JACHYMEK, Anna, GMITRZUK, Julia, MALINKA, Zuzanna, WIŚNIEWSKA, Katarzyna, OPATOWSKA, Martyna, JAKUBIEC, Joanna, KUCHARSKI, Tomasz and PIOTROWSKA, Marta. Level of knowledge of Stereotypic Movement Disorders among paediatric population. An update on proper differential diagnosis and management including physical exercise approach - comprehensive literature review. Quality in Sport. 2024;16:52749. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.16.52749
https://apcz.umk.pl/QS/article/view/52749

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 18.06.2024. Revised: 20.06.2024. Accepted: 03.07.2024. Published: 10.07.2024.

Level of knowledge of Stereotypic Movement Disorders among paediatric population. An update on proper differential diagnosis and management including physical exercise approach - comprehensive literature review

Anna Jachymek, St. Vincent de Paul Hospital, ul. Wójta Radtkego 1, 81-348 Gdynia, Poland

https://orcid.org/0009-0003-4275-5778

jachymekania@gmail.com

Julita Gmitrzuk, Nikolay Pirogov Specialized District Hospital, ul. Wólczańska 191/195, 90-001 Łódź, Poland

https://orcid.org/0009-0001-6965-290X

julita.gmitrzuk@gmail.com

Zuzanna Malinka, St. Vincent de Paul Hospital, ul. Wójta Radtkego 1, 81-348 Gdynia, Poland

https://orcid.org/0009-0000-3354-0570

zuzanna.malinka72@gmail.com

Katarzyna Wiśniewska, Central Clinical Hospital of the Medical University of Lodz, ul. Pomorska 251, 92-213 Lodz, Poland
https://orcid.org/0009-0007-5844-5829
kat.wisniewska@onet.pl

Martyna Opatowska, Faculty of Medicine, Medical University of Lodz, al. Tadeusza Kościuszki 4, 90-419 Łódź, Poland

https://orcid.org/0009-0008-6088-2742

martyna.opatowska8@gmail.com

Joanna Jakubiec, Provincial Multispecialty Center of Oncology and Traumatology named after M. Kopernik in Lodz, ul. Pabianicka 62, 93-513 Lodz

https://orcid.org/0009-0006-3246-5410

joannajakubiec1212@gmail.com

Tomasz Kucharski, Nikolay Pirogov Specialized District Hospital, ul. Wólczańska 191/195, 90-001 Łódź, Poland

https://orcid.org/0009-0005-3456-5215

tomekkuch@gmail.com

Marta Piotrowska, Central Clinical Hospital of the Medical University of Lodz, ul. Pomorska 251, 92-213 Lodz, Poland

https://orcid.org/0000-0002-0680-9789

m.piotrowska97@gmail.com

Corresponding author:

Anna Jachymek, St. Vincent de Paul Hospital, ul. Wójta Radtkego 1, 81-348 Gdynia, Poland

https://orcid.org/0009-0003-4275-5778

jachymekania@gmail.com

Abstract

Stereotypies stand out as the most debated aspect within the spectrum of repetitive behaviors observed in childhood, which encompass mannerisms, habits, compulsions, tics, and other sudden movements. Stereotypies refer to a repetitive, persistent, often rhythmic pattern of non-purposeful motor actions that may disrupt social interaction, academic performance, or other daily activities, and can potentially lead to physical harm. Many young children exhibit stereotyped behaviors, such as thumb sucking. In older children and adults, repetitive behaviors like finger tapping or drumming, self-stimulatory actions (e.g., masturbation) or leg shaking, may occur in response to boredom. These behaviors differ from Stereotyped Movement Disorder because they do not significantly interfere with daily activities nor cause self-inflicted bodily injury severe enough to warrant independent clinical attention. Stereotyped movements are commonly categorized into two groups: primary and secondary, based on the presence of additional signs or symptoms. The former are perceived as physiological, as opposed to the latter, which are considered pathological. There is growing evidence supporting a neurobiological mechanism despite some perceiving stereotypic movements as behaviors aimed at modifying arousal states. Both behavioral and pharmacological treatments have been employed with mixed results, hence, there is a need for further research in this area, including physical exercise. Conclusively, a more profound comprehension of the underlying risk factors and biology of motor stereotypies will eventually bring us nearer to developing more effective targeted therapies, which will alleviate the suffering of children who are affected.

Aim of the study: This review aims to summarize the current perception/knowledge of motor stereotypies in paediatric population, with an emphasis on accurate differential diagnosis and the currently accepted and applied treatment methods, particularly focusing on the various underlying causes of stereotypies, their proper identification during the differential diagnosis stage, and a comprehensive review of current therapeutic options, including physical activity.

Material and methods:

In order to find the relevant literature, an electronic search of PubMed database was performed. Keywords used in the search included: stereotypic movement disorder in children, tics, hyperkinetic movement disorders, pediatric movement disorders, involuntary movement, stereotyped behaviors, physical exercise. For this publication, data were collected from 72 scientific articles. After reviewing the content of those articles, 21 publications were rejected and the data used in the publication originates from 51 articles. Additionally, the latest ICD-11

classification from the WHO website and resources from Cardiff University's website were utilized.

Conclusion: Currently, there are several effective, though not perfect, treatment options for SMD, including cognitive-behavioral therapy, pharmacological treatment, and physical activity. Nevertheless, motor stereotypies are prevalent yet inadequately understood phenomena that necessitate deeper scientific inquiry.

Keywords: stereotypic movement disorder in children, tics, hyperkinetic movement disorders, pediatric movement disorders, involuntary movement, stereotyped behaviors, physical exercise

Introduction

Stereotypies are characterized as repetitive, apparently purposeless motor behaviors, and seemingly compulsive (e.g., body rocking, hand flapping or waving, self-biting, hitting, or head banging), typically emerging during early development. According to current diagnostic criteria for stereotypic movement disorder, only individuals whose repetitive motor behaviors disrupt academic, social activities, or cause self-injury meet the requirements for this diagnosis. Accurate diagnosis is crucial for implementing psychoeducation and targeted treatment interventions, especially when stereotypies are severe enough to raise the level of patient and family distress. [10]

As up to 60% of neurologically typical children shows some stereotypic behaviors or movements Stereotypic Movement Disorders are categorized as primary when they occur in an otherwise typically developing children, or secondary if they accompany another neuropsychiatric disorder mentioned above. Unlike stereotypic movements co-occurring with other conditions, primary stereotypic movements do not require invasive diagnostics and treatment. [14]

Several practical criteria for distinguishing stereotypies from other conditions have been suggested and widely adopted, but misdiagnoses are still common, particularly in non-specialized settings. [2] The main challenge in addressing stereotypies in childhood stems from their occurrence across various conditions, including ASD, developmental disabilities, sensory impairments, and various genetic syndromes. It is crucial to have knowledge and understanding

of differential diagnosis, as it prevents unnecessary tests and the adoption of an inappropriate treatment approach.

Nonetheless there are still some uncertainties regarding the classification, terminology, and suitable thresholds for determining whether a pattern constitutes a disorder. Classification is complex due to the individual variations, diverse range of movement types, and natural progressions. While some patterns may diminish over time, others may persist, and multiple patterns may occur simultaneously. [8]

This review will focus on providing the most comprehensive presentation of the issue of stereotypies in the paediatric population, primarily concerning the mechanisms of their formation, proper diagnosis, and the most effective and up-to-date therapeutic interventions available.

