"Optimizing Deep Brain Stimulation Parameters to Enhance Treatment Efficacy in Obsessive Compulsive Disorder and Autism Spectrum Disorder: A Focus on Electrode Size, Current Steering, and Stimulation Directionality".

Akshar Ammu

Abstract: Optimizing Deep Brain Stimulation (DBS) parameters is essential for enhancing treatment efficacy in developmental disorders such as Obsessive Compulsive Disorder (OCD) and Autism Spectrum Disorder (ASD). This study evaluates the impact of electrode size, current steering, and stimulation directionality on DBS outcomes, aiming to refine therapeutic strategies. A systematic review of high-impact journal studies with sample sizes of 30–50 participants was conducted to analyze the effects of these parameters on symptom reduction and side effect profiles. Results indicate that smaller electrodes provide greater precision, minimizing off-target effects by focusing on specific neural circuits, making them superior to larger electrodes. Current steering was found to be more effective than unipolar stimulation, as it allowed for precise modulation of targeted brain areas, which is particularly beneficial in conditions like OCD. Directional stimulation, by enabling focused activation of specific neural tissues, further improved treatment outcomes by fine-tuning the spatial distribution of electrical fields. These findings suggest that optimizing DBS with smaller electrodes, current steering, and directional stimulation enhances efficacy and safety, offering a more targeted approach to treating OCD and ASD. Future guidelines should prioritize these configurations to maximize therapeutic potential while minimizing adverse effects.

Introduction: Optimizing Deep Brain Stimulation (DBS) parameters to enhance treatment efficacy in developmental disorders requires an in-depth examination of key factors such as electrode size, current steering implementation, and stimulation directionality. This investigation aims to improve outcomes in Obsessive Compulsive Disorder (OCD) and Autism Spectrum Disorder (ASD) by understanding how these variables influence DBS effectiveness and developing more targeted and efficient treatment protocols. Electrode size significantly impacts neural modulation precision and extent. Smaller electrodes target specific neural circuits with greater precision, minimizing adverse effects from off-target stimulation. This precision is crucial in developmental disorders, where accurately modulating dysfunctional brain regions can greatly alleviate symptoms. Conversely, larger electrodes may stimulate broader areas, potentially enhancing or diminishing therapeutic outcomes depending on the disorder and patient characteristics. Thus, optimizing electrode size is essential for balancing efficacy and safety. Current steering implementation is another critical aspect of DBS optimization. It allows directional control of the electrical current, enabling more precise targeting of specific brain regions. This technique is particularly beneficial in OCD, where precise modulation of areas such as the subthalamic nucleus or the anterior limb of the internal capsule can significantly improve symptoms. Adjusting the current flow maximizes therapeutic effects while minimizing

unintended stimulation of adjacent areas. Stimulation directionality, referring to the orientation and spread of electrical current within the brain, is vital for optimizing therapeutic outcomes. Directional stimulation enables focused activation of neural tissue, enhancing DBS specificity. Adjusting stimulation directionality fine-tunes the spatial distribution of the electrical field, potentially improving treatment effectiveness for individual patients. This customization is crucial in disorders with heterogeneous presentations, such as ASD and IED, where symptoms and affected brain regions vary widely. The next steps involve comprehensively analyzing recent studies and clinical trials to gather empirical data on these parameters' impact on DBS outcomes. This analysis will provide insights into optimal DBS configurations and contribute to developing standardized clinical guidelines, ultimately enhancing DBS's therapeutic potential in developmental care.

Methods: Optimizing Deep Brain Stimulation (DBS) parameters for the treatment of Obsessive Compulsive Disorder (OCD), Autism Spectrum Disorder (ASD), and Intermittent Explosive Disorder (IED) involves a detailed examination of peer-reviewed research. A systematic review will be conducted on articles from high-impact journals such as Neuropsychopharmacology, The Journal of Neuroscience, and Biological Psychiatry. Emphasis will be placed on studies with large sample sizes, preferably between 30 to 50 participants per trial, to ensure statistical significance. Data extraction will focus on various DBS parameters, including electrode size, contact points, current steering, and stimulation techniques, alongside treatment outcomes and side effects. Meta-analysis techniques will be employed to synthesize findings from multiple studies, allowing for the identification of patterns and the evaluation of the overall effectiveness of different DBS configurations in treating OCD, ASD, and IED. This approach aims to refine DBS parameters to enhance therapeutic efficacy and minimize adverse effects.

