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Pediatric Deep Brain Stimulation for Therapy and Neuroenhancement: Ethical, Clinical and Legal Dimensions

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Abstract

Deep Brain Stimulation (DBS) is traditionally applied in adults for the therapy of certain neurological and psychiatric disorders. Except for adults, it can also be implemented in children, but its applications in pediatrics are limited. A groundbreaking scenario regarding the future of DBS is its potential use beyond the restoration of human health, in the field of neuroenhancement. However, the new applications of DBS present serious ethical, clinical, and legal concerns, which are examined in this paper.

In the beginning, the applications of pediatric DBS are presented, along with the method's potential short- and long-term effects. Subsequently, the concept of "neuroenhancement", contrasted with "therapy", and the potential role of pediatric DBS in this domain are analyzed. Moving on to the ethical considerations of pediatric DBS, a wide range of topics are covered, involving safety issues, authenticity, decision-making, and social concerns. In the section on clinical dimensions, the importance of conducting relevant clinical trials as well as their challenges are elucidated. Afterward, as the legal framework of DBS devices is examined, regulations both for medical and non-medical devices are provided, depending on the specific DBS application. These discussions serve as a preparation for the proposal of recommendations, from an ethical, clinical, and legal perspective.

The overall purpose of this paper is to provide pathways for the alignment of scientific advancement with the welfare of children.

Keywords: pediatric DBS, therapy, neuroenhancement, ethics, clinical trials, regulations.

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Περίληψη

Η εν τω βάθει εγκεφαλική διέγερση (DBS) εφαρμόζεται παραδοσιακά σε ενήλικες για τη θεραπεία ορισμένων νευρολογικών και ψυχιατρικών διαταραχών. Πέρα από τους ενήλικες, μπορεί επίσης να χρησιμοποιηθεί σε παιδιά, αλλά οι εφαρμογές της στην παιδιατρική είναι περιορισμένες. Ένα καινοτόμο σενάριο αναφορικά με το μέλλον της DBS είναι η εφαρμογή της πέρα από το κομμάτι της αποκατάστασης της ανθρώπινης υγείας, στον τομέα της ενίσχυσης του εγκεφάλου. Ωστόσο, οι καινούργιες εφαρμογές της DBS παρουσιάζουν σοβαρά ηθικά, κλινικά και νομικά ζητήματα, τα οποία εξετάζονται στην παρούσα εργασία.

Αρχικά, παρουσιάζονται οι εφαρμογές της παιδιατρικής DBS, μαζί με τις δυνητικές βραχυπρόθεσμες και μακροπρόθεσμες επιδράσεις της. Στη συνέχεια, αναλύεται ο έννοια της "ενίσχυσης του εγκεφάλου", σε αντιδιαστολή με τη "θεραπεία", και ο πιθανός ρόλος της παιδιατρικής DBS σε αυτόν τον τομέα. Προχωρώντας στα ηθικά ζητήματα της παιδιατρικής DBS, καλύπτεται μία ευρεία γκάμα θεμάτων, μεταξύ των οποίων είναι τα ζητήματα ασφάλειας, η αυθεντικότητα, η λήψη αποφάσεων και οι κοινωνικές ανησυχίες. Στην ενότητα των κλινικών διαστάσεων, επισημαίνεται η σημασία της διεξαγωγής σχετικών κλινικών δοκιμών, καθώς και οι προκλήσεις που αντιμετωπίζονται. Στη συνέχεια, εξετάζεται το νομικό πλαίσιο των συσκευών DBS, με την παράθεση κανονισμών τόσο για ιατρικές όσο και για μη ιατρικές συσκευές, ανάλογα με τη συγκεκριμένη εφαρμογή της DBS. Αυτές οι συζητήσεις αποτελούν προετοιμασία για την παρουσίαση συστάσεων, από ηθική, κλινική και νομική άποψη.

Ο απώτερος στόχος της εργασίας είναι να παρέχει μονοπάτια για την ευθυγράμμιση της επιστημονικής προόδου με την ευζωία των παιδιών.

Λέξεις κλειδιά: παιδιατρική DBS, θεραπεία, ενίσχυση εγκεφάλου, ηθική, κλινικές δοκιμές, κανονισμοί.

