinejad et al., 2021).

Neuroimaging studies provide evidence supporting the multiple pathways model. An fMRI study confirmed the activation of the DLPFC as a key region across "cool" executive function subdomains (Niendam et al., 2012). Many neuroimaging studies also confirmed the activation of the OMPFC when reward, emotional, motivational, and social evaluations were assessed (Salehinejad et al., 2021). Consequently, both pathways are interdependent and should not be seen as distinct entities, even though ADHD may initially appear as an impairment in "cool" EF pathways (Zelazo & Muller, 2002). For example, the "hot" pathways of motivational and reward systems can affect the "cool" pathways of inhibition

control and working memory.

The developmental aspects of ADHD can influence individual differences in executive dysfunction, indicating that both pathways and all cognitive processes involving executive functions should be assessed for a clear diagnosis. For example, a study of the cortico-striato-thalamo-cortical circuits (a circuit involved in many psychopathologies) concluded that the OMPFC "hot" pathways of emotion and motivation directly impact the DLPFC "cool" executive functions pathways (Haber, 2003).

A holistic view of the individual provides a framework for future directions in this field, especially concerning cognitive and emotional disturbances affecting ADHD (Salehinejad et al., 2021). However, these pathways are intrinsically related to many NDD and not just ADHD, underscoring the importance of conceptualizing NDD as traits. The existing individual differences that influence executive dysfunction can alter the severity of the disorder within the neurodevelopmental continuum. Instead of assigning specific executive dysfunctions to different disorders, assessments and diagnoses should include different cognitive profiles and identify where the deficit lies, proposing a more inclusive approach. The analysis will be more effective by considering individual variability, such as environmental factors, different pathways' influences, comorbidities, and genetics.

In conclusion, analyzing the clinical aspects and executive dysfunction of NDDs raises the question of what could serve not just as a research method but also as a treatment and intervention for these disorders. This could have an early impact and provide a strong framework for developing cognitive processes.

Chapter 3 - Exercise interventions in neurodevelopmental disorders

3.1 - Exercise and neurophysiological/cognitive function changes

Improving Access and Efficacy of Treatments for Neurodevelopmental Disorders

Clinical interventions for NDD are varied, encompassing a wide range of approaches, from different types of psychotherapy to pharmacological treatments. Research indicates that the effectiveness of these treatments in improving symptoms is significantly enhanced when they are introduced early in life. However, there are numerous barriers to accessing these essential treatments. Many families face significant financial burdens and endure long waiting periods to receive appropriate care or medication through public services, which can adversely affect their quality of life (Brown, 2006). Socioeconomic inequalities significantly impact access to healthcare and the realization of the right to health, particularly in developing and least-developed countries. In these regions, pronounced disparities in socioeconomic status make accessing social services much more challenging.

In the context of medication, studies have revealed that approximately one-third of children with ADHD either struggle to respond to medication or do not respond at all (DuPaul et al., 2020). Although this research primarily focused on children with ADHD, similar issues may arise with other NDD. This is often due to comorbidities and the common prescriptions shared across these disorders. Furthermore, adhering to these medications can be time-consuming, as they are often difficult to obtain due to governmental regulations and can be prohibitively expensive (Xie et al., 2021).

Exercise Interventions as an Alternative

To address these limitations, the proposed exercise intervention offers a more natural and accessible treatment option for these disorders. Exercise interventions have the potential to be more cost-effective than many traditional behavioral therapies because they require little to no investment, do not

necessarily need specialized support, and can be carried out in most community environments (Bremer et al., 2016). Exercise is already an integral part of many people's lives and cultures, making it a promising alternative for clinical intervention with numerous benefits—physical, social, and cognitive.

Physiologically, physical activity can enhance cognitive functions and improve blood flow, which increases arousal levels and neurotransmitter production (Sung et al., 2022). These factors are crucial components of brain activity and can influence the development and severity of disorder symptoms. Physical activity is also linked to the increased production and secretion of neurotransmitters like serotonin (Chan et al., 2022), endorphins, dopamine, and norepinephrine (Zhu et al., 2023). These neurotransmitters play critical roles in cognitive processes and the activation of the central nervous system. Exercise also promotes neuroplasticity, strengthening adaptation, information processing, and the ability to form new neural connections (Medina et al., 2010). Additionally, physical activity boosts the secretion of brain-derived neurotrophic factor (BDNF), a protein associated with the development of neuronal plasticity in the brain (Medina et al., 2010).