How does electrode size in DBS treatment impact symptom mitigation in OCD cases?

The impact of electrode size in Deep Brain Stimulation (DBS) treatment on symptom mitigation in Obsessive Compulsive Disorder (OCD) is a critical factor influencing clinical efficacy and patient safety. Joel S. Pelmutter(Perlmutter & Mink, 2006) in his study noted that DBS, which involves the implantation of electrodes within specific brain regions to modulate dysfunctional neural circuits, has shown promise in treating refractory OCD. According to the Shanghai Mental Health Center (Tingting et al., 2022), the size of the electrodes used in this procedure can significantly affect the outcome by altering the extent and precision of neural stimulation. Larger electrodes are capable of delivering stimulation over a broader area, potentially engaging multiple neural circuits implicated in OCD. This expansive stimulation might lead to more comprehensive symptom alleviation, as a wider range of pathological neural activity could be modulated. However, a study done by the Cumming School of Medicine

(Ramansabbu et al., 2018) found that the broader stimulation area also presents significant challenges. By affecting non-targeted regions adjacent to the intended stimulation site, larger electrodes may inadvertently induce undesirable side effects. Unintended stimulation of nearby brain structures could result in alterations in mood, cognition, or motor function. Such side effects may not only compromise patient safety but could also limit the therapeutic utility of DBS in clinical practice (Haynes & Mallet, 2010). Conversely, smaller electrodes provide a more localized and precise form of neural stimulation, concentrating the electrical field on specific neural circuits that are most relevant to OCD (Frey et al., 2022). This precision minimizes the spread of stimulation to non-target areas, thereby reducing the likelihood of adverse effects. The targeted approach facilitated by smaller electrodes could lead to improved patient outcomes, with a reduction in OCD symptoms accompanied by a lower incidence of side effects. However, the limited spatial coverage associated with smaller electrodes may also pose a limitation, as not all relevant neural circuits might be adequately stimulated, potentially resulting in suboptimal symptom control. (Xing et al., 2023) To optimize DBS treatment for OCD, it is imperative to conduct a detailed comparison of clinical outcomes associated with different electrode sizes. This involves systematically analyzing data on symptom reduction, side effect profiles, and overall patient satisfaction across various studies. Such comparative analyses would provide critical insights into the delicate balance between efficacy and safety in DBS therapy, helping to inform clinical decisions regarding electrode size selection. A comparative study (Paffi et al., 2015) underscores the importance of electrode size and placement in achieving the desired therapeutic outcomes in DBS. The authors demonstrate that different trends in neural response can be observed between microstimulation and macrostimulation (Maggio et al., 2010), depending on the specific neural fibers and tissue regions being targeted. Their findings suggest that to replicate the therapeutic effects of intraoperative microelectrode stimulation with a chronic macroelectrode, it is crucial to ensure that the electric center of the macroelectrode coincides with that of the microelectrode. This alignment is necessary to produce consistent trends in key parameters such as voltage and activation function (AF) (Appali et al., 2019)along the fibers connecting critical brain structures, such as the subthalamic nucleus (STN) and the globus pallidus (Gp). Furthermore, Paffi's study highlights the necessity of integrating dosimetric models with biophysical models of neurons and neural networks to achieve a quantitative evaluation of neural fiber responses. These biophysical models require precise input parameters, such as transmembrane potential, which can be rigorously evaluated using microdosimetric techniques at the cellular level (Lin et al., 2020). By calculating electric quantities at the microscopic level, such as membrane potential, researchers can establish a critical link between macroscopic tissue dosimetry and neuronal models. This multilevel approach is essential for developing practical clinical protocols that optimize DBS parameters for individual patients, ultimately enhancing the effectiveness and safety of OCD treatment. In addition, an experiment conducted on rat models, focusing on the hippocampal response to electrical stimulation using various electrode types (Desai et al., 2014). In this study, rats were implanted with macroelectrodes, microelectrode arrays, or sonicoplated microelectrode arrays in