Introduction

DBS constitutes a neurosurgical procedure whose traditional role is the treatment of neurological and psychiatric disorders. Not only is it applied for the management of movement disorders in adults, including Parkinson's disease (PD), essential tremor, and dystonia, but currently it is also being investigated for psychiatric conditions like schizophrenia, depression, as well as anorexia nervosa.[1]

During the process, tiny electrodes are surgically implanted in specific regions of the brain. An Implantable Pulse Generator (IPG), which is placed in the area of the chest, is connected to the electrodes and modifies neuronal activity with the delivery of electrical pulses.[1,2]

In the last decades, DBS has been rapidly evolving, and its applications have immensely expanded. For example, the advent of techniques that facilitate the study of neural networks, like optogenetics, has contributed to the surge of DBS.[3]

A major update is the initiation of the method for underage patients. Pediatric populations can significantly benefit from the adjustability and the reversibility of the method. These special characteristics render DBS promising for the improvement of pediatric healthcare.[3]

In addition, an exciting scenario is the use of DBS for neuroenhancement purposes. This means that DBS has the potential to be applied in non-disordered children with the aim of augmenting their emotional, cognitive, and social capacities.[4]

This paper underscores the ethical, clinical, and legal concerns which arise from the use of pediatric DBS, in the context of therapy and neuroenhancement. These discussions will highlight the importance of ensuring the welfare of children as medicine and technology advance.

Materials and Methodology

Existing literature was thoroughly examined using the databases PubMed, Academia, and Google Scholar. Case studies, academic papers, and scholarly articles were extracted from these databases, focusing on the prospects of DBS for treatment and neuroenhancement. Furthermore, targeted Google searches were employed with the aim of gathering additional information. More specifically, by visiting technological and legal organizations' websites, information regarding the latest DBS approvals and relevant regulations was obtained. Used keywords included "pediatric DBS," "therapy," "neuroenhancement," "ethical considerations," "clinical trials", and "DBS approvals."

Therapeutic Application

1. Overview

Pediatric DBS can be a useful tool for the treatment of pediatric disorders characterized by a low remission rate over time, but clinical studies focusing on this topic are limited. Additionally, technological advancements, such as the development of smaller and longer-lasting batteries, as well as rechargeable systems, have made DBS more suitable for pediatric patients.[3,5]

In this section, the use of DBS for the treatment of pediatric dystonia, epilepsy, and obsessive-compulsive disorder (OCD) is presented. Subsequently, the short- and long-term effects of the procedure are elucidated, providing a basic grasp of the risks and benefits associated with pediatric DBS.

2. Dystonia

Dystonia constitutes "the most common indication of DBS" in underage patients. It is a neurological disorder characterized by uncontrollable movements and abnormal postures which are caused by prolonged muscle contractions. Therapeutic approaches for dystonia include botulinum toxin (BoNT) injections, dopaminergic medications, baclofen, and anticholinergic medications. Even though these methods have shown promise in some cases, they are not effective for all patients, and evidence supporting their efficacy is limited. With various etiologies and phenotypes, dystonia necessitates individualized approaches for its treatment. Thanks to its personalized nature, DBS is alleged to be effective for the condition.

Findings actually suggest that DBS is more successful when it comes to alleviating the symptoms of younger patients with genetic dystonias, rather than secondary dystonias, which arise from another underlying disorder, such as traumatic brain injury. Notably, DBS has received Humanitarian Device Exemption (HDE) from the U.S. Food and Drug Administration (FDA) for refractory dystonia in both adult and underage patients.[3,5,6]

3. Epilepsy

Neurological disorder epilepsy causes repetitive seizures, which are sudden bursts of abnormal electrical activity in the brain. The International League Against Epilepsy (ILAE) categorizes seizures into "focal (partial), generalized, and unknown types". Childhood absence epilepsy (CAE) is a type of genetic generalized epilepsy that affects children aged 2 to 13 years. While antiepileptic drugs (AEDs) and vagus nerve stimulation (VNS) are among the methods intended to manage epilepsy, their efficacy is often insufficient. Additionally, neurosurgical resection, while effective, is associated with inherent risks. DBS)appears to be a promising new solution for epilepsy. Initial studies suggest its potential to successfully treat seizures, although its mechanism is not fully understood. DBS has even received FDA approval for patients aged 18 and older who suffer from refractory focal epilepsy.[7,8,9,10]