Description and Classification

Stereotyped movement disorders are defined as repetitive, coordinated, stereotyped, voluntary, seemingly purposeless and often rhythmic movements which should last at least several months. More often then not they lack clear function. Onset occurs during the developmental period, typically under three years of age; up to 80% of children who demonstrate complex motor stereotypies begin to show these behaviors before the age of two.[4] The characteristic features include the unprovoked nature of the movement disorders and the possibility of immediately interrupting the performance of a specific stereotyped activity in response to a sensory stimulus (e.g., touching or calling the child) or by distracting attention. [2] In typically developing children, stereotypic movements tend to diminish or become suppressed over time. However, in individuals with Intellectual Development Disorder and Autism Spectrum Disorder accompanied by Intellectual Development Disorder, these stereotyped (and self-injurious) behaviors may persist, although their manifestation may change as time progresses. [12]

To be classified as SMD the patient should signalize significant interference with the ability to engage in normal daily activities or be assessed as self-inflicted bodily injury. According to ICD-11 SMD is classified as subsection of neurodevelopmental disorders with a qualifier to indicate the presence or absence of self-injury, similar to the classification of stereotypic movement disorder in DSM-5. [3] Movements with self-injury potential (6A06.0) to the affected individual typically include face slapping, eye poking,head banging and biting of the

lips, hands or other body parts. Those that are considered as non-injurious (6A06.1) consist of head or/and body rocking, hand flapping and flicking mannerisms. [4]

The precise determination of the impact of performed movements on the patient's functioning, both in terms of motor and social aspects, is possible thanks to the division of stereotypes into simple and complex. Simple motor stereotypes include activities such as bending fingers, leg bouncing, thumb sucking,tapping foot while listening to music, nail biting, teeth clenching and/or grinding, nail biting. Complex motor stereotypes, as the name suggests, have a more complex motor nature and involve movements like waving arms, twisting arms, shaking shoulders, waving fingers in front of the eyes, opening mouth, facial motor stereotypes and opening and closing hands. Both simple and complex motor stereotypes can be accompanied by breathing pattern disturbances.[6]

Due to the co-occurrence of other neurological or psychiatric symptoms, stereotypic movements are classified into primary and secondary stereotypies. Primary stereotypies are motor disturbances that occur in typically developing children, not impairing their daily functioning, often appearing periodically, though they typically cause significant concern for the child's caregivers.Singer in the group of primary stereotypies distinguishes three categories. Common stereotypic movements: thumb sucking, hair twirling, nail biting, finger or foot tapping, etc. They occur in approximately 22–72% of individuals. Head nodding – it may take the form of "yes-yes," "no-no," or from shoulder to shoulder. Complex stereotypic movements: opening and closing hands, head shaking, waving arms. The movements predominantly involve the hands and arms. [10]

Secondary stereotypies are those that occur in children with impaired psychomotor development and genetically conditioned communication disorders. Examples of these syndromes include Angelman syndrome, Rett syndrome,MECP2 duplication syndrome, Joubert syndrome, Cornelia de Lange syndrome and Fragile X syndrome. Secondary stereotypies also occur among patients with sensory deficits such as blindness and after the use of certain medications e.g. neuroleptics, amphetamines, cocaine. Additionally, secondary stereotypies have been reported in patients with brain tumors and neuroinfections. [9,8,10]

Aetiological concepts and pathophysiology

The literature has explored multidirectional the functional and etiological foundations of stereotypes movements. Even though the pathophysiology of motor stereotypies is not

completely understood, both psychological and biological (neurochemical, brain function and structure, genetic,) factors have been explored in the complex aetiology of these movements. In spite of the fact that psychological factors may contribute to some extent, there is significantly more evidence supporting a biological basis. This review will focuse on both biological and psychological predisposition as it will provide us with a broader perspective for later discussion and understanding of differential diagnosis and treatment methods.

PSYCHOLOGICAL APPROACHES

Psychological hypotheses suggest that stereotypies may substitute for imaginary activities, channel excess cognitive capabilities into movements,compensate for external sensory deficits, or manifest as part of obsessive-compulsive or anxiety-related behaviors. [10]

A widely discussed theory in the pathomechanism of stereotypic movements is the functional theory, which focuses on explaining this behavior as an attempt to modulate the level of arousal the child receives from the environment. This perspective suggests that stereotypies might be more prevalent in children with disabilities because they lack creative ways to enhance their engagement in understimulating environments. Additionally, these children might receive less stimulation due to their disabilities e.g. individuals with sensory deficit or environmentally neglected. One study examined surveys from 85 blind children and discovered that every child exhibited at least one stereotypic behavior per week as eye poking, body rocking, etc. The report also highlighted the circumstances in which children displayed the most stereotypic behaviors when delighted, tired, left alone, bored or excited. [19]

Other study in which 26 congenitally blind children were assessed through videotape recording and through a questionnaire demonstrated stereotypic characteristics in 73% of blind individuals and noted a higher occurrence in environments characterized by limited mobility, reduced sensory stimulation and restrictions. [20]

A functional explanation for stereotypies can also be extended to social deficits resulting from isolation. That randomized controlled trial examined the occurrence of stereotypies in children in foster care in Romania compared to those who remained in institutional care. The 136 children with a history of early institutional care were assessed. During the initial evaluation before being placed in foster care, over 60% of children in institutional care displayed stereotypies. Subsequent assessments at 30, 42 and 54 months showed that transitioning to

family placements significantly decreased the occurrence of stereotypies. Moreover, reductions in stereotypies were more pronounced with earlier and more extended placements. [21]

On the other hand, motor stereotypies may also be exhibited by children with autism and anxiety related behaviors as a means to reduce overwhelming internal or external environmental stimulation. [23] One study on nonhuman primates as a model for the human condition suggests that some children with autism spectrum disorders undergo overstimulation and display repetitive behaviors as a means to mitigate the heightened arousal caused by incoming sensory stimuli.[37]
Therefore, stereotypy functions as a type of self-stimulation that may compensate for a lack of external arousal or serve as an effort to minimize external disturbances by channeling actions into movement.

Another concept explaining the pathomechanism of stereotypies is the behavioral theory which is based on the principle of positive or negative reinforcement.[6,8] The individual learn to perform a response in order to avoid a negative situation (negative reinforcement) or to achieve a desired goal (positive reinforcement), therefore, this behavior is repeated to evoke a similar desirable reaction.

NEURAL CIRCUIT AND BRAIN STRUCTURE APPROACHE

Another basis for stereotypes movements is developmental, proposing that the movements reflect external manifestations of neurological maturation happening at various stages of development as well as malfunctioning of specific brain structures.