the dorsal hippocampus. The researchers assessed the extent of neuronal activation by examining the expression of c-fos, a marker of neural activity, in response to electrical stimulation. Their findings revealed that electrical stimulation led to c-fos expression confined to the area immediately surrounding the electrode track, indicating a limited radius of activation. Notably, this activation was largely restricted to neurons, as evidenced by the co-expression of c-fos and NeuN, a neuronal marker. This suggests that the effects of electrical stimulation were highly localized, with most of the activation occurring near the site of electrode implantation. The study also demonstrated that the type and size of the electrode significantly influenced the radius and density of neural activation. Macroelectrodes, which have a larger surface area, produced the broadest radius of activation at approximately 200 μm when stimulated at 25 Hz, ±1 V, for 4 hours. This broad activation radius is consistent with the ability of larger electrodes to stimulate a wider neural field, a factor that could potentially enhance the therapeutic effects in clinical settings (Robinson, 2011). However, it also underscores the challenge of managing side effects, as a broader activation zone may inadvertently engage non-target neural circuits, leading to unwanted outcomes. In contrast, microelectrodes demonstrated a more limited radius of activation, approximately 100 μm, reflecting their capacity for more precise stimulation. The sonicoplated microelectrodes, which were modified to have reduced impedance, showed an intermediate activation radius of 150 μm. The reduced impedance of the sonicoplated electrodes allowed for greater current passage at the same fixed voltage, resulting in a more extensive activation compared to unplated microelectrodes. This finding highlights the potential of electrode surface modifications to enhance the efficiency of neural stimulation, providing a balance between the precision of microelectrodes and the broader coverage of macroelectrodes. Interestingly, the study found that while microelectrodes, particularly the sonicoplated ones, exhibited higher activation densities in the immediate vicinity of the electrode track, this activation density decreased sharply with distance. In contrast, macroelectrodes displayed a more gradual decline in activation density, suggesting a more uniform distribution of stimulation across a larger area. This difference in activation patterns is critical for understanding how electrode size and configuration can be optimized for specific therapeutic goals in DBS. The research by Desai et al. reinforces the importance of electrode size in determining the spatial extent and intensity of neural activation in DBS. These findings align with those of Paffi who also emphasize the need for precise electrode placement and configuration to achieve desired therapeutic outcomes. The study's focus on the hippocampus, a region critical for memory and spatial navigation, also provides insights into how DBS might influence cognitive functions, particularly when considering applications in OCD. In conclusion, the study supports the use of smaller electrodes in DBS for ASD to enhance precision, minimize side effects, and optimize clinical outcomes. The careful consideration of electrode size, integrated with advanced imaging and trajectory planning, is essential in tailoring DBS treatment to the specific neural dysfunctions present in individuals with ASD.

Is omnidirectional stimulation or directional deep brain stimulation the most effective method in countering neurological stunts resulting from OCD and ASD?

Omnidirectional deep brain stimulation (DBS) is a neuromodulation technique that uses cylindrical electrodes to emit electrical pulses uniformly in all directions around the electrode. This method has been the traditional choice in treating various neurological disorders, including obsessive-compulsive disorder (OCD). The effectiveness of omnidirectional DBS lies in its ability to broadly modulate target brain regions, particularly those with widespread pathological activity. In the case of OCD, omnidirectional DBS typically targets regions such as the subthalamic nucleus (STN) or the anterior limb of the internal capsule (ALIC), which are integral components of the cortico-striato-thalamo-cortical (CSTC) loop (Zhang et al., 2021). This loop is a key circuit involved in OCD pathology, characterized by hyperactivity that leads to the repetitive and intrusive thoughts and behaviors associated with the disorder.

The advantage of omnidirectional DBS in this context is its capacity to cover large areas of brain tissue, ensuring that the dysfunctional circuit is sufficiently modulated. This broad stimulation is particularly beneficial in cases where the precise anatomical location of the pathological circuitry is not well defined or when the dysfunction is more diffuse. By delivering a wide electrical field, omnidirectional DBS can effectively modulate the entire region of interest, potentially alleviating symptoms by disrupting the abnormal neural activity that underlies the disorder. However, this non-selective stimulation also presents significant drawbacks. The broad electrical field can inadvertently stimulate adjacent structures or fiber tracts that are not involved in the pathology. This unintended activation can lead to a range of side effects, including cognitive, mood, or motor disturbances. For example, stimulation of the internal capsule, which lies near the ALIC, can result in mood changes or motor side effects, reducing the overall therapeutic efficacy of the intervention (Zhou et al., 2020). This issue is particularly pronounced in disorders like autism spectrum disorder (ASD), where the neural substrates are more complex, diffuse, and less well-mapped. In ASD, broad stimulation might interfere with non-pathological circuits, leading to unpredictable and potentially detrimental outcomes.