4. OCD

Neuropsychiatric disorder OCD is characterized by "obsessional symptoms and compulsive acts that cause distress and interfere with daily activities." These unwanted and persistent symptoms typically appear during childhood or adolescence and constitute a source of discomfort and unease. The combination of behavioral therapy with medications like antipsychotics and selective serotonin reuptake inhibitors (SSRIs) is a standard approach for the management of OCD, but it is ineffective in a significant number of cases. Another alternative is stereotactic ablation, which is still under examination. Lately, healthcare professionals have shown growing interest in using DBS for OCD, but there is not sufficient evidence supporting its efficacy in pediatric populations. For this reason, the HDE granted by the FDA is restricted to adult OCD patients who do not respond to other treatments.[3,11,12]

5. Short- and Long-Term Effects of DBS

There is a wide variety of DBS effects due to the fact that the treatment is personalized and there are multiple variables affecting the process. The presence of both short- and long-term effects shows the importance of both pre- and post-operation surveillance. In addition, discussing DBS health outcomes prior to its implementation suggests ethical oversight and is essential for the protection of young patients' health.

In the context of short-term effects, patients' symptoms like respiratory distress and muscle spasms can be immediately alleviated, providing relief to the patient. At the same time, though, studies indicate that DBS poses multiple risks to patients' health, and children are particularly vulnerable to them in comparison with adults. Effects can be classified as reversible, when they can be resolved with additional interventions, or irreversible, which are considered to seriously impact children's health. The existence of reversible and irreversible effects raises ethical considerations that need to be meticulously taken into account when estimating the risk-benefit ratio of the procedure. Reversible effects are related to surgical risks, device-related complications, and neuropsychiatric effects. On the other side, irreversible effects can encompass severe surgical site infections at the site of the electrodes' implantation. When serious infections occur, the complete removal of the hardware might be needed.[1,3,5,6]

Managing DBS in the long term is quite challenging. Long-term follow-up studies have shown that, even though some patients may experience significant relief of their symptoms, in other cases, symptoms may gradually worsen. What is more, IPG's lifespan can vary greatly, depending on the condition of the patient, the type of the device, and its settings. The battery is then replaced

with a relatively simple surgical procedure that may pose additional risks to the individual's health. It can be inferred that underage patients are more vulnerable than adults because it is likely they will undergo more battery replacements throughout their lives.[3,6,13]

Neuroenhancement

1. "Therapy" vs "Enhancement"

In the present study of pediatric DBS, "therapy" and "enhancement" are two key terms that need to be clarified. It is important to remember that distinguishing these terms is vital, as this has practical effects.

According to the US President's Council on Bioethics, "therapy" is defined as "the use of biotechnical power to treat individuals with known diseases, disabilities, or impairments, in an attempt to restore them to a normal state of health and fitness." On the other hand, "enhancement" can be conceptualized as "the directed use of biotechnical power to alter, by direct intervention, not disease processes but the normal workings of the human body and psyche, to augment or improve their native capacities and performances."[14]

These definitions point out that "therapy" aims to restore the health of disordered individuals and seeks "improvement up to the species-typical level". On the contrary, "enhancement" strives for "improvement beyond species-typical functioning".[14,15]

The distinction between the two terms meets certain challenges that should be carefully examined. Firstly, clinicians' critical thinking abilities and experience are highly needed, as the concepts "typical" and "normal" can be diverse and subjective. In addition, because of the involvement of various normal factors like sleep deprivation and aging, sometimes it is hard to tell whether the individual is healthy or disordered.[14,15]

Distinguishing "therapy" from "enhancement" is crucial and has important practical implications. These implications are mainly related to the allocation of resources and the accessibility of these interventions.[15]

2. Definition and Methods

The term "neuroenhancement" can be described as "a variety of interventions and technologies aiming to improve human performance above the subject's normal performance." Neuroenhancement targets various domains, including attention, concentration, memory, perception, creativity, emotional regulation, and reasoning skills. Enhancing the individual's skills beyond the levels of "physiologically normal", it has the potential to optimize their mood, cognition, and sociality.[14,15,16,17]