One longitudial observation of 20 normal infants during the first year of life allowed to indentifie 47 repetitive movement patterns that appeared at specific developmental stages. These behaviors demonstrated developmental regularities along with consistency in form and distribution. The emergence of specific groups of stereotypies was strongly linked to motor development. This study suggested that rhythmic stereotypies are expressions of incomplete cortical regulation of internal patterning in developing neuromuscular pathways. [24]

Another study conducted on deer mice models suggestes that providing a nurturing environment during early childhood development can reduce the development/quantity of

repetitive behaviors. They believe that early environmental enrichment could potentially have lasting neuroprotective effects.The correlation between the suitable environment and reduction of repetitive behaviors was associated with elevated levels of neurotrophin (BDNF) in brain regions involved in cortical-basal ganglia circuitry, greater density of dendritic spines, and higher metabolic activity in neurons. [38]

There is uncertainty regarding possible alterations in the volume of the basal ganglia, as some research indicates an increased volume, while others suggest no change or a decrease in volume. [50,51] Studies have demonstrated that the volume of cerebellar white matter has been linked to the severity of symptoms and the larger volumes of the caudate nucleus and putamen are associated with increased repetitiveness. [35]

It is believed that the cortical-striatal-thalamo-cortical brain circuit plays a role in the expression of motor stereotypies. These cognitive pathways have been associated for a long time with the initiation, continuation, and termination of movements, and has a link to the other psychiatric disorders like Tourette's disorder, ADHD, and OCD. [34]
A series of cases suggests that the cause of stereotypic behaviors may be a disruption in the cortico-striato-thalamo-cortical pathway or connections between the prefrontal cortex and subcortical nuclei. [10,11,25] One study suggested a potential malfunction in the cortico-striatal-thalamo-cortical circuitry in children exhibiting non-autistic, physiological motor stereotypies. The examination of 6 males with complex stereotypies and average intelligence using volumetric magnetic resonance imaging showed disproportional reduction in frontal white matter when compered to total cerebral white volume, and in the left and right caudate nuclei. [26]

While stereotypies can be altered, halted, or partially inhibited, an electrophysiological investigation differentiated them from voluntary movements by analyzing EEG recordings of movement-related cortical potentials in children with primary complex motor stereotypies. This research revealed the absence of MRCPs in the prefrontal cortex preceding stereotypies, contrasting with their presence prior to voluntary movements. This suggests that premotor areas are probably not involved in preparing these complex movements, indicating that stereotypies are initiated by mechanisms distinct from those of voluntary movements.[28]

NEUROCHEMICAL APPROACH

A recent proton magnetic resonance imaging studies evaluated the metabolism of glutamate, GABA and glutamine, N-acetylaspartate, and choline levels were measured in 4 frontostriatal regions of patients with Primary Complex Motor Stereotypies. The results showed decreased levels only of GABA in the anterior cingulate cortex (emotional regulation) and striatum (motivation,decision-making, reward processing, motor and action planning, and reinforcement,) but not the dorsolateral prefrontal cortex or the premotor cortex. Moreover, the decrease in the GABA/Cr index in the anterior cingulate cortex correlated with more severe clinical symptoms. These findings suggest potential GABAergic dysfunction within corticostriatal pathways in children with primary complex motor stereotypies.[7]

Dopamine is another neurotransmitter also associated with the occurrence of stereotypies. Excessive dopaminergic stimulation can lead to the onset of repetitive movements after the use of levodopa, amphetamine, or cocaine. The studies on rat models showed that elevated levels of extracellular dopamine in the dorsal striatum were linked to reduced levels of acetylcholine release. Improving cholinergic transmission to optimal levels using acetylcholinesterase inhibitors in the prefrontal striatal region resulted in the cessation of motor stereotypies. Additionally, the administration of Raclopride (a dopamine D2 antagonist), interrupted the stereotypical movements. It occurred only when injected into the prefrontal dorsal striatum. No effect observed when injected into the sensorimotor area of the dorsal striatum.That imbalance between dopamine and acetylocholine was associated with the severity of motor stereotypies. [27] The relationship between dopamine and acetylcholine outlines one of the possible treatment methods, which will be described in the final chapter of the thesis.

Some researchers who wanted to broaden the topic of basal ganglia circuit dysfunctions administered psychomotor stimulants and a direct dopamine receptor agonist to induce varying levels of stereotypy in rats. They observed increased ratio of activation in the striosome (the primary input provider to the basal ganglia) to the extrastriosomal matrix, known as the striomal predominance value, which is a strong indicator of the severity of stereotypies. [36]

GENETIC APPROACH

Last but not least factor considered as pathomechanism of motor stereotypies is the genetic theory. There haven't been any documented gene variants linked to an elevated risk of stereotypies, yet many scientists are conducting research in this field.

A study of 100 nonautistic children with stereotypic disorders presented that 17% of participants had a first-degree relative and 25% have a second-degree relative with motor stereotypy while 75% of cases seemed to be sporadic. [12] The discovery suggests that identifying both inherited and spontaneous mutations could be effective methods for uncovering genes, mirroring their success in previous ASD studies. [39] A recent review in area of motor stereotypies proposed a Mendelian pattern of inheritance for stereotypies, citing a positive family history in 25% of cases. [10] In a particular case, two siblings exhibited atypical movements before the age of one, which didn't meet the diagnostic criteria for tics but were characterized by purposeless involuntary actions, occasionally lasting for extended periods. Their father, who suffered from severe obsessive-compulsive disorder, recalled experiencing very similar movements during his childhood. This familial case provides additional support for a probable genetic origin of these movements. [8,30] Comprehensive genetic investigations have commenced concerning Rett syndrome, given that stereotypies are a prominent characteristic. Video data from study involving 144 females diagnosed with Rett syndrome, showed that 96.4% of individuals with a pathogenic mutation exhibited stereotypies. Moreover, among participants with a mutation in the MECP2 gene, 61.8% demonstrated a midline hand-wringing stereotypy. [29]

The observation that certain children exhibit a genetic predisposition to stereotypies implies the potential utility of employing a biopsychosocial framework. This approach acknowledges that multiple factors, including levels of environmental stimulation, can contribute to the likelihood of individuals displaying stereotypies. That leads to better understanding of underlying biology and potential treatment targets of Stereotyped Movement Disorder. [8,23]

Epidemiology

The prevalence of primary simple stereotypic movements is estimated at 20–70%, while complex primary stereotypic movements are observed in about 3–4% of typically developing children. Secondary stereotypic movements are observed in 61% of patients with intellectual disabilities , 88% of patients with autism and 100% of individuals with Rett syndrome. [6,9]

Stereotypes movement frequently manifest as a physiological and temporary occurrence, with up tp 60% of typically developing children displaying certain stereotypic movements or behaviors between the ages of 2 and 5 years. [14] The first stereotypic movements typically appear before the age of three, with a peak incidence around 12 months. [17]. One cohort study

found that 80% of children with stereotypies exhibited these movements before reaching 24 months old, while only 8% showed signs after 36 months of age.[12]

Stereotypies seem to persist throughout life. One study from 2008 found that only 6% of the 100 children surveyed experienced a resolution of their stereotypies. Children with arm or hand stereotypies, whose movements persisted for more than a year, were more likely to continue having stereotypies into adulthood compared to those with head-nodding stereotypies (38% cases resolving.).[12] In children with persistent stereotypies, the movements either remained the same, worsened or improved as they aged but most of them tend to be milder and easier to control. [18] In the largest longitudinal study of children and adolescents with primary complex motor stereotypies (49 participants aged 9-20 years), 98% of participants continued to exhibit stereotypies. Additionally, 18% reported the emergence of new stereotypic movements, and 45% experienced changes in their original stereotypic movements but approximately 80% noted that their movements were improved or more manageable as they got older. [17,18]

Assessment of children with stereotypies

The boundary between motor disorders and physiological motor activity is subtle and can present diagnostic challenges. Everyone periodically experiences involuntary movements that are rhythmic, regular, non-induced, and coordinated which can be easily interrupted, such as leg shaking, foot movement while listening to music, or finger tapping. Additionally, if a child exhibits only simple primary motor stereotypies, in-depth diagnostics may not be necessary. However, it is recommended to explain the nature of the child's symptoms to the parents and to conduct periodic check-ups by family general practitioner. For patients with complex primary stereotypies, invasive neurological diagnostics are not required; instead, regular monitoring in a neurology clinic is recommended, and a psychological consultation can be considered to assess cognitive functions. If secondary stereotypies are suspected, neuroimaging, electroencephalographic, psychological assessment, metabolic and genetic diagnostics, and continuous neurological care are recommended. Expanding diagnostics in both simple and complex primary stereotypies is advisable if additional symptoms appear or if there is an exacerbation of previously observed symptoms.