Directional DBS offers a more advanced and refined approach by utilizing segmented electrodes that allow clinicians to steer the electrical field toward specific anatomical targets. This precision is achieved by controlling the activation of individual electrode contacts, thereby shaping the electric field to focus on the desired area while minimizing stimulation of non-target regions. This approach is especially valuable in OCD, where the pathological circuitry within the CSTC loop is often highly localized. For instance, targeting the STN or ALIC with directional DBS allows for precise modulation of the hyperactive circuits without affecting adjacent structures such as the hypothalamus or internal capsule. Clinical evidence supports the superiority of directional DBS in providing better symptom control with fewer side effects compared to omnidirectional stimulation. By avoiding unintended activation of nearby structures, directional DBS can reduce the cognitive or affective side effects commonly associated with

broader stimulation. Additionally, the increased precision of directional DBS allows for lower stimulation intensities, which can reduce energy consumption and extend the battery life of the implanted pulse generator—a critical consideration for long-term DBS therapy. This energy efficiency not only reduces the frequency of surgical interventions required to replace the battery but also improves the overall quality of life for patients who rely on DBS for symptom management.

While the use of directional DBS in ASD is still in the experimental stages, its potential to selectively target dysfunctional circuits related to core symptoms such as repetitive behaviors, social cognition, and communication deficits is promising. ASD is a heterogeneous disorder, with symptoms that vary widely across individuals. This variability necessitates a flexible and adaptable treatment approach, which directional DBS could provide. By focusing the stimulation precisely on the affected neural circuits, directional DBS may offer a more tailored and effective intervention compared to the more generalized approach of omnidirectional DBS (Schnitzler et al., 2022). For example, targeting specific areas within the amygdala or prefrontal cortex—regions implicated in social cognition and emotional regulation—could potentially alleviate some of the social and communicative challenges faced by individuals with ASD without affecting other, non-pathological areas of the brain.

Despite the clear advantages of directional DBS in terms of precision and side-effect minimization, it is not without its limitations. The complexity of programming and adjusting directional electrodes requires advanced imaging techniques, computational modeling, and technical expertise that may not be accessible in all clinical settings. High-resolution imaging, such as diffusion tensor imaging (DTI) or tractography, is often necessary to map the neural pathways and optimize electrode placement. Furthermore, the programming of directional DBS systems is more time-consuming and requires a greater degree of expertise compared to omnidirectional systems. Clinicians must carefully balance the electrode contacts, adjust the stimulation parameters, and monitor the patient's response to achieve the desired therapeutic effect. This complexity can increase the cost and time associated with treatment, making it less feasible in resource-limited settings. Additionally, not all patients may benefit from the high precision offered by directional DBS, particularly if their pathology involves broader or less well-defined areas. In such cases, the simpler and more generalized approach of omnidirectional DBS may be preferable, providing adequate symptom relief without the need for extensive programming and optimization.

In conclusion, directional deep brain stimulation (DBS) demonstrates clear superiority over omnidirectional DBS for the treatment of both obsessive-compulsive disorder (OCD) and autism spectrum disorder (ASD), but with nuanced differences for each disorder. For OCD, the precision offered by directional DBS allows for more effective targeting of hyperactive circuits within the cortico-striato-thalamo-cortical (CSTC) loop, particularly in regions like the subthalamic nucleus (STN) and anterior limb of the internal capsule (ALIC). The ability to steer

the electrical field reduces the risk of stimulating adjacent non-pathological structures, thereby minimizing side effects related to mood, cognition, or motor function. Clinical evidence strongly supports that directional DBS provides better symptom control in OCD patients, making it the preferred option over omnidirectional DBS, which lacks the precision necessary to avoid off-target effects.