There are diverse strategies that serve the role of neuroenhancement, and they can be divided into pharmacological and non-pharmacological ones. The prescription of drugs like benzodiazepines (BDZs), antidepressants (ADs), and antipsychotics is the most common approach for neuroenhancement and constitutes a pharmacological strategy.[17,18]

In the context of non-pharmacological strategies, behavioral interventions like meditation, formal education, and mnemonic strategies are included. Choosing the most appropriate intervention is determined by the targeted domain. For example, when it comes to improving memory, mnemonic strategies are preferred, while meditation is usually practiced for the improvement of attention. In addition, physical measures may be preferred, such as DBS and transcranial magnetic stimulation (TMS), which is non-invasive. Further novel non-pharmacological strategies are also being investigated, like implants of neural tissue derived from stem cells.[14,15,17]

3. Neuroenhancement in Education

Education in developed countries is a widely accessible form of non-physical and non-biomedical neuroenhancement. As Nelson Mandela once said, "Education is the most powerful weapon which you can use to change the world." It is of paramount importance because it equips and endows students with knowledge and skills that contribute to their character development and prepare them to become independent and active young citizens.

Apart from traditional teaching methods, in certain educational settings, other neuroenhancement strategies are deliberately applied to augment students' capacities. For example, in the context of diet, specific nutrients associated with improved brain activity are included in schools' meal programs.[17]

In addition, studies suggest that 1-3% of American and Canadian students use pharmacological neuroenhancers on a weekly basis. This method is becoming more and more popular among students, and an increase in the percentage is observed with the transition from high school to college. However, the use of certain drugs like Ritalin is limited to students suffering from cognitive disorders like Attention Deficit Hyperactivity Disorder (ADHD) .[18]

The consumption of vitamins, which are beneficial for the neurological development of the fetus, constitutes a widely preferred method among pregnant women. This practice can assist children with their studies in the long run.[17]

Furthermore, novel strategies, including DBS, are being considered to enhance student performance and, thus, maximize the results of traditional educational techniques. Nonetheless, the impact of DBS on educational settings remains unknown because its use for neuroenhancement purposes has not been thoroughly examined yet.

4. DBS for Neuroenhancement

The use of DBS for neuroenhancement is a very intriguing scenario. However, the development of this innovative application is confronted with challenges, mainly because of the unique nature of each individual. To facilitate the process, Neuralink and IMEC have invested in the development of new technologies.[4]

One interesting application of DBS could be the enhancement of memory beyond typical levels. This is considered feasible by targeting the medial temporal lobe (MTL) circuitry, which is related to memory. The technique has had success in epileptic patients, but it can also potentially extend to healthy children. This is a groundbreaking application, yet it raises an abundance of ethical concerns.[19]

A study was conducted to examine and compare the views of adaptive DBS researchers in the US regarding the implementation of DBS for the purpose of neuroenhancement. 61% of them expressed worries about the method's inherent risks, which are linked to its invasiveness. What is more, 43% found it unnatural and stated that they would remain opposed to the method, even if its risks were eradicated. It is also particularly interesting that some researchers drew parallels to plastic surgeries.[4]

The findings of this study highlight the importance of addressing the ethical issues of DBS when it is used for neuroenhancement. In case the method is applied in pediatric populations with the same purpose, greater attention is needed because of the additional concerns that emerge.

Ethical Considerations

1. Overview

DBS is associated with a wide variety of ethical issues, including safety, authenticity, decision-making, as well as social concerns. When examining the ethical considerations of pediatric DBS, the interplay of concerns related to neuroethics and child-specific issues is a major source of intricacies.