Clinical Implications of Exercise

From a clinical perspective, physical exercise can significantly reduce anxiety and depression while improving cognitive and academic skills (Fedewa & Ahn, 2011). In rehabilitation settings, it can enhance cognitive function, motor coordination, and interpersonal skills, and reduce emotional distress (Huang et al., 2017). More broadly, physical activity benefits executive functions, emotional regulation, memory, learning, mood, and social relationships (Schwarck, 2019). For instance, a study conducted with children supports the finding that higher levels of physical activity lead to improved executive functions performance, such as working memory, inhibitory control, and information-processing speed (Gapin & Etnier, 2010).

Overall, exercise interventions have the potential to significantly impact neurophysiology and consequently improve an individual's life. Future studies should focus on broader interventions that include physical activity for individuals

with NDD, as most existing research has primarily involved neurotypical individuals. Conducting longitudinal studies to observe long-term developments in various disorders is crucial. It has been observed that exercise interventions can reduce the risk of age-related cognitive decline (Erickson et al., 2019). Additionally, examining how different types of exercise affect brain physiology and cognition is essential. For instance, aerobic exercise is known to increase blood flow, metabolism, and the secretion of serotonin and dopamine (Chan et al., 2022). However, different physiological and cognitive outcomes might emerge if diverse exercise forms are analyzed.

A Holistic Approach to Exercise Interventions

A holistic approach that considers individual differences may influence how people adhere to exercise interventions and the effects they can produce. Embracing the heterogeneity found in studies may offer various pathways in clinical contexts. The outcomes of these studies can vary based on exercise frequency, intervention duration, and session length (Monteiro et al., 2022). The type of physical activity, individual adherence, and environment also play significant roles. This implies that exercise interventions are adaptable, not only in their application to individuals but also in the physiological and cognitive outcomes they can produce.

3.2 - Potential of exercise to reduce executive dysfunction

The Impact of Exercise Interventions on Executive Function in Individuals with Neurodevelopmental Disorders

Executive functions are crucial for managing everyday tasks, extending beyond sports and academic contexts to include ordinary activities like waiting for a traffic light to turn green or choosing and ordering food in a restaurant. These actions require executive function processes to be carried out effectively. Unfortunately, individuals with NDD and other conditions often experience impairments in executive functions, known as executive dysfunction, which can significantly hinder their daily lives. However, research indicates that exercise

interventions can alleviate executive dysfunction and promote executive functions development, particularly when introduced from a young age (Best, 2010).

Various types of executive dysfunction can benefit from exercise interventions. The learning experiences provided by these interventions contribute to cognitive development and subsequently strengthen executive functions (Adolph, 2008). For example, consider a person playing football: they must focus on the players' movements and the ball (attentional control), ignore irrelevant distractions like the crowd cheering (inhibitory control), plan the next strategic move to improve their position (organization and planning), and remember and execute team instructions (working memory). These sensorimotor engagements in physical activities are vital for enhancing EF (Christiansen et al., 2019).

Exercise and Executive Function Improvement

Physical activity has been shown to improve executive dysfunction in individuals with NDD. A recent study involving children and adolescents with ASD found that exercise interventions had a small to moderate positive effect on executive functions, particularly in cognitive flexibility and inhibitory control, compared to controls who did not receive the treatment (Liang et al., 2022). Other studies have linked chronic aerobic exercise to improvements in working memory and increased brain activation in young students (Pan, 2019).

A six-week study involving boys with ADHD demonstrated improvements in the participants' executive functions (Song et al., 2022). Another study comparing open-skills activities (e.g., football, tennis, basketball) with closed-skills activities (focused on aerobic exercises like running and swimming) found that open-skills physical activities are more promising for enhancing executive functions, especially inhibitory control systems, due to the dynamic interaction with the environment that these activities require (Zhu et al., 2023). Conversely, closed-skills activities were found to be more effective in improving working memory, making them potentially the best type of exercise intervention for treating ADHD symptoms (Zhu et al., 2023). However, multicomponent exercises, which incorporate both open and closed skills activities, were identified as particularly beneficial for developing cognitive processes (Zhu et al., 2023).

Executive Dysfunction in Children with NDD

Children with NDD are particularly prone to developing executive dysfunction (Demetriou et al., 2018). Recent findings indicate that individuals with lower cognitive abilities compared to the general population benefit the most from cognitive training. This suggests that exercise interventions have a more pronounced effect on individuals with NDD who have lower baseline cognitive performance compared to neurotypical individuals (Ludyga et al., 2021). Although some findings were reported in studies with small sample sizes, they highlight the potential of exercise as a promising clinical intervention for reducing executive dysfunction.