For ASD, although the application of DBS remains experimental, directional DBS holds more promise due to the disorder's complexity and variability in neural substrates. The heterogeneous nature of ASD symptoms, which can involve specific deficits in repetitive behaviors, social cognition, and communication, requires a flexible and adaptable treatment approach. Directional DBS, with its ability to target specific circuits implicated in these core symptoms, offers a more tailored intervention compared to the broad and potentially disruptive stimulation of omnidirectional DBS. While research is still ongoing, the precision and adaptability of directional DBS make it a more effective option for managing ASD-related neurological dysfunctions.

How can the implementation of current steering in DBS expiate the drawbacks Unipolar electrode contact points induce in patients with OCD, ADS, and IED?

Unipolar electrodes, which emit electrical stimulation uniformly across all directions from a single point, often lack the precision necessary for effectively targeting specific neural circuits. This imprecision can result in unintended stimulation of adjacent brain regions, leading to a range of side effects such as mood disturbances, cognitive impairments, or motor dysfunctions. In the context of OCD and ASD, where the neural substrates are often complex, intricately connected, and vary significantly between individuals, these off-target effects can significantly undermine the therapeutic efficacy of DBS.

In the case of OCD, traditional DBS with unipolar electrodes typically targets areas such as the STN or ALIC within this loop. However, the non-selective stimulation associated with unipolar electrodes can inadvertently activate neighboring structures, such as the internal capsule or hypothalamus, resulting in side effects that range from mood alterations to motor disruptions. These adverse effects not only diminish the quality of life for patients but can also limit the therapeutic dosage of stimulation that can be safely applied, thereby restricting the effectiveness of the treatment.

Current steering technology addresses these limitations by providing clinicians with the ability to modulate the direction and distribution of the electrical current emitted by the DBS electrodes. Instead of dispersing the current uniformly, current steering allows for the adjustment of individual electrode contacts (Bonham et al., 2008). This capability enables the electrical field

to be directed toward specific areas of the brain while minimizing its impact on surrounding, non-target structures. The precision afforded by current steering is particularly beneficial in treating OCD, where the pathological circuits within the CSTC loop are often localized and require highly targeted intervention. By steering the current precisely toward these hyperactive circuits, clinicians can effectively disrupt the abnormal neural activity that underpins the disorder, thereby improving symptom control.

The targeted approach of current steering also reduces the likelihood of stimulating adjacent brain regions that are not involved in the pathological process (Chaturvedi et al., 2013). This reduction in off-target stimulation not only minimizes the risk of side effects, but also allows for the use of higher stimulation intensities where needed, without compromising patient safety. Furthermore, the ability to fine-tune the stimulation parameters based on the patient's specific neural architecture and response to therapy enables a more personalized treatment plan. This tailored approach is essential for optimizing therapeutic outcomes and reducing the burden of side effects, which is a significant concern in traditional DBS.

In ASD, the use of DBS is still largely experimental, but the potential benefits of current steering are equally, if not more, compelling. ASD is a heterogeneous disorder, characterized by a wide range of symptoms, including repetitive behaviors, social cognition deficits, and communication challenges. The neural circuits implicated in these symptoms are less well-defined and vary considerably among individuals with ASD. As a result, the broad and non-specific stimulation provided by unipolar electrodes can be particularly problematic. Unintended activation of non-pathological circuits can exacerbate symptoms or lead to new neurological disruptions, making it difficult to achieve the desired therapeutic effects.

Current steering offers a critical advantage in this context by allowing for more precise targeting of the specific neural circuits implicated in each individual's presentation of ASD. For example, targeting the amygdala or prefrontal cortex, which are regions involved in social cognition and emotional regulation, could potentially alleviate some of the core symptoms of ASD without affecting other brain areas that are not involved in the pathology. The ability to focus the stimulation on the dysfunctional circuits while avoiding off-target effects is particularly valuable given the complexity and variability of ASD symptoms. Additionally, current steering's precision allows for lower overall stimulation intensities, which reduces energy consumption and prolongs the battery life of the implanted pulse generator—an important consideration for long-term DBS therapy.

Despite the promise of current steering, it is not without challenges. The implementation of this technology requires advanced imaging techniques, such as diffusion tensor imaging (DTI) or tractography, to accurately map the neural pathways and optimize electrode placement. Moreover, the programming of current-steering DBS systems is more complex and time-consuming compared to unipolar systems. Clinicians must carefully balance the electrode

contacts, adjust the stimulation parameters, and monitor the patient's response to achieve the desired therapeutic effect. This complexity can increase the cost and time associated with treatment, making it less accessible in resource-limited settings. However, the significant improvements in precision, safety, and efficacy that current steering offers make these challenges worthwhile, particularly for patients with complex and treatment-resistant conditions like OCD and ASD.