To be more specific, neuroethics is a subfield of bioethics that can be defined as "the study of the ethical, moral, social, and legal issues raised by our continually improving understanding of the brain, and by consequent improvements in our ability to monitor and influence brain function". In addition to neuroethics, pediatric DBS presents challenges that are unique to children because of their vulnerability and developmental stage.[15]

The potential of DBS for enhancement purposes gives us food for thought regarding the "goals of medicine". A main question that arises is whether pediatric DBS should extend beyond the restoration of human health. At this point, it is important to reflect on how the purposes of medicine ought to evolve, in

response to the new challenges that emerge.[15,20]

2. Safety Issues

2.1. Health Risks

As previously discussed, DBS can have unfavorable short- and long-term outcomes. However, health risks in children remain unclear, and evidence largely stems from studies involving adults. More years of investigation are required to unveil long-term effects in pediatric populations. This highlights the need for caution and thorough discussions with families about the practice's potential risks.[21,22]

It is also important to take into consideration that "children are not small adults". Adult-sized leads and batteries can possibly cause harm to underage individuals, such as skin erosion and higher infection rates in comparison to adults.[22]

Generally, estimating the risk-benefit ratio is quite challenging, especially in the case of considering DBS in non-disordered individuals for enhancement purposes. In therapeutic applications, the potential adverse effects are outweighed by the urgent need to address health issues. Consequently, the risk-benefit ratio appears to be more favorable in contrast to enhancement interventions. The disagreement on where specific brain functions are localized constitutes another root of confusion. Additionally, the fact that children's and adolescents' brains are not fully developed yet makes the prediction of the ratio even harder.[4,12,14]

2.2. Neurosecurity Threats

Despite its multiple benefits, DBS poses risks to children's well-being, which are linked to neurosecurity threats. "Brainjacking" is a novel term that has emerged in regard to this topic. The term refers to "the exercise of unauthorized control of another's electronic brain implant." In response to brainjacking, "neurosecurity"—the development of defense mechanisms against the breach of neurological implants—has evolved.[2,23]

There are several ways in which hackers could possibly exert influence, but for the time being, they remain mainly theoretical. Depending on their level of sophistication, attacks are either blind or targeted. They can be detrimental to health or even fatal, and this can cause distress not only to children but also to their families.[1,2]

Hackers can possibly cause harm by controlling different parameters, including voltage, frequency, and pulse width. They have the potential to provoke pain with excessive frequency, exacerbate symptoms with the impairment of the IPG, and even trigger emotional and behavioral changes, such as hypersexuality.[2,23]

Neurosecurity threats are expected to become a palpable threat in the near future, and considering them will be essential for the formation of the risk-benefit ratio.

3. Authenticity

3.1. Definition and Views

Philosopher Charles Guignon has defined the authentic self as "the constellation of feelings, needs, desires, capacities, aptitudes, dispositions, and creative abilities that make the person a unique individual."[24]

DBS is linked to authenticity concerns, and this is particularly worrying in the case of underage individuals, let alone adolescents, because they go through a transitional period where their identity is formed. DBS can interfere with children's character development and identity formation by provoking personality and emotional changes, including anxiety, mania, and increased libido. Additionally, it can potentially affect the perception of body image, but responses vary among individuals.[24]

From a philosophical point of view, there is a wide range of perceptions and approaches regarding personal identity. For instance, Platonic and Aristotelian philosophies support that it is an "ontological entity" that remains unchanged over time. On the contrary, according to social constructionist views, personal identity is continuously shaped through social interactions and cultural norms.

Transhumanist viewpoints advocate for the enhancement of human capabilities through technology, but bioconservative approaches are against it, as they prioritize the preservation of human nature. Moreover, the importance of self-perfection is illustrated in the "Ethics of Authenticity" by Charles Taylor. It is clear that viewpoints that support the optimization of human skills are in favor of DBS for neuroenhancement.[15,18]

When considering DBS for children, it is imperative to take into account the preservation of their authentic selves. However, the diversity of views surrounding this topic makes the process very complex. Careful consideration is needed to maximize positive outcomes and, simultaneously, protect children's identity, especially during this crucial period of their life.

3.2. Nature of Personal Accomplishments

Drawing upon authenticity, a debate focusing on the nature of personal achievements unfolds. A main argument against DBS for neuroenhancement purposes is that accomplishments are less meaningful due to the fact that they require less effort. When human skills are enhanced, there is a diminished sense of responsibility, and authenticity is undermined. On the other hand, natural accomplishments reflect the personal identity of the individual on the grounds that they stem from their dedication and commitment. In response to opponents, DBS supporters assert that augmenting cognitive abilities does not replace genuine effort but enhances its effectiveness instead. In fact, neuroenhancement is highly beneficial in terms of productivity and efficacy of work.[15]