A key tool in diagnosing motor stereotypies is the video documentation of the child's daily behaviors recorded by caregivers or parents, as well as the observation of the child during examination in the office or during a hospitalization. To establish a further diagnostic plan, it

is recommended to assess the child's development, obtain a history of co-morbid conditions, conduct a neurological examination and determine the family history.

To assess the functioning of patients with stereotypic movement disorder, three questionnaire scales completed by caregivers are used. [6]

1. The Repetitive Behaviour Questionnaire-3 (RBQ-3) is a new and improved version of the RBQ-2 to assess for stereotyped behavior, compulsive behavior, sameness behavior, restricted behavior, self-injurious behavior, and ritualistic behavior. Updates include the ability to assess repetitive behaviors across the lifespan which is important especially in longitudinal studies and the introduction of both self-report and other-report versions that can be used together when cross-informant comparison is relevant. The development of the RBQ-3 has been led by researchers at Cardiff University, supported by collaborators at Newcastle University, UK, Aston University, UK, and Stanford University, USA. [31,33]

2. Behavior Problems Inventory/BPI with three subscales for stereotyped behavior, destructive/aggressive behavior and self-injurious behavior. It is an informant-based behavior rating tool designed to assess maladaptive behaviors in individuals with intellectual and developmental disabilities, including autism spectrum disorder. [32]

3. Motor Stereotypy Severity Scale/SSS consisting of three components: a Linear Analog Scale, SS Impairment to characterize global impairment, an SSS Motor (number, frequency, intensity, interference). [33]

Differentiating from other conditions

The term stereotypic disorder is used to describe isolated motor activities, benign and developmental, observed in normally developing children, as well as to describe movement disorders among patients with autism spectrum disorders, blindness, intellectual disabilities, blindness and many genetic and metabolic syndroms like Williams syndrome, Rett syndrome, Down syndrome, fragile X syndrome, Phenylketonuria, and adenylosuccinate lyase deficiency. But there are many other types of movement disorders that may occur in the above or other conditions, such as motor mannerism, tics, compulsions, habits, paroxysmal dyskinesias. [2,8]

MOTOR MANNERISM - a repetitive, characteristic behavior exhibited by an individual, which does not necessarily interfere with daily life or cause self-injury

TIC - a non-rhythmic, quick, sudden, repetitive motor movement or vocal sound, frequently linked to a premonitory urge and a sense of relief after performing the tic. Typically suppressible and suggestible, and they tend to fluctuate in intensity, with their type and location often changing.

COMPULSION - an uncontrollable and compelling urge to carry out a specific act or ritual

HABIT- a regularly repeated routine or behavior that may not have the distinctiveness of mannerisms. It does not need to interfere with daily life or cause self-injury, nor does it need to originate from motor actions

PAROXYSMAL DYSKINESIAS - a group of movement disorders marked by episodes of hyperkinesia while maintaining full consciousness

In typically developing children, it is essential to rule out those non-stereotypic movements as significant differential diagnoses before confirming a primary stereotypy. A thorough list of differential diagnoses to consider includes: dystonias, psychogenic movement disorders, chorea, focal seizures, restless leg syndrome, hyperekplexia, myoclonic jerks, drug-induced movements, and Sleep-Related Rhythmic Movement Disorder, *Tourette Syndrome and other Tic Disorders, Trichotillomania and Excoriation Disorder, and anxiety and compulsions in OCD. [4,8,1]*

BOUNDRY WITH SIZURES

Key distinguishing features of stereotypes include specific situational triggers for movements, such as moments of boredom or excitement. In contrast, seizures are not usually provoked by changes in cognitive tasks, emotions, or attention. Additionally, stereotypes often occur multiple times a day, while most seizures are less frequent and occur in distinct episodes with relatively clear start and end points. Another important distinguishing factor is the ability to redirect the child or interrupt the movements in stereotypes, as seizures generally can not be interrupted or controlled. It is crucial to distinguish SMD from seizures to prevent unnecessary use of antiepileptic medications. [4,8]

BOUNDRY WITH TOURETTE SYNDROME AND OTHER TIC DISORDERS

Stereotyped Movement Disorder is distinguished from tics and Tourette Syndrome by its onset at a younger age, the potential for the movements to be perceived as pleasurable, absence of a premonitory sensory urge, longer duration compared to typical tics and tendency to constant pattern throughout lifetime. Gilbert has provided a general guide for differentiating stereotypes from tics. [40]. Tics typically appear in children aged three or older, whereas stereotypes tend to start before the age of

three. Both tics and stereotypies can be temporarily suppressed, but while tics are generally internally suppressed, stereotypies are typically externally suppressed by teacher or parent. Tics often affect discreet muscle groups in a distinct repetitive pattern, whereas stereotypies can vary more in their movements from one instance to another. [4,6] However, the available evidence suggests that tics and stereotypies frequently co-occur. One review noticed that up to 25% of patients diagnosed with stereotypic movement disorder also exhibit tics, and up to 8% of patients with Tourette syndrome display both tics and stereotypies. The co-occurrence of tics and stereotypies in the same patient has practical implications due to the differing treatment approaches required. A better understanding of stereotypies in patients with tic disorders can help prevent misdiagnosing these symptoms as refractory tics and avoid inappropriate treatment interventions. It is important to consider that treatment-resistant repetitive movements may actually be persistent stereotypies. [5]

BOUNDRY WITH COMPULSIONS

Unlike stereotypes, compulsions are frequently aimed at alleviating distress and anxiety and are carried out within the framework of rigid rules and intrusive thoughts.[4,8]

BOUNDRY WITH AUTISM SPECTRUM DISORDER

ASD is distinguished from Stereotyped Movement Disorder by the presence of notable impairments in reciprocal social interactions and communication. Both diagnoses may be appropriate if the stereotyped movements become a distinct area of concern, such as when they lead to self-injury. [35,4]

BOUNDRY WITH BODY-FOCUSED REPETITIVE BEHAVIORS DISORDER

Body-Focused Repetitive Behavior Disorders, such as Excoriation Disorder and Trichotillomania involve repetitive behaviors directed at the body's integument. Conversely, in SMD, such behaviors rarely involve skin-picking or hair-pulling. However, if they do occur, they typically consist of coordinated, patterned movements utilizing specific muscle groups in a particular sequence. Additionally the onset typically occurs in later childhood or early adolescence comparing to SMD which is usually under 3 years of age. [4]

BOUNDRY WITH DISEASES OF THE NERVOUS SYSTEM

If stereotyped movements are linked to specific nervous system disorder or neurodevelopmental condition, SMD should not be diagnosed unless the movements become a distinct area of clinical concern. In such instances, both diagnoses might be assigned. [4]

While treating the movement pattern itself may not be necessary, accurate diagnosis and differentiation from other disorders are crucial to provide valuable information to parents and teachers about this poorly understood condition. By adhering to above criteria, diagnosing a stereotypy relies on excluding other potential causes. When uncertainty arises, it is advisable to refer the individual to a specialized center for further evaluation. [2] Before starting pharmacological or therapeutic treatment of stereotypes, it is crucial to begin with management of any coexisting conditions mentioned above as they may interfere with the actual level of movement disorders.