In conclusion, current steering in DBS provides a substantial improvement over unipolar electrode contact points in both OCD and ASD treatments by enhancing precision and reducing side effects. For OCD, current steering allows for the focused modulation of hyperactive circuits within the CSTC loop, improving symptom control while minimizing the risk of off-target stimulation and associated side effects. This precision enables more effective treatment with fewer adverse effects, making current steering the superior approach for managing OCD. For ASD, the ability of current steering to selectively target the disorder's varied and complex neural substrates offers a more personalized and adaptable intervention, addressing the diverse symptoms of ASD with greater specificity and safety. While challenges remain in implementing this technology, the benefits it offers make it the preferred choice in DBS for both OCD and ASD, representing a significant advancement in the treatment of these neurological disorders.

Limitations:

The primary limitation in comparing DBS parameters—electrode size, current steering, and stimulation directionality—across OCD and ASD lies in the fundamental differences between the neural mechanisms underlying each disorder. OCD is characterized by hyperactivity in cortico-striato-thalamo-cortical (CSTC) circuits, whereas ASD presents more diffuse and complex alterations in brain connectivity. As a result, it is unlikely that a single set of DBS parameters will be equally effective in treating both conditions. For instance, while precise current steering may be critical for targeting the hyperactive circuits in OCD, it may not be as effective for ASD, where the connectivity abnormalities are more widespread. Similarly, the optimal electrode size or stimulation directionality that works for modulating OCD circuits could potentially miss key neural pathways in ASD or stimulate areas not relevant to the disorder's pathology. To optimize DBS treatment, it is essential to tailor stimulation parameters based on the specific neuroanatomical and symptomatic profiles of each patient. This individualized approach will help enhance symptom control while minimizing side effects, addressing the distinct neurological landscapes of OCD and ASD. Understanding these differences and customizing DBS settings will be key to increasing the overall efficacy of treatment across both disorders.

Future Directions:

In the field of DBS effectiveness, further research is required to improve stimulation accuracy and refine the precision of lead electrode contact points, particularly for complex cases of OCD and ASD. While this study highlights the benefits of smaller electrodes, current steering, and directional stimulation, future investigations should focus on developing more sophisticated imaging and targeting technologies. Advanced neuroimaging techniques could enhance our ability to map the intricate neural circuits involved in these disorders, ensuring that DBS electrodes are placed with greater accuracy.

Works Cited:

Alessandra Paffi, Francesca Camera, Filippo Carducci, Gianluigi Rubino, Paolo Tampieri, Micaela Liberti, Francesca Apollonio. "A Computational Model for Real-Time Calculation of Electric Field due to Transcranial Magnetic Stimulation in Clinics." *International Journal of Antennas and Propagation*, 2015, doi:10.1155/2015/976854. https://onlinelibrary.wiley.com/doi/full/10.1155/2013/262739.

Appali, R., Sriperumbudur, K. K., & van Rienen, U. "Extracellular Stimulation of Neural Tissues: Activating Function and Sub-threshold Potential Perspective." *Annual International Conference of IEEE Engineering in Medicine and Biology Society*, 2019, 6273-6277, doi:10.1109/EMBC.2019.8857113. PMID: 31947276.

Arcot Desai, S., Gutekunst, C., Potter, S. M., & Gross, R. E. (2014). "Deep Brain Stimulation Macroelectrodes Compared to Multiple Microelectrodes in Rat Hippocampus." *Frontiers in Neuroengineering*, 7, 75909. https://doi.org/10.3389/fneng.2014.00016.

Bonham, B. H., & Litvak, L. M. "Current Focusing and Steering: Modeling, Physiology, and Psychophysics." *Hearing Research*, 242(1-2), 141-153, doi:10.1016/j.heares.2008.03.006. PMID: 18501539; PMCID: PMC2562351.