The debate goes on as critics point out that, despite its benefits, DBS may negatively influence other domains that have not been targeted directly. The unintended consequences of DBS can potentially have a significant impact on education. For example, in the case of intentionally enhancing memory, the performance of students is bound to improve in subjects requiring memorization. At the expense of this improvement, there may be weaker performances in subjects where critical thinking and problem-solving skills are needed. Hence, neuroenhancement may imbalance the skills of students.[15]

4. Decision-making

4.1. Autonomy

According to philosopher Dan Brock, autonomy "involves the capacities of individuals to form, revise over time, and pursue a plan of life or conception of their good. It is a broad concept, applicable at both the levels of decision and of action."[2]

Given the challenges and probable risks of certain medical procedures, it is of utmost importance to strike a balance between the individual's autonomy and the clinician's medical duty. Even though the individual's preferences should always be taken into consideration, the clinician might need to take initiatives that are not in perfect alignment with the individual's wishes. This is important when it comes to ensuring safety and making decisions in the best interests of the individual. Practically, this is a way of respecting beneficence and non-maleficence.[20]

In the context of pediatric DBS, it is complicated to determine the extent to which children should participate in decision-making processes, as they constitute a vulnerable population with limited decision-making capacities. In many cases, especially when children have suffered serious cognitive damage, the engagement of guardians might also be needed, along with the intervention of healthcare professionals.[2]

Children's age and cognitive capacities can immensely influence the procedure. Generally, children who are more mature and at a higher intellectual level can understand to a greater degree the role of DBS and the nature of their condition. What is more, they are better at maintaining a dialogue with their parents and physicians, at communicating their ideas, and at expressing their desires and objections. For these reasons, their engagement in the process is higher. The same applies in the case of children with previous experiences of surgery, even if it was not related to DBS, as they are more familiar with the process.[22,25]

Overall, a number of factors are examined regarding the participation of children in decision-making. Preserving children's autonomy is paramount and necessitates thorough ethical introspection from the part of healthcare professionals. However, ensuring that children participate in decision-making may delay the treatment process and, hence, result in harm caused by the decline of their disease.[22]

4.2. Treatment Exhaustion

The concept of treatment exhaustion may further complicate decision-making. Alternative treatments are exhausted when they have been proven to have inadequate or even adverse results. A useful example is the case where baclofen therapy for pediatric dystonia is ineffective or causes harm to patients. In this instance, DBS may be seriously considered, even though it is associated with potential risks.[22]

Nevertheless, before DBS is applied, it is pivotal that the refractoriness and severity of the condition are assessed. Patient selection may be challenging because there might be disagreement when classifying a disease as refractory. Before labeling a patient as refractory, clinicians should also make sure that conventional treatments have been exhausted and that there are no gaps in the treatment of the patient.[12]

4.3. Parental Approach

Parents have the duty to make well-informed decisions in the best interest of their children. Through their open dialogue with clinicians, they receive comprehensive information as well as ethical guidance. Parents' participation in decision-making is a challenging task, which requires the assessment of the child's developmental stage and other available treatments.[22]

A major issue is that, because of their emotional attachment, parents might experience a variety of emotions, mainly associated with uncertainty and inadequacy. Parents' emotional state may impact their capacity to make responsible decisions and this necessitates their productive partnership with clinicians, who serve as gatekeepers thanks to their medical expertise.[22,26]

Despite the complexity of pediatric DBS, research indicates an overall willingness of parents to consider DBS as a therapeutic option for adolescents, especially when they have previous experiences with it. Nonetheless, more challenges may arise when parents consider DBS for neuroenhancement, because its nature is more uncertain, and taking into account societal norms would also be needed.[25]

5. Social Concerns

Issues related to justice, fairness, and equality come up when DBS is considered. A critical issue is the high cost of the technology, particularly when it is not offered under insurance coverage. This can widen the gap between the families who can afford DBS for their children and those who cannot. The negative impact of high expenses may be more noticeable among children who come from a lower socioeconomic background. This may perpetuate inequalities and reinforce the process of class stratification.[4,15]

On the other side, if DBS were available for every person, it would pose a serious threat to societal diversity. Especially in the case of neuroenhancement, universal access to DBS leads to increased homogenization, and this could disrupt the division of labor.[14]

In addition, stigmatization of children constitutes one of the most serious social implications of DBS. This is usually observed in terms of less studied and practiced applications of DBS due to the lack of societal familiarity with them. For instance, this is prevalent in psychiatric conditions and neuroenhancement practices.