Management strategies

The main pathway for treating stereotypies involves various forms of therapy aimed at changing habits. So far, no satisfactory randomized clinical trials have been conducted to invent or test a medication for Stereotypic Movement Disorder in normally developing children. Stereotypes that appear alone generally do not require pharmacological treatment because the potential benefits do not outweigh the risks. However, when stereotypes are highly limiting, involve self-injury, or accompanied by other conditions, using a pharmacological approach may be appropriate.

Currently, effective pharmacological treatments for repetitive behaviors in children with autism spectrum disorder and other neurodevelopmental disorders do not exist. This is partly because there is insufficient knowledge about the specific neural circuits involved in the development and manifestation of these repetitive behaviors.

The experimental research of co-administration of adenosine receptor agonists in C58 mice identified new potential therapeutic targets for the development of drug treatments for repetitive. They used combination of adenosine A1 and A2A receptor agonists (since neither alone decreased repetitive behavior) which modify the firing rate of dorsal striatal neurons in the indirect pathway of the basal ganglia. The combination of these drugs significantly and specifically decreased repetitive behavior in both female and male mice over a six hours period, and continued to be effective in reducing such behavior over the course of seven days. [16]

A variety of psychotropic medications have been used to treat motor stereotypies and self-injurious behaviors in ASD. However, their effectiveness is often inconsistent and insufficient, and their use is restricted due to the risk of long-term adverse side effects. Furthermore there is still no established drug-based treatment.

In an extensive review on pharmacological approach in managing behavioral symptoms linked with autism spectrum disorders throughout lifetime researchers described various antipsychotics used in attempts to reduce motor stereotypies in children with ASD. Overall, risperidone, olanzapine, haloperidol, fluvoxamine, fluoxetine, venlafaxine, citalopram, clomipramine, and sertraline have demonstrated some effectiveness in reducing stereotypic movements and behaviors, although the majority of these medications were restricted due to undesirable side effects at times. [41]

As a contrast one longitudial study involving 100 normally developing children with complex motor stereotypies found that neither the children nor their caregivers observed any decrease in the intensity, duration, or frequency of the stereotypic movements in spite of treatment with a range of medications as : pimozide, levetiracetam, carbamazepine, risperidone, acetazolamide topiramate, divalproex, clonidine, clonazepam, oxcarbazepine, phenytoin, and fluoxetine. [12]

There are some researches indicating that cognitive behavioral therapy (CBT), particularly methods like differential reinforcement and habit reversal, can be effective for treating primary complex motor stereotypies in children.

One longitudial studies followed the group of 12 non-autistic children (6–14 years of age) with primary stereotypies. To evaluate the impact and effectiveness of habit reversal and differential reinforcement therapy on stereotypies, various scales were used for measurement such as Stereotypy Linear Analog Scale, Stereotypy Severity Scale motor portion and Child Global Assessment Scale and Stereotypy Severity Scale global portion. After 12,1 months follow-up motor stereotypies demonstrated notable improvement as it resulted in both scales; $p = 0.009$ for Stereotypy Linear Analog Scale and $p = 0.046$ for Stereotypy Severity Scale. Therapy also led to improvements on the Child Global Assessment Scale. However, unlike the two aforementioned scales, no positive correlation was observed between the improvement in stereotypies and the frequency of therapy sessions or the patient's motivation. Unfortunately, as the researchers point out in this study, very young age and intellectual disability, which is often

accompanied by the most severe and frequent stereotypies, are factors that exclude the possibility of therapeutic treatment. [42]

Another study conducted on 4-year-old autistic male with communication delay and vocal stereotypies demonstrated that response interruption and redirection significantly reduced the frequency of stereotypies compared to baseline levels. Each occurrence of vocal stereotypy was interrupted by taking away the item the child was engaged with, followed by presenting the child with a vocal task, which required repeating a mastered sound three times without exhibiting stereotypy.[43]

Johns Hopkins University recently pioneered the development of a parent-guided DVD home-based intervention designed to target the suppression of complex motor stereotypies through the application of behavioral therapy methods. In this research, group of 54 children were prompted to deliberately engage in stereotypic movements to enhance awareness and mindfulness while carrying out these actions. Additionally, parents underwent training to verbally praise their children when stereotypic behaviors were absent. Reductions in all motor stereotypy screening scales such as SSS Motor, SSS Impairment, and SLAS were observed (all $p<0.001$).[44]

Treatment strategies employed to diminish hand-related stereotypies in individuals with severe-to-profound intellectual disabilities and multiple difficulties were collected in a comprehensive review of 41 studies conducted between 1995 and 2007. The interventions were categorized into five groups: diverse contingency adjustments; response blocking; non-contingent stimulation (enhanced environment); programs centered on microswitch clusters, and mechanical restraints either independently or in conjunction with other intervention factors. While mechanical restraints were found to be effective, they can cause significant distress for the individual and may present emotional challenges for caregivers. In contrast, non-contingent stimulation was perceived as less aversive by the individuals involved and was easier to implement. Overall, he results of the studies generally showed positive outcomes, although occasional failures were also noted. [45]

ISCP IMPLEMENTATION

There is a promising treatment method that required further research cause only 11 studies among individuals with autism were published so far. Inhibitory stimulus control procedures

are a type of behavioral intervention that relies on antecedents. It involves teaching an individual through discrimination training to recognize situations where engaging in a specific behavior is appropriate or not, based on the presence or absence of particular and noticeable external stimuli. Labeling ISCPs as a developing treatment for stereotypy in individuals with autism suggests that while early research has shown beneficial outcomes from this approach, additional methodically robust research is necessary before deeming this intervention as established or evidence-based practice. [22]

RELATIONSHIP BETWEEN PHYSICAL EXERCICES AND STEREOTYPIC BEHAVIOR IN CHLDREN

Over recent decades, the WHO has acknowledged the significant impact of exercise and physical activity on health and well-being, extending this recognition to individuals with stereotypic disorders. Substantial evidence suggests that physical exercise can effectively reduce stereotypical behaviors in children with autism spectrum disorder.