A study using electroencephalogram technology has provided significant evidence regarding the impact of aerobic exercises on the P300 component, a measure of event-related potentials. The P300 latency is associated with cognitive processing speed, while the P300 amplitude is related to attentional resources and working memory (Polich, 2007). The evidence suggests that aerobic exercise can alter P300 latency and amplitude in children and adolescents (Hillman et al., 2014). Additionally, a review supports that these alterations can be observed across different age groups (Kao et al., 2020), concluding that the relationship between motor skills and EF is mediated by the P300 amplitude (Ludyga et al., 2021). Physical activity elicits the P300 response, benefiting cognitive processes throughout the intervention.

Future Directions for Exercise Interventions

Exercise interventions have the potential to significantly alleviate executive dysfunction. Future studies should explore the different levels of executive functions and how various exercises influence them. Expanding research in this area and exploring new approaches to exercise interventions could provide valuable insights for the treatment of NDD and other conditions, paving the way for more effective clinical practices.

3.3 - Exercise Interventions as Developmental Tools for NDD

Exercise interventions are important developmental tools that can significantly benefit individuals with NDD. As previously mentioned, these interventions reduce executive dysfunction, improve cognitive processes, and optimize brain physiology. When applied to treat symptoms of NDD, they can lead to successful outcomes for those affected by these conditions.

For children with ADHD, closed-skill activities, such as aerobic exercises, have been shown to standardize behavior and reduce symptoms of impulsivity and aggression (Sun et al., 2022). In particular, swimming, a form of closed-skill activity, has been found to decrease hyperactivity, impulsivity, and aggression while also improving short-term memory, which is closely related to working memory function (Zhu et al., 2023). One possible explanation for these effects is that swimming helps regulate dopamine levels, which is particularly beneficial for individuals with ADHD (Ko et al., 2013). The dopamine deficiency often observed in individuals with ADHD can be mitigated by exercise interventions, as physical activity naturally boosts dopamine production, thereby alleviating symptoms (Zhu et al., 2023). In this way, physical activity acts similarly to stimulant medications by increasing neurotransmitter production (Zhu et al., 2023). The endogenous stimuli produced by exercise enhance the neurotransmitter system, promote brain-derived neurotrophic factor (BDNF) production, and stimulate neuron formation (Christiansen, 2019). As a result, these processes improve learning mechanisms and executive functions, which are frequently impaired in individuals with ADHD.

For individuals with ASD, exercise interventions can reduce stereotypic behaviors and enhance socio-emotional functioning (Bremer et al., 2016). Recent studies have examined various exercise interventions, including jogging, swimming, martial arts, yoga, and dance, and confirmed that these activities reduce stereotypical behaviors and improve socio-emotional functioning (Bremer et al., 2016). Among these interventions, jogging was found to have the most pronounced effect in reducing stereotypic behaviors, while yoga, dance, and swimming were more effective at enhancing socio-emotional functioning (Bremer et al., 2016). Martial arts and horseback riding demonstrated benefits in both areas. These findings suggest that different exercises have varying impacts on ASD symptoms, highlighting the importance of selecting appropriate activities for

targeted outcomes. However, the motor skill and socio-emotional challenges associated with ASD might hinder engagement with physical activities. Children with ASD often display sensory motor weaknesses, making it difficult to participate in motor activities (Liu, 2013). Nonetheless, a meta-analysis showed that physical activity can significantly improve motor skills in children with ASD (Monteiro et al., 2022), which are closely linked to executive function and sensory processes.

Comorbidities are common in many NDD, and exercise interventions have the potential to alleviate their symptoms. For instance, a study confirmed that physical activity is beneficial for children with ADHD comorbid with Tourette syndrome, aiding in the self-regulation of tics (Chan et al., 2022; Jackson et al., 2020). Given the prevalence of NDDs comorbid with tic syndromes, these findings suggest that exercise can improve comorbid conditions. Another analysis proposed that when exercise interventions are performed at a moderately high intensity, symptoms of ADHD and comorbid conditions decrease substantially (Ng QX, 2017).

It is crucial to emphasize that individuals with lower cognitive processing speeds, such as those with NDD, benefit the most from exercise interventions. Most of the evidence supporting this claim has been gathered from studies involving children and adolescents, who experience the most promising developmental outcomes regarding NDD symptoms during this period. Although different exercises may yield varied results, a multi-component physical exercise program could be the most effective intervention. Such programs require engagement in multiple cognitive processes simultaneously, leading to improved outcomes (Zhu et al., 2023).

Challenges and Future Directions

Individuals with NDD are heterogeneous, with varying levels of overall functioning (Bremer et al., 2016). The severity of symptoms can fluctuate along the neurodevelopmental continuum model, meaning that an individualized approach can provide a clearer understanding of where symptoms lie and how exercise interventions can be tailored to offer better clinical treatment. While the impact of these interventions is well-supported by evidence, clinical practice faces

challenges in implementing these approaches due to the variability of individual responses.