In a study about the views of clinicians on DBS for OCD adolescents, a clinician expressed that stigmatization of patients happens "largely due to the history of psychosurgery and it being misused in the past." They also added that "there weren't clear guidelines for its use, and it was probably used in a lot of patients where it did more damage than good, so there is a lot of stigma surrounding psychosurgery."[12]

The debate revolving around prioritization principles further complicates matters. These principles advocate for the prioritization of children who are in greater medical need. This works to the detriment of healthy children, who, as a consequence, may have the urge to resort to the black market. This may upset the societal balance and intensify inequalities.[15]

Clinical Dimensions

Moving on to the clinical dimensions of pediatric DBS, findings regarding DBS effects on children are limited, so further clinical trials should be conducted. Pediatric clinical trials are of utmost importance on the grounds that they constitute a foundation for increasing our medical knowledge and enhancing the outcomes of pediatric patient care. Especially in the context of pediatric DBS, the role of research involving children is particularly important, as it can shed light on the risks and benefits of the method, its short- and long-term outcomes as well as its reversible and irreversible effects.

Nevertheless, conducting pediatric research is usually challenging and has encountered multiple oppositions. First and foremost, clinical trials in children are confronted with serious financial challenges. To be more specific, their costs are elevated because of the unique nature of children and their particular needs during clinical processes. Skilled personnel and adequate facilities are required and, thus, expenses considerably increase. Because of their high costs, pediatric clinical studies generally meet the reluctance of governments and the medical industry, in terms of their financial support. This highlights the need to resort to nongovernmental organizations for funding. Apart from the economic barriers, pediatric research is hindered by additional challenges, including the presence of stricter regulations in comparison to adult standards. Moreover, particularly in the case of DBS studies, there are major difficulties in recruiting underage participants. These are mainly associated with the limited number of eligible candidates, the method's invasive nature, the need for long-term surveillance, special ethical considerations that emerge, parental concerns, and the importance of interdisciplinary collaboration.[6,12,27]

Despite the above-mentioned adversities, the latest updates are favorable for the conduct of pediatric clinical studies, encompassing those focusing on DBS. Certain widely recognized organizations like the European Medicines Agency's Network of Pediatric Research, the US NICHD Pediatric Trial Network, and the World Health Organization (WHO) promote clinical studies in children, with the purpose of developing the field of pediatric healthcare on a global level.[27]

Legal Framework of DBS Devices

1. Medical device regulations

A medical device is defined by the FDA as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes".[28]

While in the US medical devices need to be FDA approved, in the EU they must obtain a Conformité Européenne (CE) Mark. To receive CE approval, they must adhere to European regulations like the Medical Devices Regulation (MDR).

The FDA further employs a risk-based regulatory system that involves the classification of devices into Class I, II, and III

categories. DBS devices belong to the Class III category on the grounds that they constitute high-risk devices. They can significantly impact patients' health and, for this reason, the FDA needs to meticulously assess their probable risks and benefits. Analogous to the FDA, the EU MDR classifies medical devices into Class I, Class IIa, Class IIb, and Class III categories, and DBS devices fall under the Class III category.[28,29]

In the US, being Class III devices, DBS devices must also obtain Premarket Approval (PMA), before they can be distributed. In addition, they also need to pass through further safety measures before their market entry, as they must also receive an HDE approval, which is for devices that target rare conditions. Manufacturers have to provide data which support the safety of the device and prove that it does not expose patients to unreasonable risk. It is also worth noting that HDE approval does not have an equivalent in the EU. Furthermore, focusing on children, the Pediatric Medical Device Safety and Improvement Act governs the development and use of safe and biocompatible pediatric medical devices.[30,31,32]

Notably, both in the US and EU, manufacturers are also required to provide clear labeling of the device. In the context of pediatric DBS, provided information should involve device indications, potential hazards, warnings, precautions, proper implantation techniques, and directions for long-term management.[29,33]