Recent non-randomized crossover study on a group of 21 children with ASD endorsed physical exercise as a possible treatment for stereotypic behaviors. The participants, who exhibited noticeable hand-flapping and body-rocking stereotypic behaviors, experienced three different conditions over separate days: a control condition (seated position while story time activity), a 10-minute ball-tapping exercise condition, and a 10-minute jogging condition, each in a randomized sequence. The results demonstrated that each physical exercise was effective in reducing stereotypical behaviors when tailored to match the specific behavior. In particular, the jogging exercise successfully decreased body-rocking behaviors, while the ball-tapping exercise effectively reduced hand-flapping behaviors ($P < 0.017$). Moreover, they noticed that only a 10-minute matched-exercise session at low to moderate intensity could significantly reduce stereotypical behaviors for about 45 minutes which makes this method practically applicable for caregivers or teachers during breaks from learning or at other convenient times. [46]

One Small-n Meta-Analyses investigated 10 studies examing the impact of physical exercise on stereotypic behaviors in individuals with autism. The findings of the current study suggests that physical exercise can reduce stereotypic behaviors across various functions of these behaviors. Analysis of the mentioned papers determined three hypotheses to explain how

physical exercise reduces stereotypic behaviors in autism: the fatigue hypothesis, the neurotransmitter hypothesis, and the matching hypothesis. [49]

NEUROTRANSMITTER AND FATIGUE HYPOTHESIS

According to the neurotransmitter hypothesis, the impact of physical exercise on stereotypical behaviors may be attributed to its influence on neurotransmitter activity. Neurobiological investigations into the potential origins of stereotypical behaviors in individuals with autism encompass abnormalities within neurotransmitter systems, particularly those involving dopamine, GABA, and serotonin particularly within the basal ganglia. A comprehensive review of research synthesizing the benefits of moderate exercise on the biological mechanisms of brain health found that exercise boosts levels of norepinephrine, serotonin, and GABA. [47]

Researchers propose that stereotypic behaviors diminish because the body becomes too fatigued after exercise. They noted that both central and physical fatigue might be linked to the dopaminergic system. To support this hypothesis, researchers assume that a disturbance in dopamine transmission could lead to fatigue, as it might decrease the activation of the basal ganglia, thereby reducing stimulation of skeletal muscles and causing fatigue.[48]. To sum up, the aforementioned meta-analyses suggest that brief sessions of aerobic exercise transiently decrease stereotypic behaviors by affecting neurotransmitters that induce fatigue. [49]

MATCHING HYPOTHESIS

Researchers started employing the notion of "matched" stimuli to externally regulate behaviors presumed to be sustained by automatic reinforcement. The aim of identifying "matched" stimuli is to pinpoint an object or activity that elicits similar automatic internal reinforcing reactions. Unfortunately according to the matching hypothesis, the present study does not offer evidence supporting the efficacy of physically nor topographical matched exercises. [49]

Empirical evidence demonstrates the benefits of both therapist-led and home-based behavioral therapy programs for primary complex motor stereotypies, making these approach the preferred treatment options. Also physical exercise is seen as potential treatment for stereotypic behaviors in children with ASD since it is an intervention that is inexpensive and simple to administer. The examination of pharmacotherapies for stereotypies in children with developmental delay has yielded inconsistent results, leading to a lack of agreement on the most effective treatment

approach for these children, who often cannot undergo behavioral therapies. To summarize, pharmacological treatment seems to be less effective than behavioral approaches. However, challenges in implementing behavioral strategies on a daily basis, especially in settings like school, as well as intellectual disability and too young age may justify the addition of medication. [22]

Conclusion

Motor stereotypies are more prevalent than previously believed and represent a frequently chronic and enduring movement disorder. Those behaviors have tendency to manifest during early childhood and can be debilitating. While they can appear in children with typical development, they have predominantly been researched in children with Autism Spectrum Disorder and Intellectual Disability. The factors contributing to the presence of motor stereotypies, and consequently their underlying causes, are still not completely understood. However, many researchers speculate that a neurobiological or genetic component is a probable etiological factor for the manifestation of stereotyped behaviors. While existing pharmacological therapies have shown limited effectiveness, cognitive-behavioral therapies like differential reinforcement and habit reversal as well as physical activity have demonstrated satisfactory outcomes in treating stereotypies. Numerous aspects of stereotypies have been discussed in the literature, including the ongoing debate regarding the clinical definition and its efficacy as a categorical tool, which remains uncertain. [15] After analyzing the existing knowledge about stereotypic movements, especially concerning the mechanisms of their emergence, differential diagnosis, as well as the most convenient and effective treatment methods, it is intended to guide deeper and more thorough approaches by researchers, scientists, and clinicians in future endeavors in this matter. Motor stereotypies will remain regarded as a spectrum of neurodevelopmental movement disorders, necessitating additional phenotypic and neurobiological investigation.

Abbreviations:

ASD – autism spectrum disorder

SMD – stereotyped movement disorder

GABA - gamma-*aminobutyric acid*

ISCP - inhibitory stimulus control procedures

SLAS - Stereotypy Linear Analog Scale

SSS – Stereotypy Severity Scale
MRCPs - movement-related cortical potentials
OCD – obsessive-compulsive disorder
ADHD - attention deficit hyperactivity disorder
SD - stereotypic disorder
CBT - cognitive behavioral therapy

Author's contribution

Conceptualization, Anna Jachymek; methodology, Anna Jachymek and Marta Piotrowska; software, Tomasz Kucharski and Anna Jachymek; check, Katarzyna Wiśniewska and Marta Piotrowska; formal analysis, Anna Jachymek and Zuzanna Malinka; investigation, Anna Jachymek and Joanna Jakubiec; resources, Martyna Opatowska and Julita Gmitrzuk; data curation, Anna Jachymek, Katarzyna Wiśniewska; writing – rough preparation, Anna Jachymek; writing - review and editing, Anna Jachymek and Marta Piotrowska; visualization, Anna Jachymek, Zuzanna Malinka and Julita Gmitrzuk; supervision, Tomasz Kucharski and Martyna Opatowska; project administration, Joanna Jakubiec, Tomasz Kucharski. All authors have read and agreed with the published version of the manuscript.

Funding Statement

Study did not receive special funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Acknowledgments

Not applicable.

Conflict of Interest Statement

The authors of the paper report no conflicts of interest.

References

1. Pearson TS, Pons R. Movement Disorders in Children. Continuum (Minneap Minn). 2019 Aug;25(4):1099-1120. doi: 10.1212/CON.0000000000000756. PMID: 31356295.
2. Freeman RD, Soltanifar A, Baer S. Stereotypic movement disorder: easily missed. Dev Med Child Neurol. 2010 Aug;52(8):733-8. doi: 10.1111/j.1469-8749.2010.03627.x. Epub 2010 Feb 24. PMID: 20187883.
3. Stein DJ, Woods DW. Stereotyped movement disorder in ICD-11. Braz J Psychiatry. 2014;36 Suppl 1:65-8. doi: 10.1590/1516-4446-2014-3606. PMID: 25388614.
4. ICD-11 for Mortality and Morbidity Statistics; description of Stereotyped movement disorder Code: 6A06, available at: https://icd.who.int/browse/2024-01/mms/en#1111628448
5. Cavanna AE, Purpura G, Riva A, Nacinovich R. Co-morbid tics and stereotypies: a systematic literature review. Neurol Sci. 2024 Feb;45(2):477-483. doi: 10.1007/s10072-023-07095-y. Epub 2023 Sep 29. PMID: 37775616; PMCID: PMC10791822.
6. Katherine Mackenzie, Stereotypic Movement Disorders, Seminars in Pediatric Neurology,doi:10.1016/j.spen.2017.12.004
7. Harris AD, Singer HS, Horska A, Kline T, Ryan M, Edden RA, Mahone EM. GABA and Glutamate in Children with Primary Complex Motor Stereotypies: An 1H-MRS Study at 7T. AJNR Am J Neuroradiol. 2016 Mar;37(3):552-7. doi: 10.3174/ajnr.A4547. Epub 2015 Nov 5. PMID: 26542237; PMCID: PMC4792666.
8. Barry S, Baird G, Lascelles K, Bunton P, Hedderly T. Neurodevelopmental movement disorders - an update on childhood motor stereotypies. Dev Med Child Neurol. 2011 Nov;53(11):979-85. doi: 10.1111/j.1469-8749.2011.04058.x. Epub 2011 Jul 12. PMID: 21749367.
9. Stallworth JL, Dy ME, Buchanan CB, Chen CF, Scott AE, Glaze DG, Lane JB, Lieberman DN, Oberman LM, Skinner SA, Tierney AE, Cutter GR, Percy AK, Neul JL, Kaufmann WE. Hand stereotypies: Lessons from the Rett Syndrome Natural History Study. Neurology. 2019 May 28;92(22):e2594-e2603. doi: 10.1212/WNL.0000000000007560. Epub 2019 May 3. PMID: 31053667; PMCID: PMC6556084.