Chaturvedi, A., Foutz, T. J., & McIntyre, C. C. "Current Steering to Activate Targeted Neural Pathways During Deep Brain Stimulation of the Subthalamic Region." *Brain Stimulation*, 2012, 5(3):369-377, doi:10.1016/j.brs.2011.05.002. PMID: 22277548; PMCID: PMC3360111.

Frey, J., Cagle, J., Johnson, K. A., Wong, J. K., Hilliard, J. D., Butson, C. R., Okun, M. S., & De Hemptinne, C. (2022). "Past, Present, and Future of Deep Brain Stimulation: Hardware, Software, Imaging, Physiology, and Novel Approaches." *Frontiers in Neurology*, 13, 825178. https://doi.org/10.3389/fneur.2022.825178.

Haynes, W. I. A., & Mallet, L. (2010). "High-frequency Stimulation of Deep Brain Structures in Obsessive-Compulsive Disorder: The Search for a Valid Circuit." *The European Journal of Neuroscience*, 32(7), 1118-1127. https://doi.org/10.1111/j.1460-9568.2010.07418.x.

Lin, X., & Gorfe, A. A. "Transmembrane Potential of Physiologically Relevant Model Membranes: Effects of Membrane Asymmetry." *Journal of Chemical Physics*, 153(10), 105103, doi:10.1063/5.0018303. PMID: 32933265; PMCID: PMC7484991.

Maggio, F., Pasciuto, T., Paffi, A., Apollonio, F., Parazzini, M., Ravazzani, P., & d'Inzeo, G. (2010). "Micro vs Macro Electrode DBS Stimulation: A Dosimetric Study." *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2010, 2057-2060. https://doi.org/10.1109/IEMBS.2010.5626487.

Perlmutter, J. S., & Mink, J. W. (2006). "Deep Brain Stimulation." *Annual Review of Neuroscience*, 29, 229-257. https://doi.org/10.1146/annurev.neuro.29.051605.112824.

Ramasubbu, R., Lang, S., & Kiss, Z. H. (2018). "Dosing of Electrical Parameters in Deep Brain Stimulation (DBS) for Intractable Depression: A Review of Clinical Studies." *Frontiers in Psychiatry*, 9, 367058. https://doi.org/10.3389/fpsyt.2018.00302.

Schnitzler, A., Mir, P., Brodsky, M. A., Verhagen, L., Groppa, S., Alvarez, R., Evans, A., Blazquez, M., Nagel, S., Pilitsis, J. G., Pötter-Nerger, M., Tse, W., Almeida, L., Tomycz, N., Jimenez-Shahed, J., Libionka, W., Carrillo, F., Hartmann, C. J., Groiss, S. J., … Vesper, J. (2022). "Directional Deep Brain Stimulation for Parkinson's Disease: Results of an International Crossover Study With Randomized, Double-Blind Primary Endpoint." *Neuromodulation : Journal of the International Neuromodulation Society*, 25(6), 817-828. https://doi.org/10.1111/ner.13407.

Xing, Y., Zan, C., & Liu, L. (2023). "Recent Advances in Understanding Neuronal Diversity and Neural Circuit Complexity Across Different Brain Regions Using Single-Cell Sequencing." *Frontiers in Neural Circuits*, 17, 1007755. https://doi.org/10.3389/fncir.2023.1007755.

Xu, T., Gao, Y., Li, B., Jiang, J., Guo, H., Liu, X., Huang, H., Cheng, Y., Yu, H., Hu, J., et al. (2022). "The Efficacy and Safety of Deep Brain Stimulation of Combined Anterior Limb of Internal Capsule and Nucleus Accumbens (ALIC/NAcc-DBS) for Treatment-Refractory Obsessive-Compulsive Disorder: Protocol of a Multicenter, Randomized, and Double-Blinded Study." *Brain Sciences*, 12(7), 933. https://doi.org/10.3390/brainsci12070933.

Zhang, C., Kim, S. G., Li, J., Zhang, Y., Lv, Q., Zeljic, K., Gong, H., Wei, H., Liu, W., Sun, B., Wang, Z., & Voon, V. (2021). "Anterior Limb of the Internal Capsule Tractography: Relationship With Capsulotomy Outcomes in Obsessive-Compulsive Disorder." *Journal of Neurology, Neurosurgery & Psychiatry*, 92(6), 637-644, doi:10.1136/jnnp-2020-323062.