Because of the restrictions regarding the approval of pediatric DBS devices, children may resort to medical DBS devices off-label. Off-label use refers to the usage of a medical device "outside of the approved instructions for use including indications" and has to be reported by manufacturers, following the General Safety and Performance Requirements (GSPR), as outlined by the MDR. In pediatric interventional cardiology, studies suggest that more than 60% of pediatric patients who receive therapeutic cardiac catheterization may be exposed to adult devices off-label. Were we to extend the implications of this finding, there is a high probability that children use adult DBS devices off-label, when they do not have legal access to pediatric DBS devices.[34,35]

2. Latest DBS approval

The Percept™ RC DBS system, launched by Medtronic, received CE and FDA approvals at the end of 2023 and the beginning of 2024, respectively. The device is groundbreaking, as it is "the only rechargeable DBS system with BrainSense™ sensing technology." Its standout features include its small size, great battery capacity, and potential for customized treatment, as it can effectively record brain signals. It shows promise for treating movement disorders like PD, dystonia, and essential tremor in adults, and it may also enhance pediatric treatment. Without doubt, it constitutes a significant innovation with numerous prospects that could profoundly impact the field of neurology in the future. Amaza Reitmeier, Vice President and General Manager for Medtronic Brain Modulation, stated, "We are transforming brain modulation through sensing-enabled DBS and will continue to drive therapy innovation with the goal of improving the lives of many more people with Medtronic DBS therapy."[36,37,38]

3. Non-medical device regulations

DBS devices for neuroenhancement are not treated as medical devices in the US, as they do not have an "explicit connection to a disease." Consequently, they are governed by regulations beyond those for traditional medical devices and are controlled by different regulatory bodies, including the Federal Communications Commission (FCC). In contrast, in the EU, the Medical Devices Regulation (MDR) may regulate "products without an intended medical purpose" in certain cases. Such devices are termed "Medical Devices without an Intended Use." Furthermore, the updated EU's MDR specifically addresses "equipment intended for brain stimulation that applies electrical currents or magnetic or electromagnetic fields penetrating the cranium to modify neuronal activity in the brain." The EU's inclination to develop its own regulations regarding neuroenhancement devices, including DBS

devices, reflects its cautious approach. On the other hand, the US approach is less comprehensive.[16,39]

Conclusion and Recommendations

In conclusion, DBS holds promise for the treatment of various neurological and psychiatric disorders in pediatric populations. Beyond the realm of therapy, it could also potentially be applied for neuroenhancement purposes in order to optimize the capacities of children, especially in the area of education.

Nevertheless, the method is still in the research stages, both in children and adults, particularly in the fields of psychiatry and neuroenhancement. Research involving underage participants is limited and usually adult findings are adapted to pediatric cases.

The advancement of technology and medicine aims to provide an explanation of DBS mechanisms and contribute to the development of better operating and more effective models. Thus, it is expected that pediatric healthcare will improve and great progress in neurology and psychiatry will be achieved.

However, various issues, concerns, and limitations are related to pediatric DBS, on multiple levels. Based on my research, the following ethical, clinical, and legal recommendations are put forth:

1. Further relevant research should be conducted to reveal the effects of pediatric DBS, particularly the long-term ones. Greater interest must be expressed from the part of governments, the medical industry, and non-profit organizations for the financial support of such trials.
2. Interdisciplinary collaboration on a global scale is of vital importance for the development of the method. It includes productive interaction and communication among researchers, ethicists, and clinicians specializing in different fields like neurology and psychiatry.
3. Education is a must, not only for healthcare professionals but also for children and their families. Healthcare professionals should be educated in depth regarding the mechanisms of DBS and its legal as well as ethical concerns. They must also share their knowledge effectively with children and their families to ensure informed decision-making. The process of decision-making can also be facilitated by the development of clear decision aids (DAs).
4. The development of clear legal guidelines is imperative. Establishing regulations that are specific to pediatric DBS, and cover the field of neuroenhancement as well, is crucial.

Following these recommendations plays a significant role regarding the future of the domains where pediatric DBS can be applied. It is worth highlighting that, regardless of the extent to which pediatric DBS advances, its ethical, clinical, and legal considerations should not cease to be carefully explored.

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