10. Muthugovindan D, Singer H. Motor stereotypy disorders. Curr Opin Neurol. 2009 Apr;22(2):131-6. doi: 10.1097/WCO.0b013e328326f6c8. PMID: 19532036.

11. Singer HS. Motor control, habits, complex motor stereotypies, and Tourette syndrome. Ann N Y Acad Sci. 2013 Nov;1304:22-31. doi: 10.1111/nyas.12281. Epub 2013 Oct 31. PMID: 24175737.

12. Harris KM, Mahone EM, Singer HS. Nonautistic motor stereotypies: clinical features and longitudinal follow-up. Pediatr Neurol. 2008 Apr;38(4):267-72. doi: 10.1016/j.pediatrneurol.2007.12.008. PMID: 18358406.

13. Zhang D, Poustka L, Marschik PB, Einspieler C. The onset of hand stereotypies in fragile X syndrome. Dev Med Child Neurol. 2018 Oct;60(10):1060-1061. doi: 10.1111/dmcn.13924. PMID: 30187465.

14. Evans DW, Gray FL, Leckman JF. The rituals, fears and phobias of young children: insights from development, psychopathology and neurobiology. Child Psychiatry Hum Dev. 1999 Summer;29(4):261-76. doi: 10.1023/a:1021392931450. PMID: 10422351.

15. Edwards MJ, Lang AE, Bhatia KP. Stereotypies: a critical appraisal and suggestion of a clinically useful definition. Mov Disord. 2012 Feb;27(2):179-85. doi: 10.1002/mds.23994. Epub 2011 Dec 9. PMID: 22161914.

16. Lewis MH, Rajpal H, Muehlmann AM. Reduction of repetitive behavior by co-administration of adenosine receptor agonists in C58 mice. Pharmacol Biochem Behav. 2019 Jun;181:110-116. doi: 10.1016/j.pbb.2019.04.006. Epub 2019 May 2. PMID: 31054946; PMCID: PMC6629027.

17. Oakley C, Mahone EM, Morris-Berry C, Kline T, Singer HS. Primary complex motor stereotypies in older children and adolescents: clinical features and longitudinal follow-up. Pediatr Neurol. 2015 Apr;52(4):398-403.e1. doi: 10.1016/j.pediatrneurol.2014.11.002. Epub 2014 Dec 19. PMID: 25661287.

18. Shukla T, Pandey S. Stereotypies in adults: a systematic review. Neurol Neurochir Pol. 2020;54(4):294-304. doi: 10.5603/PJNNS.a2020.0058. Epub 2020 Jul 24. PMID: 32706097.

19. Tröster H, Brambring M, Beelmann A. Prevalence and situational causes of stereotyped behaviors in blind infants and preschoolers. J Abnorm Child Psychol. 1991 Oct;19(5):569-90. doi: 10.1007/BF00925821. PMID: 1770186.

20. Fazzi E, Lanners J, Danova S, Ferrarri-Ginevra O, Gheza C, Luparia A, Balottin U, Lanzi G. Stereotyped behaviours in blind children. Brain Dev. 1999 Dec;21(8):522-8. doi: 10.1016/s0387-7604(99)00059-5. PMID: 10598052.

21. Bos KJ, Zeanah CH Jr, Smyke AT, Fox NA, Nelson CA 3rd. Stereotypies in children with a history of early institutional care. Arch Pediatr Adolesc Med. 2010 May;164(5):406-11. doi: 10.1001/archpediatrics.2010.47. PMID: 20439790; PMCID: PMC4086785.

22. Lydon S, Moran L, Healy O, Mulhern T, Enright Young K. A systematic review and evaluation of inhibitory stimulus control procedures as a treatment for stereotyped behavior among individuals with autism. Dev Neurorehabil. 2017 Nov;20(8):491-501. doi: 10.1080/17518423.2016.1265604. Epub 2016 Dec 23. PMID: 28010153.

23. Comparan-Meza M, Vargas de la Cruz I, Jauregui-Huerta F, Gonzalez-Castañeda RE, Gonzalez-Perez O, Galvez-Contreras AY. Biopsychological correlates of repetitive and restricted behaviors in autism spectrum disorders. Brain Behav. 2021 Oct;11(10):e2341. doi: 10.1002/brb3.2341. Epub 2021 Sep 2. PMID: 34472728; PMCID: PMC8553330.

24. Thelen E. Rhythmical stereotypies in normal human infants. Anim Behav. 1979 Aug;27(Pt 3):699-715. doi: 10.1016/0003-3472(79)90006-x. PMID: 556122.

25. Unal CT, Beverley JA, Willuhn I, Steiner H. Long-lasting dysregulation of gene expression in corticostriatal circuits after repeated cocaine treatment in adult rats: effects on zif 268 and homer 1a. Eur J Neurosci. 2009 Apr;29(8):1615-26. doi: 10.1111/j.1460-9568.2009.06691.x. PMID: 19419424; PMCID: PMC2679995.

26. Kates WR, Lanham DC, Singer HS. Frontal white matter reductions in healthy males with complex stereotypies. Pediatr Neurol. 2005 Feb;32(2):109-12. doi: 10.1016/j.pediatrneurol.2004.09.005. PMID: 15664770.

27. Aliane V, Pérez S, Bohren Y, Deniau JM, Kemel ML. Key role of striatal cholinergic interneurons in processes leading to arrest of motor stereotypies. Brain. 2011 Jan;134(Pt 1):110-8. doi: 10.1093/brain/awq285. Epub 2010 Nov 19. PMID: 21097493.

28. Houdayer E, Walthall J, Belluscio BA, Vorbach S, Singer HS, Hallett M. Absent movement-related cortical potentials in children with primary motor stereotypies. Mov Disord. 2014 Aug;29(9):1134-40. doi: 10.1002/mds.25753. Epub 2013 Nov 20. PMID: 24259275; PMCID: PMC4028443.