Discussion and conclusions

The neurodevelopmental continuum is a proposed model for NDD that reimagines these conditions as traits existing on a spectrum, rather than as distinct categories. By integrating this continuum with the existing DSM framework, clinical assessments could be enhanced. This model would account for factors such as subthreshold diagnosis, comorbidities, and early onset, which often complicate current assessments or are not included in many clinical approaches. Instead of categorizing disorders as separate entities, the continuum considers the severity of symptoms, making the clinical approach more inclusive and accessible to those who experience symptoms but do not fit the criteria for a traditional NDD diagnosis.

The inclusiveness of the proposed model aligns well with the diverse needs of individuals. Researchers Thapar et al. (2017) illustrate that obtaining an NDD diagnosis can be a long, costly, and time-consuming process. Individuals who do not meet the full criteria for a disorder may be considered neurotypical, even if they exhibit cognitive impairments. This results in overlooked impairments and wasted resources. Conceptualizing NDD as traits within a continuum can prevent this by allowing individuals to enter the spectrum and receive appropriate treatment based on the severity of their impairment and

The model places particular focus on ASD and ADHD due to their high prevalence worldwide. According to the World Health Organization (WHO), 1 in 100 children has ASD, and between 5-8% of children have ADHD. However, these statistics might underestimate the actual prevalence, as suggested by data presented in the second chapter. It is conceivable that many people live with impairments throughout their lives without ever receiving a formal diagnosis, falling below the threshold for diagnosis, or lacking the resources to seek treatment, thus being excluded from official statistics.

Further research is needed to connect the conceptualization of NDD as traits with individuals who may fall anywhere on the NDD spectrum, regardless of

the severity of their conditions. This could lead to enhanced interventions for all affected individuals.

Exercise interventions are among the most effective tools for improving NDD symptoms. They present fewer clinical limitations and can be applied to individuals across the entire spectrum. Both severely and mildly impaired patients can benefit from exercise interventions, which improve cognitive functioning, executive functions, and social communication and behaviors. In comparison to psychotropic drugs, physical activities offer a natural alternative for treatment. They induce physiological changes in the brain, stimulating neurotransmitter production that enhances cognition and overall brain function. Exercises target executive dysfunction, which is prevalent in individuals with NDD, and if incorporated into long-term clinical treatment, they can yield better outcomes, especially if initiated early in life when symptoms typically begin. Future research should focus on how different types of exercise impact various NDD conditions within the spectrum.

Exercise interventions can effectively treat executive dysfunction in individuals with ADHD. Evidence suggests that physical activity correlates with improved inhibitory control, which Barkley (1997) identifies as the primary dysfunction in ADHD. The newer, evolving ADHD model of multiple pathways may also benefit from exercise interventions that address different aspects influencing executive functions. The "hot and cool" pathways proposed by Zelazo and Muller (2004) indicate that exercise interventions should focus on the specific executive functions needs of individuals, as these pathways present different impairments among NDD individuals.

Exercise interventions for ASD individuals can be more challenging. While physical activity improves executive dysfunction, cognitive performance, and social skills in people with ASD, engaging in these interventions can be difficult due to a lack of interest in certain objects or group dynamics common in sports (Barros & Da Fonte, 2016). Initiating these interventions early in life could be the most effective approach for individuals with ASD, aiding not only cognitive development but also enhancing engagement and social skills that are often challenging for them to develop.

Exercise interventions often come with social support, which is crucial in the clinical context. Physical activity and sports can be conducted individually or in groups, both of which offer cognitive benefits. However, when performed consistently within a community context, these interventions can foster social support, which also plays a vital role in treating NDD comorbidities such as anxiety disorders, substance use disorders, and depression. Encouraging physical activity as a treatment within the NDD spectrum supports a comprehensive approach to managing these conditions.

The effectiveness of exercise interventions can vary depending on numerous factors. The type of exercise, such as open-skills versus closed-skills activities as proposed by Zhu et al. (2023), can lead to different cognitive outcomes regarding executive function. The environment, such as indoor home training versus school sports initiatives, can influence individual social skills, emotional regulation, and motivational engagement. Additionally, available resources, including infrastructure and funding, can affect and limit engagement in physical activities. Even if these interventions are feasible in a clinical context, existing variables may prevent them from being fully realized.

Existing evidence has led to new hypotheses for future studies. Understanding individuals holistically rather than merely labeling them with a disorder is a critical step toward improving future assessments and clinical interventions. Future research should explore the interplay between various exercise interventions and their effects on different severities of NDD. This knowledge will be essential for advancing clinical treatment and providing tailored interventions for individuals with neurodevelopmental disorders.

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