29. Carter P, Downs J, Bebbington A, Williams S, Jacoby P, Kaufmann WE, Leonard H. Stereotypical hand movements in 144 subjects with Rett syndrome from the population-based Australian database. Mov Disord. 2010 Feb 15;25(3):282-8. doi: 10.1002/mds.22851. PMID: 19908321.

30. Barry S, Baird G, Bunton P, Lascelles K, Hedderly H. Stereotypies of Childhood – Do they have a Genetic Link to OCD? Movement Disorder Society, 15th International Con- gress of Parkinson's Disease and Movement Disorders. Tor- onto, Canada, 2011.

31. Rojahn J, Matson JL, Lott D, Esbensen AJ, Smalls Y. The Behavior Problems Inventory: an instrument for the assessment of self-injury, stereotyped behavior, and aggression/destruction in individuals with developmental disabilities. J Autism Dev Disord. 2001 Dec;31(6):577-88. doi: 10.1023/a:1013299028321. PMID: 11814269.

32. Cardiff University: Measuring repetitive behaviours across the lifespan, available here https://www.cardiff.ac.uk/psychology/research/impact/measuring-repetitive-behaviours-across-the-lifespan

33. Mahone EM, Ryan M, Ferenc L, Morris-Berry C, Singer HS. Neuropsychological function in children with primary complex motor stereotypies. Dev Med Child Neurol. 2014 Oct;56(10):1001-8. doi: 10.1111/dmcn.12480. Epub 2014 May 10. PMID: 24814517; PMCID: PMC4162830.

34. Gao, S., and Singer, H. S. (2013). Complex motor stereotypies: an evolving neurobiological concept. *Future Neurol.* 8, 273–285. doi: 10.2217/fnl.13.4

35. Ghanizadeh A. Clinical approach to motor stereotypies in autistic children. Iran J Pediatr. 2010 Jun;20(2):149-59. PMID: 23056697; PMCID: PMC3446025.

36. Canales JJ, Graybiel AM. A measure of striatal function predicts motor stereotypy. Nat Neurosci. 2000 Apr;3(4):377-83. doi: 10.1038/73949. PMID: 10725928.

37. Lutz CK. Stereotypic behavior in nonhuman primates as a model for the human condition. ILAR J. 2014;55(2):284-96. doi: 10.1093/ilar/ilu016. PMID: 25225307; PMCID: PMC4240438.

38. Lewis MH. Environmental complexity and central nervous system development and function. Ment Retard Dev Disabil Res Rev. 2004;10(2):91-5. doi: 10.1002/mrdd.20017. PMID: 15362162.

39. Sanders SJ, He X, Willsey AJ, Ercan-Sencicek AG, Samocha KE, Cicek AE, Murtha MT, Bal VH, Bishop SL, Dong S, Goldberg AP, Jinlu C, Keaney JF 3rd, Klei L, Mandell JD, Moreno-De-Luca D, Poultney CS, Robinson EB, Smith L, Solli-Nowlan T, Su MY, Teran NA, Walker MF, Werling DM, Beaudet AL, Cantor RM, Fombonne E, Geschwind DH, Grice DE, Lord C, Lowe JK, Mane SM, Martin DM, Morrow EM, Talkowski ME, Sutcliffe JS, Walsh CA, Yu TW; Autism Sequencing Consortium; Ledbetter DH, Martin CL, Cook EH, Buxbaum JD, Daly MJ, Devlin B, Roeder K, State MW. Insights into Autism Spectrum Disorder Genomic Architecture and Biology from 71 Risk Loci. Neuron. 2015 Sep 23;87(6):1215-1233. doi: 10.1016/j.neuron.2015.09.016. PMID: 26402605; PMCID: PMC4624267.

40. Gilbert D. Treatment of children and adolescents with tics and Tourette syndrome. J Child Neurol. 2006 Aug;21(8):690-700. doi: 10.1177/08830738060210080401. PMID: 16970870.

41. Doyle CA, McDougle CJ. Pharmacologic treatments for the behavioral symptoms associated with autism spectrum disorders across the lifespan. Dialogues Clin Neurosci. 2012 Sep;14(3):263-79. doi: 10.31887/DCNS.2012.14.3/cdoyle. PMID: 23226952; PMCID: PMC3513681.

42. Miller JM, Singer HS, Bridges DD, Waranch HR. Behavioral therapy for treatment of stereotypic movements in nonautistic children. J Child Neurol. 2006 Feb;21(2):119-25. doi: 10.1177/08830738060210020701. PMID: 16566875.

43. Miguel CF, Clark K, Tereshko L, Ahearn WH. The effects of response interruption and redirection and sertraline on vocal stereotypy. J Appl Behav Anal. 2009 Winter;42(4):883-8. doi: 10.1901/jaba.2009.42-883. PMID: 20514198; PMCID: PMC2790934.

44. Specht MW, Mahone EM, Kline T, Waranch R, Brabson L, Thompson CB, Singer HS. Efficacy of parent-delivered behavioral therapy for primary complex motor stereotypies. Dev Med Child Neurol. 2017 Feb;59(2):168-173. doi: 10.1111/dmcn.13164. Epub 2016 Jun 4. PMID: 27259464; PMCID: PMC5136513.

45. Lancioni GE, Singh NN, O'Reilly MF, Sigafoos J. An overview of behavioral strategies for reducing hand-related stereotypies of persons with severe to profound intellectual

and multiple disabilities: 1995-2007. Res Dev Disabil. 2009 Jan-Feb;30(1):20-43. doi: 10.1016/j.ridd.2008.02.002. Epub 2008 Mar 26. PMID: 18372158.

46. Tse ACY, Liu VHL, Lee PH. Investigating the Matching Relationship between Physical Exercise and Stereotypic Behavior in Children with Autism. Med Sci Sports Exerc. 2021 Apr 1;53(4):770-775. doi: 10.1249/MSS.0000000000002525. PMID: 32991345.

47. Ma Q. Beneficial effects of moderate voluntary physical exercise and its biological mechanisms on brain health. Neurosci Bull. 2008 Aug;24(4):265-70. doi: 10.1007/s12264-008-0402-1. PMID: 18668156; PMCID: PMC5552589.

48. Foley TE, Fleshner M. Neuroplasticity of dopamine circuits after exercise: implications for central fatigue. Neuromolecular Med. 2008;10(2):67-80. doi: 10.1007/s12017-008-8032-3. Epub 2008 Feb 15. PMID: 18274707.

49. Tarr, C. W., Rineer-Hershey, A., & Larwin, K. (2020). The Effects of Physical Exercise on Stereotypic Behaviors in Autism: Small-n Meta-Analyses. Focus on Autism and Other Developmental Disabilities, 35(1), 26-35. https://doi.org/10.1177/1088357619881220

50. Langen M, Kas MJ, Staal WG, van Engeland H, Durston S. The neurobiology of repetitive behavior: of mice…. Neurosci Biobehav Rev. 2011 Jan;35(3):345-55. doi: 10.1016/j.neubiorev.2010.02.004. Epub 2010 Feb 13. PMID: 20156480.

51. Goldman S, O'Brien LM, Filipek PA, Rapin I, Herbert MR. Motor stereotypies and volumetric brain alterations in children with Autistic Disorder. Res Autism Spectr Disord. 2013 Jan 1;7(1):82-92. doi: 10.1016/j.rasd.2012.07.005. PMID: 23637709; PMCID: PMC3639008.